ETHICS OF SCIENTIFIC RESEARCH IN FORENSIC MEDICINE

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ABSTRACT

Background: Multiple unethical research studies conducted in the past throughout the world have cast a significant historical shadow on research involving human subjects. These studies exposed patients to diseases or unproven treatments, so the need for rules governing the design and implementation of research protocols become very evident. Research ethics provides guidelines for the responsible conduct of biomedical research. In addition, research ethics educates and monitors scientists conducting research to ensure the safety of research subjects and to prevent sloppy or irresponsible research. Research ethics have many values including honesty, objectivity, integrity, and carefulness. There are ethical issues regarding researches involving human biological materials; especially fetal tissues, human gametes and embryos, surplus biological materials from clinical procedures or from research projects and bio banks. **Objectives:** In this review, we tried to outline principles and values of research ethics, demonstrate research ethics in animals, identify ethical principles in research involving human biological materials, genetic and human stem cell research, define criteria of institutional review board (IRB), identify ethical considerations in authorship, peer review, conflict of interest, data management and cover letter, and outline research misconducts. **Conclusion:** Ethics of scientific research are group of principles or guidelines for the responsible conduct of biomedical research to ensure the safety of research subjects and to prevent sloppy or irresponsible research. These principles include social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect for enrolled subject. As well as, there are 4 Rs ethical principles in animals; Reduction, Refinement, Replacement and Responsibility. Research misconduct includes fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. The IRB is concerned with protecting the welfare, rights, and privacy of human subjects through reviewing all research involving human participants.

Keywords: *Research principles, Animal experimentation, Human biological materials, Stem cell, Research misconducts.*

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INTRODUCTION

Multiple unethical research studies conducted in the past throughout the world have cast a significant historical shadow on research involving human subjects. These studies include Nazi medical experimentation in the 1930s and 1940s, the Tuskegee Syphilis Study from 1932 to 1972, and research conducted at the Willowbrook State School in the 1950s and 1960s ***(Sims, 2010)***.

As the results of these practices, uninformed and unaware patients were exposed to disease or unproven treatments, and the need for rules governing the design and implementation of human-subject research protocols became very evident ***(Barrow et al., 2023)***. Ethics is an understanding of the nature of conflicts arising from moral imperatives and how best to deal with them. There are four fundamental principles of research ethics being underscored as autonomy, beneficence, non-maleficence, and justice ***(Avasthi et al., 2013)***.

The growth of the medical-industrial complex during the 20th and early 21st century has been paralleled by a deepening interest in the ethical conduct of research on human subjects ***(Romain, 2015)***.

In relation to clinical research, conflicts of interest occur at different levels and usually permeate through various lines. The conflicts may be related to the financial gains to participate in pharmacy sponsored trials, or

to the expected academic career boost attained with the publication of the results of the trials and also to personal interests such as the financial support for trips to international conferences ***(Rothman et al., 2009)***.

For almost two decades, multinational pharmaceutical companies have found Egypt to be an appealing place to outsource their clinical trials. Second to only South Africa, Egypt has the highest number of clinical trials being carried out by pharmaceutical companies, such as Roche and Novartis in Africa ***(Durisch, 2016; Zannad et al., 2019)***. Compared with other Arab countries in the Middle East, Egypt conducts the largest number of clinical trials and together with Saudi Arabia manages half of all clinical studies in the region ***(Silverman, 2017)***.

Egypt has established many Institutional Review Boards (IRBs) during the last ten years. There were no national ethical guidelines to guide IRBs, which resorted to international documents such as the Council for International Organizations for Medical Sciences (CIOMS), Declaration of Helsinki (DoH) and the Belmont report to guide their review process ***(Saleh, 2017)***.

There are more than fifty IRBs in Egypt. Furthermore, there is a network of IRBs managed by the Egyptian Network of Research Ethics Committees (ENREC). The network provides periodic trainings on research ethics to IRB members in Egypt and make available online resources such as Arabic templates for informed consent, a checklist for research review and training materials ***(Sleem, 2008)***.

ENREC has promoted the enhanced ethical review of research in Egypt in the last decade. However, in contrast to other countries in the Arab Region, Egypt lacks formal regulations to ensure oversight of these IRBs as well as consistency in the review of research between the different IRBs ***(Silverman, 2017)***.

In response, the Egyptian Parliament published its first clinical research law in December 2020. The official version of the law was translated to English from Arabic and back by an accredited translation service ***(Matar and Silverman, 2022)***.

OBJECTIVES

In this review, we tried to outline principles and values of research ethics, demonstrate research ethics in animals, identify ethical principles in research involving human biological materials, genetic and human stem cell research, define criteria of institutional review board (IRB), identify ethical considerations in authorship, peer review, conflict of interest, data management and cover letter, and outline research misconducts.

History of Research Ethics:

Nuremberg Code

A well-known chapter in the history of research with human subjects opened on Dec. 9, 1946, when an American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. Among the charges were that German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent. Most of the subjects of these experiments died or were permanently crippled as a result ***(Sims, 2010)***.

As a direct result of the trial, the Nuremberg Code was established in 1948, stating that "The voluntary consent of the human subject is absolutely essential," making it clear that subjects should give consent and that the benefits of research must outweigh the risks. Although it did not carry the force of law, the Nuremberg Code was the first international document which advocated voluntary participation and informed consent ***(UNLV, 2023)***.

