



MULTI-REGIONAL CLINICAL TRIALS

THE MRCT CENTER of
BRIGHAM AND WOMEN'S HOSPITAL
and HARVARD

MRCT Center: India Regulatory Update

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GHRT Webinar

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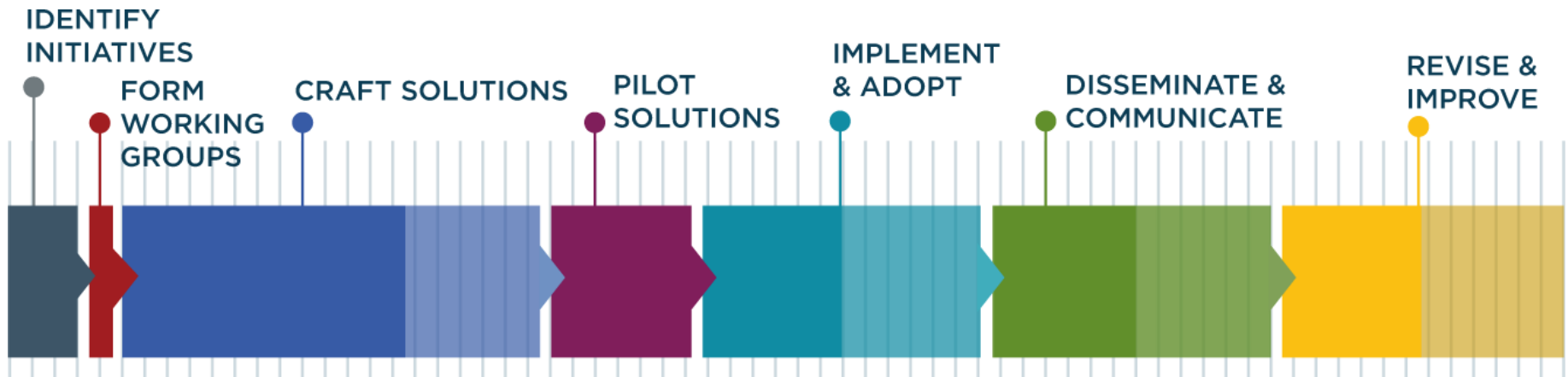
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Our Mission

Engage diverse stakeholders to define emerging issues in global clinical trials and to create and implement ethical, actionable, and practical solutions.



MRCT Current Projects



PI Training and Competency

Protocol Ethics

Return of Aggregate Results

Training

Global Regulatory Engagement

Data Sharing

Post-Trial Responsibilities

Return of Individual Results



Global Engagement: India

Agenda today: Focus on India

1. Introduce GHRT members to the MRCT Center of Brigham and Women's Hospital and Harvard (MRCT Center)
 - Overview of MRCT's regulatory focus in India.
2. MRCT update on Indian regulatory activities
 - a. Outline clinical research regulations and amendments to the Drug and Cosmetics Act.
 - b. Discuss India regulatory reforms.
 - c. Provide a high-level overview of Indian clinical trial complexities and its impact.
 - d. Describe the current status of the regulatory environment in India, its implications, pathways and future initiatives.
3. Q&A



MRCT Center major activities in India

- MRCT: >14 visits (>25 person-visits) to India over last 3 years, each time meeting with regulators (e.g. Health Ministers, Secretaries, DCGI) government representatives (e.g. ICMR), pharma, CROs, relevant organizations (e.g. ISCR, OPPI, API), academia and other collaborators
- Jan 2014 co-sponsored (with AIIMS and Apollo) Conference defining necessary changes to regulations, but nevertheless increase safety and quality, in India
- Participation in conferences hosted by ISCR, BioAsia, DIA, others
- October 2015, closed meeting with regulators, investigators, industry, CROs, content experts
- March, 2016 most recent visit to India

MRCT Center Goals in India

- To assess the changing clinical trial regulatory environment in India
- To assist the various Indian stakeholders in improving clinical trial regulation in India and, in some cases, amend or reverse prior decisions
- To revitalize the clinical trials enterprise in India, in order to promote science and public health in India



