Ethical Considerations in Interventional Studies: A Systematic Review

Ethics and Interventional Study

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Received: 24 Feb. 2022; Accepted: 21 Sep. 2022

Abstract- Interventional studies are necessary to gain new knowledge in medical sciences; they can also be associated with several risks and impose high costs on patients and healthy people, and ethical considerations must be considered, as well. Understanding the ethical challenges and issues of interventional studies is essential. Using placebo, ethical consent, and clinical trials in specific groups are some of these challenges. This systematic review study was conducted to determine ethical considerations in interventional studies with an emphasis on the four ethical principles, including autonomy, non-maleficence principle, beneficence, and justice. Researchers in interventional studies should pay attention to ethics and take the necessary steps in line with these four biological principles.

Acta Med Iran 2022;60(10):609-614.

Keywords: Interventional studies; Ethical considerations; Clinical trials; Biological principles

Introduction

Research is one of the essential foundations for the development of human societies so that no scientific- and rational-based activity can be done without investigations. In fact, the real empowerment, development, and independence of the countries are largely attributed to their ability to produce science and scientific development (1). In this regard, nowadays, along with significant advances in medical sciences, the value of research in these fields has become of great importance. In fact, the further growth of these fields, dealing with the basic sciences, is their research quality improvement (2). In the past, research was mistakenly regarded as data collection, documentation, and recording; however, the research concept is more complex. Research is a regular process of collecting and analyzing data to answer a question or find a way to fix a problem. Research is a systematic process in which the purpose, data collection, and the relationship between findings are clearly identified, and also its overall framework is defined based on the available guidelines. Several methods have been introduced to conduct research, which are selected based on the purpose, nature, subject, and extent of the study. Several methods are available to conduct the research and answer the research question, of which interventional studies are of particular importance because of their nature and type. In these studies, the researcher modifies and manipulates the independent variable, then examines the change made in the dependent variable. Interventional studies include clinical trials (CT), field trials, and community trials (1).

Clinical trials are one of the medical studies conducted on human beings. Clinical trials are mainly used to study the effects of new drugs and therapies (3). Compared with clinical trials, field trials are conducted on healthy subjects but at risk. Data collection is done in the field using normal subjects. In fact, the aim is to prevent the occurrence of the disease (4). In community

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trials, the subjects are communities rather than individuals, and they are appropriate to study diseases with a community-based origin. Although these studies are necessary to gain new knowledge in medical sciences, they can also be associated with several risks and impose high costs on patients and healthy people, and ethical considerations must be considered, as well (3).

In fact, the main problem in the ethical issues of interventional studies is that those who want to benefit from the results of these studies may not be the ones who have experienced the risks while performing the trial (5). Therefore, ethical considerations should be highly observed in conducting these studies.

Understanding the ethical challenges and issues of interventional studies is essential. Using placebo, ethical consent, and clinical trials in specific groups (healthy human subjects, people with limited knowledge, people unable to make a decision, children, etc.) are some of these challenges (6). Today, one of the most important ethical constructs of modern biomedical science is obtaining informed consent from the subjects, which is a fundamental requirement in interventional studies in medical sciences. The subjects should be well informed about the benefits and risks of the intervention and the considered procedure, blinding and randomization methods (in clinical trials), and the objectives of the study, and voluntarily participate in the study (7). Placebo is one of the major ethical issues in these studies. It is commonly referred to as "a neutral substance." According to the Food and Drug Institute's definition, a placebo "is an ineffective substance that may look like an effective agent, but has no medical value." The main problem in using a placebo is deceiving the patient. The patient believes that the taken drug acts as "real" medical treatment. Another challenge with placebo is the deprivation of active treatment that can lead to high levels of pain, exacerbation of physical condition, and even death. In addition, complications and damages to the patient while using a placebo during interventional studies are probable (5,8).

