Ethical Issues in Biomedical Research

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Human Subject Protection and GCP Training for IRB Members

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Ethical Issues to be Discussed

- Type of biomedical research
- Good laboratory practices
- Type of specimens
- Use of primary specimens/data
- Issues in human tissue research
- Issues in genetic research
- Use of archived/stored biological specimens
- Use of secondary data
- Case study

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What Is Biomedical Research?

- Laboratory based study: blood, secretions/ cells/tissues, stored specimens/clinical records/data *etc*.
- Descriptive study (prospective / retrospective)
- Clinical experimental (intervention) trial
- Medical device trial
- Drug trial (phase I-IV)
- Vaccine trial

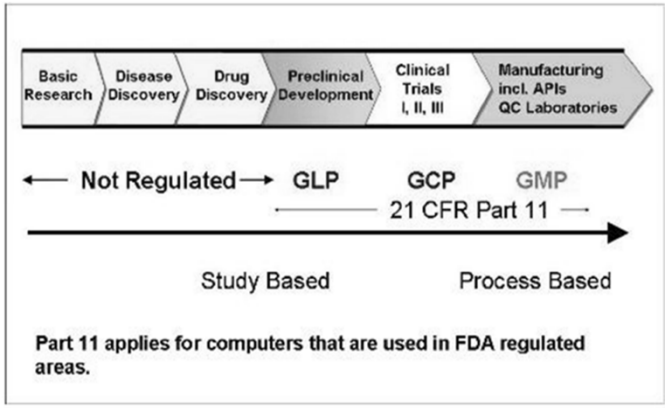
Type of Biomedical Research

- Any types of study involving human subjects (or on materials of human origin) which related to medicine and aimed at understanding human disease and improving human health
  - Primary research
  - Secondary research

Ethical Conduct in Biomedical Research

Researcher in biomedical research should maintain the highest standards of scientific integrity and ethical behavior in all phases of the conduct of research.

GLP *vs* GCP *vs* GMP



Source: Dominique Pifat: GLP vs GMP vs GCP

What Standard Applies to the Analysis of Clinical Samples?

- **Good Clinical Practice (GCP)**
- **Good Laboratory Practice (GLP): Good standard for work at the bench**
- **Good Clinical laboratory Practice (GCLP)**

What ICH-GCP says that relates to the laboratory
"Systems with procedures that assure the quality of every aspect of the trial should be implemented"

Essential Documents: certification or accreditation of laboratories

Good Clinical Practice (GCP)

WHO GCP Principle 1:

Ethical conduct research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles.

(Handbook for good clinical research practice, World Health Organization, Governance, rules and procedures, WHO Manual XVII).

ICH-GCP:

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Good Laboratory Practice (GLP) Principles

GLP

Promotes

Quality and Validity

of the Test Data

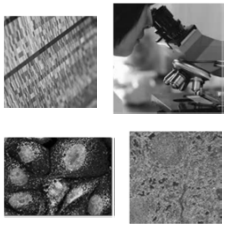
- Makes sure that the data submitted are a true reflection of the results that are obtained during the study.
- Makes sure that data is traceable.
- Promotes international acceptance of tests.

Source: WHO Handbook Good Laboratory Practice (GLP)

Good Laboratory Practice (GLP)

Whatever the type of safety study

- **Planning**
- **Performance of the study:**
  - **Biosafety: in laboratory**
  - **Biosecurity**
  - **Test systems**
- **Recording**
- **Reporting of study results**
- **Archiving of records and materials.**
- **Monitoring**
- **Standard operating procedures (SOP)**
- **Quality assurance program: audit/inspection, training, advice**
- **Personnel and test facility organization**
- **Research misconduct & plagiarism**
- **Conflict of interest**



Basic Elements of GLP

Personnel
- Study Director/PI (CV)
- Management
- Quality Assurance

Documents
- Standard operating -SOP
- Protocols
- Reports
- Archiving

Facility
- Safety Laboratory Operation
- Animal care
- Equipment
- Reagents
- Storage

