GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PAEDIATRIC POPULATION 24 NOVEMBER 2015 1. INTRODUCTION

This guideline contains recommendations on the various ethical dimensions of clinical trials conducted in children from birth up to the age of adulthood, at which legal responsibility arises. These recommendations have been prepared with a view to contributing to the protection of all children participating in clinical trials. Protecting the paediatric population (this term is used to describe all paediatric age groups and refers to the part of the population from birth up to 18 (eighteen) years of age) against the risks of trials is of great importance. However, protection must not result in this group being denied the benefits that trials may bring. In general, children are not capable of giving assent, but their consent must be obtained by way of providing information appropriate to their age. Ethics committees must obtain the opinion of a specialist in child health and diseases in order to balance the benefits and risks of trials conducted in children, and the decision must invariably include the positive opinion of the specialist in child health and diseases and the signature pertaining thereto. Research on children must only be carried out by trained investigators with paediatric experience. Pain, distress, fear and instances of separation from the parent must be prevented and, where unavoidable, reduced to a minimum. Among all paediatric age groups, newborns require much more careful consideration.

2. PURPOSE

This guideline is intended to provide recommendations on the various ethical approaches to be followed in the conduct of clinical trials falling within the scope of the relevant legislation. The conduct of clinical trials is obligatory. Trials must aim to achieve progress in the amelioration and treatment of impaired states of health, including those of children, and at the prevention and diagnosis of diseases. The same ethical principles apply to all age groups, from children to the elderly. It is acknowledged that, under the special provisions and conditions set out in the relevant legislation for the protection of children, research on children is necessary. Clinical trials involving children must be conducted in order to develop treatment options for children. Children are a group that differs from adults in developmental, psychological and physiological terms. This makes research dependent on age and development important in terms of their interests. All medicinal products, including vaccines intended for children, must be scientifically tested before being brought into widespread use. This can only be achieved through the comprehensive investigation of medicinal products that may offer significant clinical value for children. Clinical trials serving this purpose must be conducted under conditions ensuring volunteers the best possible protection. For this reason, criteria for the protection of children in clinical trials need to be established. Special protection conditions must be defined for trials conducted with children at all stages of development and of every age.

The reasons why medicinal products must be investigated in children are addressed in detail in various publications. Differences in pharmacokinetics, pharmacodynamics and adverse reactions are more common in children than in adults. In addition to growth and maturation processes, there are also certain diseases specific to children alone. Medical interventions may give rise to unique outcomes in children, some of which can only be recognised after a long time. If a clinical trial is one that can be conducted in adults and need not be conducted in children, children should not act as volunteers in clinical trials, owing to the special protection they deserve. In cases where it has been demonstrated that research on children is necessary, generally the least vulnerable among them, that is, those who are older, should be included in the trial. Where there is an obligation to include children in a clinical trial, the selection of the subsets of the paediatric population to be included in the trial must be based on the potential target population of the medicinal product to be tested, on the possibility of extrapolation, and on the scientific validity of this approach. The recommendations contained in this guideline aim to bring ethical principles together in accordance with the relevant legislation.

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

3. SCOPE

This guideline does not remove the condition of compliance with the obligations set out in the Turkish Penal Code, the Turkish Civil Code, the Basic Law on Health Services and other relevant legislation. The recommendations set out in this guideline make no distinction between commercial and non-commercial trials and cover all trials conducted in the paediatric population. Through the recommendations contained in the guideline, it is intended to contribute to the improvement and protection of the dignity, well-being and rights of vulnerable children who are unable to give informed consent. Clinical trials conducted with children must both be carried out under conditions providing the best possible protection for this vulnerable population, and children's right to benefit from trials must be recognised.

4. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS

The ethical principles addressed in this guideline are the principles set out in documents such as the current Declaration of Helsinki, the United Nations Convention on the Rights of the Child, the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), the International Declaration on Human Genetic Data (UNESCO, 2003), the Universal Declaration of Human Rights of 1948, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, and the Good Clinical Practice Guideline in force. In trials, compliance with the three fundamental ethical principles, namely respect for persons, beneficence and justice, is mandatory. These apply in their entirety to clinical trials conducted with children.

