ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/mdethic.2017-58536

Standardizing Decision-Making Processes in Institutional Review Boards in Accordance with International Guidelines and Turkish Regulations

Uluslararası Rehberler ve Türk Mevzuatı Çerçevesinde Klinik Araştırmalar Etik Kurullarında Karar Verme Sürecinin Standardizasyonu

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Received: 17.10.2017
Received in revised form: 22.11.2017
Accepted: 29.01.2018
Available online: 04.04.2018

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ABSTRACT All research on human subjects should go through objective and independent ethical review. However, there are huge inconsistencies in the decisions of the review boards, which lead the investigators to question the validity and the objectivity of the decisions. We aim to develop a standard evaluation tool to regulate the ethical decision-making process for the board members' review and to minimize the effect of subjective factors. All international and national guidelines on clinical research ethics were reviewed and relevant criteria identified to prepare a comprehensive evaluation tool. Turkish laws and legislations regarding clinical research were also evaluated in order not to exclude any item that will affect the well-being of human subjects and investigators' conduct of clinical research. Ethical evaluation criteria are grouped under six headlines, and Turkish Ethical Evaluation of Clinical Research Protocols on Human Participants Sheet (TR-EGES) was developed and is offered for use by Institutional Review Boards as a general template for decision-making process. TR-EGES will ensure that all issues in national and international documents and guidelines are covered before reaching a conclusion for the proposed research protocol and will make the decision-making process as rational and standard as possible.

Keywords: Clinical research; institutional review boards; research ethics; ethics committee; human subjects; standardization of ethical review criteria

ÖZET Gönüllü katılımcılar üzerinde yapılan klinik araştırmalar, araştırmaya başlanmadan önce objektif ve bağımsız klinik araştırmalar etik kurulları tarafından değerlendirilmektedir. Ancak, etik kurul kararlarındaki tutarsızlıklar araştırmacıların kurul kararlarının geçerliliği ve objektifliğini sorgulamalarına yol açmaktadır. Bu çalışmanın amacı, standart bir değerlendirme aracı geliştirerek etik kurul üyelerinin karar verme sürecini düzenlemek ve verilen kararlarda sübjektif faktörlerin etkisini en aza indirgemektir. Kapsamlı bir değerlendirme aracı oluşturmak üzere insan denekler üzerinde yapılan araştırmalar ile ilgili uluslararası rehberler ve yönergeler incelenmiş ve değerlendirmeye alınması gereken kriterler belirlenmiştir. Daha sonra, belirlenmiş kriterler klinik araştırmalara ilişkin Türk mevzuatı ile uyumlu olacak şekilde revize edilmiştir. Klinik araştırmalar etik kurul üyelerinin araştırma protokolünü değerlendirirken incelemeleri gereken kriterler altı başlık altında toplanmış ve etik kurul üyelerinin kullanımına sunulmuştur. Bu değerlendirme aracının kullanılması, etik kurul kararlarının verilmeden önce geçerli uluslararası ve ulusal mevzuatta yer alan tüm maddeler uyarınca gözden geçirilmiş olmasını sağlayacaktır.

Anahtar Kelimeler: Klinik araştırmalar; kurum etik kurulları; araştırma etiği; etik komite; insan denekler; etik değerlendirme kriterleri standartizasyonu

The first Turkish regulation on conducting clinical research on human subjects was released in 1993. The number and scope of clinical trials have been growing steadily in Turkey which led the country to review its legislation and align it with international guidelines and codes. In this regard, Turkish regulations were harmonized by the International Con-

ference on Harmonization (ICH), Declaration of Helsinki (DoH) and The Council for International Organizations of Medical Sciences (CIOMS) guidelines.[1,2] The requirement of objective and independent ethical review prior to the onset of the clinical trial has been considered an obligation since the first version of the regulation.

The composition and administrative structure of the review bodies has varied over time. Today, there are 977 IRB members serving in 78 Institutional Review Boards (IRB) in 34 different provinces in Turkey.[3] The qualifications and minimal training requirements for IRB members are set by the regulations, but there is no standardization or determination regarding the decision-making procedure in the IRBs.

The existing literature proves that the decisions of the IRB members are influenced by subjective factors such as personal intuitions, feelings, beliefs, interpersonal interactions, and non-rational influences on group decision-making. Moreover, the lack of knowledge on existing national and international laws and regulations, and the medical interventions in the relevant field of research result in inaccurate decisions being made.[4-9]

On the other hand, there are no standardized decision-making sheets available for IRB members. Some IRBs have developed abstract documents to guide members but none of these contains a detailed list of ethical and legal requirements to be considered before making a decision.

The literature contains challenging studies about the inconsistencies in IRB decisions.[7,9] A survey by Green et al. shows how significant the variations in IRB decisions for the same study can be. In this study of the 43 IRBs, ten decided expedited review, 31 gave full board review, and one IRB objected to the study because of the risks it involves.[10] These inconsistencies damage the investigators' trust and reliance on IRB decisions and lead them to question the validity and objectivity of the decisions on their clinical research protocols.[11-13]

The aim of this work is to prepare an evaluation sheet that goes through all ethical criteria in the international ethical guidelines and national laws and regulations for standardizing the ethical decision-making procedure of Turkish IRB members, so that the effects of subjective factors and lack of knowledge on existing national and international laws and regulations could be minimized.

MATERIAL AND METHODS

The DoH, the CIOMS, the ICH guidelines, Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants of World Health Organization (WHO) Medical Ethics Manual of World Medical Association were reviewed and all criteria for the ethical review of clinical research proposals were identified.[13-17] The identified criteria were grouped under six headlines.

