GUIDANCE ON CONDUCTING RESEARCH IN INDIA

(UPDATED JANUARY 2017)

1. INTRODUCTION

- *Regulatory Landscape*
    - Over the past few years, there have been significant changes in India's regulations relating to research and clinical trials, largely resulting from media uproar over perceived injuries to human subjects in clinical trials in India. Consequently, in 2013, the Ministry of Health & Family Welfare amended India's Drug and Cosmetic Rules, requiring sponsors of clinical trials to provide compensation for death or serious adverse events ("SAEs") (discussed in further detail below). Other new regulations, including requiring audio-visual informed consent in some instances, have consequently made India a somewhat difficult place in which to conduct research.
    - This guidance aims to summarize some of the current regulations pertaining to clinical trials; however, as suggested above, Indian regulations have been in a state of flux over the past several years and likely will continue to evolve.
- *Relevant Entities*
    - Central Drugs Standard Control Organization ("CDSCO") (India's FDA equivalent)
    - Office of Drugs Control General ("DCGI") (India's licensing authority)
    - Ministry of Health & Family Welfare ("MoH")
- *Regulatory Mechanisms*
    - Drugs and Cosmetics Act 1940; Drugs and Cosmetics Rules 1945
    - Schedule Y (the Indian regulations for clinical research, issued by CDSCO)
    - Indian Council of Medical Research ("ICMR") guidelines; Indian good clinical practices guidelines

2. DEFINITION OF "CLINICAL TRIAL"

- Indian regulations' definition of "clinical trial" is a bit unclear, as several changes to the definition have been proposed over the years. However, it appears that the current definition is as follows:
    - *"[A] systematic study of any new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including*

pharmacodynamics and pharmacokinetic) and/ and/or adverse effects with the objective of determining safety and/or efficacy of the new drug."[1]

3. DEFINITION OF "SPONSOR"

- India's regulations do not appear to define "sponsor," but it seems that the sponsor is generally the applicant to DCGI for permission to conduct a clinical trial.
- If the applicant were an industry sponsor, the company would be the sponsor.
- In general, if a pharmaceutical company contracts with a contract research organization ("CRO") to conduct a trial in India, including making the application to DCGI, then the CRO is the sponsor.
- In the case of a funder such as the NIH, if an investigator or institution applies for a grant that is then funded, the investigator or institution (not the funder) is the sponsor—and the investigator or their designee would appropriately apply to DCGI for permission to conduct a clinical trial.
- India follows the International Conference on Harmonization ("ICH") guidelines as well as the guideline on Indian Good Clinical Practices ("GCP"). These guidelines place responsibility on the sponsor for selecting appropriate investigators, research teams, and sites.[2]
- India's GCP guidelines provide that before entering an agreement with an investigator/institution, to conduct a study, the sponsor should provide the investigator/institution with the protocol and an up-to-date Investigator's Brochure. Sponsor should provide sufficient time to review the Protocol and the information provided in the Investigator's Brochure.[3]

4. PREREQUISITES FOR CONDUCTING RESEARCH IN INDIA

- *Applications and Approvals*
  - Prior to initiating a clinical trial, the sponsor must receive permission from DCGI.[4]
  - The application to seek such permission is a Form 44.[5]
    - In 2015, India launched an online submission system for clinical trials, available at: https://octams.gov.in/[6]

[1] Central Drug Standard Control Organization. Gazette Notification ("G.S.R."), G.S.R. 69(E), available at http://www.cdsco.nic.in/writereaddata/G_S_R_%2069(E).pdf.
[2] *CDSCO, Good Clinical Practices,* CDSCO.NIC.IN, http://www.cdsco.nic.in/html/GCP1.html.
[3] *Id.*
[4] Drugs and Cosmetics Rules, Schedule Y ("Schedule Y"), § 1, http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf.
[5] *Id.*
[6] *Notice,* CDSCO.NIC.IN., http://www.cdsco.nic.in/writereaddata/newNotice%20for%20website%20OCTAMS.pdf.

- Approximate timeline for processing applications: 6 months.[7]

- The protocol must be approved by an ethics committee that is registered with CDSCO before starting a clinical study.[8]
- The clinical trial must then be registered on the ICMR maintained website at www.ctri.in.[9]
  - In order to conduct research projects with collaborators in India, the Indian collaborator is required to complete an application with the ICMR.[10]

- *Academic Research*
  - As of October 2015, permission from DCGI is no longer required for "clinical trials for academic/research purposes that are non-regulatory in nature . . . provided that, the trials were approved by the respective Ethics Committee and they are not for regulatory submissions (i.e. if the trial are not for claiming permission of New Drug for marketing as per Drugs and Cosmetics Rules)."[11]
- *Drugs and Devices*
  - In 2014, CDSCO issued an order stating that the approval procedure to be followed for clinical trials with devices would remain same as that followed for approval of clinical trials with drugs and vaccines.[12]
- *Protocol Amendments*
  - If a protocol amendment becomes necessary before initiation or during the course of a clinical trial, all such amendments should be sent to the Licensing Authority[13] (*i.e.*, DCGI) in writing along with the approval by the ethics committee which has granted the approval for the study.[14]

5. COMPENSATION FOR INJURY

[7] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[8] G.S.R.72(E); Rule 122 DD.
[9] "Initiated as a voluntary measure, since 15th June 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General (India) (DCGI) (www.cdsco.nic.in)." *Clinical Trials Registry – India,* CTRI.NIC.IN, http://ctri.nic.in/Clinicaltrials/login.php.
[10] "Applications for research projects involving foreign assistance and/or collaboration in biomedical/ health research are to be submitted by the Indian investigators to ICMR for approval of Govt. of India through Health Ministry's Screening Committee (HMSC)." *Guidelines for International Collaboration/Research, Projects in Health Research,* ICMR.NIC.IN, http://icmr.nic.in/guide.htm.
[11] Circular No. 12-01/14-DC (Pt. 47), CDSCO (October 11, 2015), http://www.cdsco.nic.in/writereaddata/Requirement%20of%20permission%20for%20conductd.pdf.
[12] File No. 12-01/14-DC PL47, CDSCO (July 3, 2014), http://www.cdsco.nic.in/writereaddata/oo3.pdf.
[13] "Licensing Authority" is defined as "the authority appointed by the Central Government to perform the duties of the licensing authority under these Rules." Drugs and Cosmetics Rules, Part IV, §21.
[14] Schedule Y (2)(iii).

