Harvard MRCT

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MRCT Multi-Regional Clinical Trials

The MRCT Center at Harvard

MRCT Center at Harvard: India Regulatory Update, Causality and Compensation

Building A Learning Community Among Key Stakeholders

Parlimentary Review

In 2011, Indian Parliament formed a committee to report on functioning of CDSCO, following the deaths of seven girls who had died while on an HPV vaccine observational study.

- *The Committee concluded that subjects who died were not adequately compensated and that compensation should be paid to the next of kin.*

- *The Committee also concluded that DCGI lacked clinical/scientific expertise and not able to judge exact scientific rationale as well as the appropriateness of conducting specific trials.*

In 2012, a public interest litigation (PIL) was filed before the Supreme Court of India against the MoHFW alleging several flaws in regulatory framework surrounding clinical trials in India.

In early 2013, the Supreme Court suspended the power of CDSCO/DCGI to approve clinical trials

New regulations followed

In Jan and Feb, 2013, the government issued new rulings, that essentially curtailed or inhibited the introduction of new trials in India.

These rulings mandated:

- Compensation in the case of injury or death during a clinical trial, to be provided by sponsor (not investigator or site)
- Sponsor to provide subject free medical management for injury during trial, for as long as required
- If injury related to the clinical trial, subject also entitled to financial compensation from sponsor
- If subject dies during trial, his/her nominee is entitled to financial compensation "over and above any expenses incurred on the medical management of the subject."

“Trial-related injury or death”

Defined very broadly as any injury during a trial due to:

- Adverse effect of investigational product(s) – even if anticipated
- Violation of the approved protocol, scientific misconduct or negligence by sponsor, sponsor representative, or investigator
- Failure of investigational product to provide the intended therapeutic effect
- Use of placebo in a placebo-controlled trial
- Adverse effects due to concomitant medication, excluding standard care, necessitated as part of approved protocol
- Injury to child in-utero due to participation of parent in trial
- Any clinical trial procedures involved in the study

Compensation

Formula:

$$\text{Compensation} = \frac{B * F \times R}{99.37}$$

Base amount is 800,000 rupees.

F is a multiplier based on age and corresponding working years lost.

R is the Risk Factor (factors seriousness and severity of the disease, presence of co-morbidity and duration of disease of the subject at the time of the enrollment in the clinical trial. Multiplier 0.5-4)

Range of formula is from 400000 rupees ($6667) to 73600000 rupees ($122666)

For death: **Expert** Committee recommendation, Licensing Authority determines

For serious adverse events other than death: **Ethics** Committee recommends, Licensing Authority determines

Relationship of causality to compensation

Compensation definition extremely broad (at this time). AEs thought to be “related to” the trial are, for example:

(1) the failure of the experimental agent to have the desired effect

(2) any harmful effect of a clinical trial procedure, even if the procedure was part of the standard of care for the condition

(3) the worsening of a condition that could have been expected due to the natural history of the disease condition.

Compensation

The amendment clarifying expectations for compensation of clinical trial related injury or death states that compensation will be made for:

(a) Adverse effect of investigational product(s)

(b) Violation of the approved protocol, scientific misconduct or negligence by sponsor or its representative or the investigator

(c) Failure of investigational product to provide intended therapeutic effect

(d) Use of placebo in placebo-controlled trial

(e) Adverse effect due to concomitant medication excluding standard care, necessitated as part of approved protocol

(f) For injury to child in utero because of the participation of parent in clinical trial

(g) Any clinical trial procedures involved in the study

See Ministry of Health and Family Welfare. GSR 53(E). Central Drugs Standard Control Organization, India. 2013 Jan 30. Available from: http://cdsco.nic.in/writereaddata/ GSR%2053(E)%20dated%2030.01.2013.pdf.

