ETHICS IN MEDICAL RESEARCH AND PUBLISHING

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Abstract
This review aims to provide a concise argument on the importance of ethics in scientific endeavors. Consideration should be given to all aspects of a research project, including, study design, approval process, execution, and publication. In addition, parameters such as human roles in research and human rights are noted. Furthermore, critical questions such as confidentiality, beneficence, and non-maleficent research are emphasized. Apart from the significance of data analysis, the adverse consequences of unethical behaviors such as plagiarism, data falsification, and research bias are investigated.

Keywords: Research misconduct, Plagiarism, Study design, Informed consent, Ethics approval

INTRODUCTION
Research is the foundation of science that generates knowledge and technology with a direct impact on individuals' well-being and quality of life [1]. Historically, scientific research was limited to academic institutions with little or no impact on people's daily lives. However, during the previous century, public interest in scientific research has increased substantially, powered by rising awareness and expansion of various branches of applied science with direct influence on modern society. The massive expansion in the scientific investigation has increased concern about the quality and authenticity of the studies.

Medical research especially clinical trials is designed to understand the etiology of diseases, establish diagnostic, preventive, and therapeutic methodologies, and finally evaluate the safety, efficacy, and outcomes of the existing interventions [2]. This necessitates studies on human subjects, whose involvement is crucial and is reliant on mutual trust between the researchers and the participants. Therefore, maintaining strong ethical standards and clinical governance for the protection of the research participants is essential for the safety of the study participants and the reliability of the results [3].

Ethics is generally described as the moral values, norms, principles and rules that govern people's conduct in order to avoid harm as well as treat people fairly, equitably, and respectfully [4]. Ethics of research not only protect human rights but also consider treating the animal as well as environmental aspects. In the same line,
research ethics defined as a road map for researchers to perform research morally by adherence to a high standard of truth and accuracy. Therefore, the primary objective of research ethics is to introduce, update, govern and monitor the ethical standards required for scientific discourse.

Ethics and integrity in medical research are practices that guarantee research is carried out in compliance with the highest standards while puts patients at the least risk of adverse outcomes. Research ethics is the critical evaluation of the moral issues related to or arising from the conduct of research while research integrity is defined as the adherence to professional norms that govern the appropriate conduct of research. Collectively, they build credibility and trust in the methodology and findings of the research [5].

After the Second World War and the existence of the secrecy in the implementation of new drugs or procedures before and during the war by both Nazi, Japanese and their rivals a need for the formation of regulatory systems to control any types of manipulation of human subjects within the frame of clinical trials was mandatory [6, 7]. The first international research ethics code was initiated during the Nuremberg trials questioning the Nazi scientists involved in human torture and using human subjects for experimentation. As a result, the Nuremberg code with 10-point statements was established [7]. The most obvious feature of this code declares that participation of human subjects in any trials must be voluntary. The code also declare that participants should provide informed consent and the benefits gained from research must outweigh its associated risks. Factors such as usefulness, awareness, no suffering, and many others were confirmed.

Subsequently, Declarations of Helsinki were established in 1964 on the basis of the Nuremberg code by mostly emphasizing ethical aspects that physicians must have complied with for their patients. In 1975 [8] the Helsinki decoration was revised followed by further revisions in, 1983, 1989, 1996, 2000,2004 and 2008 [9]. The seventh revision of the Helsinki Declaration, issued in October 2013, maintained core ethical principles while considering if further advice was required [10]. In the following sections, main principles of Helsinki Declaration will briefly be discussed.

With the advancement in medical research, the emergence of new medical technologies, and progression in pharmaceutical industries, concern about human right and safety in clinical research by public and private bodies were growing throughout the world.

In this respect, in 1966 Henry Beecher, an American professor of Anesthesiology published an article in the New England Journal of Medicine (NEJM) entitled: “Ethics and clinical research [11]” raising serious concerns in ongoing clinical trials in the US and the need for human fairness. This paper was a trigger to the US society and medical science community to establish National Research act and Belmont report in the following years [12].

The process of medical ethics was further evolved by the formation of what is known as the Vancouver group. International Committee of Medical Journal Editors (ICMJE) first met in 1978 in Vancouver aiming to discuss unity in preparing the reference styles for submitted manuscripts but soon the other essential ethical issues in medical journalism were also included. The Vancouver group published a guideline for manuscript submission in the area of biomedical Journals which later revised in 1997, 1999, 2000, 2001, and 2004 entitled as “Uniform Requirements for Writing Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication” [13].

