June 18, 2014

The Hon. Secretary Lov Varma
Department of Health and Family Welfare
Ministry of Health and Family Welfare
Government of India
Nirman Bhawan
New Delhi, India

Re: Draft Rules to Amend the Drugs and Cosmetics Rules (1945): Comments and Recommendations of the Multi-Regional Clinical Trials Center at Harvard University

Dear Honorable Secretary Varma:

We write to you on behalf of the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT), which in recent months has partnered with a number of India-based organizations in projects designed to improve clinical research in India and specifically to interpret and react to changes in clinical trials regulations. For example, in January 2014, Harvard MRCT, together with the Indian Society for Clinical Research (ISCR), the All India Institute of Medical Sciences, and the Apollo Hospital Education and Research Foundation held a multi-stakeholder roundtable to discuss the recommendations of the Prof. Ranjit Roy Chaudhury Expert Committee. The executive summary of this roundtable discussion is appended to these comments, as many of its recommendations pertain specifically to the proposed changes to the Drugs and Cosmetics Rules.

More recently, in May 2014, Harvard MRCT and ISCR have partnered to develop a Causality Task Force. Its goal is to provide a guidance document and training materials to enable clinicians and ethics committee members to follow best practice procedures in determining causality for participant injuries or illnesses occurring in the course of a clinical trial, a determination that is pivotal for determining appropriateness for compensation. We anticipate this document to be available in September 2014. Dr. Prem Pais serves as the chairperson and primary expert for this effort, and Dr. Usha Pingali and Dr. Shoibal Mukherjee are additional co-chairs of this Causality Task Force.

Founded in 2009, Harvard MRCT 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 the 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. Harvard MRCT often submits comments on regulatory developments around the world, especially when, as here, the proposed regulatory changes would affect the ability of vast numbers of

people to enroll in clinical trials and, in the longer term, their ability to get access to drugs and medicines approved in other jurisdictions.

We therefore, by this letter, are submitting to you the comments of Harvard MRCT on the Draft Rules, released on April 24, 2014, which represent proposed amendments to the Drugs and Cosmetics Rules of 1945. Harvard MRCT would like to express its gratitude for the Ministry's continued efforts to refine and improve India's clinical trial regulations. Although the Draft Rules are, in some cases, a step in the right direction, many of the proposed amendments require further clarification and more careful tailoring.

Unfortunately, as the Ministry is aware, the amendments adopted to the Drugs and Cosmetics Rules in January and February 2013 have had the effect of preventing the initiation of almost all new significant clinical trials of drugs in India. This has had a secondary consequence of crippling the clinical trials enterprise in India, which before the 2013 amendments had been developing robustly and was a centerpiece of national economic development. The lack of new clinical trials being initiated in India has resulted in India's citizens being deprived of access to cutting-edge new drugs, as in oncology and cardiology, and of the health services provided in the course of those trials. Even more alarmingly, however, the current lack of new clinical trials means that in the years to come, there will be no clinical trials data from Indian populations that can be used by CDSCO to evaluate new drug effectiveness and safety, leading to delays in the availability in India of important new drugs already approved in other countries and available to other national populations.

The current proposed amendments do not, we believe, adequately relieve the problems posed by the 2013 regulatory changes, and additional amendments are necessary to protect clinical trial participants while at the same time reinvigorating the clinical trial enterprise in India. Our specific comments on these most recent proposed changes are set forth below.

Comments and Recommendations:

1. **Medical Management**

The draft rules would require that the participant "be given free medical management" until "it is established that the injury is not related to the clinical trial."

First, this amendment places the burden of proof on the trial sponsor to establish that the injury is not related to the clinical trial. This is an inversion of traditional legal concepts, which require that in order to establish liability, proof must be brought forward to demonstrate that the clinical trial participation caused the injury. It is, in fact, generally not possible to "establish" or prove that one thing is not "related to" another, and it is much more straightforward and understandable to require an affirmative demonstration of actual causation. If the Ministry is concerned that this places a burden of proof on the injured participant, then it is important to note that the Expert Committee

is to be appointed by the Ministry, which therefore has the ability to appoint competent and unbiased judges of causation. Under the current and proposed adjudication process, the Ministry itself acts as the ultimate judge of causation, and in this role can act conscientiously to assure fairness to the injured participant as well as the sponsor. But requiring proof that one thing is not related to another is conceptually flawed, and this flaw is only perpetuated in the proposed amendment.

Second, the 2013 Drugs and Cosmetics (First Amendment) Rules impose a 30 day deadline upon the Expert Committee to make its recommendation regarding causality. They further impose a three month deadline upon the licensing authority to issue its final determination regarding causality. It is not at all clear that these deadlines will routinely be met, and could be delayed for many months past the regulatory deadlines. Harvard MRCT is concerned that such delays in the causality assessment will leave sponsors providing months of costly medical treatment for injuries that the Expert Committee and Ministry may eventually determine not to have been caused by the clinical trial. It is entirely predictable that faced with this uncertainty of obligation, sponsors will self-defer from conducting significant trials in India.

