January 11, 2015

Dr. Shailendra Kumar
Director (Drugs)
Department of Health and Family Welfare
Room No-301 'D' Wing, 3rd Floor
Nirman Bhawan, New Delhi-110011

Re: Drugs and Cosmetics (Amendment) Bill, 2015: Comments and Recommendations of the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT)

Dear Dr. Kumar:

We write to you on behalf of the Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT). We are pleased to learn that the Department of Health and Family Welfare (Department) proposes to introduce the Drug and Cosmetics (Amendment) Bill, 2015 (the Bill) in the Budget Session of the Parliament. Harvard MRCT, whose mission is to improve the planning, conduct and regulation of multi-regional clinical trials throughout the world, with a special emphasis on trials in the emerging economies, often comments on regulatory developments around the world. As you may be aware, we have submitted comments and recommendations to the Department on previous occasions as well. Harvard MRCT believes that India has the potential to emerge as a destination of choice for clinical trials of significant new drugs and devices, which could give citizens of India access to cutting-edge experimental therapies. This would not only directly and immediately benefit India's own citizens but would also contribute to the overall economic development of the country.

Harvard MRCT routinely advocates for respect for research participants, efficacy, safety and fairness in clinical trials and fully agree that these issues must be of primary concern for any regulator. A holistic regulation must, however, also account for the fact that there are other participants and actors in any clinical trial including investigators, sponsors and clinical research organizations. A regime that is conducive to clinical trials must therefore necessarily also account for the interests of these actors in a manner that is fair and reasonable.

Harvard MRCT recognizes that since new clinical trials regulations were adopted starting in January 2013, the number of significant clinical trials of new drugs in India has declined drastically, as many sponsors, funders, investigators and clinical institutions have felt that the regulatory regime has been uncertain and unfair, especially in regard to assigning financial liability to them when they are without fault or culpability. In this contact, new, well-drafted and clear legislative reform could assuage many of these concerns, and the Bill is indeed a welcome step in this direction.

Our effort in this letter, therefore, is to point out to the Department some of the issues that require further clarity and more precise rule making. Our specific comments are set out below and are limited to those provisions of the Bill that relate to clinical trials.

1. Section (zc), definition of "Sponsor": In the proposed legislation, this term is defined as "a person, a company or an institution responsible for the initiation, financing and management of a clinical trial." It is possible – and indeed often the norm – that different entities may initiate, finance and manage a clinical trial. A pharmaceutical or medical device company may "initiate" a clinical trial by contacting a clinical research organization, which would then "manage" the trial, and such a trial might be "funded" by that company in combination with yet another entity, such as medical research center conducting the trial, a government research funder (such as the U.S. National Institutes of Health (NIH)) or a philanthropic foundation (such as the Bill and Melinda Gates Foundation). In this proposed definition, therefore, there is ambiguity as to which of these entities would be deemed to be the "sponsor" of that trial.. The Bill provides for specific responsibilities and imposes liabilities on "sponsors." It is therefore important to define clearly which entity under what circumstances would be regarded as the sponsor. An ambiguous definition would have the effect of preventing various organizations and entities from coming together to conduct and support a clinical trial for the fear of incurring liability as a "sponsor." It would provide clarity, in the view of Harvard MRCT –and often be more accurate and appropriate -- to define the "sponsor" as the entity responsible for initiating a clinical trial and securing the approval of any cognizant governmental agency for conducting the trial. That entity is therefore also responsible for any required reporting to that cognizant agency. Under such a definition, the mere "funding" of a trial – as by a foundation or the NIH – or the "management" of a trial by a clinical coordinating center would not, by themselves, result in any of those entities being a "sponsor" of the trial. If a pharmaceutical company contracts with a CRO for the execution of the trial, the entity that applies for and secures approval from the cognizant government agency would be the entity held responsible by the government. The contract between the CRO and the pharmaceutical company might then reflect the assignment of financial liability, but only the "sponsor" as defined would be accountable to the government.

2. Determination of casualty: We note that pursuant to Chapter 1A, Section 4B of the Bill, "whether [an] injury or death of a person in the course of a clinical trial, has been caused due to such clinical trial or not, shall to be determined by such authority and in such manner as may be prescribed." Harvard MRCT welcomes the possible revision, according to this proposed legislation, of the compensation regulations and requirements that were adopted in 2013, as these regulations have led to a marked decline in significant new clinical trials undertaken in India. In this context, Harvard MRCT earlier (on June 18, 2014) provided comments to the Department on the determination of casualty, which we have again annexed to this letter, as Appendix A. In sum, Harvard MRCT recommended that the Government appoint Expert Committees that could make expedited casualty assessments, and that causality be determined according to scientific principles, rather than according to the standards set forth in the 2013 regulations, which essentially regard nearly any injury that occurs to a participant in a clinical trial as caused by that trial. Such an expedited assessment would ensure that a research participant injured as result of the trial immediately receives medical care and compensation while at the same time ensuring that sponsors and those conducting the trial would not be liable for injuries not caused by the trial itself. The proposed legislation, insofar as it directs a reconsideration and revision of the 2013 compensation regulations, would be welcome, and would allow an opportunity for the establishment of more scientific, appropriate and fair causality assessments.

