Vulnerable Groups in the context of Clinical Studies




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Greetings from India

PAKISTAN

UTTARANCH

NEPAL

BHUTAN

BIHAR

Bihar, India

Mumbai (Bombay)

AN SEA

BAY OF BENGAL

THE EPICENTRE OF BUDDHISIM

JAPAN

Hokkaido

Sapporo

Honshu

Tokyo

Kyoto

Nagoya

Hiroshima

Osaka

Fukuoka

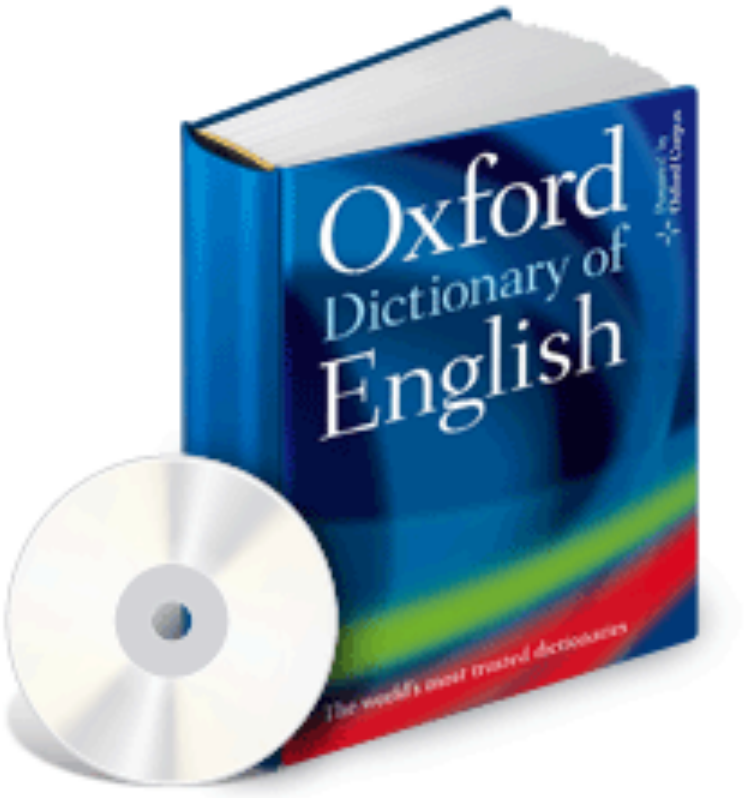
Nagasaki

Shikoku

Kyushu

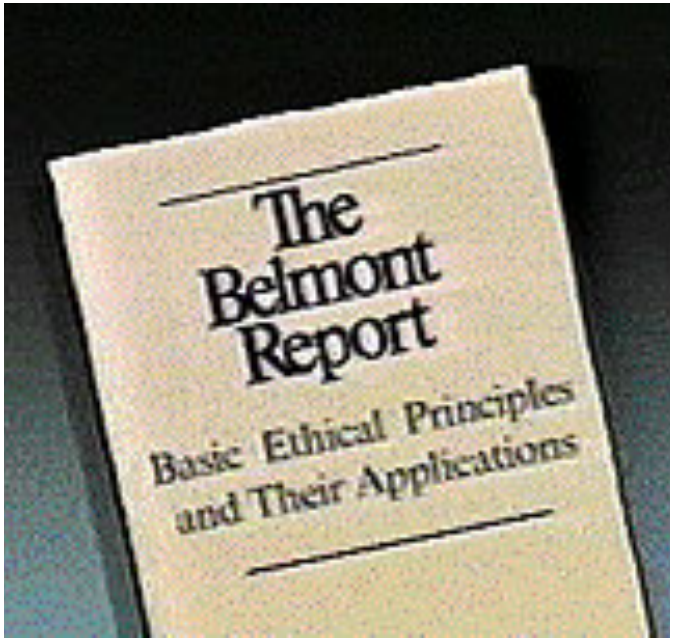
Tokyo, Japan

Who are vulnerable population?



Oxford dictionary defines vulnerable as " that which can be hurt or wounded; open to hurt by attack or criticism."

