Medical Progress, but at whose expense?

Ethical Standards for Pharmaceutical Research in India

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Outline of presentation

- The Context – India
- Opening up the global CTs; Standards setting but non-implementation
- The Framework – Vulnerability and Justice
- Some Ethical Challenges in RECs:
  - 1. Physician as investigator – how does this alter doctor-patient relationship?
  - 2. Risk-benefit assessment – Most important, the least assessed
  - 3. Informed consent – structural coercion & lack of comprehension
  - 4. Benefits and responsiveness, including post-trial benefits
  - 5. Injury treatment and compensation
- Conclusions
High economic growth of last two decades

- Booming business – Massive export of drugs, and opened to Medical tourism and Clinical Trials (CTs) to sustain health care business

At the same time

- Increased inequities - Substantial proportion of population below poverty line, illiterate or semi-literate, and discrimination in accessing health care
- No Universal Access to Healthcare; Government spends only 1.2% of GDP on health care, which is one fifth or sixth of total health care expenditure; Voluntary insurance coverage about 10%
- Weak regulations on health care, including on CTs
Within eight years of joining the WTO, India liberalised the patent laws
ICMR’s ethics guidelines (2000, 2006); and GCP
2005: Amendment in Schedule Y to allow concurrent Drug CTs (except Phase I), providing Indian entrepreneurs benefits of outsourcing of CTs by the developed countries
Phenomenal increase in numbers of CTs; but the business forecast of 1 billion $ by 2012 never achieved
Conducted at 3000-4000 sites; About 400 Institutional and about 50 private RECs involved - poorly trained members
Drug Regulator – Toothless, incompetent and riddled with conflict of interests; Regulatory capture by the regulated
Non-implementation of Ethics Standards

- Promises never kept
  - Converting Ethics Standards into a specific law
  - Establishment of health research authority to register RECs, set standards and oversee their functioning
- Outcome - Scandals/Controversies:
  - Injuries & Deaths: Jan 1, 2005 to June 30, 2012 in 475 CTs of New Chemical Entities 11,972 non-fatal & 2644 fatal Serious Adverse Event (SAEs) reported. Of them, only 80 fatal SAEs (3%) accepted as “related” and of them only 40 compensated – 1000-5000 Euros. No compensation for non fatal SAEs on record so far
  - Numerous specific cases of ethics violations: HPV vaccine demo project, Violations reported from Bhopal, Indore, Hyderabad, B’lore
- New Regulations: Work in progress
CROs marketing pitch:
- Quick and cheap CTs; treatment naïve patients, large number of patients with “diseases of interest”, cooperative doctors, lax regulations

Vulnerabilities and vulnerable groups: The so-called “heard-to-reach”, “back-region”, “hidden” populations:
- System coercion: Poverty, lack of entitlement to health care – leading to helplessness, involuntariness
- Social control: Strong family and social hierarchies - Family decision making-gender, children, old; discrimination
- Vulnerable individuals: Low education, lack of comprehension, specific disease conditions, desperation to get medical care
Pharma Companies & CROs: Used vulnerabilities to business advantage – quick and cheap trials

Ethics:
- Vulnerabilities demand more investment of resources in provision of benefits to offset systematic lack of health care provisions;
- More interaction and time for ensuring comprehension in informed consent process,
- Transparency, accountability and strong civil society involvement to ensure integrity of regulatory system and!
- Independent assistance to or advocacy for participants to exercise their rights and monitoring of trials
Some Specific Ethical Challenges in Pharmaceutical Clinical Trials
(Based on experience of working In the RECs)
The dual role – demands lots of sensitivity, understanding and negotiation of internal conflicts between the roles.

Patients trust – often blindly – the physicians; thus causing “therapeutic misconception”

Interestingly, doctor-investigators are also not immune from the “therapeutic misconception”

Three sources of doctors “therapeutic misconception” in India

- Belief that conflict between two roles is not serious
- Strong belief in scientism & less seriousness about risks involved
- Belief that by being an investigator on clinical trial, one automatically becomes scientist
- Fourth – tentative – doctors investing in pharma company business
Ethical Challenges in Ethics Committees

2. Challenge of Risk-Benefit Assessment

- Perhaps the single most difficult task in the ethics review
- Problems in relation to understanding the concepts and having data to operationalise them
  - Often, the ethics experts having knowledge of “theory” (procedure level approaches like Component analysis or Net-Risk test) do not have requisite data; and
  - those (the sponsor and investigators) who are supposed to have requisite data, do not provide relevant & context specific data
- Universalism with little concern for heterogeneity: Risks must be assessed keeping in mind the most vulnerable
- Rigorous risk-benefit assessment, in addition to skills and information, also demands time – something at premium for members of the RECs in big institutions
Problems related to participant’s comprehension everywhere – can it be made “Understood Consent?
Specific description of consent process often absent – who, where, how, in whose presence, time for consultation, independent counseling, tests for comprehension, measures of participant autonomy or voluntariness, etc.
Vulnerabilities expressed in helplessness, fear – participants often believe that saying no would diminish access to care and doctor’s interest
Ethical Challenges in Ethics Committees

4. Benefits & post-trial benefits

- A major issue at the core of debate on “exploitation”
- Covers host of issues – research must be responsive to the health needs and priorities of the health system of the community, must provide direct benefits and reasonable assurance of post-trial benefits, ancillary care etc.
- Best some RECs have achieved: Continuation of CT as open-label trial to maintain continuity of care for limited time
- Strong national regulations & political commitment needed as the following tasks are often beyond the scope of RECs
  - Need health care priority setting at the national and local level
  - Universal health care system to eliminate health care vulnerability
  - Successful drug brought to the country, determination of affordable price, technology transfer etc – they may need agreements prior to commencement of trials
Comprehensive and free medical management of all adverse events in CTs are basic rights of all participants – they must not be confused with the “compensation”

All participants, and not only those receiving experimental drug are the CT participants

Ethical & legal standards for monetary compensation in research need to be different from medical negligence compensation standards in clinical practice

Transparency and independent assessment of SAEs

International standards for the quantum of compensation
Conclusion

- Given the high disease burden, the developing countries need more research in new therapies, prevention and health system improvements.
- At the same time, given the high level of vulnerabilities in majority population, such research must have high ethical standards.
- The bioethics need to do more work to understand and design appropriate additional specific and contextual ethical standards needed for balancing different kinds of vulnerabilities. And should also design international mechanism for their implementation.
- Without such efforts, the international CTs would find it difficult to avoid exploitation of vulnerable participants.
Thank you