3. Liability: Section 4C provides that where a participant dies or is injured or disabled "*in a clinical trial*, *the person or body permitted under section 4A and the sponsor* shall provide medical treatment and compensation". First, it would be appropriate to clarify that the liability to provide medical treatment and compensation should arise only if a determination of casualty,

consistent with scientific principles, has first been made under Section 4B. Otherwise, there may be ambiguity as to whether a person who is injured while in the course of participating in a clinical trial but due to factors other than the trial is entitled to compensation..

Second, in addition to sponsors, Section 4A permits clinical research organizations, investigators and "other organizations" to conduct clinical trials. Any clinical trial is bound to include a combination of these actors, and they are not mutually exclusive. Therefore, the current language leaves room for ambiguity as to which entity would be responsible for providing medical care and compensation for participants who have been injured as a direct result of participation in a trial, and to what extent and under what circumstances.. The current language also indicates that the "sponsor" would be liable in all circumstances. As we noted earlier, the definition of the word "sponsor" is itself not sufficiently clear. In short, MRCT recommends that in the legislation, as well as in any implementing regulations, 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 actual culpability of the various parties. Therefore, for example, a sponsor should be responsible for the cost of providing medical care and compensation if the injury has been caused directly by the study drug itself. If, however, injury has been caused by negligent and inappropriate administration of a study drug, then the investigator or clinical site whose actions have caused the injury should be responsible for providing medical care to treat the injury, as well as any required compensation. Legal and financial responsibility should, in short, follow culpable behavior that has led directly to the injury at issue.

4. Section 4K Penalty: Section 4K of the Bill sets out the penalties for "whoever himself, or by any other person on his behalf *conducts* clinical trial" in contravention of Section 4A and "the *rules made thereunder*". Under the current language, there could broadly be two potential scenarios in which Section 4K would come into play. One would be in cases in which entities conduct clinical trials without obtaining a permission under Section 4A. However, due to the wording of Section 4K, it could also apply in a situation in which a permission has been obtained under Section 4A but there has been some contravention of a "*rule"* during the course of the trial. Importantly, the sub-title to Section 4K reads as "penalty for conducting clinical trial…without permission." We also note that Section 4R separately provides for penalties for contraventions of any "rules." Therefore the intent appears to be that Section 4K is to apply *only* in cases in which a trial is conducted without obtaining a permission to conduct the trial. To avoid any ambiguity, it would be advisable to clarify that the penalties under Section 4K would apply *only* in cases in which a trial is conducted without obtaining the requisite permissions under Section 4A.

   Section 4K ascribes responsibility to "…*himself*, or by any other person on his behalf…" which implies holding *an individual* responsible for the conduct of a trial, not an entity, institution or organization. Section 4K therefore appears to be referring to the situation in which an individual physician-investigator conducts an investigation of a new drug or device without having obtained adequate approval. Yet there are situations in which the need for approval for a clinical study may be less than clear (e.g., a clinical study examining the effects of decreasing the number of cycles of approved chemotherapeutic regimens from 6 to 4, or a comparative effectiveness study of the effect of common off-label uses of an approved drug) and in which there has been a true misunderstanding by the physician-investigator as to the regulatory approval that should have been obtained. It would be unfair to apply criminal penalties strictly in such cases, but this ambiguity is not contemplated by the current proposed language if Section 4K.. .

Finally, Section 4K holds the [entity or] individual responsible for the actions of "*any other person on his behalf*…." The nature of clinical medicine and of clinical research is that a team of caretakers is involved in the care and treatment of a participant. Only in situations in which the principal investigator is directly responsible or has been willfully negligent should that individual be held accountable for the actions of others. The assignment of responsibility to the individual as currently written will discourage and deter investigators from participating in clinical research, as discussed further below.

5. Penalty for violation of conditions of permission: Section 4-O makes a distinction between violation of conditions of permission that causes "adverse effects" on participants and those that do not have such an effect. While violations that result in "adverse effects" may be punishable with imprisonment, only a monetary penalty would apply to violations that do not have such an effect. This is a welcome change from the earlier draft rules of 2013, which made all violations punishable with imprisonment.