Vulnerable Population

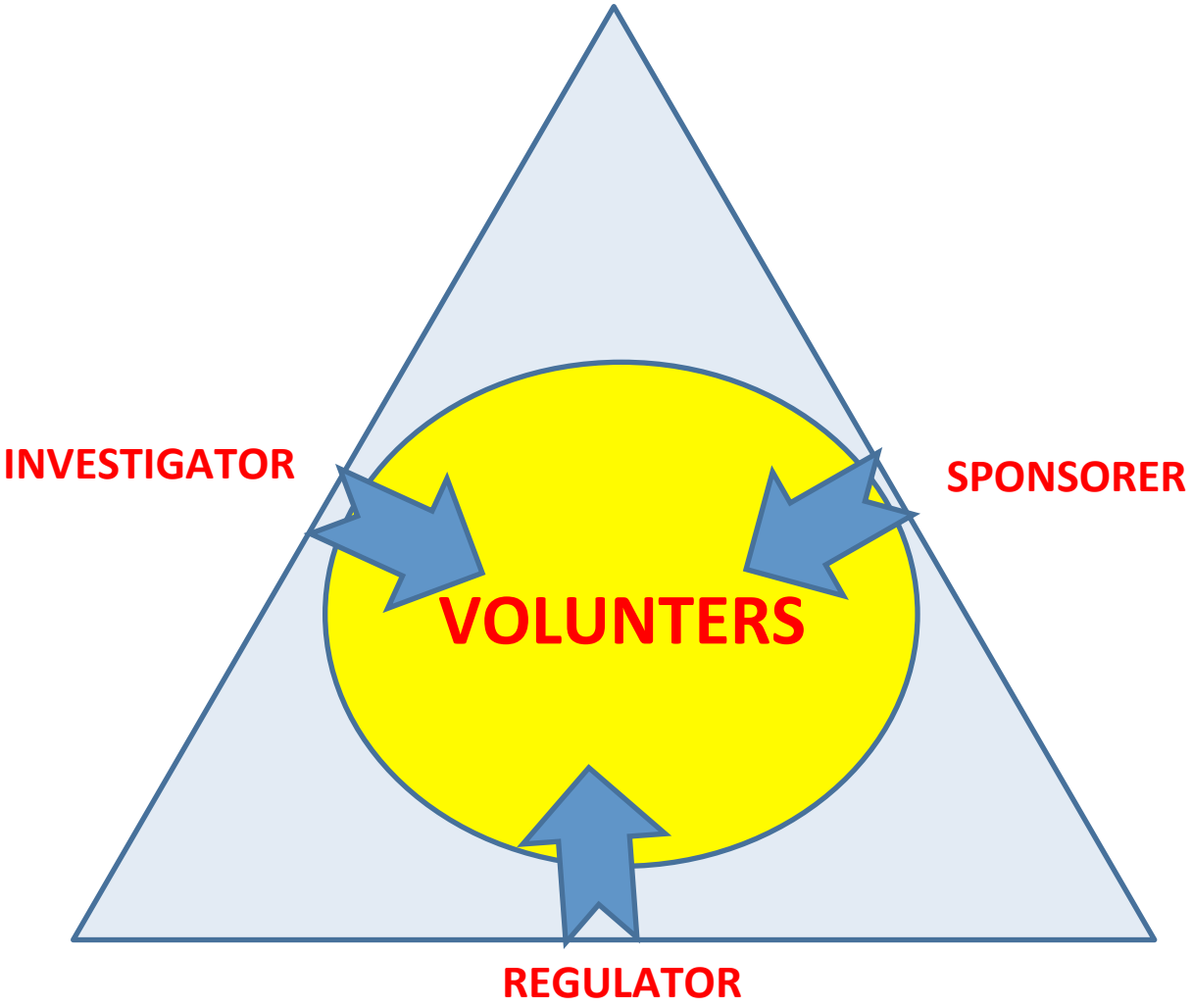


The Belmont Report (1972)

Vulnerable populations are those groups that might **"bear unequal burdens in research because of their ready availability in settings where research is conducted",** such as prisons, hospitals, institutions and camps, and called for extra protection for these groups.

My presentation is based on Indian experience which has 13.5 % world population and shares the problems of the developing world which have large vulnerable population

CLINICAL TRIALS



Vulnerability of volunteer depends on three arms of triangle and his own handicap.

