Chapter

Ethical Evaluation of Clinical Research on Complementary and Alternative Medicine

Omur Sayligil

Abstract

Traditional medicine (TM) as well as complementary and alternative medicine (CAM) practices have been used more frequently; since modern medicine has gravitated toward a dehumanistic situation due to the extensive workload of healthcare professionals and thus lack of time given to each patient and mistrust of patients due to some side effects of latest treatment options, in addition to TM and CAM practices having been more affordable, accessible, most often noninvasive, and seen as a hope during terminal periods of some diseases. In order to ensure TM and CAM complying with the standards as other healthcare services, it is necessary to address and evaluate scientific and ethical issues for these clinical researches as well. On the other hand, so far, the ethical side of TM and CAM has not been discussed in detail. Issues such as misleading information, informed consent, publications, patient-physician relationship, and confidentiality should be discussed within the framework of ethics. Ethical issues on CAM and TM research can be sorted as patient's autonomy and consent, principle of justice, patient-physician relationship, use of public resources, and health insurances. This chapter aims at evaluating CAM and TM research according to fundamental ethics principles, as well as discussing legislations on CAM and TM research in Turkey.

Keywords: traditional medicine, complementary alternative medicine, research ethics, voluntariness, beneficence

1. Introduction

According to the World Health Organization (WHO), TM consists of knowledge, skills, and practices used for protection from physical and mental illnesses, diagnosis, improvement, and treatment of these diseases, as well as maintaining the health well, which is based on theories, beliefs, and experiences indigenous to different cultures, whether explicable or not. TM practices have a long history [1]. In general terms, the use of supplementary methods in addition to modern medicine in the patient treatment process is called "complementary medicine," while the use of other methods instead of modern medicine is called "alternative medicine." Similar terms had also been used in Turkey for a long time. However, as a result of the evaluations done based on the definition of WHO, it has been

concluded that medicine cannot have an alternative, only the treatment can have one. Accordingly, the definition, "traditional and complementary medicine," has come to the fore [2].

People resort more to TM and CAM applications because these applications have low cost, are easy to access, are often free of invasive procedures, are considered promising in some chronic and terminal stage diseases, and some side effects of new treatment options can cause distrust. Also, in countries where TM and CAM applications are covered by public insurance, the inclination toward these applications will inevitably increase [3]. Friends talk about the solution to certain problems and articles about TM and CAM are frequently seen in the printed media. Many hospitals include these treatment methods in their care plans. Courses on TM and CAM are placed in the curriculum of medicine, pharmacy, and nursing faculties [4].

When the literature is evaluated, TM and CAM applications are observed to become widespread all over the world, and especially the increase in the use of TM and CAM in the western world in the last decade has increased the need for field-specific evidence-based research [5]. Although CAM has an effect, there are many unknown points about these treatments regarding scientific research that will convincingly reveal the value of individual treatments.

1.1 Scientific research and clinical research on TM and CAM

Scientific knowledge reveals the cause and effect relationship logically based on experiments. It aims to clarify the cause and effect link between events investigated as a result of accepted, proven, and reproducible experiments. Scientific research should be planned in a way to show useful results and healing in patient care. Clinical research consists of scientific studies that are carried out with the participation of volunteer people and aim to obtain medical information. For new drugs, medical devices, and other treatment methods to be beneficial to humans, scientific information should be provided on topics such as showing their safety and effectiveness, developing new treatment methods, and determining the side effects of medications and medical devices employed in treatment before they are used widely. After all treatments have been shown to be successful in the laboratory and on laboratory animals, the effects/side effects on human volunteers are investigated. Answers to questions such as the effectiveness of treatment, suitable doses for treatment, and the possible side effects can be found with clinical research results.

Medical research is carried out systematically using scientific methods based on a plan to obtain scientific information. Medical research that is conducted on humans is carried out systematically with scientific methods based on a protocol by staff (physicians) who are authorized to perform their profession in the field of medicine on patients or healthy volunteers by doing physical, chemical, or psychological medical interventions, or using biological samples taken from these people, or utilizing other personal data of these people. Medical research on humans primarily aims to obtain new and generalizable scientific data. On the other hand, its effects on the human body may not be foreseen precisely [6].

Researchers should know and apply common methods, measures, and standards so that necessary evidence can be produced and interpreted to make their decision on the use of TM and CAM treatments. Scientific thinking must remain within the ethical framework while focusing on the solution of problems. Scientific research that can be carried on human volunteers should be designed with great scientific and ethical sensitivity. Each stage of the research should be applied in a way that will protect human rights and dignity and will not cause permanent harm for future generations.