And other regulations and/or office orders:

- Ancillary care for any other illness afflicting patients in a clinical trial
- Clinical trials must be conducted in accredited site after review by accredited (and registered) IRB/REC, and only involving certified (accredited) investigators
- Clinical investigators may participate in no more than three clinical trials at any one time
- 50% of clinical trials must be performed in public hospitals with over 50 beds

Every informed consent must be video-recorded by a videographer and preserved

Structural issues

- Reorganization of CDSCO, and review of trial applications by CDSCO to be done within 3 months
- Drugs to be marketed in India must involve trials in India; BA and BE studies should not be allowed for drugs to be exported and not sold within India.
- Drugs marketed for more than 4 years outside India, may apply for a license for sale in India with ‘bridging’ studies or 4 year monitoring studies
- No regulations for devices

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MRCT has partnered with AIIMS, AHERF, ISCR, FERCI and others to assist with clinical trials reform implementation

AHERF

From left to right: Barbara Bierer (MRCT/HMS); GN Singh (Drug Controller General of India), YK Gupta (AIIMS), Ranjit Roy Chaudhury (Apollo), Shri RK Jain (Additional Secretary, Ministry of Health and Family Welfare)

Global Regulatory Engagement – India

MRCT Center in the last year has focused on India regulatory issues including:

- Proposed India regulatory reforms relating to required certification for investigators, and accreditation for research sites and or IRBs/RECs
  - Introduction of AAHRPP, ACRP, and PRIM&R
- Compensation for injury standards – global comparative research project
- Understanding of causality assessment for determination of relatedness
- Videotaping of informed consent process – confidentiality and ethics
- Limitation of involvement of most competent investigators to 3 trieals

Developments

Prime Minister Narendra Modi elected in May 2014 with majority vote and mandate for change, and clear appreciation for importance of business and innovation. Bharatiya Janata Party (BJP) in control of Parliament.

Appointment of Dr. Harsh Vardan as Minister of Health and Family Welfare on 26 May 2014.

Removal of Dr. Harsh Vardan in early November, 2014 – to Ministry of Science and Technology

Appointment of Shri Jagat Prakash Nadda as the Union Minister for Health and Family Welfare on November 10, 2014.

Many believe that little will be finalized before resolution of the pending Supreme Court PIL case

Certification and Accreditation

- Quality Council of India chosen as central agency in charge of standards and accreditation, including defining process and inspections

- QCI published draft standards, posted on National Accreditation Board for Hospitals & Healthcare Providers (NABH) this week:

  http://nabh.co/Notice_draft_accreditation_standards.aspx#sthash.ZFPCfUxD.dpuf

  Comments due by December 15, 2014

AV Recording

Audiovisual recording should be mandated only for a subset of clinical trials:

- Required when the subject is willing to participate but is not willing to provide written consent.
- Required for vulnerable populations
  - Mentally Incapacitated
  - Institutionalized Individuals
  - Children
  - Prisoners
  - Terminally-Ill Patients
  - Students
  - Subordinate Staff

General concerns and recommendations regarding Phase I enrollment.

3 Trials per Investigator

General agreement that three trials per investigator is arbitrary, not based on quality, quantity, stage or complexity of trail nor investigator capacity to conduct trials in consideration of other responsibilities.

Explicit responsibility of trial sponsors to select appropriate investigators

3 proposals pending:

1. Eliminate numerical cap and transfer responsibility to IRB/REC to review
2. “Count” only actively enrolling trials
3. Raise the ‘count’ to 6.

Compensation

- Injury must be caused by clinical trial, not just occurring while enrolled in a trial
- Eliminate liability for therapeutic failure of experimental agent
- Liability for injury in placebo arm only if standard of care has been denied
- Causality determination important

Note: even with these modifications, many questions remain

Causality Determination

Project Deliverables:

A “how to” primer detailing points to consider in determining causality of an adverse event and the likelihood it is caused by the treatment.