Clinical Trials in a Nut Shell

Approved Protocol

Investigator selection

Approval Process

Patient recruitment and participation

Data Entered and reviewed

Statistical Analysis

Presentation and publication of report

Data filed and registration obtained

Do clinical trials in India exploit people?

Studies have proved that malpractices are rampant in clinical trials in India. Recent cases include unethical testing of contraceptives, fertility drugs, cardiac treatments and cancer medicines.

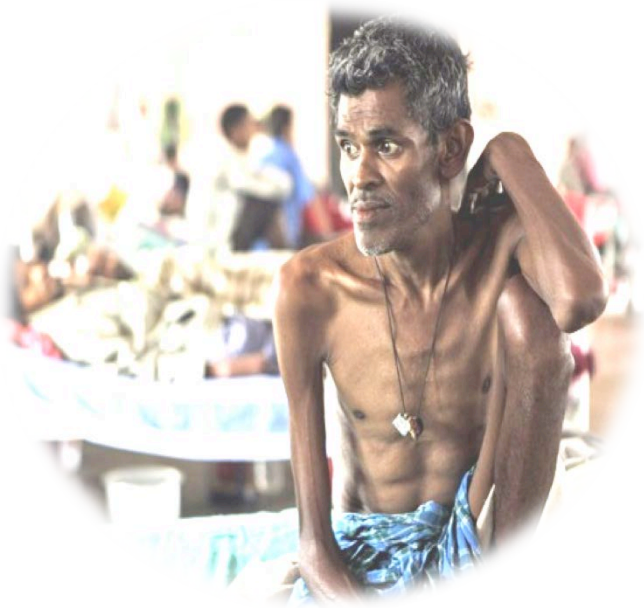
Analysts say that as many as two million Indians may be enrolled in research trials by 2012.

A major problem is that a large proportion of participants are illiterate and lured into trials by offers of free health care and financial inducements. They are often unaware of the benefits and risks of taking part in a trial, and may not even distinguish between treatment and research.

Volunteers (Indian Perspective)

Large no. of patients with wide range of disease

- 40 million asthmatic patients
- 34 million diabetic patients
- 8-10 million people with HIV
- 8 million epileptic patients
- 3 million cancer patients
- more than 2 million cardiac-related deaths,
- 1.5 million people with Alzheimer's disease;
- 15% of the population is hypertensive
- 1% suffers from schizophrenia



In order to give best treatment to above diseases research on humans is both necessary and desirable

Volunteers (Indian Perspective)

India is viewed as a favoured global site for international clinical trials of drugs. According to the **Drugs Controller General of India (DCGI),** India will be a preferred site for clinical trials because, in addition to its medical infrastructure and trained, english speaking humanpower, it has a "large, diverse and **TREATMENT-NAÏVE [UNTREATED] POPULATION with six out of the seven genetic varieties of the human race";**

Volunteers in India

A recent study reveals that outsourcing clinical trials to India may be 'rash and risky'. This opinion is drawn on the basis of concerns about timelines for regulatory approvals, deficiencies in the functioning of the ethics committees, and an unethical approach to the recruitment of illiterate and vulnerable Indian people to clinical trials.

Specific Vulnerable groups

- **Treatment Naïve population**
- Women
- Children
- Mentally incapacitated
- Elderly
- Prisoners
- Addicts
- Refugees

TREATMENT NAÏVE VOLUNTEERS

- Only 15 % of the Rs 1,500 billion spent in the health sector in India comes from the government.
- 4 % comes from social insurance
- 1 % from private insurance companies.
- Remaining 80 % is spent by individuals using private services and without insurance.
- 2/3rd of health care users bear 100 % of their health care expenses.
- 70 % of these health care users are poor.

More than half of the poorest 20 % of Indians sold assets or borrowed to pay for health care

Govt Hospital not able to provide optimum Treatment

Large group of treatment naïve population ideal for testing new drugs

Informed consent

Originally, the concept of informed consent was developed

- To promote individual autonomy
- To encourage rational decision making.
- To protect patients confronted with the power of the medical profession and with the financial domination of the drug industry.