1.2 Traditional medicine and complementary alternative medicine health surveys

Research carried out in the field of TM and CAM can be handled under two headings.

1.2.1 Clinical research into traditional and complementary medicine practices

These are studies carried out on human beings to reveal or verify the clinical or pharmacological effects of one or more products and/or methods falling within the field of traditional and complementary medicine applications, to identify their adverse events or reactions, and to investigate their safety and effectiveness.

1.2.2 Noninvasive clinical studies

These can be defined as traditional and complementary medicine applications that will be carried out using methods that will not require direct attention or intervention of a physician or dentist provided that observational studies, survey studies, retrospective studies, and traditional and complementary medicine applications are administered under conditions that are specified within the legal regulations of countries.

In studies to be conducted in the field of TM and CAM, natural, synthetic, or biotechnology-rooted active substance or combination of substances administered to human beings to prevent, diagnose, or treat diseases, correct, regulate, or change a physiological function can be defined as a drug or human medicinal product.

To ensure that studies are conducted in international scientific and ethical standards, good clinical practice titles consist of rules that should be obeyed by parties participating in the research and cover regulations about topics such as designing, conducting, following, budgeting, evaluating and reporting the research, protecting all rights of the volunteer and body integrity, providing the reliability of research data, and maintaining their confidentiality.

Randomized clinical trials, which are shown as a source of evidence for the applicability of a particular intervention, provide important data for making practical decisions. They were accepted as the gold standard by A. Hill. Although the level of evidence is evaluated according to the type of the research, each study should also be evaluated in terms of strengths and weaknesses [7].

While randomized controlled studies are considered as the gold standard of evidence for treatment effectiveness, other research models will be needed about the activity field of CAM when randomized controlled trials cannot be conducted. These models may include studies meeting randomized and nonrandomized conditions, observational cohort studies, case-control studies, studies evaluating the effectiveness of certain treatment packages as a whole, and studies measuring placebo or add-on effects [4].

Evidence-based medicine (EBM) can be defined as the systematic approach where physicians make their decisions by combining their experiences, preferences, and patient characteristics in light of the best available evidence. Today, opinion-based decision-making approach referring to individual clinical experience has been replaced by evidence-based decision-making practice because the former causes variations and inconsistencies among clinical practices, it leads to disconnections between clinical practice and medical research, and it has become difficult to follow all the sources in the rapidly growing medical literature as a result of the ever-increasing number of studies in the field of medicine [8]. EBM practices, which have replaced TM practices, necessitate that decisions should be supported

with qualified and current researches with a systematic approach to make the right decisions in the diagnosis and treatment processes. It is very important to reach information about evidence by following a conscious approach in the process of EBM applications. Evidence is determined by carefully selecting from the findings of clinical trials carried out by using real patients as subjects and applying original, powerful research methods [9].

2. Ethical aspects of traditional medicine and complementary alternative medicine research

2.1 The value of a study: its social value

Value is defined as an evaluation done in a socially accepted manner, showing the positive or negative meanings of objects in the outside world for people and society (e.g., good and bad, beautiful and ugly, underlying in nature and society phenomena) [10]. Value, as a criterion, includes the distinction between what is and what should be, and always appears as something positive or negative. The value that something has in terms of producing the desired results or the value displayed by something that acts as a tool in reaching the desired result is called instrumental or pragmatic value [11]. It can be said that the results of studies, too, have instrumental value. It should be borne in mind that research has a social value through knowledge production.

When the value of a research project is analyzed for social and scientific reasons, it increases as much as it has the promise of improving health or increasing knowledge that is important for health.

Studies that have no social value can be seen as a waste of resources and may pose participants some risks. It is an ethical imperative that in clinical trials, volunteer participants are not at risk other than investigating socially and scientifically important results. For this reason, only therapies with the greatest scientific and social importance should be selected for research purposes. Ensuring that social and scientific value prevails over commercial value is an ongoing ethical responsibility. Preliminary studies on research are absolutely valuable. The information they provide can cumulatively improve healthcare. From time to time, additions to clinical applications can be made in this way [12].

