Pharmaceutical research in developing and threshold countries

Dr. Inder Sen Gandhi,

Vimta Labs Ltd, Hyderabad, India

German Ethics Council's Annual Meeting: Medical progress, but at whose expense? Pharmaceutical research in a global context Berlin, Germany, 23 May 2013

Prime Concern :

Ethical Integrity in clinical research in developing countries

IMPORTANT POINTERS …….

Ethical Integrity in clinical research in developing countries

Year 2003	Approved Indication	Unapproved Indication	Impact
Letrozole	Breast Cancer in Post menopausal women	Induce ovulation in women	
		400 women	
		No informed consent	unethical
		No information that it is a clinical trial	unethical

Ethical Integrity in clinical research in developing countries

Year 2003	Approved Indication	Unethical conduct	Impact
Streptokinase	Acute evolving transmural myocardial infarction	Regulatory Approval from GEAC not taken	8 deaths
		Ethical Review Not done	unethical
		No informed consent	unethical
		No information that it is a clinical trial	unethical

Ethical Integrity in clinical research in developing countries

Year 2003	Approved Indication	Unethical conduct	Impact
Ragaglitzar	Diabetes	ICMR Requirements not met the results of toxicity studies on drugs for chronic diseases had to be available before phase III clinical trials begin. In the EU and the US, this is not required.	Trials suspended mouse (and several rats) treated with the drug had developed urinary bladder tumours. In India, 130 people from eight centres participated in the trials. Half of them received the experimental drug.

Ethical Integrity in clinical research in developing countries

1.EVOLUTION	**How it has evolved in India ?**
2.CLINICAL PERSPECTIVE	**Of all stakeholders, whose perspective should/must be given higher weightage ?**
3.ACTIONS	**What Action steps are necessary to ensure Ethical Integrity ?**

Ethical Integrity in clinical research in developing countries

1.How it has evolved in India ?

Ethical Integrity in clinical research in developing countries

Year	
1947	ICMR
1980	Policy Statement on Ethical Considerations involved in research on Human Subjects[2]
1996	Central Ethics Committee on Human Research (CECHR) comprised of 27 members, and 5 Sub-committees of experts, was set up for drawing up the guidelines in respective areas.
2000	"Ethical Guidelines for biomedical research on human subjects". ICMR Code
2006	ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS.

Ethical Integrity in clinical research in developing countries

ICMR CODE
Essentiality
Voluntarism, Informed consent, Community Agreement
Non-exploitation
Privacy and Confidentiality
Precaution & Risk minimisation
Professional Competence
Accountability and Transparency

Ethical Integrity in clinical research in developing countries

ICMR CODE
Accountability and Transparency
Maximisation of public interest and distributive justice
Institutional arrangements
Public domain
Totality of responsibility
Compliance.

Ethical Integrity in clinical research in developing countries

Indian GCP (2001)

[Good Clinical Practices for Clinical Research in India (2001): http://cdsco.nic.in/html/GCP.htm]

- WHO
- ICH
- USFDA
- European GCP guidelines
- Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. (2006)

Ethical Integrity in clinical research in developing countries

Clinical Trial (Clinical Study) as per Indian GCP(2001) is defined as:
A systematic study of pharmaceutical products
On human subjects – (whether patients or non-patient volunteers)
– in order to discover or verify
❖The Clinical,
❖Pharmacological (including pharmacodynamics / pharmacokinetics), and / or
❖Adverse effects,
with the object of determining their safety and / or efficacy