Interventional studies on some groups of people are of particular sensitivity and importance ethically. Choosing healthy subjects, such as children and prisoners, can be a challenge because of the easier study process; because most of these subjects are not able to pursue their rights. Paying wages and costs is also challenging. Different views have been proposed to pay for the risks of intervention to participants (9). Studies on people with limited knowledge (due to learning disorders and dementia), sick persons, and pregnant and breastfeeding women (due to the potential risks of intervention on mother and child) are also associated with specific ethical sensitivities and considerations that should be regarded (10).

The present study was conducted to determine ethical considerations with emphasis on four biological principles (respect for autonomy, non-maleficence principle, beneficence, and justice).

Materials and Methods

This systematic review study was conducted to determine ethical considerations in interventional studies with an emphasis on the four ethical principles, including autonomy, non-maleficence principle, beneficence, and justice. Research databases, such as EMBASE, ProQuest Central, CINAHL, Cochrane Library, PubMed, SID Magiran, Web of Sciences, and also the manual process of screening were used. The systematic screening, using Persian and English keywords (based on the Mesh) and their possible combinations, were used to collect studies. The English and Persian keywords were non-maleficence, Autonomy, Beneficence Community and field Trials, Interventional studies, and clinical trials. Based on the inclusion and exclusion criteria, the available articles, including descriptive (case report) and analytical articles (intervention and observational), were included. Due to the descriptive nature of the subject, no articles with a higher level of evidence were found.

Searching was conducted by two researchers and experts in systematic searching, and the studies conducted from 2001 to 2019 using the considered keywords and databases were collected. The details were also documented. Finally, 68 articles were found.

Ten articles were identified by EndNote and were excluded from the study. Based on the inclusion criteria, articles published after 2000 and those that had not been published as books were considered for the initial review. The abstracts were then studied by researchers, irrelevant articles were excluded, and the relevant studies were retrieved for full-text extraction and data extraction, of which the full-text of the two articles was not available. Finally, 53 articles were included to answer the following questions. In order to reduce human error, the needed information was extracted based on a prepared checklist by two researchers separately, and their results were matched. The variables of the checklist included: article title, author, year of publication, journal name, place, objective, methods, target population, concepts, ethical

considerations, and issues.

After filling the checklist, the quality of the data was evaluated by two other experts. In order to avoid bias, the names of the journals and authors were removed, and the data were then provided to these experts.

Results

Autonomy

Autonomy is closely linked to the self-management capacity of human beings, as it enables people to make autonomous decisions, and others must respect these decisions (11). Autonomy is achieved by providing conscious choices with no obligation (12). These choices are crucial in interventional studies. A valid informed consent process, while respecting the study participants, preserves their autonomy and human dignity and protects them against the potential risks of the study. Accordingly, the study participant must be informed about the potential risks, benefits, and alternatives to participating in the study (13). In fact, it can be said that informed consent is an important component of all interventional studies; however, obtaining valid informed consent can pose challenges for researchers and patients (10).

Informed consent is considered an ethical prerequisite for interventional studies and serves as a major tool to support study participants' autonomy. The basic ethical point of informed consent is its fully informed nature. If asking the informed consent to participate in the study is done without providing information, it is against the meaningful selection by the participant and is considered against autonomy. In fact, to maintain autonomy in research, a balance should be made in understanding and comprehension of the needed information to the participant. The information provided to the study participants should be complete enough to be used as a basis making them able to make a decision (14). The researcher should provide all information that may be effective in the participant's decision-making, including the title and purpose of the study, the length of the study, the method of study (including the possibility of random assignment to the case or control group), sources of funding, potential conflicts of interests, the organizational affiliation of the researcher, and the potential benefits and disadvantages of the research. Participants should have enough time to make decisions. They should be informed that they can withdraw from the study at any time and terminate their collaboration with the research team. Informed consent must also be obtained (15).

In some cases, those who, based on the inclusion criteria, as well as the research objectives, are eligible to participate in the study are at risk of injury, and due to the risks and benefits considerations, they should be excluded. Those who are undergoing a therapeutic intervention can be affected by the research, and the patient should be informed associated with it, so the social benefits of the study will be doubled (15).