Topics to cover

- Background
- Compensation for Trial-Related Injuries
- Causality Determination
- Audio-Visual Recording of Informed Consent
- Further Restrictions for Investigators
- Civil and Criminal Liabilities
- Accreditation of Sites and Ethics Committees and Certification of Investigators
- Academic Trials
- Other

Background: Parliamentary Review

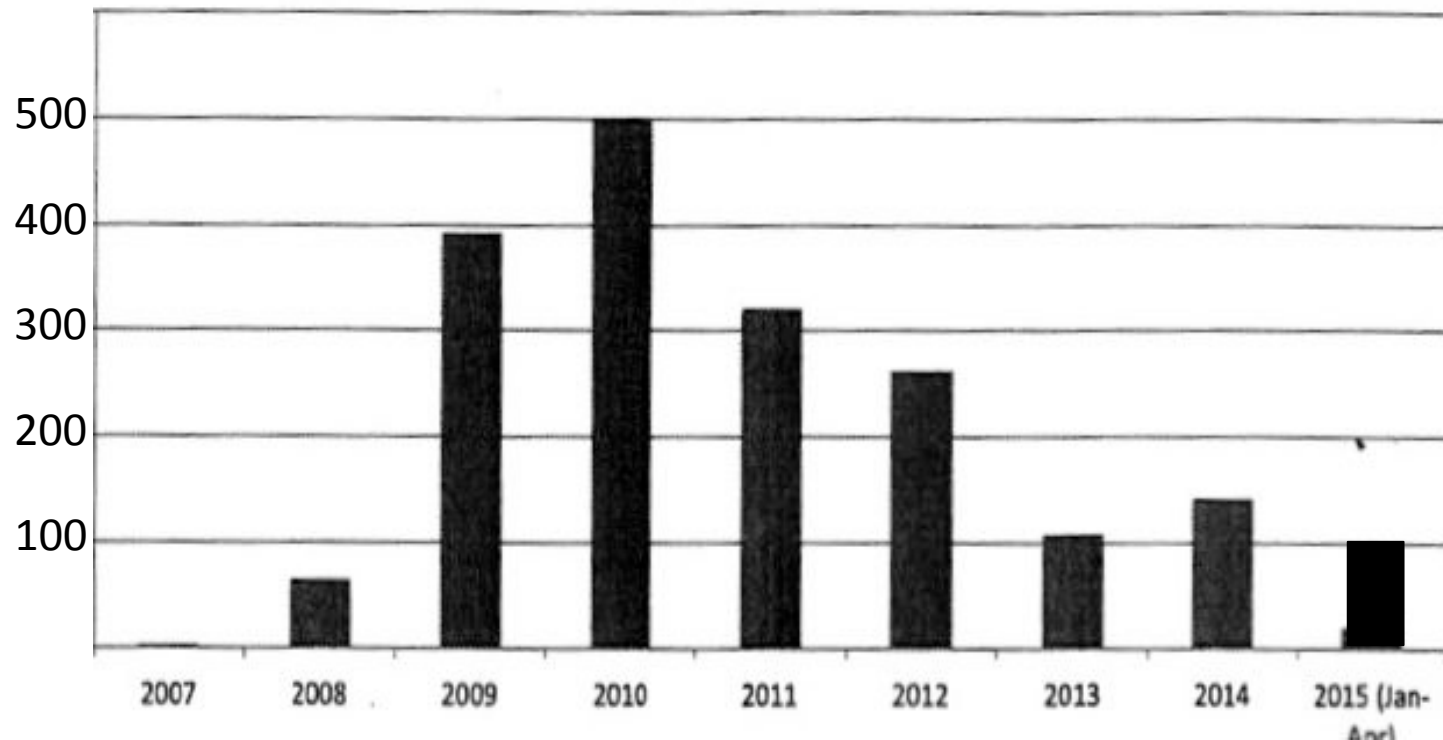
- In 2011, Indian Parliament formed a committee to report on functioning of CDSCO, following the deaths of seven girls who had died while on an HPV vaccine observational study among other issues