   A major and troubling issue that remains, however, is that this provision does not distinguish between an intentional violation of a condition of a clinical trial and an inadvertent mistake or a genuine misinterpretation of such condition. An investigator may be acting in good faith but may inadvertently misinterpret a provision of an approved protocol, or may vary from conditions of an approved protocol in order to accommodate the health circumstances or personal needs of a participant – such as when an investigator determines that a participant has a transient health condition unrelated to the trial and that a clinical procedure required by the protocol should be deferred or delayed or avoided altogether. Unintentional mistakes, misinterpretations, and deviations from protocols that are intended to assist participants or accommodate participant needs should not result in criminal penalties. Indeed, these proposals to criminalize the conduct of trials by investigators do not comprehend that the conditions, requirements and conduct of clinical trials are enormously complex, and that strict adherence to all conditions of a protocol is almost never possible, given the vicissitudes of the life and conditions of participants, the unpredictable nature of actual health care delivery, and the fact that clinical treatment of patients enrolled in trials remains one of a physician/investigator's art and skill. Conducting a clinical trial is not, as these criminalization proposals seem to assume, mere rigid adherence to rules, regardless of circumstance.

   Therefore, in the view of Harvard MRCT, only intentional and malicious violation of a condition of a clinical trial, when it results in direct injury to or death of a subject, should be punishable criminally. Injuries that occur due to investigator's unintentional actions or misunderstanding, or due to interventions required solely for a trial would already be treated and compensated through the compensation scheme already incorporated into this legislative proposal, and do not require criminal penalties.

   Harvard MRCT also notes that the possibility of imposing criminal penalties on investigators that is conveyed by this proposed legislation will have a predictable chilling effect on the willingness of all physicians in India from participating as investigators in clinical trials. The spectre of criminal punishment and imprisonment for violation of a protocol would deter any physician from being willing to engage in clinical research activities – to the detriment of patients with serious or fatal conditions who would like access to cutting-edge experimental therapies, as in oncology, and to the detriment of the development of science and research in India. Except in the most carefully defined and egregious circumstances (such as intentional, malicious violation of an approved protocol), criminalization of research is unwise public policy. There are many ways – through training, education, monitoring and oversight – to assure appropriate conduct of clinical research, but criminalization is not the answer.

Without prejudice to the above, and notwithstanding Harvard MRCT's opposition to the criminalization of clinical research, we have two further comments on the way the proposed legislation is currently drafted. First, as noted earlier, there are several actors involved in any clinical trial, including sponsors, funding institutions, contract research organizations and investigators. It is therefore important to clarify in any legislative proposal exactly who would be deemed to be "conducting" a clinical trial and consequently responsible for contravention of a condition of permission. Secondly, "adverse effects" is much too expansive a standard to justify criminal imprisonment. A research participant who may develop a mild rash or a cold or a headache for a very short period of time would arguably be deemed to have suffered an "adverse effect" -- but this should hardly justify imposition of criminal imprisonment. If any criminal imprisonment is to be imposed at all, it should only be as a consequence of an intentional deviation from an approve protocol, undertaken for no reasonable cause, that has led directly to serious injury, significant disability, or death.

We would, as a final comment, suggest that the Government consider and implement the recommendations on the recent expert committee chaired by Dr. Ranjit Roy Chaudhury as they relate to the need to devote additional and adequate resources to CDSCO/DCGI, and that the status and powers of CDSCO/DCGI be enhanced, in order that the consideration, review, approval and monitoring of clinical trials be conducted more expertly, predictably, and efficiently. Having a high-quality, efficient and well-resourced agency is essential to securing the ability of that agency to make appropriate scientific and regulatory decisions, protect the safety and welfare of human participants in clinical trials, and facilitate clinical science in India.

We at Harvard MRCT are grateful for this opportunity to provide comments and hope that the Department and the Ministry will consider these suggestions, and those contained in the attached Appendix A. Please do not hesitate to contact us should you have any questions or require any clarifications.

Respectfully submitted,

Mark Barnes, JD LLM
Rebecca Li, Ph. D.
Adarsh Varghese, LL.B., BCL
Barbara E. Bierer, MD

On behalf of:

Multi-Regional Clinical Trials Center at Harvard University (Harvard MRCT)

Enclosed: Appendix A

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:

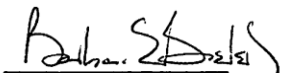
The Drugs and Cosmetics Rules must be amended to include detailed guidance on the causality assessment procedure. The rules should also allow formal opportunities for the sponsor, investigator and participant or his/her family to offer evidence of causation, or lack of causation. The rules should also 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
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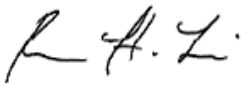

Rebecca H. Li, PhD
Executive Director, Harvard MRCT

Enclosure