- India adopted controversial regulations (Rule 122-DAB) in January 2013 (and amended in December 2014), mandating that sponsors provide compensation for injuries to participants in clinical trials.
- Rule 122-DAB: "Compensation in case of injury or death during clinical trial":[15]
    - *Medical Care for Injuries Generally*
        - Section 1 provides that, "[i]n case of an injury occurring to the subject during the clinical trial, **free medical management** shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier."[16]
    - *Compensation for Injuries Related to the Clinical Trial*
        - Section 2 states: "In case the injury . . . is related to the clinical trial, such subject shall also be entitled for **financial compensation** . . . over and above any expenses incurred on the medical management of the subject."[17]
            - If there is no permanent injury, "the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages and transportation."[18]
    - *Obligation on the Sponsor*
        - Such expenses related to medical management and financial compensation must be **borne by the sponsor** of the clinical trial.[19]
    - *Compensation for Clinical Trial Related Death*
        - In the case of death related to the clinical trial, the subject's nominee is entitled to financial compensation "over and above any expenses incurred on the medical management of the subject."[20]
    - *Totally Unrelated Causes*
        - The MoH has stated that compensation need not be paid for injury or death due to "totally proven unrelated causes."[21] In all other related cases of death or injury/disability, compensation should be paid to the participant or his legal heirs.[22]

[15] This rule was amended by G.S.R. 889(E) in December 2014, available at: http://mohfw.nic.in/WriteReadData/l892s/8492119051421383703.pdf.
[16] G.S.R. 889(E).
[17] *Id.*
[18] *Id.*
[19] Rule 122-DAB(2)(i)(4).
[20] Rule DAB-122(2)(i)(3).
[21] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[22] *Id.*

Section 5 of Rule 122-DAB provides the following illustrative list of **injuries** which must be considered **related to the clinical trial:**

(a) adverse effect of investigational product(s);

(b) violation of the approved protocol, scientific misconduct, or negligence by the Sponsor or his representative or the investigator;

(c) failure of investigational product to provide intended therapeutic effect where, the standard care, though available, was not provided to the subject as per the clinical trial protocol;

(d) use 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;

(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;

(f) for injury to a child in-utero because of the participation of parent in any clinical trial; [and]

(g) any clinical trial procedures involved in the study.

  - The MoH has also stated that institutions involved in academic trials "should create a fund" related to compensation for injury for clinical trials in order to encourage such research in institutions.[23]
  - CDSCO has issued an order specifying that compensation needs to be provided to clinical trial subjects for drug-related injury or death even if such injury is developed or death occurs after the completion of the trial.[24]

- *Compensation Covers*:
  - Payment for medical management
  - Compensation for trial related injury
  - Compensation to nominee(s) of the subject in case of death
  - Compensation for child injured in-utero due to participation of parent in trial[25]

[23] *Id.*
[24] File No. 12-01/14-DC Pt. 47, CDSCO (July 3, 2014), http://www.cdsco.nic.in/writereaddata/oo4.pdf.

- *Procedure*
    - The investigator must report all SAEs to the Licensing Authority, the sponsor or his representative, whoever obtained permission from the Licensing Authority to conduct the clinical trial, and the ethics committee **within 24 hours of the occurrence**.[26]
    - For death:
        - Compensation is determined by the recommendation of an independent Expert Committee.[27]
        - After reviewing reports from the sponsor and ethics committee, the Expert Committee gives its report to the Licensing Authority.
    - For SAEs other than death:
        - The ethics committee reviews the report from the sponsor and then passes along its opinion regarding financial compensation, if any, to the Licensing Authority within **21 days of the occurrence**.
        - The Licensing Authority must then determine the cause of injury and pass along the order.
- *Formula for Death*
    - The formula to calculate compensation for death was finalized in September 2013 with significant guidance from the Ministry's Expert Committee.[28]
        - The Expert Committee's rationale in developing the formula was to provide the nominee of the subject with a risk-adjusted and age-adjusted amount of compensation, that if placed in a bank would provide a "monthly interest amount which is at least approximately equivalent to the minimum wages [of an unskilled worker in Delhi.]"[29]

The formula is: Compensation = (**B x F x R) / 99.37**

B is the base amount equal to 800,000 rupees ($13,500)

F is the multiplier based on age and corresponding working years lost (found in an included table)

R is the risk factor based on the seriousness and severity of the subject's disease at the time of enrollment in the clinical trial (ranging from .5 for a terminally ill patient to 4.0 for healthy volunteers or no risk)

[25] G.S.R. 53(E), *available at* http://www.cdsco.nic.in/writereaddata/GSR%2053(E).pdf.
[26] *Id.*
[27] The January 2013 amendments to the Rules established an independent "Expert Committee" whose purpose is to provide the DCGI with recommendations, in individual cases of alleged clinical trial injuries, on "cause of death and quantum of compensation." G.S.R. 53(E).
[28] Compensation Formula (Clinical Trial), available at: http://www.cdsco.nic.in/writereaddata/formula2013SAE.pdf
[29] *Id* at 5.