- *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 was not able to judge exact scientific rationale as well as the appropriateness of conducting specific trials.*

Background

- January 2012, Swasthya filed Public Interest Litigation against the MoHFW (Health Ministry) alleging negligence and malpractice that had resulted in a number of clinical trial-related deaths in India.
- In response, since 2013, the Health Ministry, through CDSCO, announced a series of steps to improve regulatory oversight. We will not review the history of each, but rather focus on the current status of the regulations.
 - Compensation for Injuries and Deaths
 - Mandatory medical management and ancillary care
 - Mandatory Registration of Ethics Committees
 - Mandatory Accreditation of Ethics Committees, Sites, Investigators
 - Audio-Visual Consent (now modified)
 - Revised Expert Committee Process to Review Applications
 - Added Scrutiny for New Chemical Entities (e.g., risk vs. benefit, etc.)
 - Academic Trial exceptions and other

Impact on clinical trials approved by DCGI (CDSCO)



Note: many of the 2015 trials are extension trials, post-marketing surveillance, etc., and not new investigational agents.

ClinicalTrials.gov lists 203,394 trials being carried out worldwide; the number of trials carried out in India is 3043 (<1.5 %) of global trials (mid-2015).

Compensation: clarification and limitations

Compensation

- Sponsor provides compensation for injury or death during a clinical trial
- Sponsor to provide subject free medical management for injury during trial, for as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.
- Injury must be related to or caused by clinical trial, not just concurrent
- No liability for therapeutic failure of experimental agent unless standard care is denied
- Liability for injury in placebo arm only if standard care has been denied
- Causality determination important

Verbal reports from governmental authorities have assured us that compensation has only been awarded when SAEs and death have been determined to be causally related to investigational drug.



Compensation reform

Formula introduced, defining limit of liability:

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

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 Rs. 400000 (\$6515) to Rs. 7360000 (\$119,878)

But in case of life expectancy <30 days, 200,000 rupees should be given.

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



Compensation for injury

Definition of SAE, eligible for compensation

(i) A permanent disability

“100% permanent disability to a subject may not be considered equivalent to the death of the subject. Therefore, even in case of 100% permanent disability, the quantum of compensation should be less than that for the death of the subject.”

(ii) Congenital anomaly or birth defect

(iii) Chronic life-threatening disease or

(iv) Reversible SAE in case it is resolved.

$$\text{Compensation} = (D \times 80 \times C) / (100 \times 100)$$

D= Percentage disability the subject has suffered

C= Quantum of Compensation which would have been due for payment to the subject's nominee(s) in case of death of the subject

Causality Determination: MRCT Center and ISCR

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.

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
-
- Causality Assessment Workshop for Clinical Trial Investigators
 - On-line tool (modified WHO Uppsala monitoring scale) finalized

Compensation only one of many issues: Other regulations and/or office orders:

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

We will review these and other regulations



Proposed further revision of rule: December 12, 2014

- “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***”

Arm A = Standard Care

Arm B = Standard Care + X X = investigational agent

Response rate never 100%. In this case, standard care is provided.

No compensation for failure of X to provide intended therapeutic effect.

However:

Arm A= Standard Care (e.g. HIV drugs)