1. Scientific design and conduct of the clinical trial

2. Selection of study population and recruitment of research participants

3. Care and protection of research subjects

4. Informed consent

5. Conflict of interest issues

6. Inducements, financial benefits, and financial costs; reimbursement and compensation

This document is named the "**E**kmekci **G**üner **E**thical Evaluation of Clinical Research Protocols on Human Participants **S**heet (EGES)", and is offered for use by IRBs as a general template for decision-making.[18]

The second step was to review all Turkish laws and regulations related to clinical research, and patient rights. The laws and regulations considered were: the Constitution of the Republic of Turkey , the Turkish Regulation on Clinical Trials for Drugs and Biological Products (TRDBP), the Turkish Regulation on Clinical Trials for Medical Devices, the Turkish Regulation on Deontology, and the Turkish Regulation on Patient Rights.[19-23] A document containing all legal and ethical obligations for clinical trials emerging from Turkish legislation was listed, and all ethical obligations related to research ethics were identified.[14-18] The final step was to merge two documents to form the final evaluation sheet, the

"Ekmekci-Güner Ethical Evaluation of Clinical Research Protocols on Human Participants Sheet for Turkish IRBs (TR-EGES)". The assessment of the Investigators Brochure (IB) was added as the seventh headline owing to the obligations in TRDBP.

RESULTS

TR-EGES is composed of seven headlines.

1. Scientific design and conduct of the clinical trial

2. Selection of study population and recruitment of research participants

3. Care and protection of research subjects

4. Informed consent form (ICF)

5. Conflict of interest (COI) issues

6. Inducements, financial benefits, and financial costs; reimbursement and compensation

7. IB

The TRDBP requires the institutions to establish different IRBs for retrospective research, bioequivalence and bioavailability studies, and clinical research on human subjects.[20] Therefore, the TR-EGES starts with notes to the reviewer to make sure that the research protocol to be reviewed is not a retrospective study, or a bioequivalence or bioavailability study.

Scientific design and conduct of the clinical trial includes the assessment of the research according to the following criteria:

- The soundness of the research design;
- The provision of relevant scientific data for the need to conduct the research;
- The adequacy of the preliminary data; the definition of aims and objectives of the research;
- The sufficiency of the physical, human, and technological resources to conduct the research;
- No involvement of interventions that aim to or may lead to change or destruction of the participants' germ cells;
- The principal investigator's and the researchers' professional and scientific backgrounds, and their awareness of good clinical practice (GCP) guidelines;
- The appropriateness of the methodology of the research including the sample size;
- The selection, inclusion, and exclusion criteria of participants.

The selection of the study population and recruitment of research participants focuses mainly on the selection of the participants and ascertains if the selection is equitable. The investigator's capacity to recruit the proposed number of participants, the vulnerability of the participants, the appropriateness of the number, profile, inclusion and exclusion criteria of the participants, gender equality, the fair involvement of underrepresented groups, absence of coercive elements in the recruitment procedure, and the social value of the research are among the criteria that are evaluated in this section.

The assessment of **care and protection of research subjects** aims to guide the IRB members to evaluate the adequacy of a data and safety monitoring plan, the protection of privacy and confidentiality of participants, and evaluation of the reasonability of the risks in relation to anticipated benefits. The TR-EGES lists the criteria to be checked related to the relevant physical, mental, social, legal and economic risks, and benefits to the participants in a comprehensive framework. Particular criteria for the protection of some vulnerable participant groups are defined in separate sections. Among these, the criteria for the evaluation of research on children, pregnant or breastfeeding women, patients in the intensive care units, and incompetent patients are taken from the TRDBP.[20] The criteria for research in low-resource settings, research on individuals in hierarchical relationships, research on institutionalized persons, and non-therapeutic clinical research on incompetent participants were missing in Turkish legislation; hence, the CIOMS guidelines are used to deliberate on these criteria.[14]

The **ICF** is evaluated in two main sections: the content of the ICF and the informed consent procedure.

The criteria to evaluate the content of the ICF involve the name of the research and the names of

the researchers; identification of the institutions and sponsors of the research; the sources of funding; the aims, objectives, and methodology of the research; the experimental aspects of the research; the random assignment procedure; the risks, benefits, and compensation mechanisms if any harm occurs; the post-trial provisions; the inclusion and exclusion criteria; the expected number of participants; and the right to withdraw at any time. The second part of the informed consent procedure focuses on how the whole methodology of taking informed consent is planned in a very comprehensive way. This section has a wide range of criteria, including the qualifications of the person to take the informed consent; the timing, settings, and first approach for recruitment; the time allocated for the whole process; no coercive or undue influence being placed on the participant; and no document to waive the legal and universal human rights of the participant.

COI issues do not occur in the Turkish legislation; however, they have great potential to adversely affect the protection of participants, the recruitment procedure, the equitability and unbiased nature of the participant selection, and the research integrity. Therefore, the criteria to evaluate the existence of any COI of the principal investigator, the researchers, or the sponsor are embedded in the TR-EGES. Moreover, the IRB members are invited to declare their COI at the beginning of the TR-EGES, and withdraw from the duty of evaluating the research protocol.

The evaluation of the **inducements, financial benefits, and financial costs; reimbursement, and compensation** addresses the elimination of any coercive elements such as proposing to pay more than financial losses emerging from participating the research, or providing tempting incentives should be considered carefully. In addition, the schedules of payment or providing supplies are among the criteria for evaluating the existence of coercive elements.

The Article 28 of the TRDBP explains the responsibilities and duties of the ethics committees. The subtitle c5 of this article requires the ethics committees to review the IB of the research togerher with other relevant documents such as risk, benefit analysis, the scientific justification of the background data and hypothesis of the reserach, the obligation to have done trials on animals before submitting for clinical trial on human subjects, the research protocol, the informed consent document, the compansation mechanisim for any harm due to research, the inclusion criteria for the human subjects and the qualifications of the PI and research team.[20]

DISCUSSION

Research on pregnant women, women in the puerperal period, and breastfeeding women: The CIOMS guidelines and the ICH guidelines involve evaluation criteria for fetuses. However, the TRDBP does not mention fetuses as direct research participants.[15,16,20] Therefore, this section of the TR-EGES does not involve any evaluation criteria for research on fetuses.