- *Formula for SAEs Other Than Death*
    - On May 1, 2014, the Ministry proposed four separate draft formulas for clinical trial injuries: "Permanent Disability," "Congenital Anomaly or Birth Defect," "Chronic life-threatening disease" and "Reversible SAE in a case that is resolved."[30]
    - On December 15, 2014 the formulas were finalized, and are provided below:[31]

      Permanent Disability Amount = **(D x 90 x C) / (100 x 100)**

      D is percentage of disability

      C is Amount of Compensation due in the case of death

      Congenital Anomaly Amount[32] = **(C) / 2**

      C is Amount of Compensation due in the case of death

      SAE Causing Life Threatening Disease Amount = **(2 x N x W)**

      N is the number of days of hospitalization.

      W is Minimum wage per day of the unskilled worker in Delhi.

      Reversible SAE Amount = **2 x W x N**

      N is the number of days of hospitalization.

      W is Minimum wage per day of the unskilled worker in Delhi.

- *Penalties on Non-cooperating Sponsors*
    - If a sponsor fails to provide medical management or compensation to the subject or, in the case of death, compensation to subject nominee(s), then Licensing Authority may
        - Suspend/cancel the trial; and/or
        - Restrict the sponsor/sponsor's representative(s) from conducting any further clinical trials in India; or
        - Take any other action deemed necessary.[33]
- *Conclusion*

[30] Draft Formula to Determine the Quantum of Compensation In Case of Clinical Trial Related Injury (Other The Death), available at http://www.cdsco.nic.in/writereaddata/uploaded_for_website__1_FINAL2014.pdf.
[31] Ministry of Health & Family Welfare, Order: Compensation Formulae, file:///H:/My%20Documents/INDIA%20-%20Research/SAE%20compensation%20other%20than%20death.pdf
[32] Free medical management must also be provided to the child for as long as is required.
[33] Rule 122-DAB(7); G.S.R. 53(E).

- Under Rule 122-DAB, a clinical trial participant is entitled to have his or her medical costs covered for any injury during the clinical trial for "as long as required," regardless of whether the injury is related to the trial.
- Sponsors must also pay a participant "financial compensation" if his or her injury is related to the clinical trial, which based on Section 5 of Rule 122-DAB, broadly includes most injuries. Although such expenses must be borne by the sponsor of the clinical trial, that term is not adequately defined in the relevant regulations and therefore could potentially reach funders of a clinical trial, as well as academic institutions that are initiating a trial without external sponsorship.

6. REPORTING SERIOUS ADVERSE EVENTS

- *Definition*
  - G.S.R. 53(E) defines "Serious Adverse Events" as
    - *"[A]n untoward medical occurrence during clinical trial that is associated with death , in patient hospitalization (in case the study was being conducted on out-patient), prolongation of hospitalisation (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening."*[34]
- *Obligations on the Sponsor:* [35]
  - The sponsor must forward its report of an SAE of death and SAE other than death, after due analysis, to
    - The Licensing Authority,
    - The Chairman of the ethics committee and
    - The head of the institution where the trial has been conducted,
      - within **14 days** of the occurrence of the SAE.
- *Obligations on the Investigator:*
  - The investigator must report all SAEs to
    - Licensing Authority,
    - The sponsor,
    - Whoever obtained permission from the Licensing Authority, and
    - The Ethics Committee
      - within **24 hours** of their occurrence.[36]

[34] G.S.R. 53(E)(e).
[35] G.S.R. 889(E).

- If the investigator fails to report any SAE within the timeframe, he or she must explain the delay to the Licensing Authority along with the report of the SAE.[37]
- The investigator must forward its report of the SAE of death or SAE other than death to
  - The Licensing Authority,
  - The Chairman of the ethics committee and
  - The head of the institution where the trial has been conducted
    - within **14 days** of the occurrence of the SAE.[38]

- *Obligations on the Ethics Committee:*
  - In case of SAE of death or SAE other than death occurring to the clinical trial subject, the ethics committee must "forward its report along with "its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, to the Licensing Authority" within **30 days** of the occurrence of the SAE.[39]
    - The Licensing Authority will then forward the report of the investigator, sponsor or his representative, whoever obtained permission for the clinical trial, and the ethics committee to the Chairman of the Expert Committee.[40]

7. ETHICS COMMITTEE REQUIREMENTS

- In India, "all proposals on biomedical research involving human participants should be cleared by an appropriately constituted Institutional Ethics Committee."[41] The ethics committee must review trial protocols to safeguard the rights, safety and well being of trial subjects.[42]
- Ethics committees must consist of not less than 7 members, including a quorum of 5 members with the following representations:
  - Medical scientist
  - Clinician
  - Legal expert

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[36] G.S.R. 53(E).
[37] G.S.R. 889(E).
[38] G.S.R. 889(E).
[39] *Id.*
[40] G.S.R. 889(E).
[41] *Ethical Guidelines For Biomedical Research on Human Participants*, ICMR.NIC.IN, http://www.icmr.nic.in/ethical_guidelines.pdf.
[42] Schedule Y, Section 5, http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf.