5. INFORMED CONSENT PROCESS

5.1. When the legal representative gives informed consent, the following points must be taken into consideration.

5.1.1. Since a child cannot give legally binding permission, informed consent must be requested from the parent or legal representative on behalf of the child. In accordance with the relevant legislation, before a child is enrolled in a clinical trial, if the child possesses the capacity to express his/her consent, then in addition to his/her own consent, the written consent of the mother and father, or of the guardian if the child is under guardianship, must be obtained after they have been informed in accordance with the relevant legislation. The parent or legal representative must be informed of the purpose of the trial, its potential risks and benefits, the names of the investigators responsible for conducting the trial, their basic professional information (such as education and work experience), and the telephone number at which they can be reached for 24 (twenty-four) hours in order to obtain detailed information about the trial. The parent or legal representative must be given sufficient time and information to evaluate the benefits and risks associated with the child's enrolment in the clinical trial. If they have no experience of their child's condition, it is of great importance that the feelings of fear and uncertainty the parent may experience are taken into account when this information is provided. However, the parent or legal representative may need more detailed and clear information, and therefore more time, in order to consider the implications of the permission to be given, because, unlike trials in adults where the person assumes responsibility for himself/herself, here they assume full responsibility for the child. 5.1.2. When seeking informed consent, the responsible investigator or the investigator who is a physician or a dentist must not exert pressure on the parent or legal representative: 5.1.2.1. There must be no financial incentive for the child's inclusion in the trial. No financial incentive other than compensation and expenses should be offered. 5.1.2.2. The parent or legal representative must be informed of the option to withdraw informed consent even where it has been given in writing. 5.1.2.3. The parent or legal representative must be given assurance that refusal to participate in the trial or withdrawal from the trial will not adversely affect the child's treatment. 5.1.2.4. When permission is obtained from the parent or legal representative, the

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

child's consent must also be sought. 5.1.3. Especially in chronic diseases, rare diseases and acute severe illnesses, or in cases where the parent's level of education is low, risks arise in the relations between the parent and the physicians, namely the risk of the parent not understanding his/her obligations and the risk of emotional submission. Moreover, this situation may not be perceived by either party. The responsible investigator or the investigator who is a physician or a dentist must not take part in the decision-making process, but must ensure that the information provided is understood by the other party and that sufficient time has been allowed to reach a decision. The provision of information is a continuous process. 5.1.4. From those aged 16-18, in addition to the consent to be given by the parent or legal representative, informed consent must be obtained in writing, as is the case for any person possessing the capacity to give permission. 5.2. The following points must be observed with regard to assent at the beginning of the trial and the continuation of permission and assent during the trial:

5.2.1. Information should be provided in accordance with the relevant legislation, and sufficient time should be allowed for obtaining both the consent of the legal representative and the assent of the child. 5.2.2. It is important to be aware that the consent process is a dynamic and continuous process. For this reason, consent should be obtained before enrolling the child in the trial and should be maintained so as to ensure continuity throughout the trial. To this end, for example, the matter may be briefly discussed at each repeat visit. It is recommended that this process be documented in the medical records or in similar systems. These discussions form part of an ongoing dialogue between the child, the parents and the principal investigator or the investigator who is a physician or dentist, and should in all respects focus on the trial and, in particular, on any new information obtained in connection with the trial that may affect the willingness of the parents and the child to remain in the trial. 5.2.3. Particularly in long-term trials, the investigator should monitor the child's maturational development and capacity to give assent. 5.2.4. Although rare, where the legal representative changes during the trial, informed consent should be requested anew as soon as possible. 5.3. In the event of withdrawal of consent, attention should be paid to the following points: 5.3.1. In all cases, it should be explained that the parents or the legal representative have the right to refuse participation in the clinical trial and to withdraw the informed consent they have given without stating any reason. The parents or the legal representative should be given assurance that withdrawal from the trial will not affect the child, will not cause any harm and will not affect the treatment. Furthermore, refusal to give consent or withdrawal of consent to participate in the trial should not give rise to any obligation or discrimination for the person concerned. 5.3.2. Legal representatives who give informed consent for the participation of the child in clinical trials should be afforded the opportunity to follow the progress of the trial so that the child is able to make the decision to withdraw from the trial at any time (unless this creates a clinically inappropriate situation, for example as in operations performed under general anaesthesia). Where withdrawal takes place from a blinded trial, if the parents or the legal representative wish to follow the progress of the trial, they should be informed that the actual data will not be available until the trial has been completed. Where consent is withdrawn during a procedure such as anaesthesia, it may not be possible to discontinue the procedure in question immediately, as this could endanger the child's health. 5.3.3. It should be emphasised that the principal investigator or the investigator who is a physician or dentist has the responsibility to report trial-related events even after the child's withdrawal from the trial. In addition, the principal investigator or the investigator who is a physician or dentist should give assurance that appropriate treatment and monitoring will be provided. 5.4. When obtaining the child's assent, attention should be paid to the following points: 5.4.1. The child should, as far as possible, take part in the informed consent process together with his or her parents. The participation of children in the discussions and in the decision-making process is an approach that takes account of their stage of maturation. Sufficient time should be allowed for this process and, in order to ensure that the informed consent of the child reflects the child's will, the consent of the parents or the legal representative should be obtained in accordance with the

