

March 16, 2018

Under Secretary (Drugs)  
Ministry of Health and Family Welfare  
Government of India, Room No. 414 A, 'D' Wing  
Nirman Bhawan, New Delhi – 110011  
[Drugsdiv-mohfw@nic.in](mailto:Drugsdiv-mohfw@nic.in).

**BY E-MAIL**

**Re: New Drugs and Clinical Trials Rules, 2018, Ministry of Health and Family Welfare, G.S.R. 104(E) (Feb. 1, 2018): Comments and Recommendations of The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard**

Dear Honorable Under Secretary:

We write to you on behalf of the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard (the "MRCT Center"). Founded in 2009, MRCT Center has three primary goals: (1) to improve the design, conduct, and oversight of multi-regional clinical trials, especially trials sited in the emerging economies and developing world; (2) to simplify research through the use of best practices; and (3) to foster respect for research participants, efficacy, safety and fairness in transnational, trans-cultural human subjects research. Consequently, MRCT Center often comments on regulatory developments around the world and has submitted comments and recommendations to the Ministry of Health and Family Welfare (the "Ministry") on previous occasions.

As we have previously noted in written comments to the Ministry, the number of significant clinical trials of new drugs in India has declined in the wake of the adoption of new clinical trials regulations in India beginning in January 2013. This appears to reflect a negative reaction by many sponsors, investigators and clinical institutions to particular features of these new regulations, and in particular, provisions assigning financial liability to them irrespective of actual fault or culpability, as those concepts are traditionally understood in most jurisdictions and in clinical trials themselves. Recently, the Ministry has scaled back many regulatory requirements and made important strides in clarifying and refining its clinical trial regulations. Last year, we submitted comments on the proposed 2017 Draft Rules, in which we commended the Ministry for these changes. MRCT Center once again welcomes the Ministry's proposed new set of amendments to the Drugs and Cosmetics Rules, 1945, in furtherance of these goals (the "2018 Draft Rules"), which 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. We particularly commend the Ministry on its efforts to clarify and 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 will be manufactured and marketed in India.

MRCT Center acknowledges the Ministry's ongoing, dedicated efforts to improving India's clinical trial regulations. However, in our judgment, the 2018 Draft Rules – like the 2017 Draft Rules – require further clarification, and in our view, do not fully address the chilling effects the regulatory changes adopted beginning in 2013 have had on clinical trials activities in India. With this letter we are

submitting to you the comments of MRCT Center regarding issues that we believe could benefit from substantive change and/or greater clarity and precision. Our comments are limited to the provisions that relate to clinical trials research, specifically provisions found in Chapters I, III-VI of the draft rules, and the First, Third, and Seventh Schedules thereto. Our comments do not cover other issues, such as provisions relating to manufacturing standards.

### **Comments and Recommendations:**

#### **1. Injury Compensation and Required Medical Care**

Chapter VI of the 2018 Draft Rules provides important clarifications and refinements to the rules relating to culpability for subject injury and the obligations of sponsors or others to provide medical care to subjects. We suggest below some important areas in which additional refinements should be considered.

##### **a. List of Clinical Trial-Related Injuries**

One of the most significant regulatory changes adopted by the Ministry beginning in 2013 relates to injury compensation for clinical trial participants. MRCT Center has repeatedly commented on these provisions, and once again recommends that the Ministry consider refining these well-intentioned, yet overbroad provisions. As with the current regulations, Section 41 of Chapter VI of the 2018 Draft Rules provides an illustrative list of circumstances that, if occurring during a trial or study and leading to injury or death, must be considered “clinical trial related injury or death.” The 2018 Draft Rules’ version of this list misses the mark in the same way as its predecessor: by generally failing to acknowledge that the purpose of an investigational trial is to evaluate how the investigational product compares to the standard of care, with one of the treatment groups predictably faring worse or better than the other. Under Section 41(5)(iii) of the 2018 Draft Rules, the “failure of investigational product to provide intended therapeutic effect where, the required standard care or rescue medication, though available, was not provided to the subject as per clinical trial protocol” would constitute a compensable injury to a trial participant. However, 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. Indeed, without such results, clinical research could reach no reliable scientific conclusions. The risks of such outcomes are ever-present and are made clear to patients during the informed consent process.