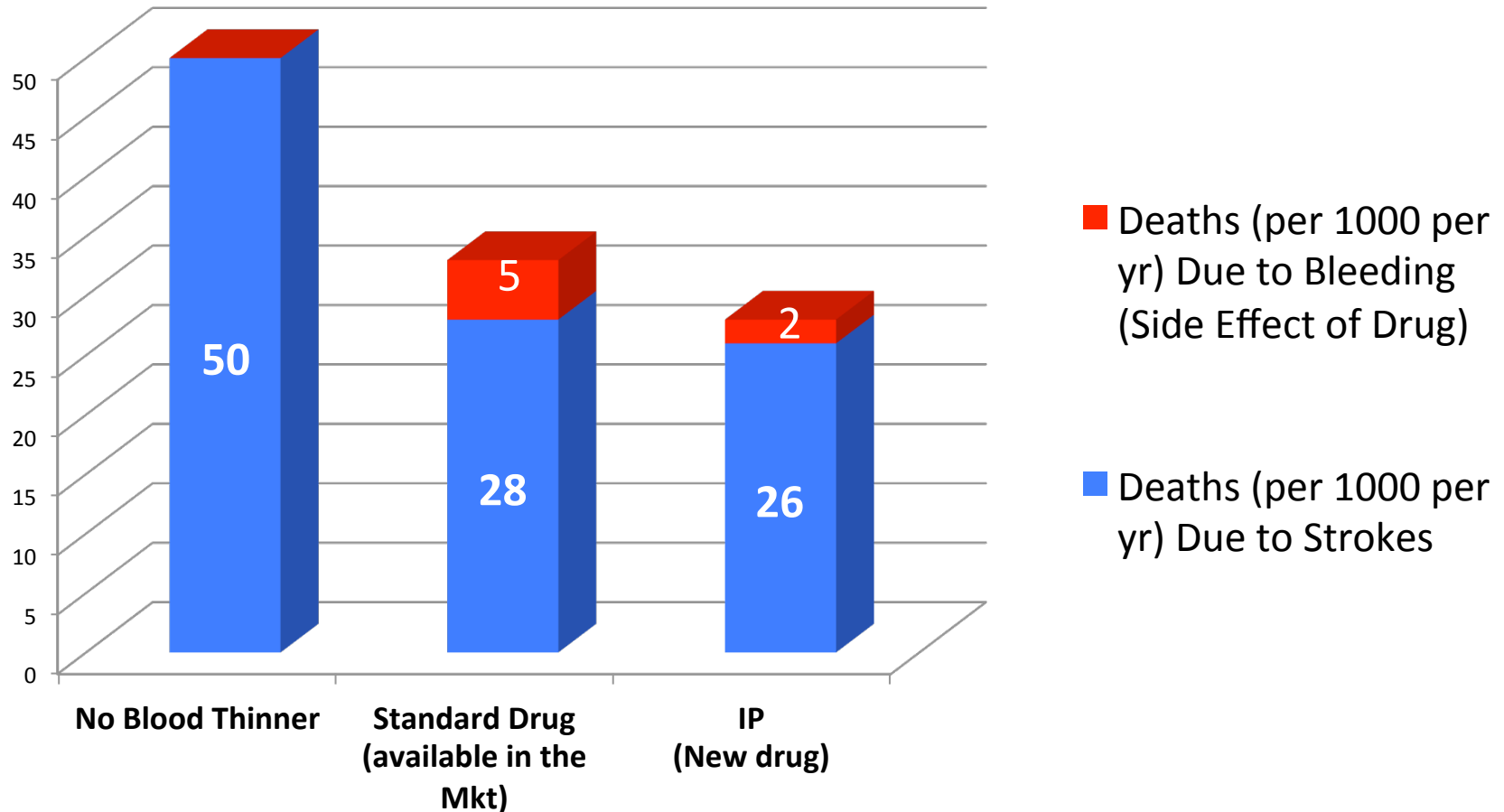
Arm B= New regimen that is apparently easier for patient to take and cheaper to provide.

Response rate never 100%, however now compensation required since standard care is not provided to patients in Arm B.

Thus, can **never** design a trial to test a replacement or improvement to current standard care unless one is prepared to pay for every failure (of which there is always a predictable number).



CT on Blood Thinners in Atrial Fibrillation Patients



Should the Researchers / Sponsors be Complimented for the 'BLUE' or Punished for the 'RED'?