- Social scientist or ethicist or representative of non-governmental voluntary agency
- Lay person

- *Registration*
  - Pursuant to G.S.R. 72(E), prior to reviewing and approving a clinical trial protocol, an ethics committee must register with the Licensing Authority.[43]
  - The registration is generally valid for three years from date of issue.[44]
- *Reporting SAEs*
  - As stated above, the ethics committee must examine any SAE reported by the investigator and send its report to DCGI along with the recommendation of compensation.
  - CDSCO's checklist and information about the format of such reports can be found here: http://www.cdsco.nic.in/writereaddata/System%20of%20Pre-screening%20for%20submission%20of%20reports%20of%20SAEs%20to%20CDSCO.pdf.
- *Other Obligations*
  - Due to the aforementioned compensation for injury regulations, the ethics committee may be responsible for reviewing and determining causality and compensation.[45]
  - Ethics committees should maintain all documents related to the clinical trial proposals, and retain all records for a minimum period of 5 years after completion or termination of the trial.[46]
  - Ethics committees should allow DCGI officials to conduct inspections and follow all related national and international guidelines.[47]
  - The committee must also prepare a constitution and standard operating procedures ("SOPs") for its operation, which should include the members, conditions of appointment, the offices and the quorum requirements.
- *Ethical Guidelines*
  - India's guidelines regarding human research protections are called the *Ethical Guidelines For Biomedical Research on Human Participants*, and are available at: http://www.icmr.nic.in/ethical_guidelines.pdf.

[43] G.S.R. 72(E), *available at:* http://cdsco.nic.in/writereaddata/G.S.R%2072(E)%20dated%2008.02.2013.pdf.
[44] *Id.;* Drugs and Cosmetics Rules, 122-DD(7).
[45] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[46] Central Drugs Standard Control Organization, Good Clinical Practices, 2.4.2.8, http://www.cdsco.nic.in/html/GCP1.html.
[47] Schedule Y, Appendix VIII(5); G.S.R. 72(E).

- The ICMR also has SOP guidelines for ethics committees available at: http://icmr.nic.in/ethics_SOP.pdf.

8. ACCREDITATION AND CERTIFICATION REQUIREMENTS FOR INVESTIGATORS, ETHICS COMMITTEES AND CLINICAL TRIAL SITES

- *Accreditation Recommendation*
  - An Expert Committee under the Chairmanship of Prof. Ranjit Roy Chaudhury formed by the MoH recommended that clinical trials should be conducted only at accredited sites by accredited investigators with the oversight of accredited ethics committees.[48]
    - The Expert Committee's report recommended that all clinical trial sites must accredited by a newly formed Central Accreditation Council.[49]
  - The report also recommends that all principal investigators be certified, although the process for such certification is not specified.
- *MoH Action*
  - In November 2013, CDSCO issued a statement that it would adopt and implement mandatory accreditation of ethics committees, investigators and research sites.[50]
  - In the short term, CDSCO stated that it would consider the non-governmental Quality Council of India for creating a system for accreditation of investigators, ethics committees, and clinical trial sites.[51]
- *Proposed Accreditation Standards*
  - The National Council of India has been given the mandate and funds to establish standards for accreditation of investigators, ethics committees, and sites. The National Accreditation Board for Hospitals and Healthcare Providers ("NABH") has developed standards for accreditation.[52]
  - These standards lack specificity, but rather express the intent that any accredited organization will have standards, including provisions for:
    - Ethics committee
      - Composition;
      - Procedures for new induction and resignation of members;

[48] *Draft Standards and Application Format for Accreditation of Ethics Committee, Investigator, and Clinical Trial Site,* CDSCO.NIC.IN, http://www.cdsco.nic.in/forms/list.aspx?lid=2074&Id=23.
[49] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[50] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[51] *Id.*
[52] *National Accreditation Board for Hospitals and Healthcare Providers (NABH),* CDSCO.NIC.IN, http://www.cdsco.nic.in/writereaddata/finalAccreditation%20Standards.pdf.

- Frequency of ethics committee meetings;
- Receipt, review and decision making of proposals;
- Review of protocol amendments;
- Procedure for deliberations and maintaining minutes;
- Periodic review and oversight;
- Procedure to be followed for vulnerable population;
- Review of informed consent document and informed consent process etc.

▪ Investigators

- Investigator's role and responsibilities;
- Investigator's education, qualification and experience;
- Investigators to follow site SOPs and study protocol for all essential trial activities

▪ Clinical Trial Sites

- Subject protection policy, informed consent, including procedures for audio-visual recording of consent;
- Medical management of adverse events;
- Adverse events and SAEs reporting (including emergency care);
- Roles and responsibilities of the study team;
- Site research team training;
- Research pharmacy (investigational product management);
- Protocol compliance and protocol deviations etc.

o *Resources*

▪ NABH's draft accreditation standards for clinical trial sites, ethics committees and investigators are available at: http://www.cdsco.nic.in/writereaddata/finalAccreditation%20Standards.pdf.

▪ The application for accreditation is available here**:** http://www.cdsco.nic.in/writereaddata/Format%20for%20Application%20for%20Accreditation.pdf

9. INFORMED CONSENT

- In India, informed written consent is required to be obtained from each study subject, and in some instances, discussed below, audio-visual consent is required.[53]
- *Basic Requirements*
    - The essential elements required for informed consent are set forth below, as well as in Appendix V of the Drugs and Cosmetic Rules:[54]
        1. Statement that the study involves research and explanation of the purpose of the research.
        2. Expected duration of the Subject's participation.
        3. Description of the procedures to be followed, including all invasive procedures.
        4. Description of any reasonably foreseeable risks or discomforts to the Subject.
        5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
        6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
        7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.
        8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials).
        9. Statement describing **the financial compensation and medical management** as under:

            (a) In the event of an injury occurring to the clinical trial subject, such subject shall be provided free medical management as long as required.

            (b) In the event of a trial related injury or death, the Sponsor or his representative, whosoever has obtained permission from the Licensing Authority for conduct of the clinical trial, shall provide financial compensation for the injury or death.[55]
        10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury.
        11. The anticipated prorated payment, if any, to the Subject for participating in the trial.