It laid down 10 clear principles to be followed by researchers and made voluntary consent essential, allowed subjects to withdraw from the experimentation at any time, banned experiments that could result in major injury or death of the subjects, and made mandatory to have preclinical data before experimenting on humans ***(Avasthi et al., 2013)***.

Declaration of Helsinki

In 1964, the World Medical Association established the "Declaration of Helsinki," which provides recommendations guiding

medical doctors in biomedical research involving human subjects. It contained 32 principles, which stress on informed consent, confidentiality of data, vulnerable population, and requirement of a protocol, including the scientific reasons of the study, to be reviewed by the ethics committee ***(Avasthi et al., 2013)***.

Tuskegee Syphilis Study (1932-1972)

An equally well-known chapter in history occurred during a research project conducted by the U.S. Public Health Service. Six hundred low-income African-American males, 400 of whom were infected with syphilis, were monitored for 40 years. Free medical examinations were given; however, subjects were not told about their disease. Even though a proven cure (penicillin) became available in the 1950s, the study continued until 1972 with participants being denied treatment. In some cases, when subjects were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment. Many subjects died of syphilis during the study. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment. In 1997, under mounting pressure, President Clinton apologized to the study subjects and their families ***(UNLV, 2023)***.

National Research Act (1974)

Because of the publicity from the Tuskegee Syphilis Study, the National Research Act of 1974 was passed. The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This commission was tasked with identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects.

It was also tasked with developing guidelines that should be followed to assure that such research is conducted in accordance with these ethical principles. The commission drafted the Belmont Report 1979, a foundational document in for the ethics of human subjects' research in the United States.

The Belmont Report ***(Barrow et al., 2023)***.

Principle	**Application**
- Respect for persons - Individuals should be treated as autonomous agents. - Persons with diminished autonomy are entitled to protection.	- Informed consent - Subjects, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them. The consent process must include three elements: Information, comprehension, and voluntariness.
- Beneficence - Human subjects should not be harmed. - Research should maximize possible benefits and minimize possible harms.	- Assessment of risks and benefits - The nature and scope of risks and benefits must be assessed in a systematic manner.
- Justice: The benefits and risks of research must be distributed fairly.	- Selection of subjects: There must be fair procedures and outcomes in the selection of research subjects.

Principles of Ethical Research adopted by National Institute of Health (NIH), USA:

1- Social Value
2- Scientific Validity
3- Fair Subject Selection
4- Favorable Risk-Benefit Ratio
5- Independent Review
6- Informed Consent
7- Respect for Enrolled Subject.

1. Social and clinical value

Every research study is designed to answer a specific question. The answer should be important enough to justify asking people to accept some risk for others. In other words, answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease to justify exposing participants to the risk and burden of *research* ***(Bitter et al., 2020)***.

2. Scientific validity

Extent to which research findings are accurate. There are two measures of scientific validity which may be external or internal. External validity means the capacity to generalize research findings and this can be verified by use of proper sample. Internal validity means ability of research design to answer the research question and this can be verified by use of proper methodology. Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose ***(NIH, 2016)***.

3. Fair subject selection (Justice)

The primary basis for recruiting participants should be the scientific goals of the study not vulnerability, privilege, or other unrelated factors. Participants who accept the risks of research should be in a position to enjoy its benefits. Specific groups of participants (for example, women or children) should not be excluded from the research opportunities without a good scientific reason or a particular susceptibility to risk ***(Tsoka-Gwegweni and Wassenaar, 2014)***.

4. Favorable risk-benefit ratio

Research risks may be trivial or serious, transient or long-term. Risks can be physical, psychological, economic, or social. Everything should be done to minimize the risks and inconvenience to research participants to maximize the potential benefits, and to determine that the potential benefits are proportionate to, or outweigh, the risks ***(Tangwa, 2017)***.

5. Independent review

To minimize potential conflicts of interest and make sure a study is ethically acceptable before it starts, an independent review panel should review the proposal and ask important questions, including: Are those conducting the trial sufficiently free of bias? Is the study doing all it can to protect research participants? Has the trial been ethically designed and is the risk–benefit ratio favorable? The panel also monitors a study while it is ongoing ***(Bitter et al., 2020)***.

6. Informed consent

Informed consent document:

A document that describes the rights of the study participants, and includes details about the study, such as its purpose, risks, potential benefits duration, required procedures, and key contacts. The participant then decides whether or not to sign the document. Informed consent **is not a contract**, and the participant may withdraw from the trial at any time ***(Rivera and Borasky, 2009)***.

Elements of Informed Consent:

Competence:

Consent is given by a competent individual (mentally efficient, conscious and more than 18years old) who can receive the necessary information, has adequately understood the information. After considering this information, he can arrive at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Disclosure:

Information disclosed to research participants must include, "research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research."

Comprehension:

The concept of comprehension requires researchers to adapt information to be understandable to every participant. This requires taking into consideration different abilities, intelligence levels, maturity, and language needs.

Voluntariness:

Participant is absolutely voluntary to participate in the study, has right to discontinue at any time and no penalty for refusal.