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

relevant legislation. The central role of the

parents in protecting their children should be recognised. Parents may also wish to discuss matters with their children on their own after receiving information about the trial and before meeting the principal investigator or the investigator who is a physician or dentist. 5.4.2. The question of whether the child is capable of giving assent should be based not only on chronological age, but also on other factors such as the child's stage of development, mental abilities (particularly in children with special needs or learning difficulties), and experience of life or disease. This should be determined following a discussion between the parents or the legal representative and the physician. Nevertheless, it is the mother or the father who knows the child best, and they are therefore generally in a position to judge the extent to which the child has understood the information provided. 5.4.3. In addition to the informed consent obtained from the legal representative, obtaining assent is also recommended. Where the child's assent cannot be obtained, it is recommended that this be documented, together with its justification, in a permission form bearing the signatures of the parents or the legal representative and of the physician providing the information. 5.4.4. Unless supported by the informed consent of the legal representative, the child's assent alone is not sufficient for participation in the trial. 5.4.5. Separate information forms for adults and for children, the language and presentation of which are appropriate to age and to the level of psychological and mental maturity, and separate consent and assent forms should be used. Consent, information forms and assent forms should be age-appropriate, should contain information on the purpose of the trial, and should set out the potential benefits and risks in honest but non-frightening language. Recommendations on this subject are set out in the annex to the guideline. 5.4.6. As stated above, assent, like consent, is an uninterrupted process and should, for example, be sought during the repeat visits of the trial. Throughout the trial, the child's objections must always be taken into account. The child's wishes should be heeded. The child should not be forced to give reasons. The child should be told that he or she may freely withdraw from the trial at any time, for whatever reason, without suffering any harm or consequence. 5.4.7. The processes of informing the child and of obtaining the child's assent should be clearly defined before the trial is initiated and documented for each child. In age groups in which obtaining assent is not possible (for example, newborns) or under certain trial conditions (for example, trials conducted under emergency conditions), the information process provided to the child and the child's responses should be documented. 5.4.8. According to age groups and level of maturity, the procedure for obtaining assent or consent should be as a minimum as follows: 5.4.8.1. Children from birth up to 3 years of age: In this age group, it is not possible to obtain the child's assent or consent; no understanding of the trial should be expected. 5.4.8.2. Children from 3 years of age onwards: In this age group, the capacity to agree is only just developing. If the child has a certain degree of understanding (pre-school children), it is still necessary to provide information appropriate to age and level of maturity, even where it has been assessed, following the provision of information, that consent cannot be obtained. Research on comprehension skills demonstrates that young children possess a considerable capacity to give assent.

It is accepted that children aged 3-4 are able to understand the notion of altruism to a certain extent. From the age of 9 onwards, children are able to understand the benefits and risks of a trial but have difficulty in understanding abstract information. This should be taken into account when drafting information forms for children. Nevertheless, it has been demonstrated that children with a chronic disease may develop an increasing ability to make independent decisions on the basis of their previous experience of life. In every case, as described above, informing the child and, where the child is of school age (6-7 years), that is to say where the child is able to read and write, obtaining the child's assent preferably in writing and rendering that assent traceable are of great importance. 5.4.8.3. Adolescents: While various threats to adolescent health are plainly evident, it is always difficult to conduct research in this group. Although adolescents possess the capacity to make decisions like adults in many other areas of life, they nonetheless fall

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

within the paediatric age group. When assent is sought, a balance must be struck between the adolescent's emerging capacity for independent decision-making and the specific need for continuous protection by the parents or the legal representative. It has been demonstrated in numerous publications that adolescents are able to take independent decisions under certain conditions. Provided that this is not contrary to the provisions set out in the relevant legislation, these decisions must be complied with. As in the younger age groups, individual capacity here is related to developing comprehension skills and to previous experience of life or disease. The information to be given to the adolescent regarding the clinical trial must be appropriate to his or her level of understanding and maturity. One of the important issues in research with adolescents is the safeguarding of confidentiality, particularly where the research is conducted on socially sensitive subjects such as drug use, sexuality or violence. In clinical trials in this age group, it should be borne in mind that disclosing to parents information concerning adolescents involves particular situations. Where an adolescent proves majority, that is to say is no longer a minor, informed consent should be requested from him or her without delay. The necessary measures should be taken to ensure that the information provided is adequately understood. 5.4.9. Every effort should be made to understand and to take account of differences of opinion between the child and the parents and the legal representative. The child's strong and definite objections should be respected. 6. STRUCTURE OF ETHICS COMMITTEES IN CLINICAL TRIALS CONDUCTED IN THE PAEDIATRIC POPULATION 6.1. The clinical trials in question should be reviewed by ethics committees established in accordance with the provisions laid down in the relevant legislation. 6.2. The Turkish Penal Code and the relevant legislation indicate the requirement that the necessary experts be present on the ethics committees when delivering an opinion on clinical trials conducted with children from every age group. The experts in question may be permanent members of the ethics committee or may be of a nature to provide advisory services under a special duty status; in that case, in addition to the ethics committee decision, they should prepare a signed opinion stating their decision.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