[53] Schedule Y, § 4.
[54] *Available at*: http://www.cdsco.nic.in/writereaddata/Drugs&CosmeticAct.pdf.
[55] Added by G.S.R. 53(E).

12. Subject's responsibilities on participation in the trial.
13. Statement that there is possibility of failure of investigational product to provide intended therapeutic effect.
14. Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have therapeutic effect.[56]
15. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled.
16. Any other pertinent information.

- *Format*
  - The format is set forth in the Drugs and Cosmetic Rules, 1942, which is provided below as **Appendix A.**
  - Prior to the beginning of the study, the investigator should obtain the ethics committee's approval for the written informed consent form and all information being provided to the subjects.[57]
  - According to G.S.R. 53(E), "the investigator shall provide information to the clinical trial subject through informed consent process . . . about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death."
  - The investigator should also inform the subject or his or her nominee of their right to contact the sponsor or whoever obtained permission from the Licensing Authority for the purpose of making claims in case of trial related injury or death.[58]
- *Audio Visual Consent*
  - In 2013, CDSCO issued an order requiring audio-visual recording of informed consent when enrolling new subjects in *all* clinical trials conducted in India:
    - "[A]n audio-video recording of the informed consent process of individual subjects, including the procedure of providing information to the subject and his understanding of such consent, shall be maintained by the investigator on record."[59]
  - However, a final amendment enacted on July 31, 2015 cut back on this requirement.[60] Now, an audio-video recording must be maintained by the

[56] G.S.R 364 (E), *available at* http://cdsco.nic.in/writereaddata/GSR%20364Ejune13.pdf; G.S.R. 611(E), *available at* http://www.cdsco.nic.in/writereaddata/Gazette%20Notification%2031%20July%202015.pdf.
[57] Good Clinical Practice Guidelines, CDSCO.NIC.IN, http://www.cdsco.nic.in/html/GCP1.html.
[58] G.S.R. 53(E).
[59] G.S.R 364 (E), *available at* http://cdsco.nic.in/writereaddata/GSR%20364Ejune13.pdf; G.S.R. 611(E), *available at* http://www.cdsco.nic.in/writereaddata/Gazette%20Notification%2031%20July%202015.pdf. cdsco.nic.in/writereaddata/Office%20Order%20dated%2019.11.2013.pdf.
[60] G.S.R. 611(E).

investigator "in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity." For anti-HIV and antileprosy drug-related trials, only an audio recording must be maintained.[61]

- The order does not explain which patients will be considered "vulnerable" and therefore trigger the audio-video recording requirement. There is some guidance in the existing language of Schedule Y, which mentions "vulnerable subjects" in the section on "Responsibilities of the Ethics Committee"—which is located just after the section on "Informed Consent"— and provides this illustrative list of such subjects:
  - Members of a group with hierarchical structure (e.g. prisoners, armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, u[n]employed or impoverished persons, patients in emergency situation[s], ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally given consent.

- Nonetheless, because it does not appear that the MoH has provided any clarification, there is uncertainty surrounding who is a ''vulnerable'' subject under the new provision in Schedule Y.

10. DATA PRIVACY

- India has an Information Technology Act, available at http://meity.gov.in/content/information-technology-act.
- *Definitions*
  - The rules apply to the "**body corporate**" handling the data. "Body corporate" is defined as "any company and includes a firm, sole proprietorship or other association of individuals engaged in commercial or professional activities."[62]
  - "Reasonable security practices and procedures" means "security practices and procedures designed to protect such information from unauthorised access, damage, use, modification, disclosure or impairment, as may be specified in an agreement between the parties or as may be specified in any law for the time being in force and in the absence of such agreement or any law, such reasonable security practices and procedures, as may be prescribed by the Central Government . . . ."
  - Providers of information are the persons who provide sensitive personal data or information to a body corporate.[63]

[61] *Id.*
[62] Information Technology (Amendment) Act, 2008, Section 43A, *available at* http://meity.gov.in/sites/upload_files/dit/files/downloads/itact2000/it_amendment_act2008.pdf.
[63] Clarification on Information Technology (Reasonable Security Practices and Procedures and Sensitive Personal Data or Information) Rules, 2011 Under Section 43A of the Information Technology ACT, 2000 PRESS NOTE, *available at* http://pib.nic.in/newsite/erelcontent.aspx?relid=74990.

- "Personal information" means any information that "relates to a natural person, which, either directly or indirectly, in combination with other information available or likely to be available with a body corporate, is capable of identifying such person."[64]
- In 2011, the Ministry of Communications and Information Technology issued a rule under the Information Technology Act, G.S.R. 313(E), which sets forth various provisions regarding "sensitive personal data or information," defined as information relating to:

    1. password;
    2. financial information such as Bank account or credit card or debit card or other payment instrument details ;
    3. physical, physiological and mental health condition;
    4. sexual orientation;
    5. medical records and history;
    6. Biometric information;
    7. any detail relating to the above clauses as provided to body corporate for providing service; and
    8. any of the information received under above clauses by body corporate for processing, stored or processed under lawful contract or otherwise. [65]

- *Transfer of Information*
    - The rules provide that sensitive personal data or information may be transferred to any other corporate body or "a person in India, or located in any other country," provided that entity ensures the same level of data protection adhered to by the body corporate.[66]
    - Such transfers are permissible only if:
        - Necessary for the performance of the lawful contract between the body corporate or any person on its behalf and provider of information; or
        - Where such person has consented to data transfer.[67]
- *Reasonable Security Practices and Procedures*

[64] Ministry of Communications and Information Technology, G.S.R. 313(E), http://meity.gov.in/sites/upload_files/dit/files/GSR313E_10511(1).pdf.
[65] *Id.*
[66] *Id.*
[67] *Id.*