- *The conceptualization of risks:* The content regarding the risk of harms related to the clinical research on vulnerable groups such as children, pregnant women, the individuals whose decision making capacity is deprives and the patients in intensive care units, in the TRDBP is different than evaluating the risk of harms for other human subjects in the TRDBP.[20] The article 6, 7, 8, and 9 of the TRDBP requires no foreseeable risks; otherwise, a general medical opinion must be formed that there are no known risks for children, fetus or infant, and participant woman. However this requirement seems unrealistic, as there has to be a clinical equipoise regarding the harms and benefits of the medical intervention to be the subject of clinical research. In fact, the aim of conducting the clinical research is determining the probability and magnitude of foreseeable harms. In the DoH, and the CIOMS, the risk of harm is considered an integral feature of research; hence they do not require the research protocol to carry any foreseeable risks but to have a reasonable balance between the foreseeable risks and expected benefits.[14,15] The research team is expected to take all precautions to minimize the negative effect of all foreseeable

harms and develop plans to compensate if any harm occurs. A revision in the related articles of the TRDBP regarding conceptualization of risks on disadvantaged or vulnerable human subjects would be appropriate in this regard.

The CIOMS guidelines require the research protocol to contain information emerging from previous research that identifies possible risks for the pregnant woman and the fetus.[14] The TRDBP is also quite abstract in this regard. No details are sought about the risk of harm to participant women and fetuses. The TR-EGES is written down in ways compatible with the perspective of the international guidelines to take every contingency into account.

■ *Research on the incompetent:* The TRDBP has particular provisions on incompetent participants, participants in intensive care units, and unconscious participants. There are no provisions designated for participants with other vulnerabilities and disadvantages.[20] On the other hand, international guidelines have a far-reaching perspective. The CIOMS guidelines have particular provisions on research in low-resource settings, individuals in hierarchical relationships, and institutionalized persons, who definitely require particular attention due to their special situations.[14]

The strategy to comply with the international guidelines when the Turkish legislation falls short is also followed in this section. The requirements of the TRDBP on incompetent participants are covered in a particular section. Three other sections are added to address the legal and ethical evaluation criteria for research in low-resource settings, individuals in hierarchical relationships, and institutionalized persons.

■ The CIOMS guidelines permit conducting non-therapeutic clinical research on incompetent participants if:[14]

■ The objectives of the research cannot be met by means of research among participants who can personally give informed consent.

■ The foreseeable risks to the participants are low.

■ The negative impact on the participant's well-being is minimized and is low.

■ The research is not prohibited by law.

■ The research is conducted in patients having the disease or condition for which the investigational product is intended.

■ Participants are particularly closely monitored and will be withdrawn if they appear to be unduly distressed.

However, the TRDBP does not allow non-therapeutic clinical research on incompetent persons, as the existence of general medical opinion that the research will provide a direct benefit to the participants is required to conduct such research, which means that such research is not legal in Turkey.[20] Hence, the TR-EGES does not involve any assessment criteria on non-therapeutic clinical research on incompetent persons.

■ *Assessment criteria for informed consent:* The TRDBP has very limited provisions regarding the ICF. The requirements for the content of the ICF occur in Article 9: The research should be directly related the health of the participants, or the research questions should only observable in these particular patients. The existing treatment options for the disease of the participants should be proved to be futile and the research should not carry foreseeable risks for the participant. There should be an existing general medical opinion that the research will provide a direct benefit to the participants.[20]

■ It is a legal requirement to provide health insurance to all participants of clinical research, except phase 4 research and observational drug research. However, the TRDBP does not oblige the researchers to involve this information in the ICF.[20] Moreover, some fundamental issues for an ethically sound ICF are left out by the TRDBP:

■ The name of the research, the affiliations of the researchers, institutions involved in the research, name of the sponsors, sources of funding, information about previous stages of the research and their significant results, experimental aspects of the research, the probability of random assign-

ment, the procedures in which the participants will be involved, the inclusion and exclusion criteria for the participants, the duration of the research, the time participants should devote to research, the possibility of unforeseeable risks' occurrence, the risk of harm to the fetus if the participant is pregnant or becomes pregnant during the research, the alternative procedures of standard of care, the right of the researchers to end the research at any time, the medical provisions to be provided after the research is completed, the compensation mechanisms for any harm occurring during and because of research, and the particular provisions if the methodology involves deception are not addressed as required information to be conveyed to the participants in the ICF.

■ In addition, the TRDBP lacks any provisions about the process of informed consent. The appropriateness of the time allocated and setting for taking informed consent, the requirement to take all precautions to avoid any coercion and undue influence on the participant, the communication skills of the person who is taking the informed consent, and the timing of approaching the participants for recruitment are not touched on at all.[22] The guide for good clinical practice that was published in 2015 by TRDBP addresses some of the missing issues related to informed consent procedure.[20]

■ The international guidelines are far more comprehensive than the TRDBP in this respect. The TR-EGES is developed to cover all issues addressed in the DoH, the CIOMS, and the ICH; hence, it may be considered too exhaustive by Turkish IRB members. However, the dearth of the national regulations should not be an excuse to disregard human subjects' rights, breach their privacy, and endanger their well-being. Conceiving the requirements of the international guidelines and reviewing all research on human subjects in line with their criteria is essential to avoid any ethical violations. This perspective is compatible with Article 10 of the DoH that requires physicians to "consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration".[13]

Moreover, the Turkish Penalty Code is, by far, more restrictive than the TRDBP related to conducting research on human subjects.[24] Article 90 of Turkish Penalty Code states that "A person who conducts a scientific experiment on human beings shall be punished by imprisonment for one year to three years unless the following conditions are met:

Article 90

1. Any person who uses a person for experimental purposes is sentenced to imprisonment from one to three years.

2. In order for an experiment carried out upon human[s] under consent not to be subject to a criminal punishment:

a) Necessary approval should be received from the competent board or authority.

b) The experiment should be initially carried out upon a sufficient number of animals without involving human subjects.

c) There is a requirement to involve human subjects in verifying scientific data obtained as a result of experiments initially conducted with animals in the absence of human subjects.

d) No harmful and persistent effects of the experiment on human subjects should be foreseen.

e) The method adopted in the experiments should not give pain in such a way as to dishonor the person involved in the experiment.

f) The objective that the experiment tries to achieve should be much more important than the risk or burden undertaken by the person.

g) The consent of the person should be obtained in writing by furnishing information about the nature and consequences of the experiment rather than by allowing the individual to expect any benefit from this experiment.