6.3. Where the ethics committee does not include a pediatrician, or where the existing pediatrician has a relationship with the trial, the opinion of a pediatrician must, in addition to the ethics committee decision, be appended. 6.4. The ethics committee is informed, on the clinical, ethical, psychological and social problems related to the trial, by a physician specialized in pediatrics, and, in the case of trials related to dentistry, by a dentist who has obtained a doctorate or specialty in the field of pediatric dentistry, and the protocol is evaluated accordingly. 6.5. All members of the ethics committee, including pediatricians providing consultancy services under a special duty status, must be independent of the sponsor of the study, the investigators and the proposed trial. 6.6. The qualifications and expertise of the ethics committee members together with the experts consulted must be documented and, where requested, appended to the opinion document they have submitted. 6.7. The ethics committee should make use of pediatricians both in the review of the initial protocol and during subsequent amendments to be made to the protocol. 6.8. Examples of consultancy obtained in clinical trials conducted in the pediatric population are as follows: 6.8.1. Use may be made, as consultants in such trials, of pediatricians, experts in pediatric ethics, medical doctor pharmacologists who have worked in the field of pediatrics, competent pediatric nurses or psychologists. It is recommended that experts possess, in addition to these qualifications, at least several years of experience in the field of pediatrics and direct experience in clinical trials conducted with children in similar age groups; for example, it is recommended that the responsible investigator, or an investigator who is a physician or a dentist, should have taken part in studies conducted with children in similar age groups. 6.8.2. In the absence of an expert possessing these qualifications, the required expert knowledge may be obtained with the contribution of a pediatrician. The ethics committee must document the expertise it makes use of and enter it in its records. 6.9. Taking into account the requirement for

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

additional protection for children enrolled in clinical trials, and in order to give its opinion on the protocol, the ethics committee should also review the content of the protocol from the perspective of pediatric protection. It should verify that the trial is scientifically valid. 6.9.1. It should be examined whether the trial is a repetition of previously conducted studies with the same purpose — which should be avoided. 6.9.2. The protection and safety of children must be guaranteed (including the minimization of risk, fear, pain and distress), and the presence of pediatricians must be ensured at all trial sites where the trial is conducted. 6.9.3. There must be justification for the inclusion of children in the trial and for the choice of age groups in terms of achieving the objectives of the trial. Depending on the age groups, the inclusion of a pregnancy test may need to be included among the inclusion or non-inclusion criteria. 6.9.4. The required non-clinical data must have been obtained before the use of the investigational medicinal product in children.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

6.9.5. There must be a comprehensive review of the existing findings relating to the investigational medicinal product in question (including relevant publications) and of the experimental studies carried out on the product, and these must be reviewed in order to confirm the initial hypothesis, the assessment of safety and expected benefit, and also the age group of the children to be enrolled in the trial. 6.9.6. The quality of the performance of the trial must be such as to ensure that the results are interpretable. Monitoring, auditing and quality assurance must be defined. 6.9.7. Age-appropriate formulations of the investigational medicinal products should be used in the trial. 6.9.8. Unless otherwise stated in the protocol, it should be specified that there is an independent data monitoring committee in the conduct of clinical trials with children. Where such a committee is not in place, the ethics committee or the Turkish Medicines and Medical Devices Agency (TİTCK) may request the establishment of such a committee. 6.9.9. The protocol must contain provisions governing the systematic and independent publication of the results, including unfavorable ones, within a reasonable time. 6.9.10. The ethics committee and TİTCK must ensure, for the purpose of protecting the health and well-being of the children enrolled in the trial, that the sponsor of the trial regularly monitors and reviews the risk/benefit balance of the trial. 6.9.11. In randomized studies, there must be an element of equipoise at the start of the study, and no participant should receive medical care known to be of lower quality than existing treatments. 7. DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE PEDIATRIC POPULATION 7.1. The design of the clinical trial depends on the objectives of the trial and the scientific questions to be asked. 7.2. In order to ensure the validity of the trials to be conducted, it is recommended that the trial design be formulated after consultation with patients or patient representatives from the age groups to be enrolled in the trial (older children or adolescents). 7.3. In children to be enrolled in the trial, particular attention should also be paid to the inclusion (and possibly the identification) of subgroups carrying certain genetic characteristics (e.g., G6PDH deficiency), in addition to the selection of age groups. Genetic variability may give rise to significant differences in drug metabolism, clinical drug responses and expected adverse reactions. 7.4. As in trials conducted with adults, all necessary measures should be taken in studies conducted with children in order to avoid bias. For example, increasing levels of bias arise in unblinded and uncontrolled studies aimed at demonstrating efficacy; therefore, such trials should, where possible, be avoided. 7.5. In open-label studies, provision should be made, as far as possible (for example, where masking is not feasible due to differences in the mode of administration of the product), for masking of the assessment. In many cases, the assessment, that is, the process of systematic review and documentation, is based on the assessment of the parents or of others involved in the care of the patient. Where feasible, the child's own assessment should also be obtained.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