Determining who will benefit from the research result is important in determining possible benefits. The potential value of each research should be outlined at the outset. The results of the research should not only be subject of scientific meetings and publications but should be disclosed to all stakeholders in an appropriate language and expression. The reason why a patient or a relative of a patient seeks remedy other than evidence-based medicine is that there is no treatment of the disease in question or probabilities are very low. We should also understand people who seek health alternatives. For TM and CAM, the social value of the research has a special importance in this sense. On the other hand, research should not be allowed to weaken the existing health system of the society. In TM and CAM research, researchers should carefully monitor the socio-cultural dimensions of disease experiences, practitioner-patient interactions, and mutual compliance with treatment instructions during the research process. Research in this field can be categorized as empirical, semi-empirical, descriptive, case presentation, and historical interviews. Regional differences, being patient-centered, using several approaches together, differences of research participant inclusion/exclusion criteria, and approaches of appropriate placebo selection can affect research outcomes. According to WHO, data supporting the global use of TM and CAM practices are insufficient. More

researches are needed to integrate CAM and TM practices in healthcare systems and understand their efficiency, safety, and mechanisms [13].

2.2 Limitation of sources

To give a definition, the source is the sum of all inputs such as money, manpower, and equipment, which are essential for any production or utilized during production. The sources to be allocated for transplantation, dialysis, or cancer treatment and the share allocated to other services such as vaccination, infection treatment, and treatment of acute diseases should be balanced. The search for balance leads to discussions on how far scientific and technical possibilities should be used to support patients. However, the limited resources make this issue controversial, imposing the necessity to make a choice [14].

When the limitations of the sources are in question, it is of significance which CAM treatments to evaluate. Research into this area may aim at understanding the biological mechanism of disease or treatment, as well as primarily addressing common disease issues. Acupuncture is used in the case of back pain, headache, migraine, knee pain, facial pain, inducing labor, nausea, vomiting, post-operative pain, essential hypertension, depression, stroke, and so forth. Analgesic effects of acupuncture practices are outcomes of patients' expectations and interaction of neurochemical, physiological, and psychological factors. One of the weakest parts of acupuncture evaluation researches may be the lack of adequate control of placebo [15]. The potential benefit may be another important topic to focus on. It is also possible to center on existing evidence that interventions are effective. Besides the pre-research geographic records, existing records can be evaluated. Regardless of what subject to be addressed, evidence to justify funding for research should be disclosed. Having evidence at hand is crucial to reveal the reliability and effects of TM and CAM treatments. There are few studies comparing treatments specific to these areas [4].

2.3 Scientific validity

In the process of scientific research, the researcher is basically seeking an explanation and answer to a question. There are two important concepts in this regard. These are validity and reliability. Validity is a concept that determines whether the answer, which is the subject of the research, can be answered with the applied research method.

Predictive validity about how predictive the research tool is in real-life situations and the construct validity regarding how much the tool correlates with the theoretical psychosocial structure of the sample that is being measured should be carefully reviewed in studies to be validated. A valid sample for the research must be calculated correctly. Neutral data collection is necessary for unbiased measurement and evaluation of the result. Science means measurement. Doing wrong measurements will lead to unreliable evidence and treatments. For this reason, utmost attention should be paid to ensure that measurement tools give valid and reliable results [16].

Scientific principles and methods are needed to produce reliable results. Scientific validity should be in accordance with the research methodology [12]. The scientific validity range and what the conditions are for the current treatment must be clarified in CAM studies. This situation is important for the social value of the research, as well as epistemologically. According to the research results in relation to CAM treatments, labels of therapies such as approved/unapproved or overridden require an epistemological and ethical evaluation.

It is claimed that cupping has a therapeutic effect on many diseases that could not be conventionally treated. It is used in conditions such as enhancing immune system, fibromyalgia, chronic pain caused by rheumatic diseases, digestive system diseases, nausea, and vomiting. It was also mentioned that cupping could also reduce side effects of some medications [17]. Evidence-based research data are needed in treatment of diseases.

2.4 Fair topic selection

The right to health is about health. The term health in national and international sources of law does not only refer to not being ill but also expresses "a complete state of physical, mental and social well-being." The WHO Constitution and the 1978 Alma-Ata Declaration define health as "not only being not ill or disabled; instead, a complete state of well-being in physical, mental, and social terms." The committee, which is the authorized interpretation body of the United Nations Convention on Economic Social and Cultural Rights, can be seen to base its interpretations of the right to health on the definitions of WHO [18].

Health, which is the value protected by the right to health, is not only a value that requires service for improvement when it deteriorates but also a value that must be respected and maintained, just like body integrity. The example that people should be protected against activities harmful to their health can be considered in this context [19].

According to the United Nations Convention on Economic Social and Cultural Rights, the right to health should not be understood as just the right to be healthy. The freedom dimension of the right to health includes a person's control over their health and body and not being a subject of medical and experimental interventions that are not based on the person's consent or end up with torture, as well as gender and reproduction freedom of the person [20].