PI – Professor Prem Pais

Guidance can be used to:

- assure causality assessments are conducted consistently across jurisdictions
- deliver training in various international settings
- delineate when unblinding is justified
- develop case studies

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Causality Assessment Workshop for Clinical Trial Investigators

Delhi, India November 22, 2014
~35 principal investigators attended
Guidance draft document circulated

Agenda:

- Background
- Important definitions
- Distinction between cause & correlation
- Steps Involved in ADR diagnosis
- Causality Assessment by different stakeholders
- Common methodologies to assess causality
- WHO-UMC system and modification thereof
- Case studies

Table 1: Recommended Data

No.	Information to be Collated	Suggested Source
1.	Adverse event description: symptoms, signs, laboratory test results, pathological findings, etc.	Adverse Event Report and Follow-Up Reports
2.	Adverse event term or phrase that fits the event described under item #1.	Adverse Event Report and Follow Up Reports
3.	List of known adverse effects of the drug.*	Safety and Tolerability Section of the Investigator's Brochure
4.	Approved labels of other drugs of the same class.	Regulatory authority database.
5.	Description of mechanism of action and pharmacological actions of the drug.	Pharmacology Section of the Investigator's Brochure
6.	Date and time of last dose of drug before onset of event.	Patient history or hospital/clinic notes
7.	Pharmacokinetic parameters of the drug: time to peak plasma concentration; half-life.	Pharmacology Section of the Investigator's Brochure
8.	Date and time of onset of event.	Adverse Event Report and Follow-Up Reports
9.	Dose of drug, frequency, duration of continuous use till last dose before onset of event.	Prescription, hospital notes and patient history
10.	Name/description of underlying disease for which the patient was receiving the drug.	Hospital/clinic notes
11.	Any complications of underlying disease present at onset of event.	Hospital/clinic notes
12.	Concomitant illnesses the patient was suffering from at onset of event.	Hospital/clinic notes
13.	Duration of pregnancy at onset of event and EDD or actual delivery date, if applicable.	Hospital/clinic notes
14.	Cause of underlying physical/mental stress or injury, if any.	Patient history, hospital/clinic notes
15.	Surgeries in the past 3 months	Hospital/clinic notes
16.	Literature linking disease and background conditions to the event, if any.	Literature search through the Internet or other sources
17.	Concomitant medicines consumed by the patient within 7 days prior to onset of event.	Patient history, hospital/clinic notes
18.	Approved labels of concomitant medicines being taken by the patient.	Regulatory authority database
19.	Action and toxicity of traditional and alternative medicines being taken by the patient.	Literature search through the Internet or other sources
20.	Addiction history and use of recreational substances by the patient prior to onset of event.	Patient history, hospital/clinic notes
21.	Action, toxicity, and interactions of recreational substances used by the patient, if any.	Literature search through the Internet or other sources
22.	Post-event history: evolution of event; changes in therapy; treatment of event, with precise details.	Hospital/clinic notes