Test and Control Articles
- Characterization
- Handling
- Storage

GLP

Management responsibility

- **There are special needs regarding facilities *eg* aseptic work areas, BSL1-4**
- **There are special needs for training personnel to perform highly critical procedures with harzardous material: biosafety, biosecurity etc.**
- **There are special needs regarding the disposal of waste materials to avoid risks of contamination to environment and other test system**
- **Emergency response preparedness**

Source: WHO Training manual "Good Laboratory Practice (GLP)"

Good Clinical Laboratory Practice (GCLP)

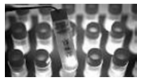
- **Provides a bridge between GCP and GLP**
- **GCLP is concerned with producing reliable results to meet the challenge of GCP compliance**
- **GCLP provides framework to organisations on facilities, systems and procedures to ensure the reliability, quality and integrity of the work and results to satisfy GCP expectations.**
- **GCLP principles should be interpreted and applied to any laboratory that analyses samples generated during the conduct of a clinical trials or clinical research**

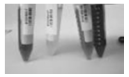
Using Biological Specimens in Research

- **IRB review is required under 2 scenarios:**
  - Retrospective use of previously stored specimens
  - Prospective studies requesting the collection, storage or use of specimens for current and/or future research.
- **Two categories of specimens:**
  - Those obtained initially for clinical or diagnostic purposes only
  - Those obtained solely for research purposes.

Human Biological Specimens

- **Blood, serum, plasma**
- **Body fluid**
- **Tissue**
- **Sputum**
- **Mucus**
- **Nasal lavage**
- **Pathology specimens**
- **DNA**
- ***Etc.***





Definition of Samples/Data

"Identified" :

Specimens or data that are still attached to a readily available subject identifier such as a name, social security number, address, telephone number, medical record number, or clear pedigree location (i.e., his or her relationship to a family member whose identity is known).

"Coded":

Collected samples or data are unidentified for research purposes by use of a random or arbitrary alphanumeric code but the samples may still be linked to their sources through use of a key to the code available to an investigator or collaborator.

Definition of Samples/Data

"Unlinked":

- **Human data or samples that were initially collected with identifiers but, before research use, have been irreversibly stripped of all identifiers by use of an arbitrary or random alphanumeric code and the key to the code is destroyed, thus making it impossible for anyone to link the samples to the sources.**
- **This does not preclude linkage with existing clinical, pathological, and demographic information before subject identifiers are removed.**

Definition of Samples/Data

"Unidentified" or "Anonymous":

- **Samples or data were collected without identifiers of any kind. Samples or data may retain demographic or diagnostic information and still be considered unidentified if such information cannot be used to reveal the identity of the source.**

Definition of Samples/Data

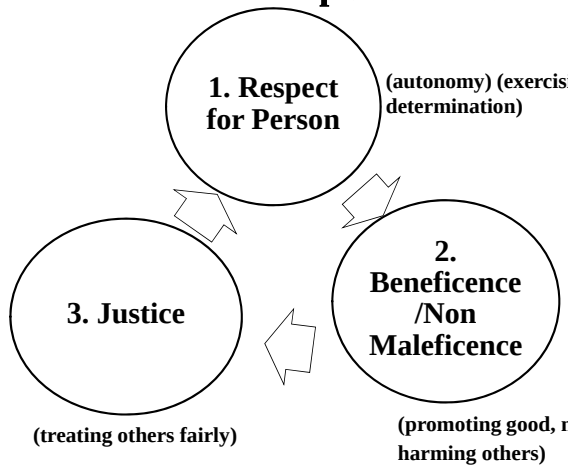
"De-identified"

- **All direct personal identifiers are *permanently* removed**
- ***No code or key* exists to link the information or materials to their original source(s)**
- **The remaining information cannot reasonably be used *by anyone* to identify the source(s)**

IRB Review of Research

- **Three categories of review:**
  - **Exempt**
  - **Expedited**
  - **Full Review**

Three Fundamental Principles of Research Ethics



Belmont Report

Issues for Ethical Justifications: Primary Research

- Valuable scientific question /Valid scientific methodology
- Reason for using human subjects
- Fair subject selection
- Favorable risk-benefit evaluation
- Possible risks, including preventive and alleviative measures
- Informed consent process
- Respect for enrolled subject
- The voluntary of the human subject is absolutely essential.
- Procedures must avoid unnecessary mental and physical suffering