From this point of view, topic selection is important for all clinical trials. Equal sharing of benefits and burdens in research is an important requirement. Various headings such as the vulnerability of volunteers, risks, socioeconomic status, and gender inequality in high-risk research are important in determining the subject of the research. In the selection of the subject of the research, vulnerable groups should be carefully monitored. The use of CAM is believed to be closely related to sociodemographic variables such as gender, age, education, income, and health complaints. TM and CAM applications are often preferred by women [21]. This general information suggests that field-specific CAM and TM studies are expected to be carried out mostly on women, as opposed to conventional medicine. EBM information shows that there are important differences between men and women in terms of diagnosis, treatment, and disease prognosis of arthritis, heart diseases, and infectious diseases. These differences exist due to the biological (sex) and social (gender) differences between men and women. For example, according to research, the side effects of antihistamines, antibiotics, antiarrhythmics, and antipsychotics are more severe and/or more common in women than in men. The effectiveness of aspirin in the primary prevention of cardiovascular disease is another example of the existence of a significant gender difference. Therefore, both sexes must be included in studies.

2.5 Vulnerable: easily affected groups

Although there are many definitions for vulnerable and easily affected groups, they are known as disadvantaged groups of society. People with vulnerable and

easily affected status had been one of the basic concepts studied in bioethics and health policies from the 1970s to 1990s. Over the years, so many groups, from old people who can be easily hurt to those with low levels of education, from individuals with insufficient resources to citizens without rights and a whole country open to exploitation, have been declared vulnerable that the scope of the term has expanded excessively [22]. There are three types of security vulnerabilities for this group. The first is vulnerability to physical harm, the second is vulnerability to damage to social stance or reputation, and the third is vulnerability to psychological and emotional distress. Vulnerable and easily affected groups include children suspected of the informed consent they deliver; individuals with inadequate mental capacity to give consent; individuals with learning difficulties, dementia, or similar ailments; individuals with cognitive impairments due to stroke; individuals with psychiatric or personality disorders; individuals who cannot socially give consent freely; students; individuals under care; members of the armed forces; juvenile criminals; prisoners and asylum-seekers; pregnant women; unconscious patients; and family members of researchers. The Belmont Report, the first document to identify vulnerable and easily affected groups, identifies individuals who cannot make decisions, are exposed to disproportionate incentives, and are involved in research due to administrative convenience as abusable [23].

The nineteenth article of the Declaration of Helsinki, titled Vulnerable Groups and Individuals, states that some groups and individuals are particularly vulnerable, and they may be more likely to be abused or damaged. Specially considered protective measures should be taken for all vulnerable groups and individuals. According to Article 20, medical research on vulnerable groups can be accepted provided that the research addresses the health needs and priorities of the group in question and it is not possible to conduct the research in a nonvulnerable group. Also, it involves the provision that the information, practices, and interventions obtained from the research should benefit the group in question. The eighth article of the UNESCO Universal Declaration on Bioethics and Human Rights (2005), which centers on the need to show respect to personal integrity and protect vulnerable and easily affected individuals and groups, emphasizes that human vulnerability should be taken into consideration in the application and development of scientific knowledge accumulation, medicine, and related technologies [24].

In research to be conducted on vulnerable and easily affected groups, risk/benefit measures, security, vulnerability, and assurances attached to privacy should be determined. It should be remembered that unethical use of personal data and privacy violations will affect the social texture of disadvantaged groups. Situations that involve sensitive issues related to stigmatization can also discredit individuals [25].

As for evidence of the effectiveness of TM and CAM approaches, the results of these studies have been found sufficient to construct a hypothesis to be tested by sound clinical trials. In many countries, TM and CAM applications are provided outside the national health system. Since the philosophy of CAM therapies is often seen as the mobilization of self-healing, there is a perception that they are safe. Due to this perception, volunteers can easily be found. These people do not think that they may be exposed to serious side effects during the research process. Side effects seen in CAM studies should be reported to the relevant authorities. As pointed out in many international documents (e.g., Helsinki Declaration, Article 12), medical research on volunteers should only be carried out by individuals with adequate ethical and scientific education, training, and qualifications. Research on patients or healthy volunteers should be conducted under the supervision of a competent and qualified physician or other healthcare professional.

2.6 Risk-benefit ratio

In any biomedical research on humans, the risks and burdens that participants may be exposed to and the possible benefits from the research must be balanced. Possible risks and burdens should always be minimal. This important rule stems from the principle of ethics that requires not to harm but to be useful. In studies involving interventions that may directly benefit the participant, higher risk and burden is acceptable. The potential risks that participants face can be not only physical but also psychological or social. Likewise, the possible benefits of the research to the participant may be of palliative as well as having a therapeutic nature [26].