Third, there should be a concern that individuals with serious preexisting medical conditions may seek to enroll themselves in trials in order to receive, for several months, free medical care until the Expert Committee and licensing authority have determined that the preexisting condition was not caused by the trial. This would not only be unfair to sponsors, but also would wrongly incentivize individuals to volunteer for trials, as it would represent "undue influence" over potential participants. Again, this possibility will only dissuade sponsors from being willing to site clinical trials in India.

Recommendations:

The Ministry should provide an expedited causality assessment (for example, three weeks from initial injury report to determination of causation) for injuries that require a high level of treatment – perhaps defined as costing more than some set rupee figure per month. In emergency situations, it is appropriate for researchers and research clinics to provide medical care to injured participants, and indeed, most established industry sponsors do reimburse research sites for these emergency care costs. However, if an expedited causality assessment determines that the injury was not related to the clinical trial, then the government or the participant and his/her family should be obliged to reimburse the sponsor for the cost of treatment during the interval before final determination of causation. Finally, a sponsor should not be required to provide medical management if it can demonstrate that the participant made material misrepresentations about a preexisting condition during the trial enrollment process.

2. **Quantum of Compensation**

The draft rules add a sub-rule stating that the quantum of compensation shall commensurate with . . . loss of wages." This suggests that each injured participant will be compensated an amount that reflects the loss of his or her actual, individualized salary

or hourly wage. Note that the promise of compensation for lost wages could be viewed as undue inducement to prolong indisposition. However, the proposed compensation formula released on May 1, 2014, suggests a standard payment for lost wages equal to the "minimum wage per day of the unskilled worker (Delhi)." The draft rules must be made consistent with the proposed compensation formula.

Recommendations:

"Loss of wages" should be replaced with "minimum wage per day of the unskilled worker in Delhi." Alternatively, the draft rules should explicitly refer to the quantum formula without mentioning individual elements of the calculation.

3. **Compensation for Failure of the Investigational Product to Provide Intended Therapeutic Effect**

Under the draft rules, a sponsor must provide compensation for failure to provide therapeutic effect if the participant was injured because the clinical trial protocol failed to provide the participant with "standard care" that was "available." However, the rule fails to give further guidance on the meaning of the terms "standard care" and "available."

Moreover, the additional language does nothing to undo the fundamental misconception at the heart of the original provision requiring compensation for the experimental agent's "lack of therapeutic effect." A clinical trial of an experimental agent is undertaken because there is significant evidence (from in vitro studies, animal studies and studies with small numbers of humans) that the agent has therapeutic promise and that the positive therapeutic effect, when weighed with its adverse effects, may be significantly greater than (or, at a minimum, non-inferior to) that offered by standard therapy. Entering a clinical trial has never been a guarantee of receiving the best therapy, or even of standard therapy, and potential participants deserve full disclosure about the risks and benefits of enrolling in a trial. Because it is experimental, a clinical trial will never provide, to those receiving the experimental agent, a panoply of "standard care." Therefore, any injury that occurs to any participant receiving the experimental agent (such as those participants in the active arm of a randomized controlled trial) would be mandatorily compensated by the sponsor, even under this new proposed language.

In short, the original provision mandating compensation for failure of the experimental agent to have therapeutic effect is fundamentally flawed as policy, and the addition of the proposed language does nothing to ameliorate this.

Recommendations:

The original provision mandating compensation for the failure of the experimental agent to have therapeutic effect should be eliminated, and replaced by rigorous requirements that sponsors fully inform prospective participants of the risks and benefits of enrolling in a trial – including the risks that the experimental agent may be ineffective

or harmful, as well as the possibility that the experimental agent may be more successful than standard therapy.

If, however, the original provision is not eliminated, then it would be preferable to define "standard care" as calibrated to local medical practice. A sponsor should not be liable for a perceived failure to have provided care, when the participant would not have received that same care from a local practitioner or hospital. Further, the draft rule should make clear that "standard care" is not considered "available" unless the participant would have sought and reasonably would have been expected to receive the standard treatment but for his or her enrollment in the trial. The sponsor should not be financially liable for failing to achieve the intended therapeutic effect if the participant would not have been received the standard treatment in the first place – due, for example, to contraindications for that participant or due the general lack of availability of standard care.

4. Compensation for Use of Placebo

Under the draft rules, a sponsor must provide compensation for giving the participant placebo if the participant was injured because the clinical trial protocol failed to provide the participant with "standard care" that was "available." However, the rule fails to give further guidance on the meaning of the terms "standard care" and "available."

When standard of care for serious illness is reasonably available, it is generally regarded as unethical for a study design to include placebo. On the other hand, for conditions that are uncomfortable but not seriously threatening to health or life, then the use of placebo may be appropriate because it allows a more rapid and definitive proof of efficacy (or lack of efficacy) of the comparator agent, but participants must be fully informed about the chance that they will receive placebo, as part of the informed consent process. (Indeed, delivery of a placebo itself is often accompanied by a beneficial effect.) Injuries that occur to participants in this limited set of circumstances are not generally regarded as being compensable, because although uncomfortable and/or inconvenient, they are not serious threat to life or health, and the participant willingly entered the trial knowing of the chance that he or she might receive placebo.