Ethical Integrity in clinical research in developing countries

CLINICAL RESEARCH

ICMR 1947

RESEARCH REVIEW PROCEDURES BY IRB/IEC/DMB

ICF

CONFLICT OF INTEREST

COMPENSATION

RESEARCH RELATED INJURY

SPECIAL TOPICS

HUMAN GENETICS & GENOMICS

ORGAN TRANSPLANTATION

ART

Ethical Integrity in clinical research in developing countries

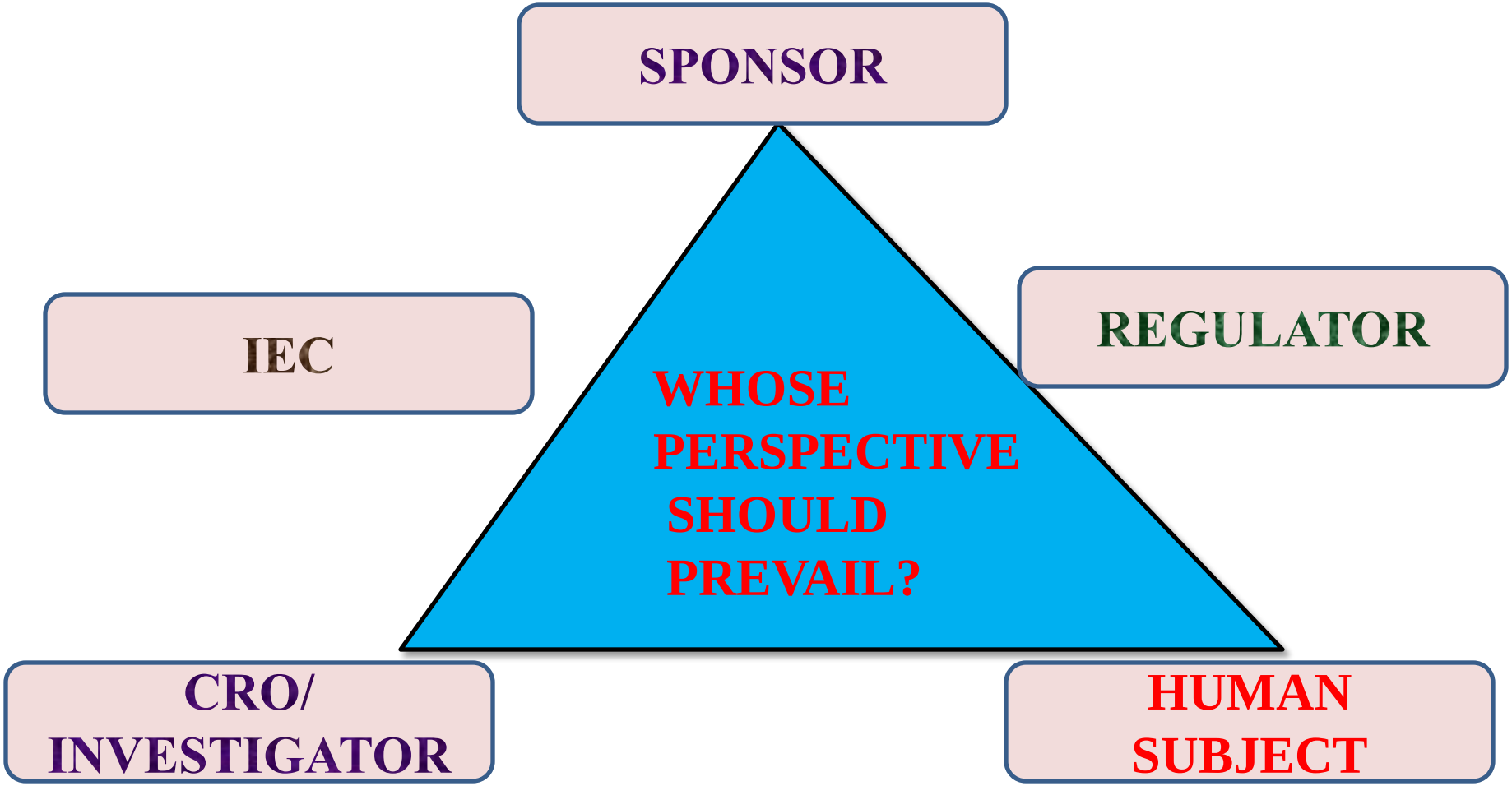
The main ethical issues involved in the Ethical Review Procedure are:

- **The Informed Consent Process,**
- **Compensation for participation,**
- **Selection of Special Groups as research Subjects,**
- **Essential Information on Confidentiality for Prospective Research Subjects,**
- **Compensation for Accidental Injury,**
- **International Collaboration,**
- **Relations with Media & Publication Practices.**

Ethical Integrity in clinical research in developing countries

2.Of all stakeholders whose perspective should/must be given higher weightage ?

Ethical Integrity in clinical research in developing countries



POINTS FOR CONSIDERATION

VULNERABILITY IS DIRECTLY PROPORTIONAL TO VARIABILITY

POINTS FOR CONSIDERATION

VARIABILITY DETERMINANTS

1.Level of literacy

2. Level of Socio-economic Status :political will & geo-strategy

3. Level of Awareness

4.Level of Autonomy

AREAS OF CONCERN

	Sponsor	CRO investigator	IEC	Regulator	Human subject
Literacy	√	√	√	√	?
Socio-Economic Status	√	√	√	√	?
Awareness	√ ? MONITORING	√ ? AUDITING	√ ? REVIEW	√ ? APPROVAL PROCEDURES ENFORCEMENT	?
Autonomy	√	√	√	√ LEGISLATIVE RECOMMENDATION GUIDELINES	?

