From the Ministry of Health:

REGULATION ON CLINICAL RESEARCH OF TRADITIONAL AND COMPLEMENTARY MEDICINE PRACTICES

FIRST CHAPTER

Objective, Scope, Basis and Definitions

Objective

ARTICLE 1 - (1) The objective of this Regulation is to regulate procedures and principles with regard to doing scientific research on human beings in the field of traditional and complementary medicine practices and protecting the rights of volunteers within the framework of international agreements that one is party to and good clinical practices.

Scope

ARTICLE 2 - (1) This regulation includes clinical research of traditional and complementary medicine practices to be conducted on human beings which are included in Regulation on Traditional and Complementary Medicine Practices published in the Official Gazette No. 29158 dated 27/10/2014, clinical research venues and natural and legal persons that will conduct such research.

(2) Clinical research other than clinical research of drugs, medicinal and biological products to be conducted on human beings, clinical research on cosmetic products and their raw materials, observational drug studies, medical device clinical research, observational medical device studies, stem cell clinical research, non-interventional clinical research, and traditional and complementary medicine practices are outside the scope of this Regulation.

Basis

ARTICLE 3 - (1) This Regulation is based on Additional article 10 of Fundamental Law of Healthcare Services No. 3359 dated 7/5/1987 and on clause (ğ) of the first paragraph of Article 355 and Article 508 of Presidential Decree Law No. 1 on Organization of the Presidency published in the Official Gazette No. 30474 dated 10/7/2018.

Definitions

ARTICLE 4 - (1) The definitions in this Regulation are as follows;

a) Adverse event: Whether there is a causality relationship with the treatment administered or not, all undesirable medical conditions that are seen in the volunteer participating in the clinical research,

b) Adverse reaction: All undesirable and unwanted responses seen in the volunteer participating in the clinical research,

c) Researcher: The person taking part in the research team under the supervision of the responsible researcher,

ç) Research leaflet: Documents about clinical and non-clinical data regarding the product or practice that is being researched,

d) Research protocol: The documents that define the objective, design and methodology of clinical research in a detailed way and that include World Medical Association Declaration of Helsinki and research forms,

e) Research product: The product that is being tested or being used as a reference in the clinical research,

f) Ministry: The Ministry of Health,

g) Unexpected serious adverse reaction: All kinds of serious adverse reactions, the nature, severity and result of which are inconsistent with safety information,

ğ) Informed volunteer consent form: The document that proves in writing the consent received by providing detailed and comprehensible information,

h) Serious adverse event: Adverse event that causes death, life-critical situation, hospitalization, longer hospital stay, permanent or critical disability or invalidity, congential anomaly or defect,

ı) Serious adverse reaction: Adverse reaction that causes death, life-critical situation, hospitalization, longer hospital stay, permanent or critical disability or invalidity, congential anomaly or defect,

i) Multi-centered clinical research: Clinical research that is conducted in more than one center in line with a single protocol and thus encompasses more than one responsible researcher,

j) Supportive entity: Person, organization or institution that is responsible for initiating, conducting or financing the clinical research,

k) Ethical committee: Traditional and Complementary Medicine Practices Ethical Committee that will be established under practice centers in order to provide scientific and ethical opinions about consents to be received from volunteers and methods and documents to be used in informing the volunteers and research related topics with regard to protection of volunteer rights, their safety and well-being,

l) Clinical research of traditional and complementary medicine practices: All kinds of research conducted on human beings in order to reveal or validate clinical or pharmacological effects of one or more than one product and/or method(s) in the field of traditional and

complementary medicine practices, define adverse event or reactions and research their safety and effectiveness,

m) General Directorate: General Directorate of Healthcare Services,

n) Non-interventioanl clinical research: Observational studies, survey studies, retrospective research, research on traditioal and complementary medicine practices to be conducted by using methods that will not necessitate care or intervention of a physician or dentist directly provided that these methods are applied in line with the conditions specified in Regulation on Traditional and Comlementary Medicine Practices,

o) Volunteer: A sick or healthy person that will take part in the research by providing their own written consent or that of their legal representative in line with provisions of this Regulation and relevant legislation,