According to the Nuremberg codes announced in 1947, the level of the risk to be taken in an experiment should never be more than the level to be determined according to the importance of solving the problem under the experiment for humanity. Appropriate measures should be taken to protect the subjects against low injury, disability, and possible death, and necessary environment and equipment should be provided. According to Articles 16, 17, and 18 under the Risk, Disadvantages, and Benefits heading of the Helsinki Declaration, before each medical research on humans, the estimated dangers and disadvantages that the research may cause compared to the benefits to be gained by the individuals or groups participating in the study of other individuals or groups who are affected by the disease that is the subject of the research should be carefully evaluated. Unless physicians make sure that risks are adequately assessed and they are satisfactorily addressed, they cannot participate in studies on human volunteers. According to the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, the dangers that the subjects of the research may be exposed to should not be disproportionate to the expected benefits of the research. Products such as plant extracts used in CAM research are likely to be pharmacologically complex. This may increase potential harm in research that tests to combine many compounds into a single product.

Use of *Hirudo medicinalis* has been a commonly used treatment method since sixth century BC. Some of the enzymes present in *Hirudo medicinalis*' saliva (e.g., calin, eglin, acetylcholine, and hyaluronidase) show anticoagulant, vasodilator, and anti-inflammatory effects. In many countries, *Hirudo medicinalis* is used in plastic surgery, traumatology, neurology, and ophthalmology fields. Point of application of *Hirudo medicinalis* can be chosen in different ways (for example, around the wound site, above the painful area). Researchers also try to make stimulating effects from on top of the acupuncture points [27]. Lack of a specific standard for TM and CAM research makes it difficult to address and assess the differences between practitioners and the risk-benefit ratio [28].

2.7 Cooperation

Without the involvement of researchers and host communities, a study is unlikely to have a lasting effect in developing countries. Without the investment of health policymakers, research results are unlikely to affect policymaking and scarce resource allocation. In almost all of the research, there is a collaborative communication between sponsors, policymakers, and research groups. In TM and CAM research, it is not always possible to predict the permanent effects of the research in question at the outset. It is difficult to be a stakeholder in the use of scarce resources without the investments of health policymakers. Emphasizing the importance of the health problem, evaluating the contribution of the research to the society, and planning, carrying out, and publishing the research all require cooperation.

Controlled clinical trials, one of the ways to access scientifically proven information, always need a competent and adequate research team with professional experience for the research. These studies are always carried out with a multidisciplinary approach. In this process, the follow-up of the volunteer participants can be maintained healthily with the work share plan within the research team. Records of the research can be taken and maintained following a protocol. Different situations arising during the research can be evaluated on time. In research based on compliance with patient rights, the safety of the patient and volunteer participants is ensured. The security profile of the applications can be followed. Patient and voluntary participant training can be maintained.

In addition to the abovementioned benefits of collaboration concerning clinical trials, there is also the opportunity that research results can be reviewed and they can be returned to the health sector as an investment. Cooperation is also inevitable for the population, in which the research has been conducted, to be able to obtain the expected benefit from the results, and to carefully follow the intellectual property rights and copyrights in the publication of the research report [29].

3. Informed consent

Human dignity is still an up to date topic as it has been in every period. As Baranzke [30] puts it, "biomedical ethics debates have raised a growing awareness that medicine may have a side that can violate human rights." Meeting people's health needs is a prerequisite for a dignified life. The existence of human dignity and what it means cannot be clearly understood anywhere other than extraordinary situations where it is seriously damaged [30]. Alan Gewirt bases human dignity on the person's opportunity to make a choice and take action based on these choices. Actions have two founding conditions and specific characteristics. Freedom is based on the control of the action performed by the person with all the information they need without any coercion. Happiness, on the other hand, can be described as the knowledge of having the skills and conditions necessary to fulfill various goals [31].

The right of the person, which is in parallel with the development of basic human rights, to make decisions about themselves, the right to determine their own destiny, has made up the rationale for a new ethical assignment to the physician in terms of giving the necessary information to the person to make an informed choice.

Informed consent can be considered as a concrete indicator of trust-based communication between physician/researcher and patient/volunteer participants. The informed consent is also an official document on the right of the patients/volunteer participants to determine their own future. It helps the communication between physician/researcher and patient/volunteer participants to conform to the law. Current literature focuses on research in which volunteering cannot be achieved in providing informed consent [32]. After the Second World War, Nuremberg Codes were developed to fill the legal and ethical gaps regarding the experiments, due to Nazi experiments carried out on humans. According to these codes, human subjects should definitely give their consent with their free will. In other words, the person participating in the experiment must have the quality to grant consent legally, must not be exposed to any sanction, deception, lie, threat or any other restriction or pressure, must be in a state to make decisions by making free choices, must be informed about the research and have enough information to make informed decision, and must understand everything.