***"Drug" refers to the investigational product**

Table 2: Revised WHO-UPC system for clinical tri

Q#	Question	T1 Ref*
1	Is the drug or other drugs of the same class known to have this adverse effect? **Guidance**: *Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable information available on the drug.*	1-4
2	If the answer to question 1 is "No", is the event consistent with the known pharmacological, toxicological or immunological action of the drug? **Guidance**: *Consult the Investigator's Brochure, approved labeling or prescribing information, and other reliable pharmacological information available on the drug.*	5
3	Did the onset of the event occur within a reasonable time after the last dose of the drug to justify an association between the drug and the event? **Guidance**: *Consider the half-life of the drug and whether the drug persists within the body. Drugs are generally washed out of the body within 5-6 half-lives, but some drugs are known to persist in isolated compartments even after they are washed out from the blood. Sometimes, some drugs can trigger a pathological process that manifests itself long after the drug has been eliminated from the body - although this is extremely rare.*	6-8
4	Was the event of acute nature that would be expected to correlate with circulating concentrations of the drug within the body? **Guidance:** *E.g., drug induced cardiac arrhythmia or convulsions are concentration dependent acute events while liver damage or pulmonary fibrosis are generally dose dependent.*	1-2
5	If the answer to question 4 is "Yes", does the time of onset of the event correspond to a period when the plasma concentration of the drug is expected to be high? **Guidance:** *Consider the time to peak plasma concentration of the drug and its plasma half-life.*	6-8
6	Does the event fit the description of a known pharmacological phenomenon (such as grey baby syndrome, tardive dyskinesia, or anaphylaxis)?	1-2
7	If the answer to question 6 is "Yes", is the dose, duration of therapy, and lag time prior to onset of event consistent with a causal relationship between the drug and the phenomenon? **Guidance:** *Base your judgment on descriptions of the phenomenon available in the literature.*	6-9
8	Did the patient have an active disease or complication at the time of onset of the adverse event? **Guidance:** *Some clinical trial subjects, such as healthy volunteers in Phase 1 studies, and those participating trials of prophylactic agents such as vaccines, may not have an active disease at the time of onset of adverse event. In some patients the adverse event may be the first sign of an active disease.*	10-12
9	Did the patient have an underlying physiological condition at the time of onset of the adverse event? **Guidance:** *E.g., pregnancy or puerperium.*	13
10	Was the patient suffering from the effect of an underlying physical or mental stress or injury at the time of onset of the adverse event?	14
11	Was the patient recovering from a surgical procedure at the time of onset of the adverse event? **Guidance***: Consider the duration of the healing process after surgery. Do not consider the effects of anesthesia for this point.*	15
12	If the answer to questions 8, 9, 10, or 11 is "Yes", is the disease, complication, condition, injury, stress or surgical procedure known to cause this adverse event? **Guidance:** *Textbook references or any other credible reports of association between underlying state and event would be valid for a "Yes" response.*	16
13	If the answer to question 12 is "Yes", does it seem possible that the disease, complication, condition, injury or surgical procedure caused this adverse event? **Guidance:** *Consider whether the severity of underlying disease/injury, temporal sequence, and evolution of the event are consistent with a causal association. If your response to this question is "No", document the reason for ruling out the underlying state of the patient as cause for the event.*	16
14	Was the patient known to be taking any concomitant medicines at the time of onset of the adverse event? **Guidance:** *Consider regular as well as intermittent or one-time use of concomitant medication. Include use of traditional and herbal medicine as well as other forms of alternative medicine and the effect of anesthetics in postoperative patients.*	17
15	If the answer to question 14 is "Yes", are any of the concomitant medicines known to cause this adverse event? **Guidance:** *Refer approved prescribing information and any other literature available, for each of the concomitant medicines being taken by the patient.*	18-19
16	If the answer to question 15 is "Yes", does it seem possible that one of the concomitant medicines known to cause this adverse event actually caused it? **Guidance:** *Consider whether the dose, duration of therapy, temporal sequence and half-life of the concomitant medicine was consistent with the time-course and severity of the event.*	18-19

Continued on next page….

Table 2: Revised WHO-UPC system (con't)