ö) Responsible person for administrative affairs: A physician or dentist with a specialty or doctoral degree who is responsible for ensuring coordination about administrative issues regarding the research in a multi-centered research while the research is being conducted among responsible researchers of these centers and ethical committee, supportive entity or legal representative of the supportive entity and General Directorate,

p) Drug or human medicinal product: Natural, synthetic or biotechnological drug substance or combination thereof administered to human beings to prevent, diagnose or treat diseases, to set right, adjust or alter a physiological function,

r) Good clinical practices: A set of rules that the parties taking part in the research should abide by and that includes regulations on issues such as designing, conducting, monitoring, budgeting, evaluating and reporting the research in order to make sure that research is conducted in line with international scientific and ethical standards, protecting all the rights and physical integrity of the volunteer, ensuring reliability of research data and ensuring confidentiality,

s) Permission: Affirmative decision of the General Directorate as to the fact that the research can be conducted in relevant center(s) in line with good clinical practices and limits set forth as per the relevant legislation,

ş) Disabled: Persons in the state of disability defined in Turkish Civil Law dated 22/11/2001 and no.4721,

t) Coordinator: A physician or dentist with a specialty or doctoral degree who is responsible for ensuring coordination among responsible researchers and ethical committee, supportive entity or legal representation of supportive entity in a multi-centered research and between them and the General Directorate if necessary,

u) Responsible researcher: A physician or dentist with a specialty or doctoral degree who is responsible for conducting the research,

ü) Contract research organization: An independent organization that operates in line with good clinical practices and to which the supportive entity has transferred all or some of its duties and authorities regarding the clinical research through a written contract,

v) Practice: Traditional and complementary medicine practices specified in Regulation on Traditional and Comlementary Medicine Practices,

y) Practice center: The center established within health practice and research center of the universities having training and research hospitals and medical faculty or faculty of dentistry to perform practices specified in Regulation on Traditional and Complementary Medicine Practicesunder the responsibility of the physician an/or dentist having a certificate in the relevant field,

z) Legal representative: The parent or guardian authorized to give consent for the volunteer taking part in clinical research on behalf of the potential volunteer in line with Turkish Civil Law No. 4721.

SECOND CHAPTER

General Principles of the Research, Principles and Procedures of the Participation in the Research

General Principles of the Research

ARTICLE 5 - (1) In order to conduct research on the volunteers, the following conditions are sought for:

a) It is a must that the research is first done in a nonhuman test environment or on a sufficient number of experimental animals. With regard to research on methods to be conducted on human beings for many years, the ethical committee will assess whether to implement the condition set forth in the first sentence of this clause.

b) Scientific data obtained as a result of experiments conducted in a nonhuman test environment or on animals must necessitate carrying out the said experiments on human beings as well in order to attain the desired objectives.

c) Scientific benefits and public interest expected of the research cannot prevail over health of the volunteer taking part in the research or potential risks that may come up in terms of volunteer health and other personal rights of the volunteer.

ç) Decisions about medical follow-up and treatment of the volunteer participating in the research are made by the physicians or dentists with necessary professional qualifications.

d) During research it is forbidden to administer methods that will inflict pain on the volunteer to an extent that is not compatible with human dignity.

e) The research is designed in such a way as to minimize pain, discomfort, fear, any risk related to the patient's disease or its development phase as much as possible. Both the risk limit and discomfort level should be specifically identified and checked constantly.

f) The objective that is aimed to be achieved through research must outweigh the inconvenience incurred on the person and the danger facing the person's health.

g) It is a must that the research does not leave a foreseeable harmful or permanent effect on the person's health.

ğ) In case it is decided by the ethical committee that the benefits to be obtained are more than potential risks that may arise, the research can be initiated with the approval of the ethical committee and permission of the General Directorate by respecting the personal rights and provided that an informed volunteer consent form is received as per the procedures. The research can only be conducted provided that these conditions are maintained.

h) Before the research commences, the person that wants to be a volunteer to take part in the research or legal representative thereof must be adequately informed by a responsible researcher having a command on the research topic on the objective of the research, its methodology, expected benefits, foreseeable risks, the personsupporting the research, challenges, inconvenient aspects in terms of the person's health or personal traits, by whom and where the research results will be used, the conditions in line with which the research will be conducted and maintained, the right to withdraw from the research whenever they want.

ı) Consent of the volunteer is received to make sure the volunteer will be included in the research of their own free will and without providing any benefit and this is documented through Informed Volunteer Consent Form drawn up in line with issues mentioned in clause (h) of this article.

i) At least one physician of the research team is assigned in order for the volunteer to be informed on their own health and the course of the research whenever they like and to get into contact with the said physician to that end.

j) The volunteers may withdraw from research of their own free will with or without giving any reason at their pleasure and they do not forfeit their rights during subsequent medical follow-ups and treatment. If the volunteers wish to withdraw from study of their own accord, it is certificated with a document signed by the volunteers.

k) It is mandatory to insure the volunteers so as to ensure that they are safeguarded against damages that may be incurred from voluntary clinical research.

l) Clinical research insurance is issued in a way to guarantee that any damage caused by clinical research is redressed and compensated.

m) Apart from insurance coverage, no other persuasive incentive or financial offer can be presented to the voluntary or legal representative with a view to ensuring that volunteers participate in research or maintaining their attendance. However, necessary expenses incurred from participation of volunteers in research as well as the decrease in income caused by working day loss are specified in the research budget and they are covered from this budget.

n) The results to be obtained following the research can be anonymously published in a way that under no circumstances can be associated with a specific or identifiable natural person.

o) No research can be conducted on germ cells of volunteers which may disrupt genetic structure.