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Issues for Ethical Justifications: Primary Research (2)

- Sample size is appropriate
- Provisions for monitoring the data collected to ensure safety of the subjects are adequate.
- Provisions for protecting the privacy of subjects and confidentiality are sufficient
- Additional safeguards are in place to protect the rights and welfare of vulnerable subjects.
- Compensation for research participants: to reimburse research participants for their time, research-related inconveniences and/or research-related discomforts.
- Research is conducted by qualified scientists

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Collection of Biological Specimens (Primary Use)

- Individual consent information (ICF/PIS):
  - Informed consent required when there is intervention/ interaction with human or private identifiable information is being collected and/or used
  - Consent is voluntary and can be withdrawn at any time and this will not affect their treatment in any way
  - Consent for collecting the specimens
    - Description of specimens/data and process used for collecting them
    - Description of the purpose of the collection and conditions for sharing with other researchers
  - Consent for storage and future use: details about where and how long the specimens will be stored

24 ……*Declaration of Helsinki, The Belmont Report…..*

Collection of Biological Specimens (Primary Use)

- **Individual consent information (ICF/PIS):**
  - **Consent for commercial use (if any), and plans (if any) for sharing profits**
  - **Consent for access to medical records and information**
  - **Consent for re-contacting the subject for more data (if any)**
- **Other information**
  - **Whether the results will be returned**
  - **Risks, including risks to privacy and confidentiality, and methods to protect risks**
  - **Genetic uses and information on the consequences of DNA typing (if any)**
  - ***Etc.***

25 ……*Declaration of Helsinki, The Belmont Report…..*

Collection of Biological Specimens (Primary Use) Issues for Consideration

- **Although consent from patient/subjects has been obtained for the use of leftover specimen in future research, approval from IRB / IEC must first be obtained for each subsequent study.**
- **Generic consent to use the tissues for future research without conditions is not permissible.**
- **Consent from children, the elderly, disabled and other vulnerable groups should be obtained as prescribed in the *Good Clinical Practice guidelines***

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Planning for Privacy and Confidentiality

- **Participant privacy and confidentiality is restricted protected**
- **Investigator should consider confidentiality protection at all phases of research**
- **Researchers should remain aware of the possibility of inadvertent (not intend to) disclosure of identities**
- **Investigators and supervisors are responsible for the safekeeping and confidentiality of signed consent forms. These must be stored separately from the data.**
- **<u>Data limit access</u> to personally identifiable**
- **Secure storage/data security**
- **Honest de-identified systems**
- **Duration of keeping data**

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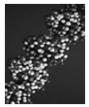
Planning for Privacy and Confidentiality

- **Investigators are responsible for keeping information (including the identity of participants) confidential and secure from interception or appropriation by secondary persons, or for purposes other than the approved research.**
  - **Coding individually identifiable data: by removal of identifying material (*eg. name, HN, social security number etc*.) from documentation whom the private information or specimens pertain has been replaced with a *number, letter, symbol, or combination* thereof.**
  - **Person(s) doing coding of data/specimens and person(s) holding codes are not part of the research team**
- **The results is presented in overview of the subject**

…ICH Good Clinical Practice…

Ethical Issues in Genetic Research

Why genetics is ethically interesting?



1. **Genetic information often identifies risks of medical conditions that *don't yet* affect the patient**

2. **Genetic information is about *families* as well as *individuals***
   - As such, it sometimes doesn't fit well into our usual individualistic ways of thinking about consent, confidentiality, etc.

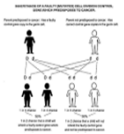
3. **Genetic research is commercially driven to a very substantial degree**
   - This raises questions about whether it is legitimate to allow genes to be 'owned' and what people should expect in return for participating in genetic research





Genetic Research: Discrimination and Stigmatization

- **The use of . . .human genetic . . . and . . . proteomic data should not . . . have the effect of infringing human rights, fundamental freedoms or human dignity of an individual or . . . lead to the stigmatization of an individual, a family, a group or communities.**



- **Appropriate attention should be paid to the findings of population-based genetic studies and behavioural genetic studies . . . .**