According to the Helsinki Declaration (Article 25), the participation of individuals who can deliver informed consent in a study should be on a voluntary

basis. Although it is deemed appropriate to consult family members or community leaders, no individual with the capacity to give informed consent can be included in any research study unless they agree with their free will. This statement has special importance in TM and CAM research in terms of not harming the participants. For instance, in countries like India, clinical research is based on the perception of the disease perceived through social values and power hierarchies in the village family based on regional values and practices and cultural values. Obtaining informed consent in these settings becomes difficult due to differences in local traditions in developing countries, including India [33].

According to the United Nations Convention on Civil and Political Rights, adopted by the United Nations on 16 December 1966, which aims to protect human rights and freedoms, no one can be subjected to torture or cruel, inhuman or degrading treatment or punishment. In particular, no one can undergo medical or scientific experiments without their free consent.

Article 16 of the Convention of Human Rights and Biomedicine on the Protection of Human Rights and Human Dignity in terms of the Application of Biology and Medicine, individuals who are the subjects of research must be informed about their rights and guarantees prescribed by law for their protection, the informed consent must be given clearly and in a specific manner, and this must be documented. According to Article 3 of the European Convention on Patient Rights (Rome 2002) titled "the right to information," each individual has the right to receive information about their health status, current health services and how they can benefit from them, and all scientific research and technological innovations.

3.1 Components of informed consent for research

Components of informed consent can be listed as voluntariness, autonomy, competence, clarity, and comprehensibility of the information supplied. Voluntariness is the situation where the person decides to do something with their free will for a purpose without expecting anything in return and realizes it. Respecting individual autonomy lies at the heart of volunteering. The concept of volunteering also includes the autonomy of a person and being free from compelling effects. For some people, volunteering can be defined as the presence of adequate information and the absence of psychological pressure and external restrictions.

The most important issue to consider regarding informed consent is whether the patient/volunteer has the capacity of giving consent. The orientation of capacity, informing, and consent to the authorized person is the first condition for a free and healthy will to form. In terms of medical intervention law, responsibilities such as respect for patient privacy, informing, and consent, which are accepted on the side of physicians, can be said to serve the patient to create an autonomous will.

The third article of the Categorical Imperative (act according to the principle of autonomy) refers to the self-governing of the will, which is ruled by the mind. It is not enough just to know what autonomy is. Active use of autonomy and the formation of personality will not be possible without moving to the autonomy stage. The basic condition of moral action is to be competent beyond being responsible. In any case, CAM studies are based on applications. Volunteer participants should always be at the center when investigating treatments. Additional efforts are necessary to inform these people if they have received multiple treatments and to ensure that the information provided is understood. In TM and CAM studies, therapeutic misunderstandings should be corrected and the components of belief and expectation should be taken into account in the informed consent process.

3.2 Information to be given about the research

The aim of giving information is to ensure that participants are in a position to decide on their own future and to increase the cooperation ability of the patient/volunteer participant.

The Belmont Report, which defines the ethical principles of human research, emphasizes that the form and context in which information is transferred is as important as the information itself. Information about the research should be clear, understandable, and accurate. It should be given to the person in a clear and comprehensible language. A person from the research team who is responsible for obtaining informed consent should provide the information. The information to be given about the research should first clearly reveal the purpose and duration of the research. Research procedures should be explained in detail. The risks and ailments related to the research, the possible duration of these conditions, and how they will be eliminated should be explained. The benefits expected from the research, alternative approaches, records regarding the research, who will reach the records and how, and the extent of confidentiality of the records should be explained. Research involving more than minimum risk should include available medical treatments for volunteers when needed; information about where to get more information, who to consult to in case of a research-related injury, and the amount of payment/compensation to be given to volunteers; explanation of who can be contacted for answers to questions about research and rights about the research (includes the patient representative and phone number of the research center); and information that participation is voluntary, the volunteer may quit the research at any time, and that there will be no loss of rights.