Participation of children in the research

ARTICLE 6 - (1) In cases where research subject directly concerns children or it is a clinical condition that can only be examined on children or where it is mandatory to ensure that data obtained from research conducted on adults also prove valid for children, and if the research does not pose any foreseeable risk for volunteers and if there is a general medical opinion that the research will have direct benefits for volunteers, it is allowable to conduct research on children within the framework of following provisions as well as the provisions set forth in Article 5 hereof:

a) It is necessary to have a general medical opinion that the products or practices under research pose no known risk for children.

b) Unless a child psychiatrist and/or a pediatrician working in universities or training and research hospitals express a positive opinion for clinical research to be conducted on children, the ethical committee cannot evaluate the protocol of this research.

c) The ethical committee evaluates the protocol after it is informed on clinical, ethical, psychological and social problems related to the research by a child psychiatrist and/or a pediatrician.

ç) If child is able to express her/his consent, the consent of child as well as the consent of her/his parents or her/his guardian -if s/he is under custody- is obtained in writing after s/he is informed as per clause (h) of the first paragraph of Article 5 hereof.

d) If the child wishes to withdraw from research at any stage, s/he is removed from research.

e) The children are given all necessary information on research in a proper manner provided that they have the capacity to assess the information and to reach a conclusion in this regard.

f) Apart from covering necessary expenses caused by the participation of children in research, no other persuasive incentive or financial offer can be presented to children, their parents or their guardians for clinical research to be conducted on children.

Participation of the pregnant, the puerperant and breastfeeding women in the research

ARTICLE 7 - (1) In cases where research subject directly concerns the pregnant, the puerperant and the breastfeeding women or it is a clinical condition that can only be examined on the pregnant, the puerperant and the breastfeeding women and if the research does not pose any foreseeable risk for volunteers and in terms of fetus or infant health and if there is a general medical opinion that the research will have direct benefits for volunteers, it is allowable to conduct research on the pregnant, the puerperant and the breastfeeding women within the framework of following provisions as well as the provisions set forth in Article 5 hereof:

a) It is necessary to have a general medical opinion that the products or practices under research pose no known risk for the pregnant, the puerperant and the breastfeeding women and for fetus or infant.

c) The ethical committee evaluates the protocol after it is informed on clinical, ethical, psychological and social problems related to the research especially in terms of embryo, fetus or infant health by a physician receiving specialization in the field of research subject.

c) The consent of the pregnant, the puerperant and the breastfeeding women is obtained in writing after they are informed as per clause (h) of the first paragraph of Article 5 hereof.

ç) If the pregnant, the puerperant and the breastfeeding women wish to withdraw from research at any stage, they are removed from research.

d) Apart from covering necessary expenses caused by the participation of the pregnant, the puerperant and the breastfeeding women in research, no other persuasive incentive or financial offer can be presented to them for clinical research to be conducted on them.

Participation of the disabled in the research

ARTICLE 8 - (1) In cases where research subject directly concerns persons in the state of disability or it is a clinical condition that can only be examined on the disabled or if they have run out of treatment options for the diseases of the disabled and if the research does not

pose any foreseeable risk in terms of the health status of the disabled and if there is a general medical opinion that the research will have direct benefits for persons in the state of disability, it is allowable to conduct research on the disabled within the framework of following provisions as well as the provisions set forth in Article 5 hereof:

a) It is necessary to have a general medical opinion that the products or practices under research pose no known risk for the disabled.

b) The ethical committee evaluates the research protocol after it is informed on clinical, ethical, psychological and social problems related to the research by a physician receiving specialization in the field of research subject or by a psychiatrist.

c) The consents of their guardians and the consent of the disabled -if they have the ability to express their consents- are obtained in writing after they are informed as per clause (h) of the first paragraph of Article 5 hereof.

ç) If the disabled have the capacity to assess the information given and to reach a conclusion in this regard and wish to withdraw from research at any stage, they are removed from research.

d) Apart from covering necessary expenses caused by the participation of the disabled in research, no other persuasive incentive or financial offer can be presented to them for clinical research to be conducted on them.