Additionally, the list of “related to” circumstances in the compensation regulations now in effect includes the “[u]se 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.” As with the 2017 Draft Rules, in these latest draft rules this provision has been modified to “[n]ot providing the required standard care, though available to the subject as per clinical trial protocol in the placebo controlled trial.” While this clarifies that use of placebo alone is not problematic, it is unclear what is meant by “standard” or “available.” On the one hand, when standard of care for 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. As we have previously suggested, a superior regulatory approach to attribute responsibility for placebo-related injury would be to not require compensation for injuries “caused by” not receiving the standard of care in a placebo-

controlled trial, but rather to ban the use of placebos when (1) the condition under investigation is serious or life-threatening and (2) some local standard of care is available.

**b. Interim Compensation & Culpability for Injury**

Of particular concern to MRCT Center is the fact that the 2018 Draft Rules not only preserve the requirement that the sponsor compensate trial participants for all injuries deemed clinical trial-related under the aforementioned broad list, but also would increase the burden on sponsors, 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 finds the injury to be “related to” the trial under the broad existing definition of “related to”, then (1) the ethics committee must determine in its opinion the compensation to be paid based on the Seventh Schedule and (2) the trial sponsor, within 15 days of the ethics committee’s determination, must pay an interim compensation of 60 percent of the full compensation.

More concerning still is the footnote explaining that this interim compensation is irrevocable; even if the Drugs Controller General of India (“DCGI”) later determines that the death or injury was not related to the clinical trial, this interim compensation is not reimbursable to the sponsor. Under this proposal, the sponsor would be automatically assessed at least 60 percent of total compensation if the ethics committee 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. These provisions run contrary to traditional views of causation and liability, and go beyond what other countries’ regulatory regimes typically demand of trial sponsors. Such onerous requirements imposed irrespective of culpability likely will continue to deter the siting of clinical trials in India, despite the country’s enormous promise as a center of clinical trials activity. MRCT Center recommends either deleting this provision in its entirety or, alternatively, revising it such that the sponsor may be reimbursed for the interim compensation if the DCGI ultimately determines that the injury is not related to the trial.

This new provision relating to interim compensation is further complicated by the process prescribed by the rules for evaluating whether a serious adverse event is “related to” the trial or study. The current regulations provide two different pathways for assessing “relatedness” of the injury to trial participation: one for serious adverse events of death, and another for serious adverse events other than death. In the 2018 Draft Rules, however, these categories would be reclassified as serious adverse events resulting in death *or* permanent disability, on the one hand, and serious adverse events other than death or permanent disability, on the other. This new approach recognizes the severe impact of a permanent disability, and accommodates the separate detailed formula in case of permanent disability outlined in the Seventh Schedule. For death or permanent disability, while the 60 percent interim compensation is based on the ethics committee’s determination of relatedness, the final determination on causation and compensation is made by the DCGI based on recommendations from an expert committee assembled for this specific purpose. The expert committee and the DCGI are likely better equipped than local ethics committees to handle these complicated questions of causation and corresponding calculations based on compensation. Under this new interim compensation process, there potentially may be two determinations of compensation: the first, by the ethics committee, based on a finding of relatedness upon which the 60 percent interim compensation is based, and the second, a final determination of compensation by the DCGI based on the recommendations of the expert committee. It is unclear, however, to what extent the expert committee and DCGI will take into account the ethics committee’s opinion regarding the amount of compensation (upon which the 60 percent interim compensation is

based); the rules simply provide that the interim compensation paid, if any, will be subtracted from the final compensation amount: “the quantum of compensation to be paid shall be an amount which is less the amount paid as the interim compensation.” MRCT Center recommends deleting these provisions relating to interim compensation.

For serious adverse events other than death and permanent disability, the 2018 Draft Rules task ethics committees with conducting the causality assessment, but as we have commented previously, these committees typically lack the capacity to determine issues of causation and compensation. The 2018 Draft Rules permit the study subject or sponsor to “appeal” the order of compensation by the ethics committee to the DCGI, but nonetheless under this process it is the ethics committee tasked with evaluating causality and the quantum of compensation in the first instance. Further, although this limited avenue for an appeal of the *order of compensation* exists, the draft rules do not address a sponsor’s or investigator’s ability to appeal the finding underlying any award of compensation: the finding that the injury is **related to** the clinical trial. Additionally, it does not appear that such a right to appeal is available in connection with the imposition of the 60 percent interim compensation based on the ethics committee’s decision that death or permanent disability is trial-related.