Regarding people with serious mental problems, consent must be obtained from their parents or guardian, and also previous studies should have confirmed the minimum risk for these subjects (16). For those with limited authority, it should be noted that they should be provided with the direct benefit of the study results. Prisoners, employees, and students are among those who are likely to participate in the study non-voluntary. They should also participate voluntarily and without pressure. It is also recommended that their representative or representatives present at the ethics committees. In patients with severe illness, consent must be obtained from the patient's guardian or legal representative. Clinical trials on these patients should also be performed when immediate intervention is needed, and also current therapies by the treatment team are ineffective (13). Regarding the children who have not yet reached their 18th birthday (in the studied countries and in international documents, childhood begins at birth and ends at the age of eighteen years), consent must be obtained from the child's parent or legal guardian, and the child also should cooperate in the intervention (17). A clinical trial should be conducted on pregnant and breastfeeding women when the study objective was designed to maintain and improve their health (13). Interventional studies on illiterate persons should be conducted to provide the necessary information in the presence of a witness, and also obtaining the consent should be confirmed by the witness (8).

Non-maleficence

In interventional studies, participants should be saved against the possible risks and dangers of the study. According to the Helsinki Declaration, all clinical trials at least should be evaluated in comparison with the best available treatments (18). It also emphasizes that medical research can only be conducted on a human subject when the importance of its objectives outweighs the potential risks and costs of research. Researchers should always try to reduce the costs and potential risks of the study (19). Creating a risk in studies can affect the participants' and public health and trust and can be associated with unfavorable consequences on the research system. The risk assessment and also evaluation of the benefits of the

research should be done by a group of individuals independent of the research team. It also should be noted that the health of the volunteers should be assessed prior to the study, and their eligibility to participate in the study is needed to be evaluated (9). In studies on the human subject, the health and safety of the subjects during and after the research prioritized all other issues. All studies on the human subject should be designed and implemented by people with the necessary and relevant clinical expertise and skills. As soon as a risk threatening the participant is found, the researcher must terminate the intervention (20). The study protocol should also provide the needed insurance for study participants and also compensate research participants (8). The issues, such as shorter length, easier methods, the researcher's convenience, cost-effectiveness, or being more practical, should not put the participant at risk of additional injury, additional costs, or imposing authority limitations on the subject (21).

Using a placebo is ethically accepted in certain cases:

- When there is no standard treatment or the standard treatment is not effective than the placebo.
- Standard treatment is not effective for the patient.
- Patients who refuse standard treatment due to another disorder and after discontinuing treatment, no serious side effects threaten the subjects.
- Adding the placebo to the standard treatment and taking the advantages of the standard treatment by all participants
- Placebo may be used in studies where the pieces of evidence indicate the standard treatment uncertainty (8,18).

Beneficence

Benevolence, kindness, and beneficence are ethical attitudes and behaviors rooted in the existential structure of human beings and are not the result of social agreements and conventions. Regarding beneficence, it should be noted that beneficence involves taking advantages, and it also has the potential to eliminate losses (22).

According to Belmont, the principle of beneficence is recognized not only as a good and honorable practice but also as an obligation. Beneficence is closely linked to non-maleficence. The principle of non-maleficence in the research context means that no person should be harmed in the study, but there may be benefits to others. However, it is important to note that any action that may be of benefit may also expose individuals to the risk (23,24). Research on human subjects is justified only if its potential benefits to each individual subject outweigh the risks. It is the responsibility of research designers, executives, research collaborators, and all councils responsible to assess or monitor the research, including the Research Ethics Committee. At the end of the study, the subject has the right to be informed about the results of the study and benefit from the beneficial used interventions or methods in the study (25). The principle of beneficence implies that medical and non-medical studies for treatment or research should be based on benevolence and be of the greatest benefit to the individual and to the community, as well. Researchers should consider the maximum benefit to the research participants based on this principle and avoid harmful practices or those associated with no physical or mental harm advantages (22).