THIRD CHAPTER

General Principles of Conducting the Research

Clinical research conditions and clinical research periods

ARTICLE 9 - (1) Period before receiving license or permission is the period when the research product is examined in terms of pharmacokinetic properties, toxicity, its impact on body functions, therapeutic dose limits, clinical effectiveness, new indication research, different doses, new administration ways/methods, a new patient population or pharmaceutical formats, and when the said product selected in accordance with the property and nature of the research is tried on sufficient number of healthy and/or sick volunteers.

(2) Period after receiving license or permission: clinical research period conducted with a view to further examining the approved indications, posology and application methods of products the licenses of which are received in Turkey as well as the safety and effectiveness of recommended using methods of products receiving permission as well as comparing the other entrenched treatment, product or methods.

Research venues and standards

ARTICLE 10 - (1) Clinical research can be conducted at training and research hospitals affiliated to the Ministry, university hospitals, or the approved research and development centers affiliated to universities which are designed to conduct clinic research, which are suitable for ensuring the safety of persons on whom research will be conducted and for implementing and following up the research on a sounder basis and for taking emergency actions when necessary, and which have personnel, equipment and laboratory facilities suitable for the properties of research. When necessary, the other health institutions and organizations meeting the specified requirements can be included in the scope of the clinical research conducted at these centers and hospitals provided that they will be carried out under the coordination or under the administrative responsibility of these centers and hospitals.

(2) Venues where clinical research will be conducted based on Good Clinical Practices Guidelines are obliged to have the followings at minimum:

a) The qualified personnel and equipment required based on the features of the research,

b) Opportunities and hardware to provide proper care service for the volunteer including cases that require emergency actions,

c) Opportunities and hardware sufficient to transfer the volunteer to an advanced health institution or organization when necessary,

ç) Opportunities and hardware sufficient to keep information and documents pertaining to clinical research and volunteers after research is completed,

d) Venues and opportunities required for storing and distributing the research product in accordance with its features.

Research application, approval of the ethical committee and permission of the General Directorate

ARTICLE 11 - (1) Research application file is prepared in accordance with the application form and its annexes on the web site of the General Directorate within the framework of Good Clinical Practices Guidelines and the other guidelines.

(2) Research application can be filed to the ethical committee and the General Directorate simultaneously by the supportive entity comprising natural or legal persons or by the contract research organization residing in Turkey which is designated by the supportive entity.

(3) The approval of the ethical committee is granted by the ethical committee within the application center where the research will be conducted, or if there isn't any ethical committee within the said center it is granted by another ethical committee nearest to the application center; on the other hand, permission is granted by the General Directorate.

(4) In multi-centered clinical research, it is necessary to receive the approval of the ethical committee within the coordinating center, or if there isn't any ethical committee within the said center, the approval of another ethical committee nearest to the coordinating center is received.

(5) It is essential that the application is finalized in thirty working days by the ethical committee and in sixty working days by the General Directorate if the application is duly lodged and if there isn't any deficiency in information and documents submitted for application.

(6) When it is considered necessary to make a change in research protocol, the ethical committee will inform the supportive entity of this situation for once only and the ethical committee inspection is ceased. The supportive entity makes necessary changes in the specified matters and submits these changes to the ethical committee in fifteen working days; otherwise, the application is deemed to be withdrawn. On the first meeting of the ethical committee, the research protocol is re-evaluated taking into consideration the changes made; the ethical committee do not grant an approval unless the requested changes have been made.

(7) If the ethical committee presents an adverse opinion, it is notified to the supportive entity with its justifications. The supportive entity may object to the opinion in fifteen working days by giving justification for once only; objections submitted after fifteen working days will not be evaluated. The research protocol as well as the justification for objection is evaluated on the first meeting of the ethical committees; no objection can be raised again against the opinions delivered during this meeting.

(8) If the General Directorate takes an adverse decision on the permission required to initiate the research, it is notified to the supportive entity with its justifications. The supportive entity may lodge application again by making necessary changes in the specified matters for once only or make an objection in fifteen working days by giving justification. Meanwhile, the inspection process is ceased. The General Directorate does not grant any permission for the research unless the requested changes are made or a reasonable justification is given in this regard in thirty working days.

FOURTH CHAPTER

Initiating, Conducting, Ceasing and Ending the Research

Initiating and Conducting the Research

ARTICLE 12 - (1) It is mandatory to receive the approval of the ethical committee and the permission of the General Directorate within the scope of this Regulation. The General Directorate cannot grant permission for research applications for which the approval of the ethical committee is not obtained.