Council for International Organizations of Medical Science (CIOMS) is also very important stake holder in the field of research ethics. In 1982, CIOMS, in collaboration with WHO, published principles guiding biomedical research involving human subjects. This work was in accordance with The World Medical Association Declaration of Helsinki and focused on developing countries and low resources settings, named “Proposed International Ethical Guidelines for Biomedical Research Involving Human Subjects” [14].

Ethical issues can occur throughout the research process including, study design, approval, execution, and publication therefore, several professional codes and laws were introduced to protect the research conduct and the dignity of participants [15, 16]. In the following sections, the ethical principles that are most frequently highlighted in the literature will be discussed.

**SEARCH STRATEGY**

This literature review aimed to discuss the various ethical aspects involved in medical research. The search was mainly through the “PubMed” database and mainly covered studies published over the past 15 years. However, it was impossible to ignore the history of medical ethics. The authors attempted to use all types of studies, mostly in English using the following keywords:
Medical research, clinical trials, ethics, research conduct, research methods, and scientific writing. After assessment of the abstracts of the chosen articles, their full text was also reviewed to determine if they passed the inclusion and exclusion criteria. Consequently, 70 articles were selected among 153 articles to be used for writing the main manuscript.

STUDY DESIGN AND ETHICS APPROVAL
Scientific research entails a variety of sequential activities, including precise study design, standard approval process of research proposals, appropriate study execution, data collection, data analysis/interpretation, and finally publication the results with the goal of developing or contributing to generalizable and reproducible knowledge. According to Committee on Publication Ethics (COPE) “good research should be well adjusted, well-planned, appropriately designed, and ethically approved”. Therefore, low-quality scientific studies may constitute research misconduct [16]. In addition, authorization from ethics committees is required in studies involving humans, their medical records, or tissues samples. The researchers should address potential ethical concerns that exist in the research. Furthermore, studies involving vulnerable individuals and communities (e.g., children, mentally or physically disabled, medically compromised, and older people) require particular care and consideration. For instance, countries with a major Aboriginal origin, such as Canada, Australia, and New Zealand, have attempted to develop community-sensitive principles for ethical research review [17, 18].

INFORMED CONSENT
Study participants should be provided with detailed information regarding the study aims, methods, and potential harms/benefits. The researchers must ensure that participants were given the necessary information to make an informed decision about their participation in the study (informed or written consent) [19]. Participants should also be informed of their right to withdraw from the study at any time and for any reason, with the understanding that their withdrawal will not influence the treatment course. In situations where the children or other vulnerable groups have limited comprehension of the situation and cannot provide consent as a result of the age, sickness and, language berries a third party (parent or guardian who act in the persons’ best interest) should be asked for consent [20].

The researchers should ensure that participants agree to take part in the study voluntarily. A mandate which clearly has been supported and recognized by the Helsinki Declaration where it states that participation in clinical research is a voluntariness decision. It further states that "no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees" [10].

Participants' Well-Being and Risk Analysis and Reduction in Human Research (Beneficence and Non-maleficence)
Clinical research has enhanced scientific knowledge and improves human lives. However, research involving human subjects must not violate the human right. As a result, over the last decades, protection of participants in health-related research acknowledged by several jurisdictions and ethical research norms have gradually been developed, mainly on account of historical events committed in the name of science [21]. Regulatory committees must authorize studies involving human subjects to prevent infringement and abuse of the subjects' rights and avoid experiments that can threaten participants’ well-being. Among those prestigious guidelines, the Declaration of Helsinki is the well-known and most applicable guideline for protecting research participants [15]. Declaration of Helsinki informs biomedical researchers about clinical research principles and to address existing ethical problems [15]. Three criteria for proper clinical practice were defined in the Helsinki declaration: respect for the person's dignity, principles of fairness, the importance of participant health and well-being (Research should not be prioritized over participant health and well-being).

In the same line, in 1987 The Canadian Medical Research Council introduced a set of guidelines for ethical research and emphasized that scientific research must be conducted in a compassionate manner. It also suggested that it is unacceptable to publish the results of research that was conducted inhumanely [22]. Accordingly, research conducted in this manner can compromise participant well-being as well as being a waste of resources by producing results that are neither generalizable nor contribute to human welfare [23]. Therefore, pursuing the ethical guidelines is mandatory to maintain participants’ dignity, rights, and welfare.