Proposed further revision of rule: December 12, 2014

Similar arguments for:

1. Shortening the course of an approved treatment

Arm A= Standard Care that is 12 month course of treatment

Arm B= Standard Care shortened to 4 months of treatment

2. Changing the dose of an approved treatment

Arm A= Standard Care

Arm B= Higher (lower) dose of Standard Care

In neither of these examples is standard care provided as recommended.

And more rarely:

3. “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”

Note however that in any clinical trial whether regulated by CDSCO or not, compensation for injury or death is anticipated.



A-V Recording of Consents

- On Oct. 21, 2013: Supreme Court issued an order allowing five clinical trials to go forward. DCGI had given approval to these five trials after having secured approval from Apex Committee.
- The Supreme Court ruled that the five trials were required to make an audio-visual record of the informed consent process.
- CDSCO issued an order on November 19, 2013, requiring audio-visual recording of informed consent to enrollment of new subjects in all clinical trials conducted in India. The mandatory audio visual (AV) record must:
 - Include the procedure of providing information to the subject;
 - Include the subject's understanding of such consent and
 - Adhere to the principles of confidentiality.
- Subject must consent to the AV recordings and without such consent, the subject cannot take part in the trial.
- CDSCO published draft guidance on 9 January 2014 on how to administer properly the audio-visual recording of informed consent



A-V Recording of Consents: 31 July 2015 Amendment

2. In the Drugs and Cosmetics Rules, 1945, in Schedule Y,—

(i) in paragraph 2 under the heading “CLINICAL TRIAL”, in sub-paragraph (4) relating to “Informed Consent”, after clause (iii), the following shall be inserted, namely:—

“(iv) An audio - video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record;

Provided that in case of clinical trial of anti-HIV and anti-Leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.”;

Definitions:

- Vulnerable Subject
- New Chemical Entity or New Molecular Entity

Audio recording for HIV and Leprosy subjects, but what about others?



Limitation of investigators to 3 clinical trials

- On July 3, 2014, CDSCO and the Drug Controller General of India published an office order limiting the number of trials with which an Investigator can be involved to three clinical trials at a time.

<http://www.cdsco.nic.in/writereaddata/officer%20order%202.pdf>, Accessed 9 Oct 2015.

- General agreement that three trials per investigator is arbitrary, not based on quality, quantity, stage or complexity of trial nor investigator capacity to conduct trials in consideration of other responsibilities.
- Explicit responsibility of trial sponsors to select appropriate investigators and of IRB/REC to review
- Issue raised and adjudicated by the Technical Committee in August, 2015, that stated ...“and the number of clinical trials, any investigator can undertake at any given point in time, shall be examined and approved by Ethics Committee.”

<http://www.cdsco.nic.in/writereaddata/Final-Minutes-of-28th-Technical-Committee-21-08-2015.pdf>

- To date, no office order has been issued revering the earlier order.



Civil and Criminal Penalties

- In August 2013, Bill 4ZE was introduced that provided that any clinical researcher (including the Sponsor, Institution or the Investigator and anyone who works on their behalf) who fails to conduct a clinical trial in accordance with “the conditions of permission” imposed by the Central Licensing Authority would be punishable with a *minimum* of two years imprisonment and a fine in the amount of Rs. 5 lakhs.
- Additionally, under section 4ZG of the Bill, any researcher who fails to provide compensation to a subject suffering a trial-related injury shall be punishable with “imprisonment which may extend to two years and a fine which shall not be less than twice the amount of the compensation.”
- The provisions of the bill were amended in draft legislation in December, 2014, but that legislation has not been introduced: no mandatory minimum sentence and lower criminal penalties
 - Chilling effect on investigators
 - No procedural safeguards



Civil and Criminal Penalties

- Prominent researchers have expressed that they will stop conducting clinical trials if section 4ZE and its counterparts become law. They believe that such penal provisions will lead to arbitrary and abusive prosecution.
- Penalties should be reserved for those who intentionally ignore Central Licensing Authority requirements or commit willful misconduct.
- Investigators who are committed to ethical practices but who have incorrectly and unknowingly misinterpreted clinical trial conditions or who intentionally deviate from the protocol for participant safety and well-being should not be subject to prosecution. Education and training should be offered, as appropriate.
- If, after education and training, there is serious and continuing non-compliance, the ethics committee should be empowered to limit or eliminate the ability of an investigator to engage in clinical research activities.

