Revised Ethical Guidelines In Indian Biobanking: Do We Need To Downregulate the Proposed Frameworks?

Juhi Tayal[1], Anurag Mehta[2] and Alok Kumar[1]

[1] Biorepository, Department of Research, Rajiv Gandhi Cancer Institute and Research Centre, India

[2] Department of Laboratory Sciences and Molecular Diagnostics, RGCI&RC, India

[1,2] Sec-5,Rohini, New Delhi, India-110085

Email: juhitayal76@gmail.com/ biorepository@rgcirc.org

isber2020 APRIL 14-18 Annual Meeting & Exhibits — ANAHEIM, CA, USA

ABSTRACT

- Clinical biobanks are gaining popularity in India and are also revolutionizing research. Indian Council for Medical Research(ICMR),Council for Scientific and Industrial Research (CSIR) and Department of Biotechnology (DBT) are the major agencies supporting research in India. The ICMR is the national organization and also the apex body for developing ethical frameworks and guidelines and also enforcing them. The ICMR issued the Policy Statement on Ethical Considerations Involved in Research on Human Subjects in 1980. Due to rapid advancement in biomedical sciences new ethical dimensions have emerged and nesseciated the updation of these guidelines time and again in 2000,2003, 2013 and very recently in 2017. The revision has introduced many new sections and also revamped the existing sections .A new Section 11 was dedicated to Biological materials, Biobanks and Datasets . This section vividly covered issues like Informed Consent Form (ICF), Storage of biospecimens and data with their personal identifiers , Ethical issues related to donors, Ethical issues related to research, Biological material/data in forensic departments of laboratories , Governance of biobank /biorepository , Special issues related to datasets and Contingency planning.
- The new guidelines though protect the research participants from exploitation ,harm and injustice by theoretically elaborating upon the principles .of essentiality, voluntariness, non exploitaion, social responsibility etc. However , there is a gross mismatch when it comes to the practical applications of these guidelines in a culturally and ethnically diverse countries like ours.
- The need of the hour is to develop a document that not only protects the research participants but also promotes research in the true spirit of altruism. The present guidelines need serious rethinking to answer questions like- Is an ICF valid in biobanking or an authorization would be more appropriate ?

NATIONAL ETHICAL CODES

1940 Schedule X of Drugs and cosmetics Act

2000 ICMR- Ethical guidelines for Biomedical Research

2001 Central Drugs Standard Control Organization (CDSCO) released Indian Good Clinical practice guidelines for clinical trials.

2006 Review of ICMR Guidelines

2007 ICMR and DBT jointly bought out guidelines for Stem Cell Research and Therapy

2013 Revision of Drugs and Cosmetics Act ; Revision of guidelines for stem cell research and therapy

2017 Revision of ICMR Ethical Guidelines for Biomedical Research on Human Participants with new additions.

Fig: 1

INTERNATIONAL ETHICAL CODES

1947 Nuremberg code ,the first international treatise on the ethics of research. highlighted the essentiality of obtaining voluntary consent

1964 The World Medical Association formulated guidelines on conducting research on humans, known as the Declaration of Helsinki.

1979 Belmont report : National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in the United States of America

1991 The Department of Health and Human Services (DHHS), USA, released the Federal Policy for the Protection of Human Subjects as the 'Common Rule'

1996 The International Conference on Harmonization (ICH) brought out the Good Clinical Practice Guidelines E6 (R1).

2001 The National Bioethics Advisory Commission, USA

2002 The Council for International Organizations of Medical Sciences (CIOMS), Geneva **.** Nullfield Council of Bioethics, United Kingdom released recommendations/ guidelines

2005 UNESCO's Universal Declaration on Bioethics and Human Rights and other international instruments on human rights further defined the Universal Codes of Ethics to be adopted by the member countries.