7.6. Uncontrolled studies aimed at demonstrating efficacy should, as a matter of principle, be avoided. Such studies are not particularly useful in demonstrating safety if they are not prospective or if they are not conducted with pre-defined subgroups. In studies conducted with children with rare diseases, the methodological standards applied in studies conducted with children with common diseases should be applied. Alternative designs or analyses must be justified. Where such studies are to be conducted for the purpose of providing data for licensing, it is recommended that the decision be taken together with the Turkish Medicines and Medical Devices Agency (TİTCK). 7.7. The scope of studies conducted with children should be as narrow as possible, but of a size sufficient, with proper statistical power, to demonstrate the efficacy that needs to be demonstrated. In the case of studies to be conducted with small numbers of children, the decision should be made by comparison, in the context of a benefit/risk analysis, with studies to be conducted with large numbers of children but with the application of minimally invasive methods. An adaptive design or other designs may be used to limit the scale of the clinical trial. 7.8. The use of placebo and control groups must be based on the element of equipoise, must be appropriate to the conditions investigated in the study, and must be justified by scientific means. 7.8.1. Use of placebo: The use of placebo in children is more limited than in adults. In particular, placebo must not be used where it would stand in the way of effective treatment in serious and life-threatening conditions. Including in pediatric studies, the use of placebo is often necessitated for scientific reasons. As in adults, the use of placebo in children may be permitted in cases where there are no findings regarding the treatability of the disease or where the placebo effect is known to be variable (such as pain, hay fever). As the findings in favor of effective treatment increase, the ethical justification for the use of placebo weakens. The use of placebo does not mean the absence of treatment; for instance, placebo may be used in addition to standard treatment. In all cases, the use of placebo should be linked with measures to minimize the effect of exposure and to prevent irreversible harm, especially in serious or rapidly progressing diseases. Where deemed appropriate, rescue treatment (treatments, such as pain treatment, administered in addition to the medicinal products used in the study in order to prevent danger or distress as soon as the patient reaches a defined level) and escape procedures (the immediate withdrawal from the study of participants whose clinical condition deteriorates during the study or who fail to reach a defined level) should be brought into effect. Among other situations requiring thorough scrutiny and restriction of the use of placebo, mention may be made of run-in periods during which, according to the protocol, no effective treatment is to be administered. Placebo may be accepted as a comparator in cases where there is no generally accepted treatment for the condition and the investigational medicinal product may be the first medicinal product capable of altering the course of the disease, or where the effect of the treatment commonly used against the disease is considered doubtful due to the abundance of undesirable adverse reactions, and in cases where the risks may far outweigh the benefits. Other study designs deemed necessary should also be taken into consideration. The interpretation of actively controlled studies may be more difficult than that of placebo-controlled ones, whereas favorable information on the comparative benefit/risk balance can be obtained through them. The debate over the use of placebo in pediatric clinical trials is as important as the debate over its non-use in clinical trials.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

7.8.2. Superiority–non-inferiority (assay sensitivity) trials: Equivalence and non-inferiority trials, particularly when conducted in the pediatric population and in connection with sample size, bring about various challenges regarding the selection of equivalence or non-inferiority margins; when these are used instead of superiority trials, they must be justified in their entirety. In addition, inconsistencies in the conduct of the trial also obscure the differences between treatments in superiority or non-inferiority trials. In this regard, reference should be made to existing guidelines on methodological issues or to relevant guidelines concerning the relevant therapeutic areas. 7.8.3. Controlled trials conducted in children using medicinal products

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

(reference) not licensed in our country: Since most medicines used in children have not been fully evaluated and licensed, careful consideration must be given to the selection of active control products. Medicinal products not licensed in our country may be used as controls if they represent evidence-based standard treatment. The definition of standard treatment may vary. 7.8.4. Clinical trials conducted in children using medicinal products containing radioisotopes: Stable isotopes should be used to prevent radiation effects, except in cases where radioisotopes are necessary for treatment. 8. MINIMIZATION OF PAIN, DISTRESS AND FEAR 8.1. Physical and emotional pain should be prevented as much as possible and, where inevitable, treated effectively. For this purpose, the intensity of physical pain and distress must be assessed, particularly in preterm infants, newborns, and other children who cannot express the pain they feel, and must be monitored regularly according to guidelines and validated scales appropriate for age and case. Effective treatment should be administered according to pain intensity and reviewed regularly in light of the assessments made. Where appropriate, patient-controlled analgesics may be used in children whose comprehension ability is sufficiently developed. Pain may be attributable to the disease, to the case itself, or directly or indirectly to medical interventions. Painful procedures should be performed at a minimum level. Validated non-invasive methods should be preferred. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples to be taken from each child. 8.2. Parents and legal representatives must be informed as to which procedure constitutes normal treatment and which is performed within the scope of the clinical trial. Before each trial procedure or intervention, an explanation appropriate for the child's age, honest but not frightening, should be provided, thereby reducing anxiety and expectation of pain. Any procedure that may lead to the child's humiliation and consequently emotional distress must be avoided. Painful procedures include, but are not limited to, the following: physical discomfort (exposure to cold, heat, light or noise), positioning and immobilization, invasive procedures such as blood sampling (capillary, venous, and particularly arterial), biopsy, lumbar puncture, sample collection, repeated examinations of injured or traumatized arms and legs and other limbs, endotracheal intubation, airway clearance, insertion of oral or nasal tubes. In addition, monitoring should be applied in cases requiring sedation, and the appropriate level of sedation required for the procedures must be maintained.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