3. Children may not be used for experimental purposes.

4. Any person who carries out an experiment upon a sick person for treatment purposes without obtaining his or her consent will be punished with imprisonment for up to one year. However, where there is no hope of treating a person by ordinary medical means, an experiment based on new scientific methods can be carried out upon a person by obtaining his or her consent. In such a case, no punishment is imposed. This consent should be obtained in writing by furnishing information about the nature and consequences of the experiment, and the treatment should be undertaken by a specialist physician in a hospital.

5. The provisions of the Law relating to felonious homicide and felonious injury are applied in case of injury to or death of the victim following the commission of the offense defined in the first subsection.

6. The security precautions specific to legal entities are applied in the case of commission of offenses listed in this section within the frame of the activities of a legal entity."

The restrictive language of the Turkish Penalty Code imputes criminal liability to Turkish researchers if they fail to comply with any of the above provisions. The general statements in Article 90, together with the abstractness of the TRDBP, can create grounds for judgments against the researchers if any complaints are made. Therefore, remaining in compliance with the international guidelines to fulfill all ethical requirements provides legal protection for the researchers to defend themselves in case of an inquiry.

■ *Conflict of Interest (COI):* The Turkish regulations on clinical research on human subjects do not address COI at all. Hence, it is plausible to think that the IRB members do not consider the COI of the principal investigator, the researchers, or the sponsor when they are reviewing the research protocol. However, there is a possible negative influence of COI on the protection of the participants, the recruitment procedure, the equitable and unbiased participant selection, and research integrity. Therefore, the section on assessing the COI is integrated as a separate section in the TR-EGES.

■ *Inducements, financial benefits, and financial costs; reimbursement and compensation:* There are clear statements in the TRDBP that no persuasive incentive or financial proposal shall be made except for the expenses incurred by the participation in the investigation.[20] This provision is in compliance with the DoH and the CIOMS.[13,16] The schedule of providing the compensation is also very important. The participants would be reluctant to express their will to withdraw if the research team makes the payment when the research is finished. Therefore, assessment criteria to cover the undue influences resulting from inducements are embedded in the TR-EGES as a separate section.

■ *The need for revision in Turkish regulations on* clinical *research on human subjects:* When the TRDBP is checked against the DoH, the CIOMS, and the ICH guidelines, some fundamental drawbacks are detected.

The definition of human subjects: The TRDBP does not define human subjects, but only volunteers.[20] According to TRDBP, "a volunteer is a healthy person or a patient, who declares written consent by herself or by a legally authorized representative (LAR) to be involved in a clinical trial." The first paragraph of the preamble of the DoH states that "The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data".[13] However, the definition in the TRDBP has no implications on identifiable human material and data.

The context of risk: The TRDBP does not conceptualize risk as an integral component of clinical research, but as a feature that should be mitigated. However, as stated in Article 16 of DoH, "In medical practice and in medical research, most interventions involve risks and burdens".[13] The TRDBP requires that there should be no foreseeable risks, or a general medical opinion must be found that there are no known risks, for the clinical research to be conducted on particular participant groups.[20] However, having no foreseeable risks may be considered as a standard that is too high to achieve and

inconsistent with the nature of research to reveal the *unknown*. Therefore, revising this perspective in line with that of the DoH that states "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects" would be plausible.[13] Moreover, an approach that excludes all foreseeable risks also casts out the requirement to take measures to minimize the risks.

The content of ICF and the process of taking informed consent: The content of ICF and the process of taking informed consent: The gold standard of clinical research on human subjects is informed consent. The idea behind all IRB actions is to protect the rights, well-being, and integrity of the human participants. Inability to address the informed consent procedure carries the risk of degrading the procedure to one where merely taking the signature of the participant suffices to fulfill paperwork requirements; this would pose a perilous risk of violating the entire value system of research ethics.

The lack of expedited review: There is no expedited review procedure and no definition of minimal risk in the TRDBP.[20] This means all clinical research protocols go through full review. Taking into account the low resources of IRBs, and high workload on every IRB member, the absence of an expedited review process has the potential to create an unnecessary burden in the system.

The lack of provisions on important issues: The Turkish regulations on clinical research on human subjects should be amended to cover informed consent regarding the use of residual material in clinical research; the requirements of conducting non-therapeutic clinical research on disadvantaged participants; the ethical issues in multi-cultural, international clinical research, involving indigenous populations; institutionalized participants; individuals in hierarchical relationships with the research team; and COI.

Placebo and sham procedure use: The use of placebo instead of the standard of care in randomized controlled clinical research has been a topic of considerable debate for a long time. The final revision of the DoH Article 33 states the conditions in which placebo use is acceptable:[13]

"The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention, and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option."

In 2015 the Turkish GCP Guidelines were published.[25] The Turkish GCP Guidelines provide harmonization of the Turkish regulations on clinical research with international legsilations such as the ICH Harmonized Tripartite Guideline for GCP.[15] Despite the fact that most of the shortcomings in the TRDBP are covered by the Turkish GCP Guidelines, the revision of the TRDBP is still a requirement, since the TRDBP is the legally binding document for the researchers and the IRBs.

CONCLUSION

It would be too idealistic to argue that all inconsistencies in IRB decisions can be eliminated. However, they can be minimized by providing tools for IRB members to go through while reviewing the research protocol. The TR-EGES would be a very helpful document for all IRB members and improve the compliance of their decisions with the requirements of international guidelines. Moreover, a comprehensive revision is needed in the Turkish regulations to be in full harmony with the international guidelines and to cover the new aspects of clinical research on human subjects.

TABLE 1: "Ekmekci-Güner Ethical Evaluation of Clinical Research Protocols on Human Participants Sheet for Turkish IRBs (TR-EGES)".