Ethical Integrity in clinical research in developing countries

3.What Action steps are necessary ?

Ethical Integrity in clinical research in developing countries

Ethical Integrity in clinical research in developing countries

CLINICAL RESEARCH PROCESS

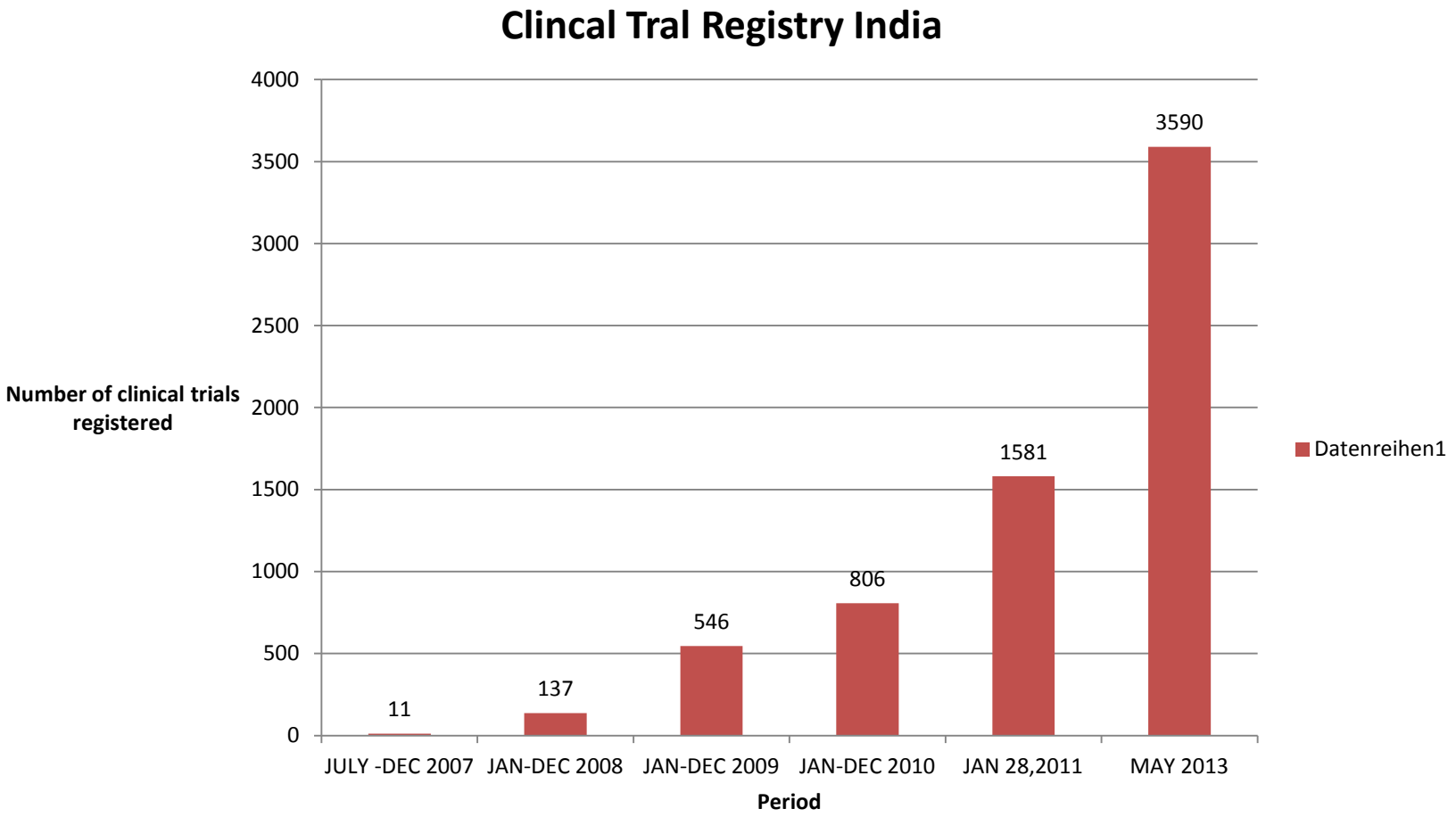
ACTION 2:CLINICAL TRIAL REGISTRY
20TH JULY 2007
15JUNE 2009

CONSORT STATEMENT REQUIREMENTS

CONTEMPLATED RESEARCH & MEDICAL PUBLICATIONS

UPDATED HELSINKI DECLARATIONS

Ethical Integrity in clinical research in developing countries



Ethical Integrity in clinical research in developing countries

Trials registered in clinicaltrials.gov :