2013 Declaration of Helsinki, Latest version

2016 Revision of ICH, GCP as E6 (R2) Revision of CIOMS

2017 Revision of Common rule by DHHS

Fig: 2

BACKGROUND

- Biomedical research in India has revolutionized with the changing times. This paradigm shift has not only bought greater complexities but also greater responsibilities for policy makers ,researchers and stakeholders. The advancement is not limited to basic research or clinical research ,it has now taken a foothold into Digital imaging and Artificial intelligence platforms as well.
- The aim of policy makers worldover was to safeguard four basic ethical principles for research involving human subjects: respect for persons, beneficence, non-maleficence and justice.
- Time and again numerous international and National ethical codes were put forth and subsequently revised.
- Fig1 and Fig 2 illustrate the various ethical code timelines.[1]

- **The four basic principles of ethical research have been expanded into 12 general principles in the ICMR Guidelines [2]**
- Principle of essentiality
- Principle of voluntariness
- Principle of non-exploitation
- Principle of social responsibility
- Principle of ensuring privacy and confidentiality whereby
- Principle of risk minimization
- Principle of professional competence
- Principle of maximization of benefit
- Principle of institutional arrangements
- Principle of transparency and accountability
- Principle of totality of responsibility
- Principle of environmental protection

Classification of Biobanks [3]

BASED ON TISSUE TYPE:
tumor tissue, cells, blood, DNA, or DNA array results

BASED ON THEIR PURPOSE/INTENDED USE :
- research, forensics, transplantation, source for therapeutics
- E.g., umbilical blood, stem cell biobank

BASED ON OWNERSHIP
- Academic and research institutions based.
- Hospitals, biotechnology and pharmaceutical companies based.
- Stand-alone biobank companies and some foundations may hold biobanks.

CURRENT CLASSIFICATION comes from the Pan-Euopean BIOBANKING AND BIOMOLECULAR RESOURCE RESEARCH INFRASTRUCTURE (BBMRI) :

1)Population-based biobanks :focused on the study of the development of common, complex diseases over time.

2)Disease-oriented biobanks : Biobanks of tissue samples and clinical data

Missing elements: Authorship Attribution[5]

It is important to acknowledge the Biobanks and Research Databases in publications and presentations as the source of the biosamples used in their research.

Three types of acknowledgment were recommended:

1. biobank acknowledgment, 2. biobank curator acknowledgment and 3). biobank and curator acknowledgment.

This approach is also recommended by the International Society for Biological and Environmental Repositories (ISBER) *Best Practices for Repositories as well as* the *Biobank Quality Standards produced by the National Cancer Research Institute* (NCRI) and the Confederation of Cancer Biobanks (CCB).

DGFT notification 2016-A Baffling Mystery [2]

These guidelines issued by Directorate General of Foreign guides regarding the lab analysis/R & D testing or export of materials to foreign laboratories to be permitted by Customs authorities at the port of entry/exit without prior approvals (import licence/export permit) from any other Government agency, provided the concerned Indian company/ agency submits an undertaking that they are following and will follow all the applicable rules, regulations & procedures for safe transfer and disposal of the biological samples being imported/ exported as per the related norms/regulations set by WHO*/DGFT**

GAP: This one page draft does not address biological transfers to academic Research Institutions abroad, Transfer of samples between two biorepositories.

Looking ahead

ICMR Guidelines serve as a starting point for grounding discourse on a range of issues.

It is not too great a claim to say that ***biobanks require a rethinking of our ethical assumptions and frameworks which we have applied generally to other issues in ethics.*** New ethical structures are required.

What are the reasons for this profusion of guidelines, and why is it apparently so difficult to devise a single universal framework?

As such a framework exists for clinical research ethics, why is the regulation of biobanks so varied?

Guideline for Indian Biobanks

The word biobank first appeared in the Pubmed in the year 1996.

Till date there are no operational guidelines or accreditations/ certifications for Indian Biobanks leaving them in a lurch to follow international guidelines .

Revised ICMR ethical guidelines 2017 first laid down an exclusive section 11 to advise on Biological materials, biobanking and datasets .

Need for Revision:The need arose due socio-cultural ethos in India, globalization of science and technology, * the ethical conflicts and dilemmas in regulating R&D and clinical trials and commercialization in private sector.