Protocol no:

Principal investigator name:

Reviewer name:

Meeting date:

Reviewer's declaration of conflict of interest

No Conflict of interest ☐

Yes there is conflict of interest ☐

(please explain.....)

Notes to the reviewer:

Please make sure that the research protocol you are about to review is not a retrospective study.

Please make sure that the research protocol you are about to review is not a bioequivalence or bioavailability study.

☐ NA: For "not applicable" options please check this box. There are no "NA" box for the items that are essential for the ethicality of the protocol.

Revision Criteria

1. Scientific design and conduct of the clinical trial

☐ 1. The research design is sound and scientific

☐ 2. Relevant scientific data is provided regarding the need to conduct the research

☐ 3. Adequate preliminary data and appropriate scientific justification is provided

☐ 4. The aims and objectives are clearly defined

☐ 5. There are adequate physical, human, and technological resources to conduct the research.

☐ 6. The principle investigator is a physician (or a qualified dentist when appropriate) and is responsible for all research-related decisions and implementation thereof.

☐ 7. The research protocol does not involve any intervention that aims to or may lead to the change or destruction in the germ cells of the volunteers.

☐ 8. A statement that the study does not have a predictable harmful and lasting impact on human health.

☐ 9. The principle investigator is a physician (or a qualified dentist when appropriate) and is responsible for all research related decisions and implementations

☐ 10. The principle investigator has adequate experience and scientific knowledge to conduct this research

☐ 11. The researchers have adequate experience and knowledge to conduct this research

☐ 12. The principle investigator and research team have appropriate ethics and scientific education, training and qualifications. The researchers meet the qualifications specified by the applicable regulatory requirement(s), and provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation

☐ 13. The protocol involves a list of appropriately qualified persons to whom the principle investigator has clearly delegated significant research-related duties.

☐ 14. Sample size is justified

☐ 15. Research is designed to involve minimal number of human volunteers and minimize all possible risks for harms

☐ 16. The research is designed to reduce any risk of pain, discomfort, fear, illness and the progression of the illness to the lowest possible level. Both the level of risk and discomfort will be controlled throughout the study

☐ 17. The proposed time table is appropriate and reasonable

☐ 18. A statement is provided indicating that the research will be registered on a publicly accessible database before recruitment of the first volunteer.

☐ 19. A statement is included indicating that negative and inconclusive as well as positive results are planned to be published or otherwise made publicly available.

☐ 20. Plans to inform volunteers about the results of the research are described and appropriate.

☐ 21. Data analyses methods are specified

☐ 22. Methodology is scientifically appropriate to answer the research question

☐ 23. The differences between research and standard operations are well-defined

☐ 24. The data collection procedure is well-defined and appropriate

If the methodology involves deception;

☐ Using deception is scientifically justified

☐ Using deception is ethically justified

continuation..→

TABLE 1: *continuation.*

☐NA 25. If the methodology involves deception;
☐ Using deception is scientifically justified
☐ Using deception is ethically justified
☐ Using deception is legally (according to local laws and regulations) justified
☐ Volunteers are informed that deception may be used in this research
☐ Economic, legal (according to local laws and regulations), social, physical and mental risks induced by deception are considered
☐ The risks emerging from deception are minimized
☐ The scientific importance of the results outweigh the risks of deception
☐ 26. The research will be conducted in a manner that minimizes possible harm to the environment
2. Selection of study population and recruitment of research volunteers
☐ 1. The investigator has adequate means to recruit the proposed number of volunteers
☐ 2. The proposed volunteer profile and number is favorable for the research
☐ 3. Groups, communities and individuals invited to participate in research are selected for scientific reasons and not because they are easy to recruit, or because of their compromised social or economic position, or their ease of manipulation
☐NA 4 If the volunteers are from a vulnerable group;
☐ The need for having this vulnerable group is justified scientifically
☐ Direct benefits to the volunteers or particular vulnerable group are properly described
☐ Necessary precautions to protect the vulnerable volunteers against legal (according to local laws and regulations), ethical, social, economic, physical and mental harm
☐ 5 Inclusion criteria for volunteers are appropriately defined
☐ 6 Exclusion criteria for volunteers are appropriately defined
☐ 7. Inclusion criteria are justified scientifically
☐ 8. Exclusion criteria are justified scientifically
☐ 9. The inclusion criteria are consistent with the research design and methodology
☐ 10. The exclusion criteria are consistent with the research design and methodology
☐ ☐NA 11. If groups in need of special protection are excluded, the reasons for exclusion are scientifically and ethically justified
☐ 12. Gender equality is considered
☐ 13. No discrimination exists due to gender, age, nationality or any other variable
☐ 14. Groups that are under-represented in medical research are provided appropriate access to participate
☐ 15. The location and settings for recruitment are well-defined
☐ 16. The location and settings for recruitment are consistent with research design and methodology
☐ 17. There are no coercive incentives to promote participation in the research against volunteers' better judgment
☐ 18. The timing of approach for recruitment is adequate and does not expose any risks for rational decision making
☐ 19. Precautions are taken to avoid any coercion indecision making
20. The research has social value;
☐ It is directly relevant for understanding or intervening in a significant health problem
☐ It has an expected contribution to research likely to promote individual or public health
3. Care and protection of research subjects
☐ 1. Relevant physical, mental, social, legal (according to local laws and regulations) and economic risks are considered
☐ 2. Required resources are available for ameliorating any harm to volunteers
☐ 3. Reasonable and probable physical, mental, social, economic and legal (according to local laws and regulations) risks for volunteers are defined
☐ 4. Reasonable and probable physical, mental, social, economic and legal (according to local laws and regulations) benefits for volunteers are defined
☐ ☐NA 5. Risk and benefit allocation among different volunteer groups are considered adequately
☐ ☐NA 6. The protocol describes appropriate arrangements for post-research provisions
☐ NA 7. For research protocols using placebo or less than the standard of care, make sure the following items are met:
☐ No proven intervention exists
☐ For compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of the intervention in the research