(2) The research is conducted as follows:

a) Clinical research within the scope of this Regulation is conducted with a team meeting the requirements of the research under the leadership of the responsible researcher.

b) Changes made while conducting the research which are notifiable and which require the approval of the ethical committee and the permission of the General Directorate are specified in accordance with the Good Clinical Practices Guidelines.

c) Without prejudice to the provisions set forth in clause (b) above; the supportive entity or the responsible researcher or a researcher who is a physician or a dentist takes emergency safety precautions against threats if a situation emerges which may have an impact on the safety of volunteers while they conduct the research or develop the research product. The responsible researcher or the supportive entity is obliged to notify the General Directorate of this situation and precautions taken in five working days. Otherwise, the research is ceased by the General Directorate.

ç) If the research is not initiated on the date specified in the application file despite the permission of the General Directorate, its underlying reasons are notified to the General Directorate in sixty working days.

d) The responsible researcher includes associate researchers, working at another institution and meeting the requirements, in research team so as to fulfill the conditions and take the measures required for patient safety and states this inclusion in the application form.

e) The supportive entity may transfer some of its duties to the contract research organization working in conformity with scientific rules and good clinical practices provided that it makes a written contract and notifies the General Directorate thereof. Transfer of duties to the contract research organization does not remove the possible legal and criminal responsibility of the supportive entity pertaining to the duties transferred. Both the supportive entity and the contract research organization are liable for the results of the said works and transactions.

Ceasing and Ending the Research

ARTICLE 13 - (1) The research is immediately ceased by the General Directorate if it is identified that one or more requirements of the research are not met during research despite being fulfilled at permission stage. The research is directly ended if these conditions are not fulfilled within the prescribed time or if it is understood that it not possible to fulfill these conditions within the prescribed time, or if it threatens the health of volunteers within this period.

(2) In cases which do not pose any direct risk for volunteers, opinion of the supportive entity or the responsible researcher may be requested. In this case, the supportive entity or the responsible researcher presents its opinion to the General Directorate in fifteen working days.

(3) If the supportive entity ceases the research before it is completed, it submits to the General Directorate an information letter containing the decision of ceasing with its justifications and measures to be taken for continuing the treatment of volunteers included in scope of the research.

(4) The supportive entity notifies the General Directorate of termination of the research in sixty working days after the research is ended.

(5) The decision of ceasing or ending the clinical research is notified to the supportive entity and the responsible researcher with its justifications.

FIFTH CHAPTER

Research Products

Responsibility of the supportive entity and the responsible researcher regarding the research product

ARTICLE 14 – (1) The supportive entity is liable for storing, distributing and delivering research products to the research center in accordance with their features after they are manufactured or imported, for maintaining these conditions after they are delivered to the research center, for ensuring that unused products are recalled from research centers and returned or properly destroyed, and for ensuring that the above-stated processes are recorded.

(2) Responsible researcher in each research center where research is conducted is liable to accept, preserve and distribute the research products in accordance with written requests or research protocol, to perform stock control for them, to keep records, and to conduct transactions for the remaining products. Responsible researcher assigns preferably a pharmacist for these procedures.

Manufacture, import and labeling of research products

ARTICLE 15 – (1) It is guaranteed that research products are manufactured and prepared in compliance with the rules stipulated in the annex of Regulation on Traditional and Complementary Medicine Practices.

(2) Necessary permissions are received from competent authorities for manufacturing or importing products to be used in research.

(3) The supportive entity that will manufacture or import the research products ensures that:

a) The fact that research products to be manufactured or imported are manufactured and controlled in compliance with the rules stipulated in the relevant Regulation is documented during the application made to the General Directorate.

b) The information and documents pertaining to products manufactured or imported so as to conduct research are stored for at least five years.

Withdrawal of research products

ARTICLE 16 – (1) In the event that the research is ceased, all products which remains unused by responsible researcher or a researcher who is a physician or a dentist are immediately returned to distribution points by the supportive entity and the General Directorate is notified thereof through a report as well as its documents in fifteen days.

(2) Withdrawal of research products as well as transactions to be conducted and measures to be taken with regard to these products will be specified in detail in the report submitted to the General Directorate.

SIXTH CHAPTER

Notifications, Research Records, Confidentiality and Transfer, Audit and Responsibility

Notification of adverse events

ARTICLE 17 - (1) The responsible researcher or a researcher to be appointed by the responsible researcher immediately notifies the supportive entity about all serious adverse events except for the ones which are not required to be promptly notified according to the protocol or the research leaflet. Following this immediate report, a detailed report shall be submitted to the supportive entity. A single code number is used in the immediate report and other subsequent reports for the volunteers participating in the study.