- Body corporate must implement security practices and standards and have a comprehensive documented information security program.
- It must also have information security policies with technical, operational and physical security control measures.
- In case of an information security breach, the body corporate or a person on its behalf must demonstrate that they have implemented such security control measures.[68]

- *Privacy Policy*
  - The body corporate, or any person who on behalf of body corporate, collects, receives, possess, stores, deals or handle information of provider of information, must provide a privacy policy for handling such information.
  - This policy must be made publicly available on the website of the body corporate.[69]

- *Consent*
  - Under G.S.R. 313(E) rule 5 provides that "[b]ody corporate or any person on its behalf shall obtain consent in writing through letter or Fax or email from the provider of the sensitive personal data or information regarding purpose of usage before collection of such information."[70]
  - The rule also provides that "[w]hile collecting information directly from the person concerned, the body corporate or any person on its behalf shall . . . ensure that the person concerned is having the knowledge of — (a) the fact that the information is being collected; (b) the purpose for which the information is being collected; (c) the intended recipients of the information . . . ."[71]

- *Disclosure*
  - G.S.R. 313(E) rule 6 states:
    - "Disclosure of sensitive personal data or information by body corporate to any third party shall require prior permission from the provider of such information, who has provided such information under lawful contract or otherwise, unless such disclosure has been agreed to in the contract between the body corporate and provider of information, or where the disclosure is necessary for compliance of a legal obligation."[72]
  - The Ministry has since clarified that the rules set forth in G.S.R. 313(E) are applicable to the body corporate or any person located within India.

[68] *Id.*
[69] *Id.*
[70] *Id.*
[71] *Id.*
[72] *Id.*

- "Any such body corporate providing services relating to collection, storage, dealing or handling of sensitive personal data or information under contractual obligation with any legal entity located within or outside India is **not** subject to the requirement of Rules 5 & 6. Body corporate, providing services to the provider of information under a contractual obligation directly with them, as the case may be, however, is subject to Rules 5 & 6." [73]

- Therefore, if an Indian corporate body collects information under a contract with an organization in or outside India, the consent and disclosure requirements do not apply to that processor Indian corporate body; it instead would be governed by the contract with the other corporate body. However, the other aforementioned requirements, including publication of privacy policy, transfer conditions, and implementation of security controls, appear to remain applicable to the processor Indian corporate body.
- The Ministry also clarified that consent includes consent given by any mode of electronic communication.

- *De-Identification*
  - It does not appear that the Ministry of Communications and Information Technology or other entity has issued guidance on de-identification or anonymization of sensitive personal data, and thus local counsel may need to be consulted when transferring or handling sensitive personal data or information in an anonymized or de-identified format, to assure that use and/or transfer of such data are not restricted by Indian law.

11. ROY CHAUDHURY COMMITTEE REPORT, MINISTRY RESPONSE

- In July 2013, the Roy Chaudhury Committee issued a lengthy report on a number of topics related to the drug approval process in India, and included in its report were recommendations related to the compensation issues posed by the amendments to 122-DAB.[74]
- The recommendations included an obligation of the sponsor to provide medical care for all ancillary conditions of enrolled subjects, even if those conditions bear no relation to the trial and the test drug.[75]
- In November 2013, the MoH responded to the recommendations, and as a result, the following changes, among others, were adopted:[76]

[73] Clarification on Information Technology (Reasonable Security Practices and Procedures and Sensitive Personal Data or Information) Rules, 2011 Under Section 43A of the Information Technology ACT, 2000 PRESS NOTE, *available at* http://pib.nic.in/newsite/erelcontent.aspx?relid=74990.
[74] In early 2013, the MoH empanelled an ad hoc committee, chaired by Dr. Ranjit Roy Chaudhury of Apollo Hospitals, to review the performance of CDSCO and DCGI and to make suggestions as to how to improve that performance. *See* Report of Prof. Ranjit Roy Chaudhury Expert Committee, July 2013, *available at* http://www.cdsco.nic.in/writereaddata/Report_of_Dr_Ranjit_Roy.pdf.
[75] *Id.*

- *Ancillary Care*
  - On July 3, 2014, CDSCO issued an order stating that "all Sponsors / Manufactures [sic]/Clinical Trial Applicants are hereby advised that such ancillary care should be provided to the clinical trial subject for brief illness in the same hospital/trial site, wherever required."[77]
  - Enrolled subjects are now entitled to medical care for all ancillary conditions, even if those conditions bear no relation to the trial. It does not appear that "ancillary care" has yet been defined in the rules.
- *Accreditation*
  - As discussed in Section 8 above, the MoH decided that clinical trials should be conducted in accredited sites by accredited Investigator with the oversight of accredited ethics committees.
- *Restrictions on Number of Clinical Trials Per Investigator*
  - India initially passed an order prohibiting any investigator from conducting more than three trials at any time.
  - However, in August 2016, CDSCO released an order removing that restriction, stating: "[the] Ethics Committee after examining the risk and complexity involved in the trial being conducted/proposed shall decide about how many trials an investigator can undertake."[78]
- *Review of Clinical Trials*
  - Applications of clinical trials and new drugs are initially evaluated by Subject Expert Committees and their recommendations will be reviewed by the Technical Review Committee.
    - However, all proposals of clinical trials and new drugs need not be evaluated by the Technical Review Committee.
  - If India participates in global clinical trials of New Chemical Entities ("NCEs") to be used for diseases prevalent in India after approval for marketing in the innovator country, approval should be sought from CDSCO for marketing these NCEs in India.
- *Placebo-Controlled Trials*
  - For placebo-controlled trials, the pharmaceutical companies, investigators, and the ethics committees must ensure that the design used in a placebo controlled clinical trial is appropriate, efficient and ethical.
- *Post-Trial Access of Investigational Product*