7. Respect for potential and enrolled participants

Individuals should be treated with respect throughout their participation and after their participation ends. This includes respecting their privacy and keeping their private information confidential, respecting their right to change their mind, to decide that the research does not match their interests, and to withdraw without a penalty, as well as, monitoring their welfare and, if they experience adverse reactions, unexpected effects, or changes in clinical status, ensuring appropriate treatment and, when necessary, removal from the study.

Values of research ethics ***(Avasthi et al., 2013)***

Honesty:

Strive for honesty in all scientific communications. Honestly report data, results, methods and procedures, and publication status. Do not fabricate, falsify, or misrepresent data. Do not deceive colleagues, research sponsors, or the public.

Objectivity:

Strive to avoid bias in experimental design, data analysis, data interpretation, peer review, personnel decisions, grant writing,

expert testimony, and other aspects of research where objectivity is expected or required. Avoid or minimize bias or self-deception. Disclose personal or financial interests that may affect research.

Integrity:

Keep your promises and agreements; act with sincerity; strive for consistency of thought and action.

Carefulness:

Avoid careless errors and negligence; carefully and critically examine your own work and the work of your peers. Keep good records of research activities, such as data collection, research design, and correspondence with agencies or journals.

Openness:

Share data, results, ideas, tools, resources. Be open to criticism and new ideas.

Transparency:

Disclose methods, materials, assumptions, analyses, and other information needed to evaluate your research.

Accountability:

Take responsibility for your part in research and be prepared to give an account (i.e. an explanation or justification) of what you did on a research project and why.

Intellectual Property:

Honor patents, copyrights, and other forms of intellectual property. Do not use unpublished data, methods, or results without permission. Give proper acknowledgement or credit for all contributions to research. Never plagiarize.

Confidentiality:

Protect confidential communications, such as papers or grants submitted for publication, personnel records, trade or military secrets, and patient records.

Responsible Publication:

Publish in order to advance research and scholarship, not to advance just your own career. Avoid wasteful and duplicative publication

Responsible Mentoring:

Help to educate, mentor, and advise students. Promote their welfare and allow them to make their own decisions.

Respect for Colleagues:

Respect your colleagues and treat them fairly.

Social Responsibility:

Strive to promote social good and prevent or mitigate social harms through research, public education, and advocacy.

Non-Discrimination:

Avoid discrimination against colleagues or students on the basis of sex, race, ethnicity, or other factors not related to scientific competence and integrity.

Competence:

Maintain and improve your own professional competence and expertise through lifelong education and learning; take steps to promote competence in science as a whole.

Legality:

Know and obey relevant laws and institutional and governmental policies.

Animal Care:

Show proper respect and care for animals when using them in research. Do not conduct unnecessary or poorly designed animal experiments.

Human Subjects protection:

When conducting research on human subjects; minimize harms and risks and maximize benefits; respect human dignity, privacy, and autonomy; take special precautions with vulnerable populations; and strive to distribute the benefits and burdens of research fairly.

Research ethics in animals

Animal model-based research has been performed for a very long time. Ever since the 5th century B.C., reports of experiments involving animals have been documented, but an increase in the frequency of their utilization has been observed since the 19th century ***(Fernandes and Pedros, 2017)***.

Most institutions for medical research around the world use non-human animals as experimental subjects. Such animals might be used for research experimentations to gain a better understanding of human diseases or for exploring potential treatment options ***(LaFollette, 2020)***.

There are many reasons that highlight the significance of animal use in biomedical research. One of the major reasons is that animals and humans share the same biological processes. In addition, vertebrates have many anatomical similarities (all vertebrates have lungs, a heart, kidneys, liver

and other organs). Therefore, these similarities make certain animals more suitable for experiments and for providing basic training to young researchers and students in different fields of biological and biomedical sciences ***(Franco, 2013)***.

Pros and cons of animal experimentation

Arguments against animal experimentation:

Animal rights advocates strongly argue that the moral status of non-human animals is similar to that of humans, and that animals are entitled to equality of treatment. In this view, animals should be treated with the same level of respect as humans, and no one should have the right to force them into any service or to kill them or use them for their own goals. In terms of suffering and the capacity of enjoying life, many animals are not very different from human beings, as they can feel pain and experience pleasure ***(Gruen, 2021)***. Hence, they should be given the same moral status as humans and deserve equivalent treatment.

Arguments support animal experimentation:

Those who support animal experimentation have frequently made the argument that animals cannot be elevated to be seen as morally equal to humans. Since, animals do not possess humans' cognitive capabilities and lack full autonomy (animals do not appear to rationally pursue specific goals in life), it is argued that therefore, they cannot be included in the moral community. It follows from this line of argument that, if animals do not possess the same rights as human beings, their use in research experimentation can be considered appropriate. The European and the American legislation support this kind of approach as much as their welfare is respected. Another aspect of this argument is that the benefits to human beings of animal experimentation compensate for the harm caused to animals by these experiments ***(Kiani et al., 2022)***.

A way to evaluate when the experiments are morally justified was published in 1986 by Bateson, which developed the Bateson's Cube. The Cube has three axes: suffering, certainty of benefit and quality of research. If the research is high-quality, beneficial, and not inflicting suffering, it will be acceptable. At the contrary, painful, low-quality research with lower likelihood of success will not be acceptable ***(Bateson, 1986; Bateson et al., 2004)***.