Informed consent

An ethically valid informed consent has four key components:

Disclosure	Understanding,	Voluntariness,	Competence

This creates challenges for researchers in Paediatrics , Psychiatry, emergency and clinical care medicine

↓

Surrogate or waived consent

↓

Makes large population of handicapped (Physical or Mental) vulnerable

Informed consent situation in India

Nov 1999 - Experimental cancer drug tested without people's consent at government-run Regional Cancer Centre in Thiruvananthapuram

- 25 Oral cancer patients were given experimental drug M4N or G4N when there was established treatment for their conditions.
- Investigator involve was not qualified or authorized to do experiments on human subjects .
- Mandatory ethical IRB (Independent Review board permission not taken
- No Ethical clearance from John Hopkins Institute but released fund.
- US government approval for export of chemicals not taken
- Patients signed the informed consent in language other than their native language
- **Research not approved by DCGI**

Not informed, denied established treatment and bypassed regulatory authorities

Informed consent situation in India

2003- *Drug promotion as "research"* , (Sun Pharmaceutical Industries Limited)

- Anticancer drug Letrozole on > 400 women as fertility drug for Ovulation induction.
- Promotion cum Research Programme conducted by Private doctors

No consent and role of Investigator doubtful

Informed consent situation in India

2003-2004 -*Research in emergency situations*
***(*Santa Biotech)**

Bioequivalence Study

Testing its " Clot buster " Streptokinase against established one in treatment of CVA

Informed consent situation in Multicentre Trial

2002 - *Diabetes drug tested on humans before toxicology studies completed* (Novo Nordisk)

- **Multicentre trial of Ragaglitazar before receiving results of animal study - Bladder cancer in rats**

- **No. of Cases -**

North America- 650
Latin America – 200
Australia / New Zealand – 100
EU- 800
Europe (Non EU) – 100
ASIA – 550 (India – 130 at eight centre)

CRO EXCEL LIFE SCIENCES TRIALS STARTING July 2008

The survey's findings on why people entered a clinical trial were enlightening:

- 15 % stated that they entered the trial because they were **looking for a cure.**
- 13 % were looking for **"observed benefits".**
- 15 % were looking for a **better treatment**.
- 16 % were looking for **higher quality care.**
- 10 % were looking for **free medication and medical care.**
- 15 % said the **doctor advised them to enter the trial**.
- 5 % said they **entered the trial to receive money for participation.**
- 11 % said they entered the trial to **help advance scientific knowledge.**

Presentation by Dan Macdonald Vice President , Business Development ,Excel Life Sciences in meeting of Institute of Clinical Research (Indian) Mumbai . October 10-11-2008

Vulnerable Children

- Children are considered vulnerable group and require additional protection as research subjects.
- Obtaining the assent of a child and the permission of a parent or guardian is not the same as obtaining informed consent from a competent adult .

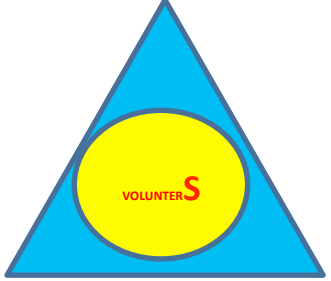
The recruitment of children, may raise concern that they are being exploited.

Payments for children

Although it seems reasonable to offer payment for the time and inconvenience of participating in research, children and their families may be unduly influenced by the offer of payments that may amount to several hundred dollars or may include gift certificates to toy or record stores.

According to the ICMR's guidelines, "… payments should not be so large or the medical services so extensive as to make prospective participants consent readily to enroll in research against their better judgment, which would then be treated as undue inducement."