	All countries	% Growth	India	% Growth	China	% Growth	Korea	% Growth
2005	10480		137		119		114	
2006	8665	-17.3	203	48.2	157	31.9	205	79.8
2007	9711	12.1	218	7.4	202	28.7	268	30.7
2008	11525	18.7	272	24.8	274	35.6	329	22.8
2009	11173	-3.1	246	-9.6	316	15.3	397	20.7
CAGR %	1.6		15.8		27.7		36.6	

SOURCE:*Confederation of Indian Industries White Paper Potential of and Challenges faced by Clinical Research Industry in India February 13, 2013*

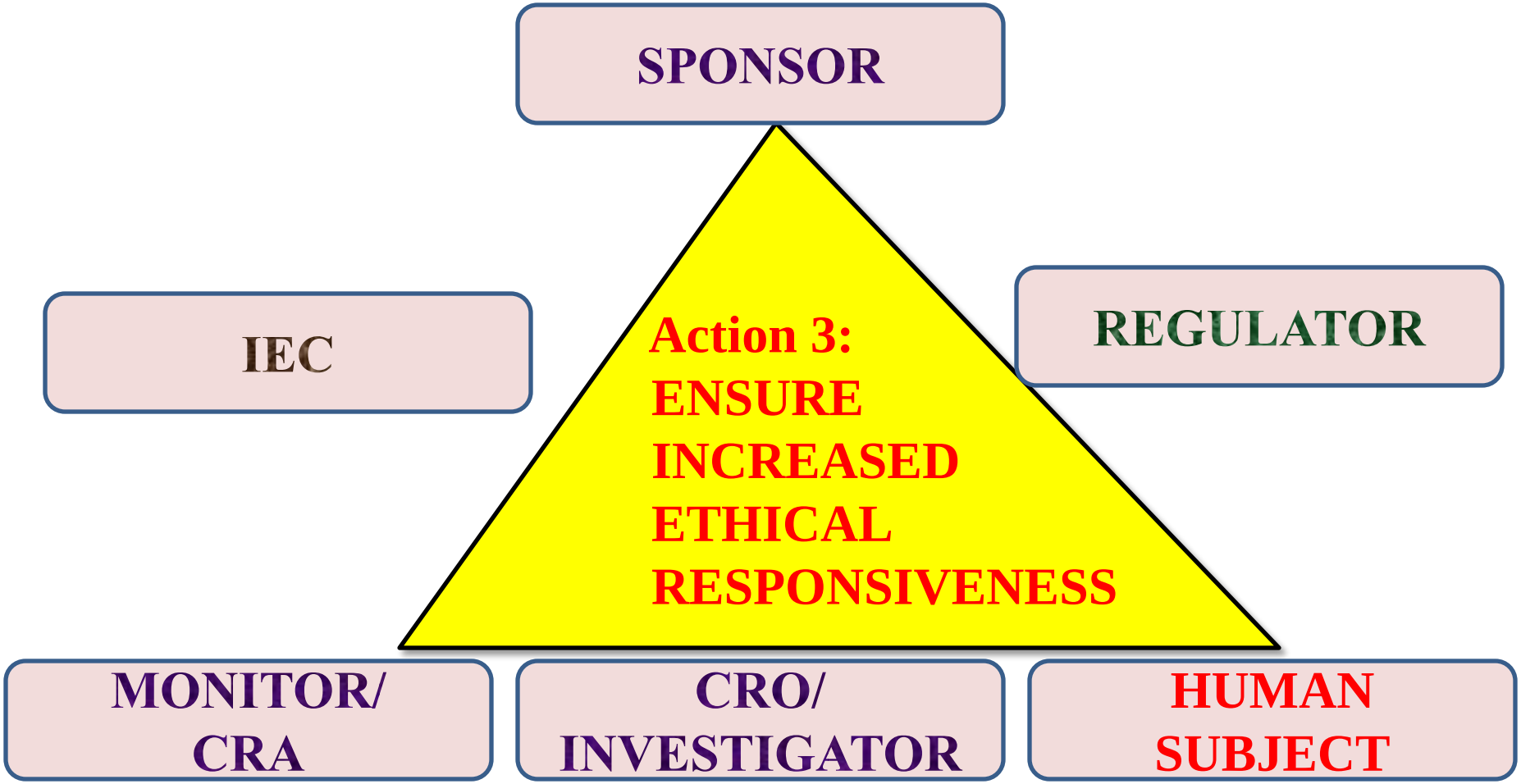
Ethical Integrity in clinical research in developing countries

Industry trials registered in clinicaltrials.gov :