Ethics, principles and legislation in animal experimentation

Ethics in animal experimentation

Legislation around animal research is based on the idea of the moral acceptability of the proposed experiments under specific conditions. The significance of research ethics that ensures proper treatment of experimental animals ***(McCance, 2012)***. To avoid undue suffering of animals, it is important to follow ethical considerations during animal studies. It is important to provide best human care to these animals from the ethical and scientific point of view. Thus, if experimental animals mistreated, the scientific knowledge and conclusions obtained from experiments may be compromised and may be difficult to replicate, a hallmark of scientific research ***(Fernandes and Pedros, 2017)***.

Principle of the 4 Rs

In practice, the proposed set of animal experiments is usually considered by a multidisciplinary Ethics Committee before work can commence ***(Hansen, 2013)***. This committee will review the research protocol and make a judgment as to its sustainability. National and international laws govern the utilization of animal experimentation during research and these laws are mostly based on the universal doctrine presented by Russell and Burch (1959) known as principle of the 3 Rs. The 3Rs referred to are Reduction, Refinement and Replacement, and are applied to protocols surrounding the use of animals in research. Some researchers have proposed another "R", of responsibility for the experimental animal as well as for the social and scientific status of the animal experiments ***(Tannenbaum and Bennett, 2015)***.

The first "R", Reduction means that the experimental design is examined to ensure that researchers have reduced the number of experimental animals in a research project to the minimum required for reliable data ***(Ferdowsian and Beck, 2011)***. Methods used for this purpose include improved experimental design, extensive literature

search to avoid duplication of experiments ***(Delahaye, 2019)***, use of advanced imaging techniques, sharing resources and data, and appropriate statistical data analysis that reduce the number of animals needed for statistically significant results ***(Di Salvo, 2017; LaFollette, 2020)***.

The second "R", Refinement involves improvements in procedure that minimize the harmful effects of the proposed experiments on the animals involved, such as reducing pain, distress and suffering in a manner that leads to a general improvement in animal welfare. This might include for example improved living conditions for research animals, proper training of people handling animals, application of anesthesia and analgesia when required and the need for euthanasia of the animals at the end of the experiment to curtail their suffering **(*Di Salvo, 2017)***.

The third "R", Replacement refers to approaches that replace or avoid the use of experimental animals' altogether. These approaches involve use of computerized techniques/software and in vitro methods like cell and tissue culture testing, as well as relative replacement methods by use of invertebrates like nematode worms, fruit flies and microorganisms in place of vertebrates and higher animals ***(Fernandes and Pedroso, 2017)***.

The fourth "R", Responsibility refers to concerns around promoting animal welfare by improvements in experimental animals' social life, development of advanced scientific methods for objectively determining sentience, consciousness, experience of pain and intelligence in the animal kingdom, as well as effective involvement in the professionalization of the public discussion on animal ethics ***(Kiani et al., 2022)***.

Animal welfare laws

Legislation for animal protection during research has long been established. In 1876 the British Parliament sanctioned the 'Cruelty to Animals Act' for animal protection. Russell and Burch (1959) presented the '3 Rs' principles: Replacement, Reduction and Refinement, for use of animals during research ***(Tannenbaum and Bennett, 2015)***. Almost seven years later, the U.S.A also adopted regulations for the protection of experimental animals by enacting the Laboratory Animal Welfare Act of 1966 ***(Hansen, 2013)***.

These laws define the breeding conditions, and regulate the use of animals for scientific research and teaching purposes. Such legal provisions control the use of anesthesia, analgesia or sedation in experiments that could cause distress or pain to experimental animals. These laws also stress the need for euthanasia when an experiment is finished, or even during the experiment if there is any intense suffering for the experimental animal ***(Ferdowsian and Beck, 2011; Rai and Kaushik, 2018)***.

Development of new products and techniques to avoid animal sacrifice in research

Certainly, in vivo animal experimentation has significantly contributed to the development of biological and biomedical research. However, it has the limitations of strict ethical issues and high production cost. Some scientists consider animal testing an ineffective and immoral practice and therefore prefer alternative techniques to be used instead of animal experimentation. These alternative methods involve in vitro experiments and ex vivo models like cell and tissue cultures, use of plants and vegetables, non-invasive human clinical studies, use of corpses for studies, use of microorganisms or other simpler organism like shrimps and water flea larvae, physicochemical techniques, educational software, computer simulations, mathematical models and nanotechnology ***(Balls and Combes, 2017)***. These methods and techniques are cost-effective and could efficiently replace animal models. They could therefore, contribute to animal welfare and to the development of new therapies that can identify the therapeutics and related complications at an early stage ***(Fernandes and Pedroso, 2017)***.

Research involving human biological materials

Human biological materials are a valuable resource in biomedical research. These materials could be obtained from living or dead persons, or fetuses. It includes blood

and other body fluids, solid body tissues and organs, gametes and embryos. The ethical issues concerning the use of human biological materials for research relate to the collection, storage, use and disposal of the biological materials ***(Amoakoh-Coleman et al., 2023)***.

Types: Biological materials for research may be newly obtained for the purpose of research or they may come from pre-existing stored specimens or surplus from a clinical procedure. They may also be identified or de-identified ***(Hoeyer, 2008)***.

Guidelines on research involving human biological materials:

A-General (*Budimir et al., 2011)*

1- All research involving human biological materials, whether identified or de-identified, should be reviewed and approved by an IRB.