8.3. In order to minimize pain, distress and fear, trial sites must be suitable for pediatric care, and staff must be trained in pediatric care. Staff should be trained in communication with both parents (or legal representatives) and children. Children enrolled in the trial should be received in an environment familiar to them, with appropriate furniture, toys, and play activities in their surroundings; where conditions permit, children's school attendance should be ensured, and their concerns should be addressed by specialist staff. 8.4. The feeling of fear should be prevented where possible, and if not possible, minimized to the lowest level; the child's need for comfort and reassurance must not be overlooked. Changes in procedures must be communicated to the child. In every possible circumstance, the child should be prevented from being separated from parents or familiar persons. If these conditions cannot be met, a member of staff associated with the trial and able to provide reassurance must always be present with the child. As soon as any sign of distress or objection is observed in the child, the procedure should not simply be stopped; a short break should be taken so that the child feels that the situation is under control; better explanation and assessment of the situation may be necessary to reassure the child, and during this time a decision may also be made to discontinue the procedure entirely. 8.5. It must be taken into account that each child's response to pain, distress and fear may differ. Different reactions may be expected in children with chronic or acute illnesses. Pain tolerance increases with age and level of maturity, at which point medical procedures are no longer perceived as punishment. 8.6. In all circumstances, trial procedures or interventions should be kept to the minimum number required to obtain valid data; these should be performed using materials and devices appropriate for age or

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

size, and the number of sampling attempts should be limited in advance. 9. RISK ASSESSMENT AND MONITORING 9.1. The interests of the child must always take precedence over science and society. This principle is the most important element in the assessment and monitoring of risks. Risks must be viewed in balance with the benefit to be obtained. 9.2. Risk assessment is the most important stage in the evaluation of the protocol and the conduct of the trial. Risk is defined as potential harm (actual or theoretical) or the potential consequences of an action. Risks may be physical, psychological, or social, and may manifest immediately or with delay. Furthermore, they may differ according to age groups. Risk must be assessed in terms of probability, magnitude, and duration. Pediatric trials should generally be analyzed in terms of potential risks, including those that may not be considered in adults, because medicines or procedures may lead to adverse events in children that are not identified in adults. It is the responsibility of the investigator to conduct a comprehensive analysis of the risks in the trial, to describe the situation in the protocol, and thereby enable the ethics committee to make its approvability decision. 9.3. Risk assessment includes the assessment of the risks of the investigational product or control being tested, and in some cases the risks of withholding effective treatment and of the disease itself. Potential harms may include the burden and intensity of the trial, the severity and seriousness of potential harms, the reversibility of adverse events and reactions, and their preventability. The concentration of research projects on the same population (excessive research on the population) is another potential harm. Conducting multiple clinical trials on a single individual should not be supported.

9.4. The timing of pediatric trials in relation to preclinical data and information obtained from adults may also be associated with risk levels; in this case, trials are either conducted too early or the study of a medicinal product likely to show effect in children is delayed because adult data are expected to be obtained. 9.5. The absence of age-appropriate pediatric formulations also constitutes a risk. In a disease without treatment, the disclosure of risk following presymptomatic diagnosis (for example, genetic diagnoses), the narrowing of opportunities and freedom of choice, may create risks. Likewise, violation of the right to privacy is also considered a potential harm. 9.6. In cases where certain issues arise during the clinical trial in which the interest of the child conflicts with the interest of the research, the protocol must provide for the management of these issues through, for example, assessment of the harm that will result from the administration of treatment versus the harm that will result from the discontinuation of treatment. In addition to the risks inherent in the trial, external risks must also be assessed. These may be, for example, risks associated with differences in the level of expertise or experience of the relevant centers. 9.7. Risk assessment is difficult in practice because probabilities are unknown. Factors affecting risks must be described in the protocol. Finally, for each identified risk, measures must be established to prevent that risk, keep it at the lowest level, and monitor it. 9.8. The determination of risk levels and associated potential benefits constitutes the essence of ethical approvability. It is recommended that the ethical acceptability of trials be decided through the risk levels described below: 9.8.1. Minimal risk: May be defined as a situation in which the probability of harm or discomfort is no greater than the ordinary risks and discomforts encountered in daily life or during routine physical and psychological examinations or tests. 9.8.2. Minor increase over minimal risk 9.8.3. More than a minor increase over minimal risk 9.9. The level of risk may increase over time, during the trial, and in light of new information. Risk must be monitored continuously and must be defined in the protocol. In particular, the protocol must include stopping rules for planned and unplanned analyses related to safety and non-compliance. The use of an independent data monitoring committee is recommended. This committee must include specialists in pediatric health and diseases. For example, if an independent data monitoring committee is not utilized in certain pharmacokinetic trials, this must be justified. 9.10. The sponsor of the clinical trial must, during the course of the clinical trial, annually or upon request, in the safety report to be submitted to the Turkish Medicines and Medical Devices Agency (TİTCK) and the ethics committee,