Beneficence and non-maleficence are two distinct but complementary aspects of research ethics. The term beneficence refers to the research's benefits, while non-maleficence states the potential harm or risks associated with research participation [24]. The essential foundation in all health research is to determine to what extent the population under investigation bears minimal risk while enjoying the benefits of the research. According to Beauchamp and Childress, “the principle of beneficence includes the professional mandate to do effective and
significant research to serve better and promote the welfare of our constituents" [4]. In case of clinical research, it may be associated with risk for participants; however, the researcher must ensure that the overall benefit gained outweighs the risk of research. The results of a study should benefit both study participant and the society, however, the advantages to the society should not come at the expense of the participants' safety [25]. Non-maleficence, on the other hand, considers the study participant's safety and assumes that the study must not bring any harm or suffering to the research participants [4, 26]. Consequently, the researchers first must explore the potential harm associated with the study (e.g., physical, emotional, and economic) while aiming to avoid/minimize them. Physical harms can be quickly detected, therefore preventable. Meanwhile, emotional, social, and economic issues may be less evident, causing harm to the subjects without the researcher's knowledge [19].

**PRIVACY AND CONFIDENTIALITY**
The importance of privacy and confidentiality has been emphasized as a foundation of research ethics by Helsinki Declaration [10]. In general, confidentiality can be described as any legal and moral effort to ensure that research is carried out with the utmost respect for participants privacy and confidentiality of their personal information [27]. The researchers must keep the confidentiality of participants' personal information, records, and other sensitive data.

Conducting human research entails safeguarding participants' confidentiality to the maximum extent possible and explaining possible harm or risk such as loss of confidentiality. Coding participants by numbers instead of using their real names and other identifying data as well as minimizing access to the participant's records are among efforts to maintain confidentiality [28]. In addition, confidentiality is crucial to the researcher-participants relationship. In the absence of confidentiality, the participant may be unwilling to provide the researcher with the necessary information, leading to invalid results [29].

Maintaining anonymity and confidentiality in qualitative research is problematic. In qualitative research, non-numerical data (e.g., text, video, or audio) is gathered and analyzed to have a deep understanding of concepts, ideas, or experiences [30]. Additionally, qualitative research deals with fewer number of participants while gathering a large amount of in-depth personal information. Therefore, protecting participants' confidentiality while addressing detailed descriptions of their experiences and believes is considered a significant challenge [31].

**STUDY EXECUTION: DATA GATHERING, ANALYSIS AND INTERPRETATION**
When conducting a research project, the researcher should ascertain that accumulated study data are analyzed precisely and study methodology clearly outlines data analysis. Deficient data analysis, although misleading, does not always imply research misconduct. However, data fabrication and falsification are well-known examples of misconduct [1].

According to WHO definition, fabrication is identified as “deliberate creation, recording, and reporting of nonexistent results while falsification is described as the deliberate manipulation of data to change or omit data, including the deceptive manipulation of images” [32]. It is frequent, particularly in pharmaceutical-sponsored research where the industries may force the researchers to under-report negative or inefficient findings in large clinical trials [33]. Therefore, falsification and fabrication are not only unethical, but they may also put individuals at risk because treatment or policy choices are made based on incorrect information.

**PUBLICATION ETHICS**
After gathering, analysis, and interpretation of the data, it is time to publish the research findings and submit it to scientific journals. However, in this step there are several ethical considerations as well. The researchers may deliberately perform unethical actions to obtain financial gain or academic promotion [34]. In the following section, some of the ethical considerations related to the publication will be discussed.

**ORIGINALITY**
The concept of originality implies the development of something new, something that has never been invented before pursuing the benefits of mankind. However, it may not manifest itself as a world-changing idea; rather, it may emerge as a particularity or improved per se, that does not conform to previous standards and is usually associated with the capacity to inspire a choice of development [36]. Originality in research publication is always desirable since it result in broadening of knowledge. On the other hand, lack of originality is an undesirable phenomenon that results in duplication of science and wastes the publishers' resources as well as the readers' time [23]. Salami papers, plagiarism/self-plagiarism, and duplication are among issues that interfere with originality.
PLAGIARISM AND SELF-PLAGIARISM

Plagiarism is described as utilizing someone else’s ideas, findings, or text without properly acknowledging them [32]. Typically, plagiarism happens when huge portions of the text are copied and pasted without proper and explicit citation. Plagiarism is caused by a variety of factors, including limited language proficiency, insufficient academic and research instruction (of what constitutes plagiarism), and limited awareness of the plagiarism consequences in the academic environment [39].

On the other hand, self-plagiarism is described as using own words or ideas repeatedly and unnecessarily. Although plagiarism and self-plagiarism are both considered as a violation of originality, self-plagiarism can probably be acceptable where it enables the growth of ideas and concepts without having a fraudulent intention [40].