2- It is essential to protect the privacy and confidentiality of donors of biological materials and their personal information.

3- Donors of biological materials should not be offered any financial incentives for their donation, although reasonable compensation of expenses may be given.

4- Researchers and those managing biobanks need to be aware of religious and cultural perspectives and traditions relating to human tissue.

B-Consent in research with human biological materials

Informed consent must be obtained before any biological materials are taken for use in research ***(Tzortzatou-Nanopoulou et al., 2023)***.

Consent may be ***general or specific***.

General consent is consent that does not limit the use of the biological materials to any particular research project. It includes consent for storage and future use of the biological materials or personal information generated from the research using these materials, without a requirement for re-consent.

Specific consent is consent for a particular research project. In the event there are surplus biological materials from this project, a fresh consent would be needed for any future research. Specific consent should be obtained if the biological materials, or information derived from research with the materials, are to be used in research deemed to be sensitive (e.g. eggs, embryo).

Consent should contain ***(Beier et al., 2011)***:

(a) The purpose of the research, and any risks or benefits;

(b) The type and amount of biological materials to be collected, and the procedures and risks involved in taking it;

(c) That the biological materials will be considered a gift and donors will not have any right or claim to any share in the commercial gain derived from the research;

(d) Whether the biological materials may be stored and used for future research, and for how long;

(f) Whether there is any possibility of being re-contacted for future research, or to be informed about clinically significant incidental findings (according her or his desire),

(h) That it is possible for donors to withdraw consent from the research, as long as the biological materials have not yet been used.

Re-consent is required in the following situations:

(a) When the proposed research is not covered by the consent

(b) For research deemed to be sensitive, such as that involving human eggs and embryos**.**

- Under the Medical Act (Therapy, Education and Research), any person who is not mentally disordered and who is 18 years of age or above may give all or any part of his or her body for research or for therapy. The gift will take effect upon death.

- Legally authorized relatives of deceased individuals (which include still-born infants and fetuses) may also give all or part of the deceased person for research after or immediately before death.

C-Fetal Tissues

Fetal tissues include membranes, amniotic fluid, placenta and umbilical cord. Fetal tissues for research should only be taken from dead or non-viable fetuses. Abortion should not be induced for the purpose of obtaining materials for research. Consent for the termination of pregnancy should be separate from the consent for obtaining fetal tissues. Consent for the use of fetal tissue for research could be obtained from either parent. Any research intention to propagate

fetal cells *in vitro* and/or to transplant these cells into a human recipient should be disclosed when consent is given ***(Wester, 2022)***.

D-Human Gametes and Embryos

Specific consent from the donors must be obtained before any gametes or embryos are to be used for research. For women undergoing fertility treatment, consent for the donation of surplus oocytes or embryos for research should be separate from the consent for treatment. The treating physician should not also be the researcher seeking consent for the donation of oocytes or embryos for research. Donors should confirm in writing that they do not require the oocytes or embryos for future use ***(BAC, 2021)***.

For women not undergoing fertility treatment must be interviewed by an independent panel. The panel must be satisfied that they are of sound mind, clearly understand the nature and consequences of the donation, and have freely given explicit consent, without any inducement, coercion or undue influence and may be compensated for legitimate expenses incurred. Human embryos created for research through *in vitro* fertilization of human eggs by human sperm, or created through any form of cloning technology, should not be allowed to develop beyond 14 days *in vitro* and should not be implanted into the body of any human or animal ***(Advena-Regnery et al., 2018)***.

E-Surplus Biological Materials from Clinical Procedures

Biological materials, such as blood, biopsy samples or even whole organs, may be left over after clinical procedures that may be therapeutic or diagnostic in nature. Such materials can be very useful for research. Consent for the clinical procedure should be separate from the consent for the use of left over materials for research. Healthcare institutions should inform patients that there is a possibility of using of their surplus biological materials for research ***(Beier et al., 2011)***.

F-Surplus Biological Materials from Research Projects

Biological materials that are collected for a specific research project may subsist after the project is completed. Such materials can be stored for future research if consent for storage and future research use had been obtained from the donors ***(RCPA, 2022)***.

G-Imported Biological Materials

When imported biological materials are to be used for research, the researcher should obtain written assurance from the source authority that the materials have been ethically and legally obtained ***(Bioethics advisory committee, 2021)***.

H-Biobanks

Institutions that maintain tissue banks or biobanks for research should ensure the following ***(Tzortzatou-Nanopoulou, 2023)*****:**

(a) That appropriate consent has been obtained for the storage and use of the biological materials;

(b) That all research involving the biological materials is approved by IRB, and also by MOH (Ministry Of Health) where relevant, before the materials are handed over to the researcher(s);

(c) Protection of the privacy of the donors and the confidentiality of personal information associated with the biological materials;

(d) Keeping proper records of all biological materials;

(e) Proper disposal of the biological materials when no longer needed.

Human genetic research

Human genetic research is the study of genes, their functions, how they are associated with health and disease, and how genetic and environmental factors influence health. This research may involve participants directly or indirectly through the use of their biological materials or personal information from medical records or other databases. It may involve the study of a specific gene, multiple genes, gene-environment interactions, or the entire genome to establish associations between genomic variants and diseases or specific traits ***(Delgado et al., 2023)***.