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

in accordance with the relevant legislation, identify and assess the risks (actual and theoretical) and harms initiated by the medicinal products under investigation. The sponsor must include in the said report a specific analysis regarding the safety of volunteers in the pediatric population enrolled in the clinical trial

GUIDELINE ON ETHICAL APPROACHES FOR CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

should provide and, in light of scientific developments and events occurring within the scope of the trial, should present an up-to-date risk/benefit assessment of this pediatric population. 10. BENEFIT AND MEASUREMENT OF BENEFIT 10.1. Direct benefit refers to the benefit provided to the individual or to the benefit provided to the group. 10.2. Benefit can be defined as an advance in treatment, diagnosis, or prevention in the relevant child or group of children. Benefit is a tangible outcome that the volunteer can also perceive. Benefit is attained either through a better risk/benefit balance resulting from an increase in efficacy and safety, or through an alternative to an existing treatment that provides at least the expected risk/benefit balance. Benefit can also be achieved through contributions made to patient care (for example, a better route of administration, a reduction in dosing frequency, an improvement in potential medication errors or compliance, a shorter treatment duration, or a clinically relevant, age-appropriate formulation). 10.3. The benefit directed at the group of children who have the same disease or a disease with similar characteristics and for whom the medicinal product may provide benefit can be defined as an increase in knowledge regarding the condition or its treatment, which in turn is likely to lead to better possibilities for diagnosis, treatment, and prevention. The measurement of this benefit is determined by the importance of the knowledge gained, the severity and prevalence of the condition in question, the likelihood of obtaining results from the proposed trial, and the usefulness of the benefits obtained. 10.4. The determination of risk levels and associated benefits constitutes the essence of ethical acceptability. The sponsor of the trial should present the risk levels, which should be evaluated by the ethics committee. The assessment of risk and benefit may be based on probabilities and assumptions, and this must be balanced against the severity of the conditions or diseases to be investigated and the risks and benefits of alternative treatments. 10.5. In the following examples, the risk levels are considered to be in balance with the benefit for a trial conducted in the pediatric population: 10.5.1. Minimal risk involving benefit to the individual or benefit to the group, 10.5.2. A minor increase over minimal risk involving benefit to the individual or benefit to the group: the benefit/risk balance is as favorable as that of existing alternative treatments, 10.5.3. More than a minor increase over minimal risk, involving benefit to the individual and particularly favorable compared with existing alternative approaches for the individual's condition. 11. STUDIES ON ASSAY METHODS RELATED TO AGE OR WEIGHT AND BLOOD SAMPLES 11.1. The assay methods, tests, and blood sample volumes related to the trial should be described and justified in the protocol. 11.2. When determining the number and types of assay methods and tests, the age or weight (body surface area, if necessary) of the children to be enrolled in the trial should be taken into account. Where possible, alternative sampling methods used in pharmacokinetic studies (urine or saliva sampling) should be preferred. In blood and tissue assays, micro-volume and micro

GUIDELINE ON ETHICAL APPROACHES FOR CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

assays should be used where possible. As a matter of principle, general or local anesthesia should be administered for painful or invasive procedures where conditions permit. 11.3. The timing of sampling should be coordinated as much as possible in order to avoid repetitions of methods and repetitions of the same sampling procedure carried out with the aim of minimizing pain, distress, and iatrogenic complications. Sampling should be performed by trained personnel. The number of sampling attempts should be kept limited. The timing of sampling and the number of sampling attempts should be described in the protocol. 11.4. In preterm and term newborns, blood volume is very limited. They are usually anemic due to frequent sampling related to age and