In short, although the 2018 Draft Rules, like the 2017 Draft Rules, contain modest improvements to the process for evaluating whether serious adverse events are related to the clinical trial, these new draft rules are even more burdensome on sponsors, who may have to pay non-reimbursable interim compensation in case of death or permanent disability of a participant, even if the death or permanent disability is ultimately found to be unrelated to the clinical trial. Further, the 2018 Draft Rules lack specificity as to how the relevant body (whether that is the ethics committee, expert committee, or DCGI) will conduct causality assessments (particularly such causality assessments for consideration of interim compensation). Lacking in this proposal is any specific procedural mechanism by which investigators or sponsors may obtain comfort that their evidence and assessments regarding causality would be considered fully as part of the serious adverse event review process.

### **c. Responsibility for Medical Treatment Unrelated to Clinical Trial**

Under existing regulations, free medical management must be provided to subjects “as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.” Under the 2018 Draft Rules, for injuries suffered by a participant during a trial, the participant continues to be entitled to “free medical management . . . as long as required as per the opinion of investigator and the Ethics Committee.” Under this new provision, “relatedness” is not mentioned, and discretion is left up to the investigator and ethics committee. Although the investigator’s and ethics committee’s opinion may turn on the relatedness of the injury necessitating the medical care, the rules do not address explicitly the relevant considerations to be weighed by the investigator and ethics committee in making such a determination. As written, this rule would continue the obligation of the “sponsor or the person who has obtained permission from the Central Licensing Authority” to provide free medical management and “ancillary care” to clinical trial participants, regardless of whether the condition or injury that necessitates such medical management is related to the clinical trial. Under the Draft Rules, sponsors are financially responsible for all participants’ other non-trial related illnesses. Unlike the 2014 order establishing the “ancillary care” requirement, this obligation is not limited to medical treatment “for brief illness” but rather extends to the entire duration of the participation in the trial. 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, would incentivize persons to seek to enroll in trials, and would result in adverse selection of subjects. MRCT Center therefore recommends removing Section 41(1)-(4) and all references thereto from the draft rules.

#### **d. Assignment of Responsibility between Sponsor, Investigator, and Others**

Under the injury compensation regulations that were adopted in 2013, the burden of providing “medical management” and compensation for injuries incurred during a trial generally falls on the sponsor of a clinical trial. The 2018 Draft Rules provide greater clarity regarding the allocation of responsibility for providing medical management and compensation, by stating that the burden of providing compensation or free medical management pursuant to these provisions is that of the “the sponsor *or* of the person who has obtained permission from the Central Licensing Authority,” instead of the sponsor alone. 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 to conduct the trial, such as a contract research organization. As we have expressed in comments on prior draft rules, 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 responsibilities, and failure of discharging responsibilities, of the various parties. For example, a study sponsor should be responsible for medical care costs incurred in connection with injuries caused directly by a study drug, while investigators or clinical sites should be responsible for injuries stemming from negligent and inappropriate administration of a drug contrary to the approved research protocol. Given that the 2018 Draft Rules provide that responsibility would lie with either the sponsor or person who obtained permission to conduct the study we assume that the intent of this rule is to allow for apportionment of liability between each of these parties, according to their relative culpability.

We note that the 2017 Draft Rules had provided additional detail in this respect that is lacking in the 2018 Draft Rules, specifically that such responsibility may be apportioned through contract and a default responsible party in the absence of such an agreement. The provision in the proposed 2017 Draft Rules stated, “[t]he responsibility for medical management or compensation . . . shall be discharged by the sponsor or the person who has obtained permission from the Central Licensing Authority, *as per agreement entered between the sponsor and the investigator and the institution . . . .* Provided that *where no such provision exists in the agreement or in case of any dispute among parties, the person who obtained the permission for conduct of clinical trial shall be responsible.*” MRCT Center recommends adding substantially similar language in the 2018 Draft Rules to address more clearly the allocation of responsibility through contract. This provision in the 2017 Draft Rules, unlike its counterpart in the 2018 Draft Rules, also provides that absent any agreement, the responsibility falls on the entity that obtained permission to conduct the trial. The 2018 Draft Rules similarly should provide a default responsible party in absence of such an agreement; otherwise, it is unclear who would be responsible between the sponsor or the person who obtained permission to conduct the trial.