Genetic information refers to any information about the genetic makeup of an individual. It can be derived from genetic testing in either a clinical or research setting, or from any other sources, including details of an individual's family history of genetic diseases ***(BAC, 2021)***.

Guidelines on Human Genetic Research are the same as that of human biological materials.

Human stem cell research

Stem cells are undifferentiated cells that have the potential to develop into specialized cell types ***(EL Barky et al., 2017)***.

Classification according to origin *(Kalra and Tomar, 2014; EL Barky et al., 2017)*:

1- Embryonic Stem Cells (ECS): They are derived from the inner cell mass of the blastocyst

2-Fetal Stem Cell: A stem cell derived from fetal tissue, including placenta.

- Cord blood stem cells
- Amniotic Fluid / Fetal Stem Cells

3-Adult Stem Cell: A stem cell derived from the tissues or organs of an organism after birth.

- Hematopoietic stem cells (HSCs)
- Mesenchymal Stem Cells (MSCs)

4-Induced Pluripotent Stem Cells: Reprogramming adult human cells to a pluripotent state, making them similar to embryonic stem cells in terms of research and therapeutic applications.

Sources of stem cells *(Bacakova et al., 2018)*

- Excess fertilized eggs from IVF clinics
- Aborted fetuses
- Fetal Membranes and amniotic fluid
- Umbilical cord and Placental stem cells
- Bone marrow derived stem cells
- Somatic cell nuclear transfer (SCNT)

Types of Stem cell research:

(a) Basic research to understand physiological cellular processes and disease mechanisms.

(b) Research into new therapies, including pre-clinical and clinical trials

Uses:

The unique capacity of stem cells to develop into various specialized cell types makes them of potential use for the regeneration or reconstruction of diseased or injured tissue. Stem cell research may thus lead to new and better ways of treating serious and debilitating diseases such as Alzheimer's, diabetes and spinal cord injury ***(Hyun et al., 2008; Daley, 2012; Kato et al., 2012: Weissman, 2012;Sipp, 2013)***.

Stem cell research may involve human-animal combinations ***(King and Perrin, 2014)*** as follow:

(a) Cytoplasmic hybrid embryos (somatic cell nuclear transfer) which are created by fusing human somatic cell nuclei with enucleated animal eggs. These embryos can be used to derive stem cells with human nuclear genetic material without the need to create human embryos or the use of human eggs

(b) Animal chimeras, which are created by injecting human stem cells, into animals at various stages of development to study stem cell integration and differentiation and to evaluate the potential usefulness and safety of transplanting human stem cells for clinical treatment.

(c)Transgenic animals are animals in which the genome has been modified to include human genes. They have been widely used in laboratory research to understand and treat diseases.

Potential risks of stem cells *(Kunter and Floege, 2011)*

- Tumor formation
- Immune rejection
- Genetic abnormalities
- Adventitious agents(viruses and other disease)

Ethical problems and Regulations

Human embryonic stem cell research is controversial because, with the present state of technology, starting a stem cell line requires the destruction of a human embryo. So it is not the entire field of stem cell research, but the specific field of human embryonic stem cell research that is at the center of an ethical debate ***(Volarevic et al., 2018)***.

Opponents of the stem cell research argue that embryonic stem cell technologies are a slippery slope to reproductive cloning and can devalue human life. They argue that a human embryo is a human life that is entitled to protection. Also the use of adult stem cells from sources such as umbilical cord blood has consistently produced more promising results than the use of embryonic stem cells ***(Assen et al., 2021)***.

Supporters of embryonic stem cell research argue that such research should be

allowed because the resultant treatments could have significant medical potential. Also they consider human embryo as a mass of cells, no different from any other biological material used for research ***(King and Perrin, 2014)***.

Regulations:

The National Academies set certain guidelines for the scientists; researchers conducting human embryonic stem cells research including the donor issues, the ethics of induction of ovulation and the transplantations protocols. The guidelines rule out that nuclear transfer must not be used in attempts to reproduce a human being (reproductive cloning), and no human embryos used in research should be grown in culture for longer than 14 days or the formation of the primitive streak **(*King and Perrin, 2014; Volarevic et al., 2018 and Assen et al., 2021)***.

Islamic point of view

نظر مجلس المجمع الفقهي الإسلامي برابطة العالم الإسلامي في دورته السابعة عشرة المنعقدة بمكة المكرمة ، في الفترة من ١٩-١٤٢٤/١٠/٢٣هـ الذي يوافقه: ١٣-٢٠٠٣/١٢/١٧م ، قد في موضوع : (الخلايا الجذعية) وهي خلايا المنشأ التي يخلق منها الجنين ، ولها القدرة - بإذن الله - في تشكل مختلف أنواع خلايا جسم الإنسان ، وقد تمكن العلماء حديثاً من التعرف على هذه الخلايا وعزلها وتنميتها ، وذلك بهدف العلاج وإجراء التجارب العلمية المختلفة .. ومن ثم يمكن استخدامها في علاج بعض الأمراض ، ويتوقع أن يكون لها مستقبل وأثر كبير في علاج كثير من الأمراض والتشوهات الخلقية ، ومن ذلك بعض أنواع السرطان ، والبول السكري ، والفشل الكلوي والكبدي ، وغيرها .