(2) The adverse events or laboratory findings which are defined as critical for safety assessments are reported to the supportive entity within the period of time and in a manner specified in the protocol.

(3) The responsible researcher or a researcher to be appointed by the responsible researcher provides all sorts of additional information required to the supportive entity, ethical committee and the General Directorate in the event of the death of one of the volunteers participating in the research.

(4) The supportive entity keeps a detailed record of all adverse events reported to it by the responsible researcher or the researcher. It submits these records to the General Directorate and to the ethical committee if requested.

Notification of serious adverse events

ARTICLE 18 – (1) The supportive entity informs the ethical committee and the General Directorate about the serious adverse reactions occurring during the research not later than seven days following the reception of such information. It conveys to the ethical committee and the General Directorate the monitoring reports which include additional information on these cases, within eight days following the reception of such reports.

(2) All other unexpected serious adverse reactions are reported to the ethical committee and the General Directorate by the supportive entity not later than fifteen days following the reception of the initial information.

(3) Furthermore, the supportive entity informs all researchers and the responsible researcher.

(4) The supportive entity submits, annually, to the ethical committee and the General Directorate the list of all unexpected serious adverse reactions occurring during the research including information on the safety of the volunteers, along with the interim report form included in the relevant guidelines to be issued by the General Directorate. The General Directorate may request reports at shorter intervals if deemed necessary.

Other notifications

ARTICLE 19 - (1) The interim report and the final report are drafted in line with the relevant guidelines and the forms to be published on the web site of the General Directorate in a way to include the reports of all centers which take part in multi-centered research.

(2) Guidelines for Good Clinical Practice are used to determine, of all assignments related to the research, the ones which require notification and the ones which require approval from the ethical committee and permission from the General Directorate. The General Directorate may cancel the assignments which require notification by giving justification.

(3) The supportive entity is responsible for regularly submitting the notifications to the General Directorate.

Research records, confidentiality and transfer

ARTICLE 20 – (1) All research within the scope of this Regulation are recorded in a public database on the condition of respecting the principle of confidentiality of personal data.

(2) All research records are regularly kept by the responsible researcher or the researcher and the supportive entity, and they shall be kept for at least fourteen years following the completion of the research in all centers.

(3) The ethical committee and the General Directorate are informed in the event of the transfer of the research by the supportive entity for any reasons. The General Directorate gives approval if it deems that the transfer is appropriate. The new owner of the data or the documents

shall be responsible for maintaining and archiving them in the event of the transfer of the research.

(4) Research data and documents shall be archived in accordance with the provisions of the guidelines.

(5) It is essential to keep research documents confidential. These documents are submitted to the authorities if legally requested by the authorized persons or by the competent authorities.

Audit

ARTICLE 21 - (1) The General Directorate audits, with or without prior notification, the research carried out in Turkey or abroad, the places where the research are carried out, the supportive entity and contract research organization, the places where the products on which the research is performed are manufactured, laboratories where the analyses related to the research are performed, and the ethical committees in terms of compliance with this Regulation and other relevant legislation provisions.

(2) The auditors of good clinical practices are selected from among the persons who have a bachelor's degree at minimum, who received adequate training on and have adequate experience in good clinical practices, and who are preferably graduates of medicine, dentistry or pharmacy field.

(3) The good clinical practice auditors are liable to respect the principle of confidentiality regarding the information they receive during the audit.

Responsibility

ARTICLE 22 - (1) Legal and financial responsibility of the research belongs to the supportive entity and contract research organization and to the researcher. The volunteer or the social security institution under which the volunteer is covered shall not be charged with any fees for any research product used in the research, for any materials appropriated to the use of the products, and for any examination, testing or treatment.

(2) Natural or legal persons who will carry out the research must specify the financing of the research in the application file.

(3) The reception of the informed volunteer consent form from the volunteer participating in the research does not annul the volunteer's right to compensation for damages incurred due to the research.

Prohibitions

ARTICLE 23 - (1) It is prohibited to carry out any research within the scope of this Regulation in contravention of procedures and principles set out in this Regulation or in other relevant legislation.

Administrative sanctions

ARTICLE 24 - (1) In the case that the provisions regarding clinical research are violated, the General Directorate may halt or end the relevant research or the part of the research that is carried out in Turkey in international multi-centered clinical research. The supportive entity informs the General Directorate after the elimination of the reasons for halting and the research continues if deemed appropriate by the General Directorate.