In our view, not only should the draft rules better address the mechanism by which such responsibility should be apportioned (*i.e.*, through contract, default falling on one agreed-upon party), but they also should not limit the potential responsible parties to the sponsor or person who obtained

permission to conduct the study; the “person who obtained permission” is typically a study sponsor or CRO, but not a study site or investigator. Therefore, to clarify what apportionment of responsibility is permissible, and to preserve the ability of parties to apportion responsibility based on actual culpability, wherever the phrase “sponsor or person who obtained permission” is used in reference to the obligation to provide compensation or medical management, we recommend other parties should be listed so that the phrase reads: “The responsibility for medical management . . . shall be discharged by *the sponsor, investigator, institution, or their contractors or agents* as per agreement entered between the sponsor and such parties.”

#### e. **Quantum of Compensation**

We commend the Ministry for clarifying provisions relating to compensation by incorporating the compensation formulae finalized in the Ministry’s December 15, 2014 order, which establishes a standard payment for lost wages equal to the “minimum wage per day of the unskilled worker (Delhi),” as the Seventh Schedule to the 2018 Draft Rules.

## **2. Reporting Serious Adverse Events**

Consistent with existing regulations, the 2018 Draft Rules require investigators to “report all serious adverse events to the Central Licencing Authority, the sponsor or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial, and the ethics committee that accorded approval to the study protocol, *within twenty four hours of their occurrence.*” As we have conveyed in previous comments, investigators may have difficulty meeting this reporting deadline given the possibility of delay between the occurrence of the adverse event and when the investigator becomes aware of the event. Further, participants may obtain care from a health care worker or facility that does not communicate with the investigator or even appreciate the potential relatedness of the event (illness/injury) to participation in the trial. Participants may live far from the research site and not be able quickly to inform the investigator, who in turn would not be able to quickly report to the DCGI. Investigators who fail to meet this timeframe are entitled to “furnish the reason for the delay to the satisfaction of the [DCGI.]” Nonetheless, the default notification period of 24 hours seems too short in some circumstances.

Similarly, the sponsor and the investigator are required to send their reports on serious adverse events to the central licencing authority, chairperson of the ethics committee and head of the institution on a compressed timeframe. Serious adverse events other than death and permanent disability must be reported “within fourteen days of the occurrence of serious adverse event.” Serious adverse events of death or permanent disability must be reported “within fourteen days of the knowledge of occurrence of serious adverse event of death or permanent disability.” The latter standard is more deferential to the concern expressed above regarding a delay in knowing when a serious adverse event occurs, and this standard of “knowledge of occurrence” rather than actual occurrence should be ported to all notification responsibilities for all serious adverse events. However, in addition to the possibility of delay between when a serious adverse event occurs and when the parties become aware of such event, many serious adverse events may require reviews that are too complex to be evaluated and reduced to writing within two weeks of being informed of such event. Therefore, additional timing flexibility for all notification requirements would be helpful.

MRCT Center therefore recommends that the words “within twenty-four hours of their occurrence” be replaced with “within twenty-four hours of reasonable knowledge of the serious adverse event.” All parties’ (the sponsor or its representative and the investigator) subsequent responsibility to “forward their reports . . . within fourteen days” should be replaced with “forward their reports . . . as soon as practicable.”

### **3. Ethics Committees**

The 2018 Draft Rules, like the 2017 Draft Rules, require institutions to have an in-house ethics committee and prescribe when use of an outside ethics committee is permissible. We reiterate that these requirements should be refined to be more flexible and better elucidate when an institution may rely on another institution’s ethics committee for review and approval of study protocols.

First, Section 6 of Chapter III appears to require institutions to have their own in-house ethics committees: “Any institution or organisation intends [sic] to conduct clinical trial or bioavailability or bioequivalence study shall be required to have an ethics committee.” However, Section 25 provides that permission to conduct a trial or study is subject to certain conditions, including that “where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the” (1) institutional ethics committee of another site or (2) an independent ethics committee provided that the approving ethics committee and clinical trial site “shall be located within the same city or within a radius of 50 km of the clinical trial site.” The provision in Section 6 requiring all institutions conducting trials or studies to have an in-house ethics committee is in tension with this provision in Section 25, which allows institutions to rely on another ethics committee *only if* the site or study centre “does not have its own ethics committee.” To rectify this discrepancy between the rules, we would recommend revising Section 6 to state the following: “*Any institution or organisation intending to conduct a clinical trial or bioavailability or bioequivalence study shall be required to conduct such trials or studies under the initial and continuing review of an internal or external ethics committee constituted in accordance with these rules.*”