	Industry	% Growth	India	% Growth	China	% Growth	Korea	% Growth
2005	6485		101		78		109	
2006	4707	-27.4	156	54.5	123	57.7	163	49.5
2007	5452	15.8	183	17.3	132	7.3	191	17.2
2008	6707	23.0	220	20.2	146	10.6	241	26.2
2009	6109	-8.9	195	-11.4	107	-26.7	249	3.3
CAGR % 2005-8	1.1%		29.6		23.2		30.3	
CAGR % 2005-9	-1.5		17.9		8.2		22.9	

SOURCE:*Confederation of Indian Industries White Paper Potential of and Challenges faced by Clinical Research Industry in India February 13, 2013*

Ethical Integrity in clinical research in developing countries



Ethical Integrity in clinical research in developing countries

Action 4:
Current Status:
Regulatory guidelines and oversight is minimal

Proactive Status: with Risk Avoidance and Risk Reduction Approach:
which should be facilitative rather than creating regulatory time consuming hurdles..

Drugs and devices are covered by legislative provision termed as “Revised Schedule Y of the Drugs & Cosmetics Act (2005)”

Ethical Integrity in clinical research in developing countries

Terms of Reference:

1. To formulate policy, guidelines, SOPs for approval of New drugs including Biologicals with special emphasis on the following:-

   a) To plan a transparent, equitable system of clinical evaluation of new drugs.

   b) Requirements of local clinical trial on Indian population for drugs approved in other countries.

   c) Specific circumstances, if any, under which local clinical trial can be abbreviated, relaxed or omitted.

   d) Types of local clinical trial, its design, sample size, sites and their distribution, inclusion of ethnic population etc. in the local clinical trial.

   e) Requirements of Post Marketing (Phase IV) trial to assess safety of new drugs in Post Marketing scenario.

Ethical Integrity in clinical research in developing countries

2. To formulate policy, guidelines, SOPs for approval of clinical trials including global clinical trials of new drug substances discovered abroad and bioavailability and bioequivalence study for export with special emphasis on the following:-

   a) Monitoring the functions of Ethics Committees.

   b) Accreditation of clinical trial sites and Investigators.

   c) Clinical trial inspections.

   d) Participation of State Authorities in monitoring of clinical trials.

Ethical Integrity in clinical research in developing countries

3. To formulate policy, guidelines and procedures for examination of issues related to continued marketing of drugs not only due to safety or other reasons but also due to launch/availability of safer and more efficacious alternative drugs in the country.

4. To formulate guidelines, SOPs on the functioning of New Drug Advisory Committees (NDACs).

5. To formulate policy, procedures for identification of experts for advising CDSCO in its various matter.

6. To advise CDSCO in other matters referred to it for advice.

Ethical Integrity in clinical research in developing countries

Action 4:
Current Status:
Regulatory guidelines and oversight is minimal

Proactive Status: with Risk Avoidance and Risk Reduction Approach:
which should be facilitative rather than creating regulatory time consuming hurdles..

Drugs and devices are covered by legislative provision termed as “Revised Schedule Y of the Drugs & Cosmetics Act (2005)”

Ethical Integrity in clinical research in developing countries

Action 5:

Regulatory requirements must insist on auditing of studies

Ethical Integrity in clinical research in developing countries

Action 6:

Auditing of total research by independent trained auditors and/or trained regulatory personnel is required to determine ethical and scientific validity of study.

Ethical Integrity in clinical research in developing countries

Action 7:

Compensation for research injury should be as per applicable regulatory requirements and International Guidelines

Gazette Notification on Compensation published by the Ministry of Health & Family Welfare on January 30, 2013.

Ethical Integrity in clinical research in developing countries

	Deaths	Related	Unrelated	Compensation
2005				
2006				
2007				
2008				
2009				
2010	668	22		
2011	438	16		
2012	436	16		2
2013				
	2868	89		45

Source:Based upon Media Reports.

Ethical Integrity in clinical research in developing countries

SAE DEATH/OTHER THAN DEATH	IEC	SPONSOR	DCGI	EXPERT COMMITTEE
IMMEDIATE REPORT	24h	24 h	24h	
DETAILED REPORT [CAUSALITY]	10 DAYS			
OPINION [RELATED/UNRELATED]	21 DAYS			
COMPENSATION RECOMMENDATION				30 DAYS
COMPENSATION APPROVAL			30 DAYS	
COMPENSATION PAYMENT		30 DAYS		

Thanks for listening

When we listen

We feel.

Felt thinking reveals inherent truth

We are here to evolve better future like a thinking child