continuation...→

TABLE 1: *continuation.*

☐ Patients who receive any intervention less effective than the best proven one, a placebo, or no intervention are not subject to additional risks of serious or irreversible harm as a result of not receiving the best intervention
☐ 8. The needs of volunteers during data collection are considered and appropriate planning to meet these is conducted
☐ ☐NA 9. The people in charge of monitoring the data are identified
☐ ☐NA 10. The procedure for and frequency of data monitoring is specified
☐ ☐NA 11. The data to be monitored is identified
☐ 12. There is a mechanism to stop the research as soon as an increase in frequency or the severity of harm is detected
☐ 13There is a plan to stop or revise the research if the benefits outweigh the harm
☐ 14The person who is in charge of informing principle investigator and IRB about unexpected harms or benefits outweighing harms is identified
☐ NA 15. If personal data will be collected;
☐ The reasons for collecting personal data is justified scientifically.
☐ The people who have access to personal data are identified and justified.
☐ The risks emerging from the collection of personal data are identified.
☐Appropriate precautions to avoid the realization of harm are taken.
☐ All risks defined in the research protocol are clearly stated in the informed consent form.
☐ 16. Appropriate provisions to secure the confidentiality of data are identified
☐ NA17. If the research protocol involves breaching the confidentiality of data
☐ The reason for the breach is justified ethically, legally (according to local laws and regulations) and scientifically
☐ Provisions to minimize the risk of harm due to breach are described
☐ 18. Data collection settings are appropriate to protect the privacy of volunteers
☐ 19. Storage and archiving settings are appropriate to ensure the confidentiality of data
☐ NA 20. If this is a multi-site research;
☐ The mechanisms to secure the confidentiality of data in various research steps (collection, storage, transfer, analyze) are planned
☐ The privacy of volunteers are revised due to cultural and religious variations
Risks for vulnerable groups
Please make sure the following criteria are met:
☐ NA21☐ The research cannot be carried out in a non-vulnerable group
☐ The research is responsive to the health needs or priorities of this vulnerable group
☐ This vulnerable group stands to benefit from the knowledge, practices, or interventions that result from the research
Research on children
Please make sure that all following terms are met:
☐NA 22 ☐ The research question is directly related to children or
☐ The research related to a clinical situation that can be investigated only on children or
☐ The results obtained from research on adults will be examined if they are valid for the children as well and
☐ The research carries no foreseeable risk for the health of the participant children and
☐ There is enough scientific proof to suggest direct benefit to participant children
☐ The IRB is well informed about the ethical, physiological, and social problems related to the clinical research by a pediatrician. Please note that this information should be provided by a dentist if the research is on dentistry.
☐ No persuasive incentive or financial proposal are made except in cases where the child is required to pay the costs incurred by participating in the trial.
☐ There is reasonable prospect of direct benefit to the individual participant
☐ The magnitude and probability of risk is allowable compared to the magnitude and probability of the benefit
☐ The expected results are scientifically very important and vital to contribute to the well-being, prospect of life of patients with that disorder
☐ The expected results are scientifically very important and vital to understand the etiology, course or prognostics of the disorder
☐ The minor is assessed due to her capability of assenting by taking into account her age, maturity, psychological state she is involved
☐ The risks are least possible for achieving the objectives of the research
☐ The provisions in informed consent part about pregnant participants and participants in childbearing age are fulfilled
Research on pregnant, women in puerperal period and breast feeding women
Please make sure that all following terms are met:
☐NA23☐ The research topic is a clinical situation that directly concerns pregnant women, puerperal or lactating women or *continuation...→*

TABLE 1: *continuation.*

☐ The research does not carry any foreseeable risk for the fetus or infant and volunteer woman and
☐ There is a general medical opinion that the research will provide a direct benefit to the volunteers
☐ A general medical opinion is found that the product and the application to be investigated have no known risks to pregnancies, pregnant, breast feeding women and the fetus or infant.
☐ The ethics committee is well informed by a physician who has expertise on the subject of research on clinical, ethical, psychological and social problems related to research, especially regarding fetus or infant health, and the protocol is evaluated in this respect.
☐ For clinical trials to be carried out on pregnant women, puerperal or breastfeeding women, no persuasive incentive or financial proposal shall be made except for the expenses incurred by the participation in the investigation.
☐ Individuals responsible for determining viability and/or providing service to reanimation of the fetus are not involved in the research team
☐ No incentives to terminate pregnancy is provided
☐ The knowledge expected to be gained out of the research is vital
☐ There is no other means to obtain the knowledge other than conducting the research on pregnant woman or fetus
☐ The research involves minimal risk
If the research involves more than minimal risk;
☐ Preclinical studies including research on pregnant animals, and clinical studies including non-pregnant women have been conducted and the involvement of pregnant or fetus in essential for the research
☐ Previous research identifies possible risks for the pregnant woman or fetus
☐ The magnitude and probability of risk is allowable compared to the magnitude and probability of the benefit
☐ The risks are least possible for achieving the objectives of the research
Research in low-resource settings
Please make sure that all following terms are met:
☐ NA24 ☐ The research is responsive to the health needs or priorities of the communities or populations where the research will be conducted.
☐ Every effort is made in cooperation with government and other relevant stakeholders to make available as soon as possible any intervention or product developed and knowledge generated to the population or community in which the research is carried out and to assist in building local research capacity.
☐ The communities are consulted and engaged in the planning of any intervention or product developed, including the responsibilities of all relevant stakeholders.
☐ If volunteers' health needs during and after the research cannot be met by the local health infrastructure or volunteers' pre-existing health insurance; prior arrangements have been made to ensure adequate care for volunteers
Research on individuals in hierarchical relationships
Define the group;
☐ NA25 ☐ students
☐ subordinate personnel
☐ workers in settings where research studies are conducted
☐ members of the armed forces or police
☐ other: ……
The research protocol includes description of provisions
☐ to protect such individuals from being conscripted into the research
☐ to avoid unduly influence of their voluntariness
☐ to avoid their agreement to participate in the study based on fear of disapproval or retaliation if they refuse
Research on institutionalized persons
Define the group;
☐ NA26 ☐ residents of nursing homes
☐ residents of mental institutions
☐ prisoners
☐ other……..
The research protocol includes description of provisions
☐ to protect such individuals from being conscripted into the research

continuation...→

TABLE 1: *continuation.*

☐ to avoid unduly influencing their voluntariness

☐ to avoid their agreement to participate in the study based on fear of disapproval or retaliation if they refuse

☐ to avoid breach of respect for autonomy if their competency is diminished

☐ The appointment of an advocate to the research ethics committee is considered.