ويمكن الحصول على هذه الخلايا من مصادر عديدة منها :

(١) الجنين الباكر في مرحلة الكرة الجرثومية (البلاستولا) وهي الكرة الخلوية الصانعة التي تنشأ منها مختلف خلايا الجسم ، وتعتبر اللقائح الفائضة من مشاريع أطفال الأنابيب هي المصدر الرئيس ، كما يمكن أن يتم تلقيح متعمد لبيضة من متبرعة وحيوان منوي من متبرع للحصول على لقيحة وتنميتها إلى مرحلة البلاستولا ، ثم استخراج الخلايا الجذعية منها .

(2)الأجنة السقط في أي مرحلة من مراحل الحمل .

(3) لمشيمة أو الحبل السري .

(٤)الأطفال والبالغون .

(٥)الاستنساخ العلاجي، بأخذ خلية جسدية من إنسان بالغ ، واستخراج نواتها ودمجها في بييضة مفرغة من نواتها ، بهدف الوصول إلى مرحلة البلاستولا ، ثم الحصول منها على الخلايا الجذعية .

وبعد الاستماع إلى البحوث المقدمة في الموضوع وآراء الأعضاء والخبراء والمختصين والتعرف على هذا النوع من الخلايا ومصادرها وطرق الانتفاع منها ، اتخذ المجلس القرار التالي :

أولاً: يجوز الحصول على الخلايا الجذعية وتنميتها واستخدامها بهدف العلاج أو لإجراء الأبحاث العلمية المباحة ، إذا كان مصدرها مباحاً ، ومن ذلك - على سبيل المثال - المصادر الآتية :

١ / البالغون إذا أذنوا ، ولم يكن في ذلك ضرر عليهم .

٢ / الأطفال إذا أذن أولياؤهم ، لمصلحة شرعية ، وبدون ضرر عليهم .

٣ / المشيمة أو الحبل السري ، وبإذن الوالدين.

٤ / الجنين السقط تلقائياً أو لسبب علاجي يجيزه الشرع ، وبإذن الوالدين . مع التذكير بما ورد في القرار السابع من دورة المجمع الثانية عشرة ، بشأن الحالات التي يجوز فيها إسقاط الحمل .

٥ / اللقائح الفائضة من مشاريع أطفال الأنابيب إذا وجدت وتبرع بها الوالدن مع التأكيد على أنه لا يجوز استخدامها في حمل غير مشروع .

ثانياً: لا يجوز الحصول على الخلايا الجذعية واستخدامها إذا كان مصدرها محرماً ، ومن ذلك على سبيل المثال :

١ / الجنين المسقط تعمداً بدون سبب طبي يجيزه الشرع .

٢/ التلقيح المتعمد بين بييضة من متبرعة وحيوان منوي من متبرع .

٣ / الاستنساخ العلاجي .

Institutional Review Board (IRB)

The Institutional Review Board (IRB) is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB is charged with the responsibility of reviewing, prior to its initiation, all research (whether funded or not) involving human participants. The IRB is concerned with protecting the welfare, rights, and privacy of human subjects ***(Grady, 2015***). Federal regulations give the IRB the authority to: approve, disapprove, or modify research; conduct continuing reviews; observe and verify changes to research; suspend or terminate approval; and observe the consent process and the research procedures ***(Oregon State, 2019)***.

Criteria for IRB Approval *(UCLA OHRPP, 2021)*

IRB review is necessary for all human subjects research that does not qualify as exempt research or for expedited review.

a) In order to approve research, IRB determines that all of the following requirements are satisfied:

1. Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes (Beneficence) .
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may

reasonably be expected to result. In evaluating risks and benefits, the IRB will consider only those risks and benefits that may result from the research, as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research (Beneficence).

3. Selection of subjects is equitable. In making this assessment the IRB will take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special considerations of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, mentally disabled persons, or economically or educationally disadvantaged persons (Justice).
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal regulations (Respect for Persons).
5. Informed consent will be appropriately documented in accordance with, and to the extent required by the Federal regulations (Respect for Persons).
6. When appropriate, the research plan makes adequate provision for monitoring the data collected to assure the safety of subjects (Beneficence).
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data (Respect for Persons and Beneficence).

b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects (Respect for Persons and Beneficence).

Ethical considerations in:

(Authorship, peer review, conflict of interest, data management and cover letter).

Authorship:

It is the process of deciding whose names belong on a research paper. In many cases, research evolves from collaboration and assistance between experts and colleagues. Some of this assistance will require acknowledgement and some will require joint authorship. The International Committee of Medical Journal Editors is much more systematic. They argue that if but one of the follow criteria are not met by an individual, then that individual should be acknowledged as a contributor (e.g., in a footnote) but not ascribed authorship. These criteria are as follows ***(Ponomariov and Boardman, 2016)*:**

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

There are a couple of types of authorship:

Co-author

Any person who has made a significant contribution to a journal article. They also share responsibility and accountability for the results of the published research.

Corresponding author

If more than one author writes an article, one of them is chosen to be the corresponding author. This person will handle all correspondence about the article and sign the publishing agreement on behalf of all the authors. They are responsible for ensuring that all the authors' contact details are correct, and agree on the order that their names will appear in the article.

Researchers should discuss authorship at an early stage in a research project to establish; Who will be listed as an author on potential research outputs, the order in which the authors will be listed and the responsibilities of each author ***(UQ , 2024)***.