[76] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[77] Order, File 12-01/14-CD (Pt. 47), CDSCO (July 3, 2015), http://www.cdsco.nic.in/writereaddata/oo5.pdf.
[78] Circular, File 12-01/14-CD (Pt. 47), CDSCO (August 2, 2016), http://www.cdsco.nic.in/writereaddata/restricion%20of%20conducting%20three.pdf

- MoH's position is that if an NCE is found to be beneficial in the clinical trial, the trial participants should have post-trial access to such NCE.[79]
- According to the February 16, 2015 meeting minutes of the Drugs Technical Advisory Board, "[t]he DTAB after deliberation recommended that Post Trial access of the investigational products may be provided to the subject found beneficial during the course of the trial on the basis of the recommendations of the investigator and ethics committee especially in the cases where no alternative therapy is available to the patient. However, such Post Trial access of the investigational product should be permitted after obtaining the consent of the patient, however, there would not be any liability of the sponsor in use of the drug. The sponsor shall arrange to provide the drug in such cases free of cost as the drug might not yet have been permitted to be marketed. Drugs and Cosmetics Rules, 1945 may be amended appropriately."[80]
- ICMR Guidance cites favorably to the Declaration of Helsinki, stating, "at the end of the trial every participant should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."[81] It also states: "[W]henever possible I\EC should consider such an arrangement in the a priori agreement. Sometimes more than the benefit to the participant, the community may be given benefit in indirect way through improving their living conditions, establishing counseling centers, clinics or schools, and giving education on maintaining good health practices."[82]
- The guidance acknowledges that "[f]or smaller scale or student projects post trial benefit to the participants may not be feasible but keeping in mind the post trial responsibility conscious efforts should be made by the guides and the institution to initiate steps to continue to support and give better care to the participants."[83] Finally, later in the guidance it states: "After the clinical trial is over, if need the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in the country and thereafter at a

[79] Actions on the Recommendations of Prof. Ranjit Roy Chaudhury Expert Committee, November 6, 2013, available at http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf.
[80] See Minutes of the 68th Meeting of Drugs Technical Advisory Board Held on 16th February, 2015 at CDSCO, HQ, FDA Bhawan, Kolsta Road, New Delhi, http://www.cdsco.nic.in/writereaddata/newMinutes%20of%2068th%20DTAB%20meeting.pdf. CDSCO acknowledged, but did not provide any guidance on, the status of this DTAB meeting in its report: "In the 68th meeting of DTAB held on 16.02.2015 recommendations were made in respect of . . . Post Trial Access of the new investigational product and consideration of compensation in the cases of injury or death discerned at later stage and collection of ADRs in the country, prescreening meetings with the applicants in respect of clinical trials." *Steps Taken By CDSCO in February, 2015 In Making Its Services Responsive, Efficient and Transparent,* CDSCO.NIC.IN, http://cdsco.nic.in/writereaddata/Steps%20taken%20in%20Jan%20&%20Feb,%202015%20docx%20(1).pdf.
[81] *Ethical Guidelines for Biomedical Research on Human Particpants,* ICMR.NIC.IN, pg. 30, http://www.icmr.nic.in/ethical_guidelines.pdf.
[82] *Id.*
[83] *Id.*

reduced rate for the participants whenever possible. A suitable a priori agreement should be reached on post trial benefits."[84]

- *Penalties for Informed Consent Violations*
  - An investigator can be debarred from clinical trials for any violation of the informed consent process.
- *Information Technology*
  - Those involved with clinical trials must use information technology to ensure total transparency in the system. Beginning with the filing of the application, each step in the clinical trial must be recorded and "made available in the public domain."
- *Approval of New Drugs*
  - The MoH decided to continue the current practice of allowing all NCEs/NMEs undergoing clinical trials anywhere to undergo parallel Phase II and Phase III Clinical trials in India after carrying out safety assessment of Phase I Clinical Trial data generated abroad.
  - For new entities developed in India and to be marketed in India, it is not necessary for all phases to be conducted in India:
    - Phase I and Phase II trial may be conducted in India or outside India.
    - Phase III trials should be conducted in India before the drug is considered for approval in the country.
    - Phase IV trials are required to be conducted in India to assess the safety of such drug in post market scenario.
- *Regulatory Bodies*
  - The MoH also said that CDSCO will be bolstered and given additional resources, and that the status of DCGI will be upgraded.[85]

12. DRAFT BILL 2015 AND OTHER UPDATES

- *Drugs and Cosmetics Act (Amendment) Bill, 2015*
  - On December 31, 2014, the government released a draft of a new bill that would amend the Drugs and Cosmetics Act of 1940.[86]

[84] *Id.*
[85] *Id.*
[86] *Available at:* http://www.cdsco.nic.in/writereaddata/D&%20C%20AMMENDMENT%20BILL(1).pdf. Amendments to the statute must go through a parliamentary process, while the government in power can amend rules on its own. Therefore, even if the 2015 reform bill is passed in its proposed form by the Indian Parliament, the government would then need to issue relevant rules to define in detail how the statute will be implemented.