Research on incompetent participants

Please make sure that all following terms are met:

☐ NA27 ☐ The research topic is directly related to incompetent persons or

☐ The research questions are only observable in incompetent persons and

☐ The existing treatment options for the disease of the incompetent are proved to be futile and

☐ The research does not carry foreseeable risks for the incompetent participant and

☐ The general medical opinion exists that the research will provide a direct benefit to the incompetent person.

If the incompetent has the capacity to declare her claims,

☐ Her consent is sought together with the written informed consent of her legal guardian.

☐ A statement that if the incompetent has the capacity to develop opinion by evaluating the information provided and refuses to participate in the research or declares her will to withdraw she will immediately be excluded from the research.

☐ A physician who has expertise related to the research topic and a psychiatrist informed the ethics committee about the clinical, ethical, psychological and social problems related to the research and the protocol should be evaluated in this respect.

☐ No persuasive incentive or financial proposals are made except for the expenses incurred by the participation in the investigation.

Research on participants in intensive care units and unconscious

Please make sure that all following terms are met:

☐ NA28☐ The research is directly related the health of the participants or

☐ The research questions are only observable in these particular patients and

☐ The existing treatment options for the disease of the participants are proved to be futile and

☐ The research does not carry foreseeable risks for the participant and

☐ The general medical opinion exists that the research will provide a direct benefit to the participants.

If the participant in intensive care unit has the capacity to declare her claims, or unconscious become conscious and has the capacity to declare her claims,

☐ Her consent is sought together with the written informed consent of her legal guardian.

☐ A statement that if the participant has the capacity to develop opinion by evaluating the information provided and refuses to participate in the research or declares her will to withdraw she will immediately be excluded from the research

☐ No persuasive incentive or financial proposals are made except for the expenses incurred by the participation in the investigation.

If the legal guardian or relatives of the patient in intensive care unit or unconscious patient cannot be contacted, and if this patient will be involved in the research under the responsibility of principle investigator or a physician from the research team please make sure all requirements below are met:

☐ The research is directly related the health of the participants or

☐ The research questions are only observable in these particular patients or

☐ The existing treatment options for the disease of the participants are proved to be futile and

☐ The research does not carry foreseeable risks for the participant and

☐ The general medical opinion exists that the research will provide a direct benefit to the participants.

☐ There is a general medical opinion about the immediate benefit to patients with cardiac arrest, head trauma, central nervous system infections, and intracerebral hemorrhages, where the physician should immediately intervene and where current treatment options are proven to be futile.

Non-therapeutic clinical research on incompetent participants

☐ NA29 The research protocol includes the following:

☐ The objectives of the research cannot be met by means of a research in participants who can give informed consent personally

☐ The foreseeable risks to the participants are low

☐ The negative impact on the participant's well-being is minimized and low.

☐ The research is not prohibited by law.

☐ The research is conducted in patients having the disease or condition for which the investigational product is intended.

☐ Participants are particularly closely monitored and will be withdrawn if they appear to be unduly distressed

continuation...→

TABLE 1: *continuation.*

4. Informed consent

a. Please make sure all the following items are included in informed consent document

☐ 1. The name of the research

☐ 2.The names and affiliations of the researchers

☐ 3. The names of institutions involved in the research

☐ ☐NA 5 The name of the sponsors and supporting institutions

☐ 6. The sources of funding

☐ 7. A statement that this is a research not standard care/procedure

☐ 8. The aim and objective of the research

☐ 9. Information about previous stages of research

☐ 10. Information about any significant results of the previous stages of research

☐ 11. The methodology of the research

☐ 12. The research procedures including all invasive procedures

☐ 13. Aspects of the research that are experimental

☐ 14. The aspects of the research those are not favorable for the heath and/or personal qualifications.

☐ ☐ NA 15 If it is not a phase 4 or an observational research; a statement that the volunteer will be insured for any harms emerging from research.

☐ ☐ NA 16. Information about treatment protocols that will be used during the research

☐ ☐ NA 17. Research treatments and the probability of random assignment to each treatment

☐ 18. Procedures in which volunteer will be involved

☐ 19. A statement that participation is voluntary

☐ 20. The right to withdraw consent to participate at any time without reprisal

☐ 21. Criteria for inclusion and exclusion

☐ 22. Expected number of volunteers

☐ ☐ NA 23. An explanation of the incentives to be provided to the volunteer and schedule of providing them

☐ 24. Responsibilities of the volunteer

☐ 25. Duration of research

☐ 26. The time volunteers should devote to the research and stay in the research center or hospital

☐ 27. The expected benefits for the individual volunteer

☐ 28. The possible risks of harm to the individual patient

☐ ☐ NA 29. A statement that currently unforeseeable risks may occur

☐ if the volunteer is pregnant:

☐ a statement that clearly lists all possible risks to the fetus

☐ a statement that currently unforeseeable risks may occur to the fetus

☐ if the volunteer is of childbearing age:

☐ a statement that lists all possible risks if she becomes pregnant during the research

☐ 30. The expected contribution of the research to generalizable scientific knowledge

☐ ☐ NA 31. Alternative procedures and standard of care

☐ 32. The contact information of whom to be contacted if the volunteers;

☐ need to ask a question about the research

☐ have an unexpected medical condition

☐ have an emergency situation

☐ 33. A statement that guaranties the approval of administrative authorities (Ministry of Health, Drug and Medical Devices Agency etc…)

☐ 34. The principal investigator's right to end the research without providing any reason