The information provided to volunteer participants regarding the research to obtain informed consent should be completely understood by the patients, but it has quite a complex content. This complexity poses a major barrier for nearly a quarter of adults with low literacy skills to grasping the information supplied. Research communities are responsible for developing innovative forms of consent, which increase patients' willingness to read and skills to understand. To speak of fully informed consent, it is important that the information provided is well understood and that the person can fully grasp what is to be done to their body and participate in the process. Readability is a language-specific concept developed in the United States (USA) in the early nineteenth century. Among the factors affecting the readability are average word length, word frequency, number of words with multiple syllables, average sentence length, number of words with multiple meanings, and average number of syllables. As the number of words in the sentence increases, the readability of a sentence decreases. Readability means full understanding of the text. Readability is highly impacted by issues such as the level of reading, the format of writing, the shortness of sentences and paragraphs, and the technical language. Therefore, to increase the readability, short sentences and paragraphs should be selected and text appropriate for the reading level should be created [34].

3.3 Person providing and provided with information

As a rule, the person to provide information is the person from the research team who undertakes the task of obtaining informed consent. The person to be provided with information is the person who is competent and adequate to give consent, who is invited to the research, and who meets the criteria for participation in the research. In the case of giving information and obtaining consent for the research, separate procedures are followed for children and vulnerable groups. As stated

in the Helsinki Declaration, for a volunteer candidate who is deemed not having the capacity to grant an informed consent can give consent to participate in the research, an additional approval of a physician and the legal representative is necessary. If the person does not give consent, this should be respected. According to the World Medical Association, children, the family, and the legal representative have the right to actively participate in the medical practice decisions [35].

Pediatricians must take medical responsibility as a responsible researcher or assistant researcher in any research on children. One of the main points of Helsinki Criteria is that physicians who are specialists in the research topic take part in scientific research on people. Pediatricians should be included in the team in all studies on children. Responsibilities awaiting pediatricians who will take part in this matter are discussed in other approaches.

3.4 Time of the informing

The provision of information about the research should be done during the process of the invitation of the volunteers to the research without time pressure, and the volunteer should be given some time to decide.

4. TM and CAM research in Turkey

In Turkey, the frequency of use of TM and CAM applications in the general population and the distribution rate by methods are not known. Also, a few available studies include specific patient groups.

The first regulation governing traditional and complementary medicine practices in Turkey was the "Regulation of Acupuncture Treatment," which was published in 1991. The Department of Traditional, Complementary and Alternative Medicine Practices was established in 2012 under the Ministry of Health. It was renamed as the Department of Traditional and Complementary Medicine Practices in 2014, and the Regulation on Traditional and Complementary Medicine was published in the Official Gazette with the date October 27, 2014, and issue 29158. The regulation involves the definition of 15 traditional and complementary medicine applications (acupuncture, apitherapy, phytotherapy, hypnosis, leech applications, homeopathy, chiropractic, cup application, larva application, mesotherapy, osteopathy, prolotherapy, ozone application, reflexology, and music therapy). It also includes the personnel who can perform these applications, indication/contraindication, and materials to be found at the application center [36].

Regulation on Traditional and Complementary Medicine Practices Clinical Research was published in the Official Gazette with the date March 9, 2019 and issue 30709. The purpose of this Regulation is to regulate the principles and procedures for conducting scientific research on people and protecting the rights of volunteers in the fields of traditional and complementary medicine within the framework of international agreements and good clinical practices. This regulation covers clinical studies on medicine, medicinal and biological products on humans, and clinical studies with cosmetic products and raw materials; observational drug studies; clinical studies of medical devices; stem cell clinical studies; noninterventional clinical studies; and traditional and complementary medicine applications. In cases where the research topic directly concerns children or is a clinical condition that can only be examined in children, or data obtained as a result of research on adult individuals have to be validated in children, the research is delivered to the assessment of the ethics committee after a child psychiatry specialist and/or child

health and diseases specialist at the university or training and research hospital gives a positive opinion of the research on children if the research does not pose a predictable risk for the health of volunteers and there is a general medical opinion that the research will provide direct benefit to volunteers. Apart from children, another group of vulnerable—easily affected—subjects is pregnant, postpartum, or lactating women. In cases where the topic of the research is directly related to pregnant, postpartum, or lactating women or is a clinical condition that can only be examined in these women, and the research does not pose a predictable risk for the volunteer and the fetus or the infant, and there is a general medical opinion that the research will directly benefit the volunteers, then research on pregnant, postpartum, and lactating women may be allowed provided that the general research principles are followed. In cases where the subject of the research is directly related to the persons with limitations or is a condition that can only be examined in people with limitations, or where the current treatment options related to the disease of the person with limitations have completely been exhausted, the research does not pose a predictable risk for the health of the person with limitation, and there is a general medical opinion that research will provide a direct benefit to the people with limitations, then people with limitations can be the participants of TM and CAM research. The aforementioned regulation covers the provisions for starting, executing, stopping, and terminating the research, the responsibilities of the responsible researchers and supporters, and the details of the research product. Where and how the adverse events or serious adverse reactions will be reported detail the confidentiality of research records.