UNESCO Int'l Declaration, Art. 7

Genetic Association Research
Concerns related to privacy

- **Careful due to the risks of bias, discrimination and social stigma increase.**
  - **Detection of single-gene mutations associated with rare, inherited diseases (*highly selected donors*)**
  - **Genome-wide association studies (GWAS) Search for genetic patterns associated with common diseases requires *large sample sizes***
  - **Genomes may be *shared* with central repository**
  - **Genomes may be *posted on-line* for further research use**
- **Information about the *potential for developing a disease* in the future**
- **Either disease being researched or incidental finding**
- **Risk of employment or insurance *discrimination***
- **Genetic status of relatives who did not choose to donate specimens**

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Human Genetic Data

- **Clear, balanced, adequate and appropriate information shall be provided to the person whose prior, free, informed and express consent is sought.**

- **Information shall . . . specify the purpose for which human genetic data . . . are being derived, . . . used and stored**

(International Declaration on Human Genetic Data Adopted by the UNESCO General Assembly on 16 October 2003)

Genetic Association Research
Key Ethical Challenges

- **Informed Consent** ◦
  - Challenge of consent for future research that is not fully anticipated at the time of sample collection
  - Option in *vs.* option out
- **Sample/Data Sharing**
  - Risks associated with sharing potentially identifiable information with third parties

Human Genetic Data:
Withdrawal of Consent

- **Consent may be withdrawn by the person concerned unless such data are irretrievably unlinked to an identifiable person.**
- **When a person withdraws consent, the person's genetic data, proteomic data and biological samples should no longer be used unless they are irretrievably unlinked to the person concerned.**
- **If the person's wishes cannot be determined or are not feasible or are unsafe, the data and biological samples should either be irretrievably unlinked or destroyed.**

UNESCO Int'l Declaration, Art. 9

Genomic Research Practices
Privacy, Confidentiality and Integrity

- **Respect the privacy of the subject, the confidentiality of the patient's information and minimize the impact of the study on the subject's physical and mental integrity**

(Daclaration of Helsinki #21)

Genomic Research Practices
Privacy, Confidentiality and Integrity

- **The private information or specimens were not collected specifically for the proposed research**
- **The investigators cannot readily ascertain the identity of the individual(s)"**

Certificate of Confidentiality (CoC)

- CoC's allow the investigator and others who have access to the research records to refuse to disclose identifying information in any civil, criminal, administrative, legislative, or others
- **Examples of sensitive research activities include:**
  - Collecting genetic information
  - Collecting info on psychological *well-being* of subjects
  - Collecting info on subjects' sexual attitudes, preferences, or practices
  - Collecting data on substance abuse or other illegal risk behaviors

(NIH, USA)

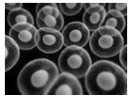
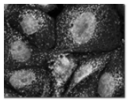
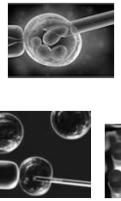
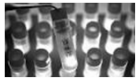
Ethical Issues in Tissue/ Cell Line Research: What is supposed to be reviewed?

- **Covered stem cell line means a culture-derived, human stem cell population that is capable of:**
  1. Sustained propagation in culture
  2. Differentiation along multiple cell lineages
  3. Self-renewing to produce daughter cells with equivalent developmental potential.

This definition includes both *embryonic* and *non-embryonic* human stem cell lines regardless of the tissue of origin

Human Tissues Research: Relevant Materials

- **Blood**
- **Tissue**
- **Stem cells**
  - **Adult, "tissue-specific" stem cells (from bone marrow, umbilical cord blood, brain, heart)**
- **Sputum**
- **Foetus**
- **Mucus**
- **Nasal lavage**
- **Lungs**
- ***Etc.***


Human Tissue Authority/Property Right

Codes of Practice:

- **Consent**
  - **Donation of organs, tissue and cells for transplantation**
  - **Post-Mortem Examination**
  - **Anatomical Examination**
  - **Removal, storage and disposal of human organs and tissue**
  - **Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation**



www.hta.gov.uk/guidance/codes_of_practice.cfm

Case Study

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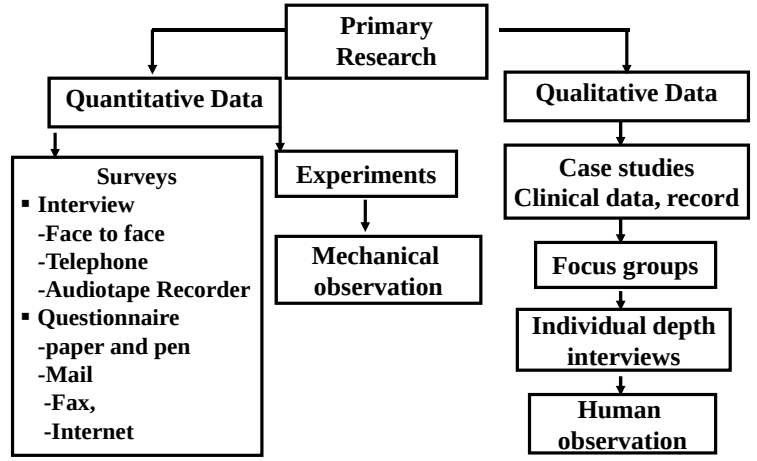
Collection of Data (Primary Use) Methods & Techniques



Ethical Consideration for Obtaining Data (Primary Use)

- Permission of the people/community to conduct research
- Physical or emotional harm to the subjects/ community must be avoided.
- Interview: avoid the word sensitive or difficult questions
- Both sides fair consideration: Objectivity *vs.* subjectivity in research is important consideration. Be sure not to get the personal biases and opinions
- Many types of research, such as surveys or observations, should be conducted under the assumption to keep the findings anonymous.

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Ethical Consideration for Obtaining Data (Primary Use)

- Many interviews are not done under the condition of anonymity. The subject should know whether the research results will be anonymous or not.
- Fair selection of the study subject or focus group. Do not take advantage of easy-to-access groups of people The subject has to choose fairly based on the most benefit of the research.
- Informed consent required when there is interaction with human or private identifiable information is being collected and/or used
- Privacy and Confidentiality are strictly protected: limiting access to the data
- To be honest to write the report

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Risks and Minimize Risks

Example

- **Social risk/community risk**
  ***eg.* psychological risk (social), family violence): from questionnaires, interview, focus group**
- **Economic risk**
  Economic risks may exist if knowledge of one's participation in research, for example, could make it difficult for a research participant to retain a job or to find a job, or if insurance premiums increase or loss of insurance is a result of the disclosure of research data.

Minimizing risks: protecting confidential data, including not only the data collected, but the fact of participation in the research project itself. (confidentiality process)

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PIS/ICF: Collecting the data

- **The purpose of the research**
- **Consent for collecting data**
  - Description of data and use
  - Description of the purpose of the collection and conditions for sharing with other researchers
  - Consent for future use
- **The time use for participating in the study eg. giving information, answer the questionnaire, time for interview *etc.***
- **Benefit of the study**
- **Possible risk**
- **Protection of privacy and confidentiality**
- ***Etc.***

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Secondary Research

- **Analysis**
  - **Retrospective study on leftover/stored biological specimens /clinical data / *etc.***
  - **Secondary data analysis**
- **Review: systemic, simple (narrative)**
  - **Case series**

Interaction between researchers and participant data is a key feature

Secondary Use of Biological Specimens/Data

- **Research use for a purpose other than that described in the primary protocol**
- **Research should be compatible with the informed consent under which the specimens were collected.**
- **Retrospective study using stored or leftover specimens: blood, serum, other body fluids, DNA, tissues, cells, teeth, urine blood, and other direct derivatives from human tissues *etc.***
- **Retrospective study using human data including medical histories, clinical data, clinical records and diagnoses, responses to questionnaires or surveys, etc.**

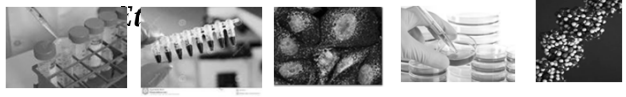
GCLP/GLP

Source of Stored Biological Specimens

- Leftover specimens after routine diagnosis

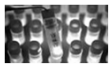
- Archived/Stored specimens (in individual research laboratories)

- Biobanks



Study Using Stored/Leftover Specimens from Routine Clinical Care/Diagnosis or Surgical Procedures

- The specimen was originally obtained for non-research purposes by someone other than the researcher *eg* diagnostic purpose
- Specimens provided to the investigator are accompanied by only minimal clinical information such as age, sex, and existing laboratory results
- No identifiable private information about the person from whom the specimen was obtained is transmitted with the specimen
- Participants are not consented
- No results returned



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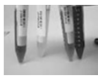
Study Using Unlinked Stored/Leftover Specimens

When an investigator proposes to create unlinked samples from coded or identified materials already under his or her control, IRB may exempt the research from IRB review if it determines that……..