☐ ☐ NA 35. Medical provisions to be provided after the research has ended

☐ 36. Compensation mechanisms for any harm incurred during the research

☐ ☐ NA 37. If biological materials left over after clinical diagnosis or treatment (so-called "residual tissue") is used in the research and broad informed consent is substituted by an informed opt-out procedure, sufficient information are provided about the existence of their right to opt-out needs the patients are told that they can withdraw their data any time

continuation...→

TABLE 1: *continuation.*

☐ ☐ NA 38. The volunteer is well informed if the research protocol includes deception

☐ 39. A statement that any knowledge discovered during research, which can affect the willingness of the volunteer to continue the research will be shared immediately

☐ 40. A statement that records identifying the volunteer will be kept confidential and to the extent permitted by the applicable laws and/or regulations will not be made publicly available

☐ 41. A statement is included indicating that if the results of the research are published, the volunteer's identity will remain confidential

☐ 42. No relevant information is withhold from the volunteers

☐ 43. The readability of document is adequate

☐ 44. The informed consent document is available in the mother tongue of the volunteers

☐ 45. No technical and medical terms volunteers may find difficult to understand are included

☐ 46. An understandable language appropriate for the education level of volunteers is used

☐ 47. The informed consent addresses the second person

b. Informed consent procedure

☐ 1. The protocol gives the volunteers the option of being informed about the general outcome and results of the study

☐ 2. Written informed consent forms are available and formally documented

☐ NA 3. If written informed consent will not be taken;

☐ Not obtaining written informed consent is scientifically justified.

☐ Not obtaining written informed consent is ethically justified.

☐ Not obtaining written informed consent is legally justified according to local laws and regulations.

The informed consent type is identified:

☐ verbal

☐ presumed

☐ deferred

☐ other (e.g., information sheet)

☐ Non-written consent is formally documented and witnessed.

☐ 4. Volunteers are adequately informed about the content and nature of the personal data collected

☐ 5.The person who will be taking informed consent is identified and qualified

6. ☐ The person in charge of taking informed consent can communicate in an understandable language to the volunteer/ parents

If not,

☐ a translator is provided

☐ 7. Potential volunteers are not in a dependent relationship with the person who takes the informed consent

☐ 8.The persons from whom the informed consent will be taken is identified

☐ Patient

☐ Legal guardian

☐ Parent

☐ 9. The person to take informed consent is the principle investigator or a physician or a dentist from the research team who has enough knowledge about the research protocol.

☐ 10. The timing of obtaining informed consent is appropriate

☐ 11. Enough time is allocated to answer the questions of the volunteers/legal guardians to facilitate decision making

☐ 12. The informed consent procedure provides enough time to the volunteer to think and consult before deciding

☐ 13. The settings for obtaining informed consent minimizes possibility of undue influence or coercion

☐ 14. If the potential participant volunteer is an adult who is incapable of giving informed consent;

☐ The informed consent is obtained from the legally authorized representative of the participant.

☐ A statement is included indicating that the legally authorized representative considers the participant's previously formed preferences and values.

☐ A statement is included indicating that if participants become capable of giving informed consent during the research, their consent to continued participation will be obtained.

☐ The consent of the participant has been obtained to the extent of that person's capacity.

continuation...→

TABLE 1: *continuation.*

☐ NA 15. If a volunteer is unable to read or if a legally (according to local laws and regulations) acceptable representative is unable to read,
☐ An impartial witness will be present during the entire informed consent discussion
☐ The witness will sign and personally date the informed consent form together
☐ The volunteers will sign and personally date the informed consent form if capable
☐ 16. In case of volunteers' withdrawal, the volunteer/parents are guaranteed not to face any disadvantages
☐ 17. A copy of the form will be provided to the volunteer
☐ 18. No document to waive the legal and universal human rights of the volunteer is involved in the informed consent document
☐ NA 19. If the research involves pediatric participants
☐ Consent is taken from both of the parents
☐ the assent of minor is taken (if the pediatric participant has the capability to assent)
☐ For a partially competent child, the right to withdrawal from the research is defined and secured
5. Conflict of interest (COI) issues
☐ ☐ NA 1. The sponsor/ principal investigator/ researchers did not disclose COI
☐ NA 2. If the sponsor/ principal investigator/ researchers disclosed COI;
☐ The COI does not adversely affect the protection of volunteers
☐ The COI does not adversely affect recruitment procedure
☐ The COI does not adversely affect the equitability and unbiased nature of volunteer selection
☐ The COI does not adversely affect the research integrity
6. Inducements, financial benefits, and financial costs; reimbursement and compensation
☐ 1. No coercive payments or supplies are promised to the volunteers for opting in the research
☐ 2. The schedule of payment or providing supplies do not have an undue influence on the volunteer for not withdrawing from the research
☐ 3. All financial losses of the volunteers are compensated
7. Investigators Brochure (IB)
1 IB includes a title page with the
☐ sponsor's name,
☐ the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date.
☐ An edition number,
☐ A reference to the number and date of the edition it supersedes
☐ 2. IB includes a confidentiality statement
3 The content of the IB includes:
☐ Table of contents
☐ A brief summary
☐ A brief introductory statement
☐ Physical, chemical, and pharmaceutical properties and formulation
☐ Nonclinical studies ☐ Nonclinical pharmacology
☐ Pharmacokinetics and product metabolism in animals
☐ Toxicology
☐ Effects in humans
☐ Pharmacokinetics and product metabolism in humans
☐ Safety and efficacy
☐ Marketing experience
☐ Summary of data and guidance for the investigator
☐ References related to publications and reports

Acknowledgments

The authors declare no conflict of interest. We would like to express our gratitude to Susan Kornelsky from Boston Children's Hospital for her gracious contribution.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept**: Perihan Elif Ekmekci, Müberra Devrim Güner; **Design:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Control/Supervision:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Data Collection and/or Processing:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Analysis and/or Interpretation:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Literature Review:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Writing The Article:** Perihan Elif Ekmekci, Müberra Devrim Güner; **Critical Review:** Perihan Elif Ekmekci, Müberra Devrim Güner; **References and Fundings:** Perihan Elif Ekmekci, Müberra Devrim Güner.*

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