Good clinical practice, which is based on the principles of the current Helsinki Declaration, is an ethical and scientific quality standard for the design, execution, recording, and reporting of clinical trials on humans.

Good clinical practice assures the society that the rights, health, and privacy of the volunteers participating in the research are protected and that the data obtained from the research are reliable. The purpose of the Good Clinical Practices Guide is to provide a single standard to facilitate the international mutual acceptance of clinical data. Traditional and Complementary Medicine Practice Good Clinical Practice Manual (May 14, 2019) guides the collection of clinical data to be presented to the Health Services General Directorate and of their respective ethics committees and explains the details and principles of the traditional and complementary medicine practices clinical research that is carried out or scheduled to be conducted in Turkey [37].

Whether volunteer's participation will is accepted or not, these subjects are individuals whose free decision-making willpower can be affected due to the expectation of benefit of participation or the expectation of retaliation by individuals in a hierarchical structure if they refuse to participate. The examples of these individuals include people who are in a certain hierarchical structure such as medical, pharmacy, dentistry, and nursing students; hospital or laboratory staff working in the research setting; those working in the pharmaceutical industry; members of the armed forces; and soldiers and detainees. Also, the group involves patients with an incurable disease; those who live in nursing homes; unemployed or poor people; people who need urgent medical attention; and children or people who cannot give consent. Clinical research is defined as studies conducted on humans to reveal or confirm the clinical or pharmacological effects of one or more research products or traditional and complementary medicine methods, to identify adverse events or reactions, and to investigate their safety and efficacy. In scientific, medical, and ethical terms, TM and CAM research is evaluated in ethics committees assembled according to the Regulation on Traditional and Complementary Medicine Practices

Clinical Research. According to the current legislation in Turkey, ethics committee members are required to receive basic training on good clinical practices and clinical research before starting to work in these boards. If possible, an equal gender distribution among members should be provided in ethics committees.

5. Conclusion

Development of good empirical practices have been guiding ethical discussions and specifying a normative approach and framework for human research at the same time. CAM field necessitates evidence-based results on clinical research. Due to their approaches of preventing illnesses and providing treatment that have been preferred by many individuals, TM and CAM practices and research are expected to progress. Clinical research is essential in ensuring medical advances, and it establishes the bond between theory and practice in the field of medicine. In addition to determining effectiveness of a treatment, strength of the evidences on the medical application should be evaluated. The right path with CAM and TM clinical research and practices would include not to disacknowledge them, but to pave the way for the scientific research on the ones that have the potential to be beneficial and to bring the proven benefits to modern medicine. One challenge with these practices would be the fact that a considerable amount of CAM and TM data are not systematic and standardized, which have made them difficult to scientifically accept. In order to assist the international acceptance of CAM and TM data to pave the way for CAM and TM databases, meta-analyses and so on, good clinical practice guides being made specific to these areas is essential. For all human research, informed consent must be obtained from the voluntary participants. Throughout this process, it is imperative to show respect to participants' dignity, to omit forcing potential voluntary participants in any pecuniary and nonpecuniary way, to care on their confidentiality, and to pay utmost attention on privacy of their data. New treatment procedures and medications as results of clinical research are for public welfare, but the benefit of the voluntary participant must be prioritized.

When it comes to CAM and TM clinical research, a framework to their ethical evaluation is suggested herein. For clinical research on CAM and TM, legal arrangements are necessary regardless of geographical region, belief and cultural differences. Ethical committees for clinical practices and researches should be established specifically for CAM and TM research. In these committees, physicians from different fields of specialization who participated in clinical research conducted according to good clinical practices, physicians having expertise on CAM and TM, legal experts with specialization on medical law and patients' rights, pharmacology and pharmacognosy specialists, along with medical ethics and public health experts. Instructions should be prepared to cover how these committees to work and make decisions; number of members and their employment periods, duties and authorities in these committees; how the applications to these committees are to be done, and how the decisions are to be delivered to the researcher(s); within the legal framework of the countries that the ethical committees belong to.

Conflict of interest

The author declares that there is no conflict of interest.

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Author details

Omur Sayligil
Eskisehir Osmangazi University, Faculty of Medicine, Department of History of Medicine and Ethics, Eskisehir, Turkey

*Address all correspondence to: sayligil@ogu.edu.tr

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