Justice

Based on the principle of justice, the benefits and burdens of the research should be distributed fairly. Injustice in research becomes apparent when the participant is deprived of part of the benefits of the research without sufficient and persuasive reasons. In fact, the subjects participate in a study to benefit from research through treatment, medical care, and disease monitoring. In an interventional study, participants should have fair access to the potential benefits of the research (26). In an interventional study, justice is achieved by finding the answers to basic questions; basic questions of the research (Who will be studied? When and where will the study be conducted, and what are the expectations of the researcher (s)? -To what extent the effectiveness of the research is estimated? - Is research worth doing? -Is the research designed to answer the research question? And -Who will benefit from the research? (12).

Study participants should also have the opportunity to take advantage of the research even after conducting the research. In cases where the participants are deprived of the health care and benefits of the study because the research process is finished, this is considered an injustice and abuse of the participants. Another common example of injustice is research sampling from developing and low-income countries, however, developed and the research industrialized countries benefit from the research. In fact, participants from developing countries should benefit as those from developed countries. Accordingly, if the research has no benefit to the participants, they should not be selected, which is based on the Belmont report. According to this report, based on the principle of justice, the research benefits should not be limited to those who can benefit from them, and also, the research should not be conducted on people who are

deprived of its benefits (24).

Discussion

Interventional studies are essential to acquiring new medical knowledge. However, these studies are associated with the risk of injury to the patient. These studies also are costly. Therefore, researchers, research designers, funding agencies, and publishers must determine, at least through scientific potential, whether these studies are ethically justified or not (3). In these studies, four ethical principles, including autonomy (one's ability to make decisions based on personal values and beliefs), non-maleficence (a commitment to prevent intentional harm), beneficence (providing benefits to people and balancing them with risks and costs fairly) and justice (equitable distribution of benefits and burdens of research) should be considered (18).

The main challenge of interventional studies is the fact that those who want to benefit from the results may not be the same ones who have experienced the risks of the trial. Participation in such studies is inherently associated with the risks for subjects compared with current conventional practices. The risks cannot be offset by prospective clinical benefits because the primary endpoint of an interventional study is not treating the participants, whereas, in general, it aims at the production of medical knowledge (5).

Informed consent is an essential requirement for participation in interventional studies. According to the Nuremberg Code, informed consent is respect for individuals and their autonomy. It has three main characteristics: voluntary, conscious, and honest. Accordingly, the study participant should be aware of the diagnostic or therapeutic procedure and also be informed about the potential benefits and risks (27). Using a placebo in interventional studies can be linked to some challenges. According to the Helsinki Declaration, the placebo can be used for scientific and methodological reasons if there is no standardized treatment, provided that patients receiving the placebo do not notice its hazardous and non-hazardous effects (28). In interventional studies, there is a large gap between those participating in the study and others who want to benefit from the study results, which can be the next patients and the community, as well. Due to this gap, participants should be protected from the risks and burdens of the research. According to the Helsinki Declaration, the health of individuals participating in the research prioritizes other issues. Prisoners, children, and individuals in the lower classes are at risk of injustice distribution of the risk of research. They may not have access to the results of the research because of their economic condition. They can not also pursue their rights properly; therefore, the research subject should be selected with particular sensitivities and considerations (9).

Researchers in interventional studies should pay attention to and take appropriate measures regarding ethics, including respect to the rights, health, and safety of all study participants, especially specific groups, obtaining necessary documentation, such as clinical trial protocol and its revisions, the written informed consent form, evaluation of the protocol and documentation received through a reasonable time, and approval, disapproval, or recommendation of revisions to the protocol in writing, the continuous review conducted at intervals appropriate to the risk level, asking for additional information if necessary to increase the respect for rights, safety and health of the participants, and method of paying the participants. In addition, considering the cultural, social, and religious conditions of the study participants by researchers should also be considered by the researchers of interventional studies.

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