- process used to unlink the samples will be effective
- unlinking of the samples will not unnecessarily reduce the value of the research.



Further Use of Stored/Leftover Specimens from Approval Research Project (1)

1. Such leftover specimen has *received the informed consent* from the research participants in the *original EC approval* research project with the permission from the research participants for further use.

<u>Ethics Consideration</u>

- Letter of permission for leftover specimen from the principle investigator of such research project
- Providing the approval number and title of the original project
- Providing the inclusion criteria/ exclusion criteria/ discontinuous criteria
- Coding of specimens/data: identifying information never released to investigators

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Further Use of Stored/Leftover Specimens from Approval Research Project (2)

2. **Leftover specimen that has not received the permission (informed consent) from the research participants for further use in the original research project when the specimens were collected, cannot be used for further research purpose.**

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Further Use of Stored/Leftover Specimens from Approval Research Project (3)

3. **If the study objectives are not included in the approval research project, some additional data from the participant are needed.**
   - **Re-Consent is required**
   - **Possibility of withdrawing specimen**
     - **Permission from the participant to use and store specimen/ data (medical records, pathological records / personal data) for future (if any)**
     - **Keep privacy and confidentiality (coding system)**
     - **Results returned (disclosure if necessary)**

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Case Study

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Secondary Use of Data: Protection

- **Personal data for secondary use: seems likely that data can be used for a secondary purpose which was not first considered ('Research')**
- **As long as secondary use cannot cause harm or distress to the data subject and safeguards his/her rights**
- **Results of the secondary research must not be identifiable.**

Secondary Use of Data

When are "privacy and confidentiality" NOT required?

- **In the public domain:**
  - **Observation of public behavior**
  - **Use of public records/data eg. commercials, public message boards**
  - **When research participants give informed consent for disclosure of information**

Note: Investigator's judgment should always apply and research protocols must be approved by the Institutional Ethical Committee

Ethical Consideration for Using Secondary Data

- **Research involving the study of existing data that can be linked to the participants**
  - **Permission to use the data**
    - Participants
    - Authorized person
  - **Privacy and confidentiality**
  - **Secondary person is required** to do coding of data and is not part of the research team
  - **Limiting access**
    - Limiting access to paper or electronic records
    - Password protection of electronic records
    - Defined privileges for electronic data users
  - **Other ethical consideration**

Study of Existing Data that Can be Linked to the Participants

- **Need to be aware of the impact on how data is collected when sharing later.**
  'Fair obtaining and processing' requires that the research participant is informed about
  - The purpose of data collection
  - The persons or categories of persons to whom the data may be disclosed
  - Any other information that is necessary to ensure the processing is fair.
- **For re-use, research participants should know the re-using the data and the categories of data being used.**

FTM Criteria for an Exempt Review of Research Proposal

Research that is exempt from the regulatory requirement for prospective IRB review and approval. This includes "research involving the collection or study of

- **Existing pathological specimens (if publicly available or rendered unidentifiable)**
- **Anonymous leftover diagnostic specimens (anonymous)**
- **Existing data, documents, pathological specimens (de-identified/ no identifiers maintained such as online survey)**

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When is Specimen/Data Research Exempt ?

- **Research involving the study of existing data, documents, records, specimens (pathological or diagnostic), if these sources are publicly available**
- **Absolutely no identifiable private information about the person whose specimen was obtained.**
- **Cell lines which could not be identified directly to the owner subjects *eg.***
  - Human cell lines obtained from a commercial provider (e.g. ATCC)
  - Human cells about which all information has been published.
- **Isolated microorganisms from the specimens which cannot link to the subjects**

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NIH, USA

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Thank you

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