REGULATOR

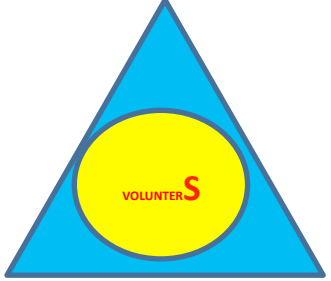


REGULATOR

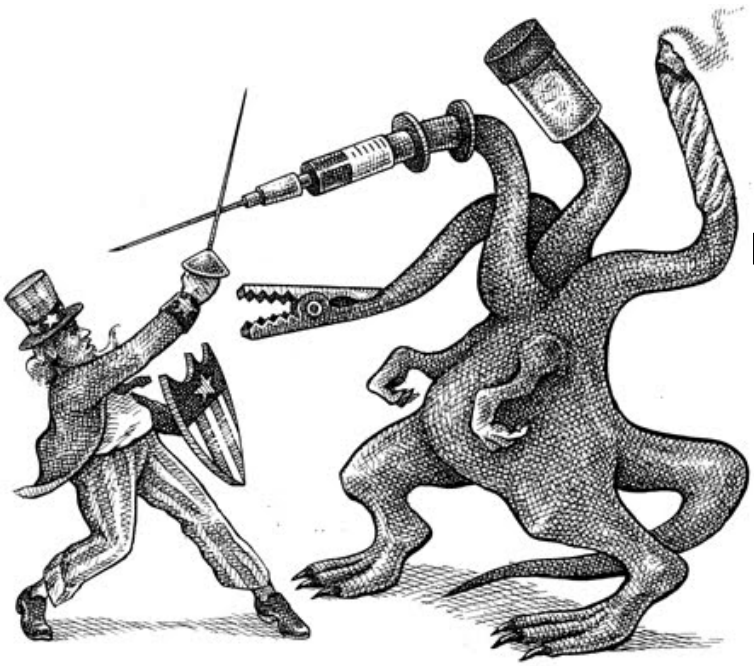
Indian Acts / Orders related to clinical trial

- Drug & Cosmetic Act : 1940
- Medical Council of India Act 1956 (Amended in 2002)
- DCGI (Drug Controller General of India)
- ICMR (Indian council of Medical Research)
- Guidelines for Exchange of Biological Material (MOH order 1997)
- Right to Information act (RTI 2005)
- The Biomedical Research on Human Subjects (Regulation , Control & Safeguard) bill 2005

REGULATOR

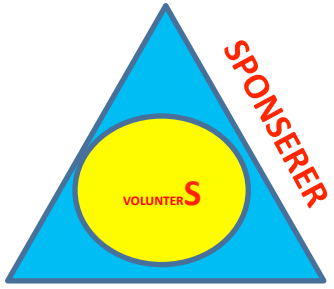


Loose control on trials



The phenomenal growth in clinical trial unfortunately has created a situation where regulatory mechanism cannot keep pace. Ethical review is now mandatory for clinical trial but there is little review of the functioning of the ethics committee by the DCGI. There is little interaction between ethics committees in different locations, thereby allowing the practice of 'Ethics Committee Shopping', - sponsors whose trials are rejected by one ethics committee approach a different centre for approval.

SPONSORER



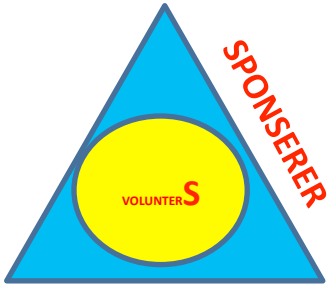
Why attracted to India

1. Huge patient base with diversity of diseases

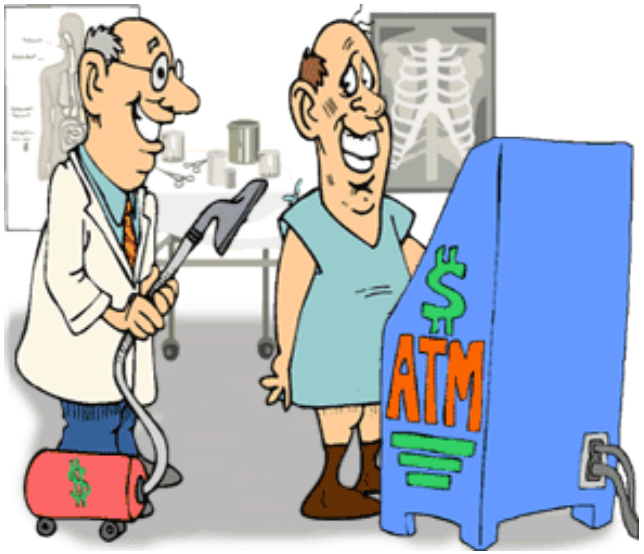
2. The average cost of drug discovery in US is estimated at US$ 800 million. Cost of conducting clinical research in India is much lower as compared to the developed countries. Drug companies can save up to two - third of overall cost of conducting trials in India compared to the west.

4. English-speaking technical workforce, good IT infrastructure and low infrastructure costs can reduce expenditures for clinical trials by as much as 60 percent.