- Based on CDSCO's website, this remains a "draft" bill and has not yet been finalized.[87]
- The 2015 proposed reform bill appears to build and modify the existing compensation framework, primarily by requiring that the relevant regulatory authority develop new rules— instead of simply rehashing the rules in Rule 122-DAB—prescribing how a clinical trial should be conducted and when an injury is "due to" a clinical trial and therefore compensable.
- The 2015 bill would add a new chapter to the Drug and Cosmetics Act, 1940—Chapter 1A, entitled ''Clinical Trials.''
  - Section 4A of that chapter leaves no question that all parties involved in carrying out a clinical trial—regardless of the precise definition of ''sponsor'' or ''investigator''—will be subject to the regulatory authority's "prescriptions:"
    - "No person, sponsor, clinical research organisation or any other organisation or investigator, shall conduct any clinical trial in respect of a new drug, [or] investigational new drug . . . in human participants except under, and in accordance with, the permission granted by the Central Licensing Authority in such form and manner as may be prescribed."
- Also, similar to a draft bill proposed in 2013, the 2015 bill contains significant criminal penalties for those who conduct trials without proper authorization to do so, or who conduct trials in violation of clinical trial regulations.

- *Drugs and Cosmetics Act (Amendment) Bill 2013*
  - In August2016, the Indian government decided to withdraw the Drugs and Cosmetics (Amendment) Bill, 2013.
  - CDSCO also released a notice stating that the MoH plans to "re-visit the Drugs and Cosmetics Act, 1940 and Rules, 1945 to match up with the current regulatory requirements related to safety, efficacy and quality of drugs, medical devices and cosmetics." The government has therefore suggested that it plans to draft a fresh law. It is unclear what effect if any this has on the 2015 Bill, but CDSCO still has it listed on its website.[88]
- *Bed Requirements for Trial Sites*
  - India formerly required that trials be conducted at sites with more than 50 hospital beds, but in August 2016, CDSCO released an order essentially eliminating this

[87] *Acts and Rules*, CDSCO.NIC.IN, http://www.cdsco.nic.in/forms/contentpage1.aspx?lid=1888.
[88] F. No. D-21013/63/2016-DC, CDSCO (June 6, 2016), *available at* http://www.cdsco.nic.in/writereaddata/Noticedatede06_6_2016.pdf; *The Drugs and Cosmetics (Amendment) Bill, 2013*, prsindia.org, http://www.prsindia.org/billtrack/the-drugs-and-cosmetics-amendment-bill-2007-2903/.

requirement, stating that the ethics committee simply must decide whether the trial site is suitable.[89]

- *Preclinical/Toxicology Studies*
    - In November 2015, CDSCO released a circular stating that "if a new drug was already approved outside India after conducting pre-clinical/toxicological studies on animals, such studies are not required to be repeated while approving their proposal for import/manufacture in India unless there were specific concerns."[90]
- *Adding Trial Sites and Investigators*
    - In November 2015, CDSCO also released a circular stating that ethics committees can approve requests for new clinical trial sites and new investigators to be added to a clinical trial without CDSCO's approval as long as the ethics committees conduct "due diligence."[91]
    - The ethics committees would still have to inform DCGI of the changes, and DCGI would be able to object to any such additions or deletions of sites or investigators.[92]
    - CDSCO published an additional circular in August 2016 providing that clinical trial sponsors no longer must obtain a no objection certificate (NOC) from DCGI each time they add a site or investigator to a study.[93]

13. ADDITIONAL RESOURCES

- CDSCO has a checklist for various types of applications:
    - http://cdsco.nic.in/writereaddata/Checklist%20of%20New%20Drugs.pdf
- The MoH's Actions on the Recommendations of the Chaudhury Expert Committee (setting forth various changes to the approval of new drugs, clinical trials, and banning of drugs):
    - http://www.cdsco.nic.in/writereaddata/Action_RR_Choudhury_Committee__06.11.2013.pdf
- ICMR Ethical Guidelines:
    - http://www.icmr.nic.in/ethical_guidelines.pdf
- Schedule Y (regulations on clinical trials):

[89] Circular, File 12-01/14-CD (Pt. 47), CDSCO (August 2, 2016), http://www.cdsco.nic.in/writereaddata/requirement%20of%2050%20bedded%20.pdf.
[90] Circular, File 12-01/14-CD (Pt. 47), CDSCO (November 11, 2015), http://www.cdsco.nic.in/writereaddata/removing%20the%20practice%20of%20repetition.pdf
[91] Circular, File 12-01/14-CD (Pt. 47), CDSCO (November 11, 2015), http://www.cdsco.nic.in/writereaddata/NOC%20for%20DCGI.pdf
[92] *Id.*
[93] Circular, No. 12-01/14DC (Pt-47), CDSCO (August 3, 2016), http://www.cdsco.nic.in/writereaddata/noc.pdf.

  - http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf

- Checklist for submitting registration of ethics committee:
  - http://www.cdsco.nic.in/writereaddata/CHECKLIST%20FOR%20SUBMISSION%20192013.pdf
- Checklist for good manufacturing/good laboratory practices:
  - http://www.cdsco.nic.in/writereaddata/publicnoticechecklist28_5_2016.pdf

APPENDIX A

FORMAT OF INFORMED CONSENT FORM

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name:_____

Date of Birth / Age: _____

Address of the Subject: _____

Qualification: _____

Occupation: Student / Self-Employed / Service / Housewife / Others (Please tick as appropriate)

Annual Income of the subject: _____

Name and address of the nominee(s) and his relation to the subject: _____ (for the purpose of compensation in case of Trial related death)[94]

	Please initial box (Subject)
(i) I confirm that I have read and understood the information sheet dated ___ for the above study and have had the opportunity to ask questions.	[ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my	[ ]

[94] From "Address of the Subject" until "Name and address of the nominee(s) was added by G.S.R. 53(E).

medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____ Date:
_____/_____/_____

Study Investigator's Name: _____

Signature of the Witness _____ Date:_____/_____/_____

Name of the Witness: _____

(Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject or his/ her attendant)[95]

[95] G.S.R. 53(E) added this.