(2) The General Directorate warns the ethical committee which does not act in conformity with ethical principles or which does not fulfill the principles of the Standard Operating Procedures for Ethical Committee published by the General Directorate or if it is found out as a result of the audit that the ethical committee lacks in space, secretariat, archive and other equipment required for conducting its activities. The approval given to the ethical committee by the General Directorate shall be canceled if no corrective action is taken within the period of time specified after the warning and the membership of the ethical committee chair shall be canceled for two years.

(3) Turkish Criminal Code No. 5237 dated 26/09/2004, Misdemeanor Law No. 5326 dated 30/03/2005 and other relevant legislation shall apply to those who behave and act in contravention of the provisions set out in this Regulation based on the nature of the acts.

SEVENTH CHAPTER

Structure, Operating Procedures and Principles, and Duties of the Ethical Committee

Structure of the ethical committee

ARTICLE 25 – (1) The Ethical committee is constituted with the purpose of providing scientific and ethical opinions about the consents to be received from volunteers and methods and documents to be used in informing the volunteers and the research related topics with regard to the protection of volunteer rights, safety and well-being, and it consists of minimum seven and maximum fifteen members most of whom are healthcare professionals with education at doctoral or specialty-in-medicine level.

(2) The Ethical Committee is established with the proposal of rector in universities, of head physician in training and research hospitals, and with the approval of the General Director of Health Services, and it commences to function as of approval date. When any committee member leaves the office, the person determined by the relevant managers is submitted for the approval of the General Directorate.

(3) A separate ethical committee or a committee or structure that will perform the functions of the ethical committee shall not be constituted by other institutions and organizations in order to provide opinions about topics falling within the scope of this Regulation.

(4) A person who takes part in another ethical committee may also take part in the ethical committee to be established within the scope of this Regulation.

(5) The Ethical Committee consists of members with qualifications specified below:

a) If available, a person with doctoral degree in medical ethics or medical deontology or a specialty in medicine,

b) If available, a person who holds a doctoral degree in pharmacology or pharmacognosy, or completed his/her education for specialty in medicine,

c) Specialist physicians who, preferably, participated as a researcher in international clinical research organized in accordance with good clinical practices and who are selected preferably from different specialties,

ç) Persons who are competent in one or more traditional and complementary medicine practice fields,

d) If available, a person with a doctoral degree or specialty in biostatistics or public health who, preferable, is a healthcare professional,

e) A graduate of the faculty of law who, preferably, has experience in health law, patients' rights or clinical research,

f) A person who is not a healthcare professional.

Operating procedures and principles of the ethical committee

ARTICLE 26 – (1) The operating procedures and principles of the ethical committee are as follows:

a) The ethical committee acts independently when it comes to assessing clinical research applications in scientific and ethical terms and to making a decision.

b) The members of the ethical committee must follow the principle of confidentiality regarding any information conveyed to them.

c) The members of the ethical committee begin performing their duties after signing the confidentiality document and commitment letter prepared by the General Directorate.

ç) A member of the ethical committee who is associated with or takes part in the research which is being inspected shall not participate in discussions and voting in the ethical committee of this research and sign the ethical committee decision.

d) The members of the ethical committee convene with at least two-third of the total number of members and make a decision with simple majority of the members participating in the meeting.

e) The term of office of the ethical committee members is two years and the members may be re-elected.

f) The membership of those who do not participate in three meetings in a row or five meetings at intervals without any excuse during her/his membership is automatically annulled. A new member with the same qualifications within the framework of the fifth paragraph of article 25 of this Regulation shall be selected to replace those who complete his/her term of office or whose membership is annulled.

g) The ethical committee may receive written opinion of another person or other persons who is/are competent in the examined topic or may invite them as a counselor to the meeting, if needed.

ğ) Standard operating methods of the ethical committee are determined by the General Directorate and published on the web site of the General Directorate. The ethical committee conducts its duties within the framework of these standards.

Duties and powers of the ethical committee

ARTICLE 27 – (1) The duties and powers of the ethical committee are as follows:

a) The ethical committee assesses the following at a minimum when forming an opinion about the research application;

1) The analysis of benefits, harms and risks expected from the research,

2) Whether or not the research is based on scientific data and a new hypothesis,

3) For the research that will be performed on human beings for the first time, the necessity to perform the research in a non-human test environment or on a sufficient number of animals at first,

4) Whether the research has grown to the maturity to be performed on human beings in terms of achieving the desired objective in line with the scientific data obtained as a result of the tests performed in a non-human test environment or on animals, and the necessity of conducting the research on human beings,

5) The research protocol,

6) The content of the research leaflet and whether this leaflet is prepared in due form,