Additionally, as we have noted in previous comments, there has been a recent, worldwide shift toward greater use of centralized ethics committees that are responsible for initial and continuing review of all, or many, study sites within a multi-site trial or study, such that even large, sophisticated research institutions with their own active ethics committees frequently are deferring to a central ethics committee. For India to remain an attractive site for clinical trials, these rules should reflect such trends, and therefore we would recommend loosening the pre-conditions described in Section 25. Specifically, clinical trial sites and bioavailability and bioequivalence study centres should be permitted to use an outside ethics committee even if such site or centre has its own ethics committee, and the requirement for outside ethics committees to be located within the same city or within a radius of 50 km of the site or centre should be eliminated. These provisions unnecessarily restrict an organization’s ability to rely on a central ethics committee for review, particularly in light of the myriad safeguards in place serving to ensure that the use of an external ethics committee does not result in diminished human subjects research oversight, such as the requirement that all ethics committees be registered with the DCGI and that clinical trials and bioavailability or bioequivalence studies of new drugs or investigational new drugs may only be carried out upon applying for and receiving permission from the DCGI to conduct such trial or study.

### **4. Biomedical and Health Research Ethics Committees**

The 2018 Draft Rules include a broad definition of “biomedical and health research,” touching upon any research designed to generate scientific knowledge about diseases and conditions. Although earlier proposed rules largely discussed ethics committees only in the context of clinical trials, the 2018 Draft Rules require “any institution or organization [that] intend[s] to conduct biomedical and health research” to have “an Ethics Committee to oversee the conduct of such research.” This requirement, coupled with the broad definition of “biomedical and health research,” would appear to oblige any entity conducting any sort of biomedical research— whether interventional human subjects research, observational human subjects research, or even most forms of non-human subjects biomedical research—to do so under the review of an ethics committee. MRCT Center recommends that the rules be revised into a more narrowly tailored set of parameters detailing the types of research that should be reviewed by a biomedical and health research ethics committee. For example, ethics committee review of an investigator’s protocol describing review of sensitive information within subjects’ medical records is often required in other jurisdictions and helps to protect the research subjects’ privacy rights. However, there are other types of important scientific research, *e.g.*, *in vitro* experiments done without generating any data identifiable to any living human, for which ethics committee review is altogether unnecessary. Requiring research institutions that focus on such research to have an ethics committee would pose a substantial burden on the ability to carry out many types of research in a cost-effective manner.

Therefore, we recommend that the Ministry narrow the scope of the rules regarding “biomedical and health research” so that this requirement applies only to interventional research with living humans or research that produces data identifiable to a living human.

## **5. Audio-Visual Consent**

The 2018 Draft Rules maintain the requirement within the current Schedule Y of the Drug 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.” 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.” 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.

## **6. Continuation of Experimental Drug after a Trial Has Concluded**

Section 27 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 ethics committee 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.” In case of agreement of the investigator, research participant and ethics committee, the sponsor

appears to be required to continue to provide the experimental drug, on a free basis. Although the provision appears to allow the investigator to declare to the participant that the sponsor shall have no liability for post-trial use of the investigational new drug or new drug, this proposed requirement is overly broad and would be unworkable in some circumstances. 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 ethics committee. This provision as drafted would also presumably require the sponsor to provide the former trial participant with a lifetime of free experimental drugs, including a drug treating a chronic condition. The obligations that would be imposed on sponsors by this provision would predictably discourage sponsors from undertaking trials of new drugs in India, to the detriment of patients and of national technological development.

\*\*\*

We at MRCT Center are grateful for this opportunity to provide comments, and we thank the Ministry for its attention to this submission.

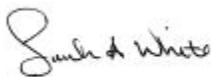
Respectfully Submitted,



Mark Barnes, JD, LLM  
**Faculty Co-Director & Co-Chair, MRCT Executive Committee**



Barbara Bierer, MD  
**Faculty Co-Director & Co-Chair, MRCT Executive Committee**



Sarah White, MPH  
**Executive Director, MRCT Center**