17	Was the patient known to be taking any recreational substances at the time of onset of the adverse event? **Guidance:** *Include use of tobacco, alcohol, and abuse of prescription medicines as recreational use.*	20
18	If the answer to question 17 is "Yes", are any of the recreational substances known to cause this adverse event?	21
19	If the answer to question 18 is "Yes", does it seem possible that any one of the recreational substances known to cause this adverse event actually caused it? **Guidance:** *Consider whether the extent of abuse and time sequence is consistent with a causal relationship of abuse to event.*	21
20	Was the drug dose reduced or the drug withdrawn at any time after the onset of the adverse event? **Guidance:** *Enter "No" if, after the onset of the adverse event, the patient continued to receive the same dose of the drug at the same frequency as before onset of the event. Enter "Not Applicable" if the patient was expected to receive only one dose, or if the event occurred after the last scheduled dose of the drug, or if the patient died before the next dose could be given or before any effect of drug discontinuation can be expected (keeping drug half-life and reversal time of drug effects in mind).*	22
21	Was the dose of any of the concomitant medicines reduced or withdrawn at any time after the onset of the adverse event? **Guidance:** *Enter "Not Applicable" if the patient was not receiving any concomitant medicines at the time of onset of the adverse event.*	22
22	Was the nature of the event such that withdrawal of the causative agent would be expected to lead to reduction/disappearance of manifestations in the days after withdrawal? **Guidance:** *Adverse events resulting from the direct pharmacological action of a drug are generally rapidly reversible, while recovery from effects of drug-induced injury to cells depends on the pace of regenerative processes in the affected tissue. Drug-induced degenerative changes and fibrosis may not be reversible. Choose your response based on the nature of the event and the withdrawal period that was available to observe the effect of drug withdrawal. You may choose "Not Applicable" if withdrawal was not possible.*	22
23	If the answers to questions 20 and 21 are both "Yes", were the dose reductions/withdrawals of drug and concomitant medicines sequential? **Guidance:** *Enter "No" if one or more concomitant medicines were withdrawn (or their dose reduced) at the same time as withdrawal or dose reduction of the drug. Enter "Yes" only if there was sufficient gap between withdrawal of drug and the concomitant medicines to allow for a de-challenge effect to be observed for the drug and the concomitant medicine/s separately.*	22
24	If the answers to question 20, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on drug dose reduction/withdrawal? **Guidance:** *Confine your response to the effect of withdrawal or dose reduction of the drug, irrespective of the effect of withdrawal or dose reduction of concomitant medicines, and irrespective of whether withdrawals and dose reductions happened simultaneously or sequentially.*	22
25	If the answers to question 21, 22 and 23 (if applicable) are all "Yes", did severity of the event reduce or did manifestations of the event disappear on concomitant medicine dose reduction/withdrawal? **Guidance:** *You need to respond to this question only if withdrawal or dose reduction of one or more concomitant medicines occurred sequential to withdrawal or dose reduction of the drug.*	22
26	If the answer to question 24 or 25 is "Yes", are there any confounding factors that make the de-challenge results ambiguous? **Guidance:** *Specific treatment of a drug-related adverse event may confound the de-challenge results as both will reduce severity of the event.*	22
27	If the answer to question 20 is "Yes", was the drug restarted after a period of withdrawal?	22
28	If the answers to questions 24 and 27 are both "Yes", did the manifestations of the event reappear after the drug was restarted?	22
29	If the answer to question 28 is "Yes", are there any confounding factors that make the re-challenge results ambiguous? **Guidance:** *A positive re-challenge result would be ambiguous if drug and concomitant medicines were restarted at the same time.*	22

***Corresponding Table 1 row numbers for reference**

Table 3

Q#	Response Options			CERTAIN		PROBABLE		POSSIBLE		UNLIKELY	
				(+)	(-)	(+)	(-)	(+)	(-)	(+)	(+)
1	Y	N	-	Y							N
2	Y	N	-								N
3	Y	N	-	Y	N	Y	N	Y	N	N	Y
4	Y	N	-								
5	Y	N	B			Y/B	N				
6	Y	N	-	Y	N						
7	Y	N	B	Y	N						
8	Y	N	-								
9	Y	N	-								
10	Y	N	-								
11	Y	N	-								
12	Y	N	B	N/B	Y						
13	Y	N	B			N/B	Y	Y			Y
14	Y	N	-								
15	Y	N	B	N/B	Y						
16	Y	N	B			N/B	Y	Y			Y
17	Y	N	-								
18	Y	N	B	N/B	Y						
19	Y	N	B			N/B	Y	Y			Y
20	Y	N	NA								
21	Y	N	NA								
22	Y	N	NA								
23	Y	N	B								
24	Y	N	B	Y/B	N	Y/B	N				
25	Y	N	B	N/B	Y						
26	Y	N	B	N/B	Y	N/B	Y				
27	Y	N	B								
28	Y	N	B	Y/B	N						
29	Y	N	B	N/B							

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Causality Assessment for Clinical Trial Investigators

Open workshop in February 2015
Revised training and guidance

Pilot of WHO-UHS revision
- Test inter-rater reliability
- Test understanding and applicability

Broaden implementation

Develop on-line training module for dissemination

India: still pending

- Requirement for placement of trials in 50-bed hospital
- Compensation revisions for situations not modified (e.g. Phase 4 trials, post-marketing surveillance, noncompliance)
- Compensation formula for injury
- Definition of “ancillary care” expectation for intercurrent illness during clinical trial
- Structure, education and training of regulatory authorities
  - Elevation of CDSCO/DCGI to higher authority and status in government
  - Increased investment in regulatory offices and competence of officials
  - Transparency of regulatory processes and decisions

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Questions and Discussion