SPONSORER



Clinical trials are conducted by **contract research organisations (CROs)** which are developing the infrastructure for trials by making inroads into small towns, identifying trial sites in small private hospitals and developing databases of potential trial participants. Medical professionals are given substantial incentives to recruit their own patients into clinical trials.



Creates a major conflict of interest that threatens the well-being of patients

INVESTIGATOR

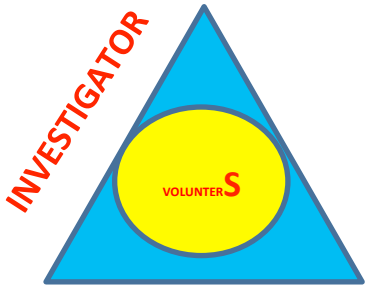
Who is Investigator ?

- **76% of patients said the trial's principal investigator was their primary physician.**
- **21 % of patients said they were referred by their primary care physician.**

97 % of patients entered the trial because of their primary care physician.

CRO Excel life science trial 2008

INVESTIGATOR



Doctor-patient relationship in India is unequal.

Patients may not question their doctors' judgement. They may be easily influenced by the doctor's advice.

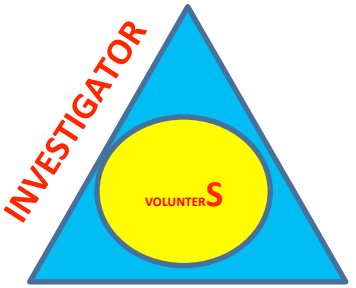
They may also believe that refusal to follow the doctor's advice to enter a trial would affect their access to care.

INVESTIGATOR

PRIVATE HOSPITAL

- **The investigator is paid according to the number of patients recruited .**
- **Additional benefits include all-expenses paid trips abroad to attend conferences.**
- **Oncology trials get higher payments because the trial takes a comparatively longer time and there are fewer patients available for recruitment.**

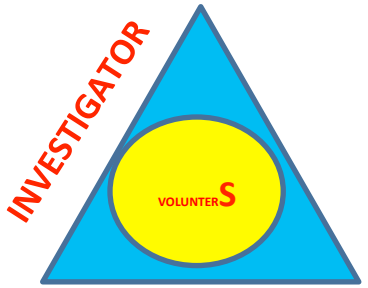
INVESTIGATOR



Public Hospitals

- Resource-starved public hospitals see trials as a source of funds for much-needed improvements in infrastructure.
- Many trials conducted in government hospitals are in fact the last resort for poor patients.
- It is argued that the patients benefit since they get free, focused and more frequent medical supervision for the duration of the trial.

INVESTIGATOR



Unseen Concern and Challenges

- Failure to obtain informed consent.
- Falsified data.
- Ethics unawareness.
- Inadequate source documentation.
- Protocol noncompliance.
- Delinquent or inaccurate data submission.
- In the field of rare diseases sometimes the number of patients might be the limiting factor for a clinical trial.
- Physicians are not as familiar with the clinical trial process as they are in the West.

CONCLUSION

Contd..

a) Regulators needs to generate effective monitoring mechanism for continuous evaluation of trials throughout the study period ensuring regular and periodic scientific and ethical review. Strategies should be developed to prevent fudging the data.

b) Studies should follow strict adherence to ethical guidelines.

c) All persons involved in study should undergo basic training concerning counselling and preventive strategies.

d) All persons should be recruited in any study after ensuring receipt of proper informed consent for participation.

e) Adequate care and protection should be provided to vulnerable groups.

f) Community involvement at all stages of the studies.

g) Sharing results with all persons involved in research.

h) Ensure global justice, narrowing gap between developed and developing worlds.

CONCLUSION

l) To favour the promotion of clinical trial in India (Developing countries), restrictions are necessary to ensure that the health of the trial subjects is adequately protected in case of any contingency. Comprehensive health insurance for all the participant volunteers must be provided by the sponsorer in the form of a viable bank guarantee ensuring the obligation of any direct / indirect consequences.

m) If the intervention being tested is not likely to be affordable in the host country or if the health care infrastructure cannot support its proper distribution and use, it is unethical to ask persons in that country to participate in the research, since they will not enjoy any of its potential benefits.

n) Clinical trials sponsored or regulated by external agencies should be limited to those that are responsive to the host country's health needs


Thank
you !