Roy Chaudhury Committee Recommendations on Accreditation and Certification

- All clinical trial sites must be accredited by a newly formed Central Accreditation Council:
 - “Conducting clinical trials at centers that have not been accredited would be illegal.”
 - Government would propose accredited sites for each proposed trial.
- Each organization conducting research must have an ethics committee (IRB/REC) that is accredited by the Central Accreditation Council.
- All principal investigators must be certified.
 - Process for such certification is not specified.



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)

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

- Training has been offered, inspectors trained, and uptake is beginning.
- There has been little communication as to the status of accreditation of ethics committees, investigators, and sites.
- We are unclear where the accreditation process stands and how this is impactful to the international community.

Note that no country as of today has a sustained, comprehensive system for mandatory, uniform accreditation or certification of ethics committees, investigators and research sites.



India Update

- In November 2015, CDSCO issued four Circulars to revitalize the clinical trials industry in India:
 - Academic/Research Clinical Trials Not for Regulatory Purposes (Academic/Research Circular)
 - Addition of New Clinical Trial Sites or Investigators
 - Preclinical/Toxicological Studies of New Drugs Approved Outside of India
 - Simultaneous Review by DBT and DCGI of Recombinant Products
- Two of these issues were discussed with the regulatory authorities in our recent exchange

Academic/Research Clinical Trials Not for Regulatory Purposes

- January 6, 2016 the Indian Ministry of Health & Family Welfare (Health Ministry) introduced the 2016 Draft Rules that attempts to codify the November 10, 2015 Circular-1 issued by CDSCO to relax the requirements for academic/research-oriented clinical trials.
- Exemption from permission from the Drug Controller General of India (DCGI)/licensing authorities for trials:
 - The trial is for an approved drug formulation for any “new indication”, “new route of administration”, or “new dosage form”;
 - The trial is approved by the Ethics Committee; and
 - The data generated is not intended for submission to a licensing authority for approval of the drug.
- Ethics Committee must inform the DCGI/licensing authorities of all approved cases and give DCGI/licensing authority 30-days to object

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)
- Finalized 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, competence, and training
 - Transparency of regulatory processes and decisions
 - Continued commitment to regulatory timelines for decisions

“...and in such manner as may be prescribed”

2015 Reform Bill

Introduced on December 31, 2014 with comments due by 1/19/2015 (then 1/26/2015)

Amendment to the Drugs and Cosmetics Act, 1940

2013 introduced changes by way of amendment to the Drugs and Cosmetics Rule, 1945

Inclusion of device trials

No change in compensation *per se*

“[w]hether the injury or death of a person in the course of clinical trial, *has been caused due to such clinical trial or not*, shall be determined by such authority and in such manner as may be prescribed.”

No significant change in criminal and civil penalties as described



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



India Update

- In a recent submission by Swasthya to the Supreme Court of India, received under RTI, 2,209 clinical trial related deaths occurred between 2011 and October 20, 2015 for a total of 5,077 in the past decade. How this number was determined is not clear.
- Many believe that the PIL must be settled before real progress can be made.
- We plan to continue our advocacy in India, through work with our collaborators there, including ISCR and advisors to DCGI/CDSCO.

In conclusion

There are several unique and laudatory principles in the Indian clinical trial regulatory framework, including mandatory compensation for death and injury, and mandatory universal accreditation of sites, investigators, and ethics committees, among others.

We hope and trust that the clinical trial enterprise in India will recover to lead the international community in regulations and processes that demonstrate the ethical, fair and responsible treatment of all participants. For that, clarity and definition are necessary, training and education essential, and appropriate accountability held by each of the cooperating stakeholders including sponsors, investigators, sites, ethics committees, regulators, participants and civil society.



Thank you
Questions and Discussion