Therefore, a superior regulatory design would not compensate for injuries "caused by" use of placebo, but instead would not allow the use of placebo when (1) the condition under investigation is serious or life-threatening and (2) some local standard of care is available. Compensation for injury related to use of placebo in trials of treatments for less serious conditions would not be appropriate, as the underlying design would have been judged to be ethical and participants, fully informed, would have chosen to enter the trial and endure the risk of receiving placebo, as well as the chance of the possible benefit of receiving the active comparator agent.

Recommendations:

Under the rule as originally drafted, "standard care" should be defined so as to be calibrated to local medical practice. This standard of care must reflect not only local medical practice for the patient's primary condition but also local medical practice for adverse events, side effects, or other incidental medical issues that arise during the course of the trial. A sponsor should not be liable for a perceived failure to have provided care, when the participant would not have received that same care from a local practitioner or hospital. Further, the draft rule should make clear that "standard care" is not considered "available" unless the participant would have sought and reasonably would have been expected to receive the standard treatment but for his or her enrollment in the trial. The sponsor should not be financially liable for failing to achieve the intended therapeutic effect if the participant would not have received the standard treatment in the first place – due, for example, to contraindications for that participant or due the general lack of availability of standard care.

However, a superior regulatory design would allow placebo only under certain limited conditions, described above; would require full informed consent for potential participants about the use of placebo; and would not compensate "injuries" from use of placebo in place of standard care when the study design and protocol has been approved by an ethics committee.

5. Responsibility of Sponsor to Report Serious Adverse Events

The draft rule requires that "any report of the serious adverse event be forwarded by the sponsor to the Licensing Authority . . . within fourteen calendar days of the ***occurrence*** of the serious adverse event."

Harvard MRCT is concerned that sponsors may have difficulty meeting this deadline because of significant delay between the occurrence of the adverse event and when the investigator has informed the sponsor of the event. Further, participants may obtain care from a health care worker or facility that does not communicate with the investigator or the sponsor or even appreciate the potential relatedness of the event (illness/injury) to participation in the trial. Many participants live far from the research site and may lack access to a method of quickly communicating with the investigator, who in turn would not be able to communicate rapidly with the sponsor.

Recommendations:

The words "occurrence of the serious adverse event" should be replaced with "reasonable knowledge of the serious adverse event."

6. Responsibility of Investigator to Report Serious Adverse Event

The draft rule requires that "any report of the serious adverse event be forwarded by the investigator to the Licensing Authority . . . within fourteen calendar days of the ***occurrence*** of the serious adverse event."

Harvard MRCT is concerned that investigators may have difficulty meeting this deadline because of significant 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. Many participants live far from the research site and may lack access to a method of quickly communicating with the investigator, who in turn would not be able to communicate rapidly with the Licensing Authority.

Recommendations:

The words "occurrence of the serious adverse event" should be replaced with "reasonable knowledge of the serious adverse event."

7. Causality Assessment

The Drugs and Cosmetics Rules give no guidance as to how Ethics Committees and the Expert Committee will conduct causality assessment. Ethics Committees are a body constituted to assess the risks, benefits and ethics of clinical trials. They currently lack the capacity to determine causation and compensation. Further, the existing process allows no formal opportunity for the investigator or the sponsor to make, and have considered, their own assessments of causation, and contains no method of appeal or neutral review of causation assessments by the Expert Committee. This is fundamentally unfair to sponsors and investigators, whose reputations – even leaving aside the liability risk to sponsors – may be impugned by inaccurate judgments of causation. This procedural unfairness is enhanced by the inversion of the burden of proof in these provisions, under which, for the sponsor to avoid liability, the lack of causation of the trial intervention must be proven – that is, requiring proof that something did not happen, rather than proof that it did.

To reiterate: the fundamental problems inherent in the current compensation regulations, even if all the present proposed changes are adopted, will yield a high level of regulatory uncertainty. This will continue to discourage sponsors and investigators, and will continue to deprive Indian citizens of the ability to choose to enroll in trials of promising treatments for serious illnesses.

Recommendations:

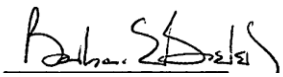
The Drugs and Cosmetics Rules must be amended to include detailed guidance on the causality assessment procedure. The rules should also allow formal opportunities for the sponsor, investigator and participant or his/her family to offer evidence of causation, or lack of causation. The rules should also provide the sponsor (and the participant) with a formal mechanism for appeal to a neutral adjudicator of Expert Committee findings related to causation.

* * *

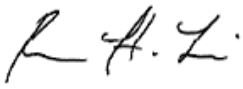
We hope you will give consideration to our points and recommendations, and we thank the Ministry for its attention to this submission.

Respectfully submitted,

Mark Barnes, JD, LLM
Harvard Faculty Co-Chair, Harvard MRCT



Barbara Bierer. MD
Harvard Faculty Co-Chair, Harvard MRCT



Rebecca H. Li, PhD
Executive Director, Harvard MRCT

Enclosure