Peer review:

Peer review is the system used to assess the quality of a manuscript before it is published. Independent researchers in the relevant research area assess submitted manuscripts for originality, validity and significance to help editors determine whether a manuscript

should be published in their journal. When a manuscript is submitted to a journal, it is assessed to see if it meets the criteria for submission. If it does, the editorial team will select potential peer reviewers within the field of research to peer-review the manuscript and make recommendations ***(Steer and Ernst, 2021)***.

There are four main types of peer review ***(BMC, 2024)***:

Single-blind: the reviewers know the names of the authors, but the authors do not know who reviewed their manuscript unless the reviewer chooses to sign their report.

Double-blind: the reviewers do not know the names of the authors, and the authors do not know who reviewed their manuscript.

Open peer: authors know who the reviewers are, and the reviewers know who the authors are. If the manuscript is accepted, the named reviewer reports are published alongside the article and the authors' response to the reviewer.

Transparent peer: the reviewers know the names of the authors, but the authors do not know who reviewed their manuscript unless the reviewer chooses to sign their report. If the manuscript is accepted, the anonymous reviewer reports are published alongside the article and the authors' response to the reviewer

Conflict of interest:

Conflicts of interest represent circumstances in which professional judgments or actions regarding a primary interest, such as the responsibilities of a medical researcher, may be at risk of being unduly influenced by a secondary interest, such as financial gain or career advancement ***(IM, 2009)***. The secondary interest may be financial or non-financial, and the resultant bias may be conscious or unconscious. The presence of conflicts of interest poses a problem for professional, patient, and public trust in research and the research enterprise. Effective means of identifying and managing conflicts are an important element in successfully achieving the goals of research. These strategies typically focus on the investigator and rely upon disclosure ***(Romain, 2015)***.

Research Data Management (RDM):

Research data management is the organization, documentation, storage, and preservation of the data resulting from the research process, where data can be broadly defined as the outcome of experiments or observations that validate research findings, and can take a variety of forms including numerical output (quantitative data), qualitative data, documentation, images, audio, and video ***(NLM, 2024)***.

In respect to research ethics, RDM includes three issues:

1-The ethical and truthful collection of reliable data;

2-The ownership and responsibility of collected data; and,

3-Retaining data and sharing access to them with colleagues and the public

Ethical data collection refers to collecting data in a way that does not harm or injure someone. **Harm and injury** could range from outright physical injury to harmful disclosure of unprotected confidential health information. **Truthful data** collection refers to data that, once collected, are not manipulated or altered in any way that might impact or falsely influence results. **Responsibilities** include the following important issues; Oversight of the design of the method of data collection, Protecting research subjects from harm and Securing and storing data safely to preserve the integrity and privacy of data ***(UM, 2003)***.

Data sharing is considered to be a hallmark of the scientific community due to the following: Data sharing achieves many important goals for the scientific community, such as reinforcing open scientific inquiry, encouraging diversity of analysis and opinion, promoting new research, testing of new or alternative hypotheses and methods of analysis, supporting studies on data collection methods and measurement, facilitating teaching of new researchers, enabling the exploration of topics not envisioned by the initial investigators, and permitting the creation of new data sets by combining data from multiple sources. Protecting intellectual property while at the same time encouraging data sharing is highly

important in order to ensure valid and reliable research ***(Ross et al., 2018)***.

The cover letter:

It must attest that the manuscript represents original work and that it is not under consideration for publication elsewhere. The cover letter should also state that all authors meet the criteria for authorship and that the authors will sign a statement attesting authorship and disclosing all potential conflicts of interest ***(Springer Nature, 2023)***.

Research misconduct

Research misconduct is defined as: "fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting *research* ***(US DHHS, 2024)***.

- Fabrication is making up data or results and recording or reporting them.
- Falsification is changing research materials, equipment, or processes or altering or omitting data or results so that the research record does not accurately reflect the research findings.
- Plagiarism is using another person's ideas, processes, results, or words without giving appropriate credit.

Identifying Research Misconduct ***(Resnik et al., 2015)***

- There be a significant departure from accepted practices of the relevant research community; and
- The misconduct be committed intentionally, or knowingly, or recklessly; and
- The allegation is proven by a preponderance of the evidence.

CONCLUSION

Ethics of scientific research are group of principles or guidelines for the responsible conduct of biomedical research to ensure the safety of research subjects and to prevent sloppy or irresponsible research. These principles include social value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent and respect for enrolled subject. As well as, there are 4 Rs ethical principles in animals; Reduction, Refinement, Replacement and Responsibility. Research misconduct includes fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. The IRB is concerned with protecting the welfare, rights, and privacy of human subjects through reviewing all research (whether funded or not) involving human participants.

RECOMMENDATIONS

1- Making training workshops for researchers on ethics of sound scientific research

2-Researchers should be aware of research misconducts in order to avoid them.

3- Researchers seeking to begin a study must submit a full research proposal to the IRB to ensure the ethical conduct of research.

4- Continuous monitoring for researcher during experiment to ensure good data management.

5- Researcher should declare any conflicts of interest to maintain the integrity of research and public trust.

6- Researcher should be aware of conditions of authorship to avoid writing those who haven't right to be on research paper.

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