Medical Progress, but at whose expense?

Ethical Standards for Pharmaceutical Research in India

Amar Jesani
Editor, *Indian Journal of Medical Ethics*
Trustee, Centre for Studies in Ethics and Rights
Mumbai, India

German Ethics Council, Annual Meeting
May 23, 2013

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

Context: About India

- 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

Global CTs in India – Standards setting

- 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

Framework: Vulnerability and Justice

- 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

Framework: Responses to vulnerabilities

- **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)

Ethical Challenges in Ethics Committees

1. Physician as Investigator

- 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

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

3. Informed consent: Process & Documentation

- 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

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

5. Injuries & deaths: treatment compensation

- 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