- Responsible Conduct of Research
- Informed Consent Process
- Vulnerability
- Public Health Research
- Social and Behavioural Sciences Research for Health
- Biological materials, Biobanking and Datasets
- International Collaboration
- Research during Humanitarian Emergencies and Disasters
- The guidelin es also highlight the need for capacity building in the area of ethics in order to improve the ethical conduct of research and has segregated varied roles of researchers as well as the ethics committee.

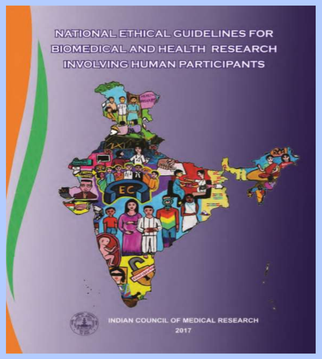
ROLE OF RESEARCHER

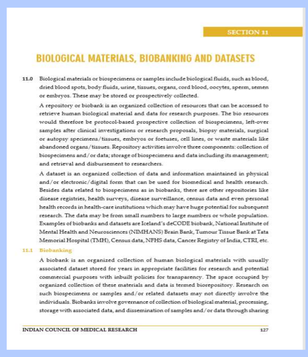
- For protecting the dignity, rights, safety and well-being of the participants enrolled in the study.
- They should have the appropriate qualifications and competence in research methodology and should be aware of and comply with the scientific, medical, ethical, legal and social requirements of the research proposal.
- To obtain the written, informed consent of the prospective participant or legally acceptable/ authorized representative (LAR). In absence of LAR, a literate impartial witness should be present during the informed consent process.
- To safeguard the confidentiality of research related data of participants and the community.

ROLE OF ETHICS COMMIITEE(EC)

- EC should attempt to maximize benefits and minimize risks to participants .
- To decide on the merit of the research before approving it.
- To assess any altered risks in the study at the time of continuing review.
- To classify risks as : Less than minimal risk, Minimal risk, Minor increase over minimal risk or Low risk, More than minimal risk or High risk.
- Data of individual participants/ community may be disclosed in certain circumstances with the permission of the EC .

How is ethical landscape of biobanking different : Gap Analysis of Section 11 of Revised 2017 ICMR Guidelines[2]




SECTION 11

BIOLOGICAL MATERIALS, BIOBANKING AND DATASETS

11.0 Biological materials or biospecimens or samples include biological fluids, such as blood, dried blood spots, body fluids, urine, tissues, organs, cord blood, oocytes, sperm, semen or embryos. These may be stored or prospectively collected.

A repository or biobank is an organized collection of resources that can be accessed to retrieve human biological material and data for research purposes. The bio resources would therefore be protocol-based prospective collection of biospecimens, left-over samples after clinical investigations or research proposals, biopsy materials, surgical or autopsy specimens/ tissues, embryos or foetuses, cell lines, or waste materials like abandoned organs/ tissues. Repository activities involve three components: collection of biospecimens and/or data; storage of biospecimens and data including its management; and retrieval and disbursement to researchers.

A dataset is an organized collection of data and information maintained in physical and/or electronic/digital form that can be used for biomedical and health research. Besides data related to biospecimens as in biobanks, there are other repositories like disease registries, health surveys, disease surveillance, census data and even personal health records in health-care institutions which may have huge potential for subsequent research. The data may be from small numbers to large numbers or whole population. Examples of biobanks and datasets are Iceland's deCODE biobank, National Institute of Mental Health and Neurosciences (NIMHANS) Brain Bank, Tumour Tissue Bank at Tata Memorial Hospital (TMH), Census data, NPHS data, Cancer Registry of India, CTRI, etc.