DUPLICATION AND DUPLICATE SUBMISSION

The simultaneous or successive submission of the same article into multiple journals is called duplicate submission. On the other hand, a redundant or duplicated publication described as publication of a research that considerably overlaps with a previously published article by the same author [41]. Duplicate publishing covers not only the text of an article, but also previously published figures and data sets. In contrast to duplicate submission, which is viewed as research misconduct, duplicate publication is regarded as unethical behavior.

While submitting a manuscript, the author must always notify the journal's editor of any prior submissions that might be regarded as redundant or duplicate publications of the same or substantially comparable content. The editors are also required to determine the degree of overlap and validate the authors' level of disclosure [41]. Hanke et al. described duplication as "deliberate transformation of a manuscript from an original into an altered state in an effort to create the illusion of two independent publications." They also indicated that “it has nothing to do with increasing the fund of medical knowledge and everything to do with adding bulk to an author’s C.V” [42]. Duplication is considered a waste of time and resources and leads to distortion of the research record and putting public health at risk [43]. Entering duplicated research into the pool of meta-analysis studies derives conclusions favoring the duplicated publications.

PUBLICATION BIAS

Publication bias can be described as the researchers’ tendency to over-report positive findings since positive findings are associated with more citations in the medical literature. It has been reported that studies with positive findings are significantly more represented in literature than studies with negative/no effect [44]. Physicians and policymakers rely on research findings, whether it is managing a single patient or establishing guidelines. Therefore, underreporting negative findings apart from wasting time and resources can lead to a distorted result and positive bias [45, 46].

DECLARING CONFLICT OF INTEREST

Research is grounded in trust, and the researchers are in the position of trust aiming to provide unbiased findings to promote human lives. Conflicts of interest are described as circumstances where personal interests or preferences can affect or entirely compromise individuals’ ability for professional judgments [47, 48]. Although conflicts of interest are widespread in research, they must be appropriately addressed to safeguard research integrity and public trust. WHO also indicated that “conflict of interest arises in research when the objectivity, accuracy, efficiency, and/or impartiality of an individual or group engaged in the research is threatened by an interest outside the scientific and ethical interests of the research” [32]. A common example of conflict of interest is where the researcher directly chooses study participants. For instance, the researchers must avoid using their own students who may act for the researchers’ best interest since they found themselves in a vulnerable position to the researcher. The vulnerability situation can oppose the voluntary nature of participation and provision of consent [49]. Controlling conflicts of interest is the researchers’ primary...
responsibility in medical research to obtain valid findings that protect research integrity and promote public health.

AUTHORSHIP MANIPULATION
Overall, there is disagreement on what constitutes authorship and who is considered as an author. In general, authors are individuals who collaborated in a research project [50]. According to the International Committee of Medical Journal Editors (ICMJE), the author should have made a significant contribution to the intellectual content of the paper, including conceptualizing and research design, as well as collecting, analyzing, and interpretation of the data [51]. The author is also defined as the one who represents the research to the public and is responsible for the validity of the research [52]. Authors are generally listed in order of the value of their contribution, and authorship order has significant implications in academia since it is utilized for researchers' evaluation and promotion [53]. Non-principal authors, on the other hand, are individuals who made little contribution to the research, such as assisting in the data collection, grammar and language editing, and other routine duties that do not constitute authorship on their own. Non-principal writers are sometimes assigned authorship as a matter of previous or future favors, which is another ethical issue in research publication (also known as gift/guest authorship) [1, 54].

In recent years, other challenging issues related to medical ethics emerged as a result of new advancement in biomedical sciences. Of note, the research outsourcing here is exemplified and briefly discussed.

RESEARCH OUTSOURCING
Several authors have expressed their concern toward an increasing trend of outsourcing in medical research, especially in clinical trials as a solution to reduce cost and improve efficiency [55, 56]. Pharmaceutical companies aim to test their products in developing countries such as Africa, India, and Brazil, where ethical principles and regulatory practices are considerably more relaxed. In the meantime, outsourcing is reported as a strategy for pharmaceutical companies to speed up drug development and remain viable in this industry [57, 58]. Several factors resulted in outsourcing, including difficulties in recruiting sufficient participants in high income countries, limited regulatory barriers in low and middle-income countries, and the necessity for the pharmaceutical industry to speed up drug development. In addition, medical research outsourcing has become increasingly appealing as it brings some development in targeted regions [59, 60]. In 2016, a study investigated the financial and ethical consequences imposed by clinical trials conducted in Latin American countries by evaluating the effectiveness and safety of 33 FDA-approved products in these countries. The study concluded that outsourcing clinical trials among Latin American countries resulted in significant side effects, imposed a financial burden, and put patients at high risk [61].