7) The written information provided with regard to the research, the method followed to receive the volunteers' consent, the sufficiency of the justification about the research that will

be performed on the disabled, children, pregnant women, puerperae and breastfeeding women, patients in the intensive care unit, and unconscious patients,

8) The responsibility of the responsible researcher or the researcher or the supportive entity in the event of injuries or deaths including permanent health problems probable to occur due to the research,

9) The payment of compensation in the event of an injury or death that may be associated with the research,

10) The arrangements with regard to engaging volunteers in the research,

11) The appropriateness of the research team taking part in the research to the nature of the research.

b) The ethical committee does not give approval for the research which will be carried out in places other than the ones specified under the relevant practice section in the annex of the Regulation on Traditional and Complementary Medicine Practices or which will be performed with the products which do not have the specified requirements.

c) The ethical committee may observe those with approved applications during the research and on site, when necessary.

ç) The ethical committee provides its opinion to the applicant within maximum thirty business days as of application date.

d) If additional information and explanations are needed during the ethical committee's inspection, all necessary requests shall be conveyed to the applicant at a single time. The inspection shall be ceased until the requested information and documents are submitted to the ethical committee.

e) All secretariat works of the ethical committee are carried out by the health research and application center of the training and research hospital or the faculty of medicine or the faculty of dentistry to which the application center is affiliated.

Objection to the approval of the ethical committee

ARTICLE 28 - (1) Upon the request of General Directorate, Clinical Research Advisory Committee organized within Turkish Medicines and Medical Devices Agency and mentioned in the Regulation on Clinical Research Conducted on Drugs and Biological Products published in the Official Gazette No. 28617 dated 13/4/2013 expresses opinions with regard to the objections raised against the approval of the ethical committee for all clinical research subject to the provisions of this Regulation and against the matters requiring the opinion of an expert presented to the Turkish Medicines and Medical Devices Agency by the parties of the clinical research.

Insuring the volunteers

ARTICLE 29 – (1) It is obligatory to make sure that volunteers taking part in research under this Regulation are covered by the clinical research insurance against any damages that may be caused by clinical research. However, some clinical research is outside the scope of this insurance since it does not pose any risks for volunteers or since the risk is at an acceptable level. The clinical research included in or outside the scope of this insurance is as follows:

a) Non-interventional clinical research is outside the scope of this insurance.

b) Clinical research conducted through traditional and complementary medicine tools and methods is outside the scope of this insurance provided that it is conducted in line with practices and conditions set forth in Regulation on Traditional and Complementary Medicine Practices. However, the ethical committee and/or the General Directorate may request the insurance to be issued for the research stated herein by giving justifications.

c) Clinical research of traditional and complementary medicine practices conducted with a human medicinal product, traditional herbal medicinal product, herbal product, medical device, cosmetic product or homeopathic products to which a license or an approval is granted by Turkish Medicines and Medical Devices Agency is outside the scope of this insurance provided that these products are used in indications, doses and for populations stated in their licenses; otherwise, it is mandatory to take out an insurance.

ç) The procedures of bloodletting, taking urine, saliva or similar material samples which are routinely conducted at health institutions and organizations are outside the scope of this insurance.

d) The provisions apart from those which are stated in this paragraph and which are to be fulfilled with regard to the insurance of volunteers against the other examination, diagnosis, prophylaxis and treatment methods applied to volunteers during clinical research are regulated as per the guidelines prepared by the General Directorate.

Training

ARTICLE 30 - (1) The General Directorate may organize trainings or seminars with a view to training qualified responsible researchers or researchers, healthcare personnel and other individuals working in this field who have undergone training on good clinical practices and clinic research included in the scope of this Regulation, or it grants authorization to the institutions or organizations to organize these trainings or seminars in parallel with the guidelines to be published.

The Guidelines

ARTICLE 31 - (1) The guidelines which provide guidance and explanations to implement this Regulation are published by the General Directorate.

EIGHTH CHAPTER

Miscellaneous and Final Provisions

Situations for which there are no provisions

ARTICLE 32 - (1) Provisions set forth in the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, the Medical Deontology Regulation which came into effect through Cabinet Decree no. 4/12578 dated 13/1/1960, the Patient Rights Regulation published in the Official Gazette no. 23420 dated 1/8/1998, and Regulation on Traditional and Complementary Medicine Practices as well as the provisions of the other applicable legislation depending on the venues where clinical research is conducted are applied to the situations for which there are no provisions in this Regulation.

Entry into force

ARTICLE 33 - (1) This Regulation enters into force on its publication date.

Enforcement

ARTICLE 34 - (1) The provisions of this Regulation are enforced by the Ministry of Health.