11.1 Biobanking:

A biobank is an organized collection of human biological materials with usually associated dataset stored for years in appropriate facilities for research and potential commercial purposes with inbuilt policies for transparency. The spare occupied by organized collection of these materials and data is termed biorepository. Research on such biospecimens or samples and/or related datasets may not directly involve the individuals. Biobanks involve governance of collection of biological material, processing, storage with associated data, and dissemination of samples and/or data through sharing

INDIAN COUNCIL OF MEDICAL RESEARCH 637

Section No and Title	Subsection No and Title	States	GAP Analysis in the Biobanking concept
11.3 Ethical issues related to donors	-	• An informed consent document is to inform the participant of the goal of research, possible risks and adverse event, and the possibility to refuse or withdraw from research at any time. • **Reconsenting** For a new study or after death of the participant and at multiple stages of data utilization or possible commercialization	**1) Inappropriateness of Informed consent in the biobank setting because :** • Most of the biobanks used leftover/ residual samples from hospitals or pathology laboratories after an initial confirmed diagnosis is made. These samples would have been otherwise discarded. • Biobanks are not research studies with specific end points rather they are frameworks or organized collections. An authorization to allow the use of biosamples would be more apt. 2) It is daunting as well as an operational challenge to reconsent the participant after 10 years of initial consent.
11.4 Ethical issues related to research	**11.4.1 Ownership of the biological samples and data:**	**Who rightfully own the samples-The biobank, the researcher who collects it or the specimen contributor?** The present guidelines gives full leverage and ownership to the contributor by allowing the participant to withdraw consent at any point of time.	•However the biobanks collect samples in thousands and some banks have a daily disbursal or utilization in cell culture experiments. Withdrawl in such settings will not be possible as the tissue would already be used up. • The same hold true for the clinical annotations and National Cancer Registry Data as well.
	11.4.2 Mandatory material transfer agreements (MTA)	The EC should oversee the process of the in-country and international material transfer. Mandatory regulatory clearances with appropriate MoU are required if biospecimens are to be sent overseas	The vetting of MTA for overseas material transfer by ICMR is done six monthly .How do we propose to hold the research study for that long a duration? DGFT Gazette is too brief and not explanatory.
	11.4.4 Return of research results to Individual/groups	Results of the study to be communicated back to the participant. The guide;ines suggest an opt-in and opt –out ,odel of receiving the results of the research .	• Possible only with disease specific biobanks. • Not applicable for academic research studies where there is hardly any translation. • Not applicable in cancer biobanks where the results are delayed. • Also depends on the study type. For eg- Incidental findings to 100,000 or 500,000 participants of a genomic study could represent a remarkably expensive and time-consuming effort. (4)
	11.4.5 Benefit Sharing [4]	The guidelines mention Benefit sharing *as an important tool to achieve justice* for research.	However, donation for biobanks should be based on mutual trust and community service especially where banks store leftover samples. If revenue is associated with sample donation the essence of altruism would be lost. The benefit sharing model is apt for research involving clinical trials.
11.6 **Governance of biobank /biorepository**	-	The current guidelines emphasize the importance of a separate technical authorization committee and drafting SOP's for biobank management.	Biobanks have turned out as rather unruly phenomena, and challenges in governance are far from implementation of guidelines or codes of good practice. The need is to laydown governance models which are biobank specific and handle issues not only dealing with the establishment and operation of the biobank, but also with the relationships with participants, research users and society. The governance model to be robust and flexible enough to develop both -legislatively created and regulated biobanks as well as self regulatory / self binding biobanks.

References

1. Chaturvedi, S., and Muthuswamy. 2016. Biobanking and privacy in India. *The Journal of Law, Medicine & Ethics* 44: 45–57.
2. Mathur, R., and Swaminathan , S. 2017. "National ethical guidelines for biomedical & health research involving human participants, The Indian Council Of Medical Research : A Handbook.
3. Kinkorová, J. 2016 .Biobanks in the era of personalized medicine: objectives, challenges, and innovation. *EPMA Journal* **7**, 4 .
4. Edwards, T., Cadigan, R. J., Evans, J. P., & Henderson, G. E. 2014. Biobanks containing clinical specimens: Defining characteristics, policies, and practices. *Clinical Biochemistry, 47*(4), 245-251.
5. Kleiderman E, Pack A, Borry P, and Zawati M. 2018. The author who wasn't there? Fairness and attribution in publications following access to population biobanks. PLoS ONE, 13(3): e0194997.