CONCLUDING REMARKS
The fundamental goal of research is to improve human well-being through the progress of knowledge [23]. Research involves many organized steps and processes, and commitment to research ethics standards is mandatory to the research investigations. A huge spread of research organizations, universities, and other higher education institutes at the same time, obliged the researchers to adhere to high ethical standards and regulatory systems throughout all stages of the study including design, execution, and presentation of the findings [62].

It is the researchers' responsibility to address various ethical issues at various stages of the process. Honesty, accuracy, objectivity, and efficiency are among shared values for responsible conduct [62].

Therefore, ethical principles can be used as a guide to keeping the researcher away from engaging unethical behavior. Every phase of scientific research, including data collection, analysis, and publication is embraced by research ethics and ethical guidelines. Indeed, unethical publication may happen in several ways. Plagiarism, data manipulation, and duplicate publication are examples of research misconduct that can damage the scientific literature and public trust. Although these practices may be more prevalent among younger researchers, they can also be seen among recognized academics [63].

Over the past few years, there has been a growing consensus on the importance of responsible conduct of research (RCR) and establishing a culture of integrity and transparency in research environments. Several attempts have been made to introduce the guidelines and regulatory protocols developed to minimize research misconduct in scientific research and publication [64, 65]. But an increasing trend in the expansion of universities and research institutions from one side and on the other side the explosion of the science and technology into a new and wide horizon of benches of science all together have provided a milieu in parallel for growing of misconduct. Another aspect associated with research misconduct mainly targets scientific journals of note the fast the growing area of predatory journals. The predatory Journals, the emergence of a new definition as
results of uncontrolled growth and expansion of the research organizations and journals completely generated as a business incentive with unhealthy and fraudulent function [66, 67]. Chawla showed predatory journals reported 8-fold rise in the number of published paper between 2010 and 2014, while they appear to hardly question the validity and authenticity of the studies. Such publication results in limited/no citation [68].

There are factors that allow the research misconduct stile remain and regarded as an issue creating agony and distress for young early career researchers even in well-developed nations with high regulatory standards and controls when the competition to keep the position is matters. The extent and magnitude of research misconduct is unclear and there is no straightforward way to evaluate it. Our knowledge relies only on the reported circumstances, but current evidence described it as “tip of an iceberg” [69]. However, a basic estimate is derived from the perspective of researchers and journal editors on research misconduct.

Another study in 2003 aimed to investigate editors' perspectives about research duplication in clinical investigations. The author indicated that although editors agreed on the causes of research duplication, there was no consensus on what constitutes acceptable research overlap [70]. A study in 2009 investigated the knowledge of journal editors about a range of publication ethical issues. Results of this study showed that most scientific journal editors were unconcerned about publication ethics and believed research misconduct is infrequent in their journals [71]. Therefore, it is essential to develop explicit principles that clarify the existing ambiguity about unethical behavior in research publications.

To this end lack of institutional guidelines, unavailability, or access to updated verification software as a gatekeeper of preventing and detecting misconduct are also exemplified. By dissecting the causes and contributing factors associated with research misconduct, in order to reduce the risk of such behaviour, an educational policy or program for early career researcher is crucial.

Ethics are considered moral principles serving as a guide for scientists. The ethical issue has become more current in scientific writing due to uncertainty in the definition and dimensions of ethics, as well as a lack of clarity in ethical norms. In addition, controversy exists between ethical guidelines around the world that exacerbate the existing condition, urging the development of a unified and comprehensive code of academic conduct. Such a principle should provide a decisive framework for addressing studies involving human subjects, including research outsourcing.

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ЭТИКА В МЕДИЦИНСКИХ ИССЛЕДОВАНИЯХ И ПУБЛИКАЦИЯХ

Резюме
Данный обзор представляет собой краткую аргументацию важности этики в научной деятельности. В нем уделяется внимание всем аспектам исследовательского проекта, включая план исследования, процесс утверждения, выполнение и публикацию. Кроме того, в статье были отмечены такие параметры, как роль человека в исследованиях и права человека. Также рассмотрены такие важные вопросы, как конфиденциальность, благотворность и безвредность исследований. Помимо важности анализа данных, были рассмотрены неблагоприятные последствия незтичного поведения, такого как плагиат, фальсификация данных и предвзятость исследований.

Ключевые слова: неправомерное проведение исследования, плагиат, дизайн исследования, информированное согласие, одобрение этики.

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