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

pathological conditions. The fact that blood transfusion (or iron or erythropoietin supplementation) can be given to children, especially in this age group, should not be used as a justification for drawing blood in larger volumes or drawing blood frequently. 11.5. The blood volume limits set out below are recommended for blood sampling. If investigators do not comply with these limits, they must duly justify the situation. The blood loss in each individual within the scope of the trial (including that occurring in preventive interventions) should not exceed 3% of the total blood volume within a four-week period, and 1% in a single procedure. In rare concurrent trials, it is recommended that 3% be the maximum level. The total blood volume is estimated to be 80-90 ml per kilogram. 3% means 2.4 ml of blood per kilogram. 11.6. In preterm and term newborns, actual blood loss must be routinely monitored. In all trial protocols, the expected blood loss should be explained in detail. The expected blood loss should also be specified in detail in the patient information forms. 12. TRIALS CONDUCTED IN NEWBORNS (TERM AND PRETERM) 12.1. Whether preterm or term, newborns are the most vulnerable group of the pediatric populations. A newborn who contracts a serious illness becomes a multiple drug user whose potential interactions must be taken into account. This pediatric subset may differ pharmacologically from older age groups. In trial protocols for this population, the complexity of the condition and long-term effects, which may also be developmental, should be taken into account. Therefore, ethics committees and investigators need to carry out a comprehensive review in this field. 13. TRIALS CONDUCTED IN HEALTHY CHILDREN 13.1. As a matter of principle, a healthy child should not be enrolled as a healthy volunteer. Trials that can be conducted in adults should not be conducted in children. There may be exceptions to this; healthy children may, for instance, participate in consumability tests such as a chew-and-spit test performed for a newly flavored medicinal product. 13.2. In some cases, trials need to be conducted in children who are healthy during the trial. Pediatric vaccine trials, including preventive trials or immunogenicity trials, fall into this category, and the target population is highly likely to benefit from them. Conducting clinical trials in children with intermittent diseases (such as relapsing diseases or seizures) is accepted, because even in the healthy phase these children are in fact patients. Where possible, it should be preferred that older children, rather than younger children, be enrolled in trials first.

13.3. Proof of concept should first be established in relevant animal models or in adults. The type of pharmacokinetic study that cannot be conducted in adults, namely studies conducted in those affected by the disease, should be performed on the target population as far as possible. However, it is acknowledged that data in children affected by the disease may show variability. 14. VACCINES 14.1. Immune responses should be investigated taking into account the maturation level of the immune system in the target population. 15. PEDIATRIC FORMULATIONS TO BE USED IN CLINICAL TRIALS TO BE CONDUCTED IN THE PEDIATRIC POPULATION 15.1. The formulations used in the trial should be described in the protocol in accordance with the relevant legislation. In addition, the formulations used in pediatric clinical trials should be reported in publications. 15.2. Age-appropriate formulations should be used in order to eliminate the risk of adverse reactions (for example, tablets choking small children), dosing errors, or mistakes. Where a pediatric formulation exists, it should be used. In cases where extemporaneous (prepared at the time of use) preparations are used due to the absence of an appropriate formulation, their preparation conditions and doses should be specified and good manufacturing practices should be complied with. 15.3. In the excipients used in formulations, the age of the children participating in the trial should be taken into account (for example, benzyl alcohol is contraindicated in newborns). The conditions for preventing bacterial contamination and deterioration of the investigational product should be specified in the protocol. 16. PROTECTION OF PERSONAL DATA 16.1. The sensitivity of data protection in children is also linked to the future (unknown) use of the data obtained from children. The storage of biological material samples and the requirement for permission for such uses should be discussed in the protocol. The archival retention period of trial documents should

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

be determined taking into account that long-term review (long-term safety) may be required in trials conducted with children. 16.2. It has rarely been seen that children object to records concerning themselves. For this reason, investigators have the additional duty of protecting the right to confidentiality and access to data. In cases where trials are conducted in schools, the level of protection (access, modifications, and disclosure) of the educational performance records contained in the trial documents and of the information given to parents or legal representatives should be specified in the protocols. This condition is particularly prominent in trials in which adolescents participate and in which issues of sexuality, illicit drug use, or violence are addressed. 16.3. If a child's personal information is being collected, stored, used, accessed, or destroyed, the responsible investigator and the other investigators must ensure that the volunteer's rights to private life and privacy, cultural sensitivities, and the community in which the volunteer lives are respected. Children participating in a trial have the right to be informed of all information collected about their own health status. The other personal information collected in research projects, personal

made accessible to these persons in accordance with the applicable legislation on data protection. When disclosing genetic findings that may pose a risk in clinical trials, an appropriate setting should be selected and advisory assistance from experts should be obtained.

17. UNNECESSARY REPETITION OF TRIALS

17.1. Unnecessary repetition of trials in children is considered unethical.

17.2. If pediatric clinical trials are systematically registered, results including negative ones are published, and the literature is analyzed in a comprehensive manner, trials with similar objectives and similar designs will be identified, thereby preventing unnecessary repetition of trials involving children.

17.3. Ethics committees should not accept pediatric protocols that prevent investigators from publishing independently. The timing of such publications should be specified in the relevant protocols.

18. ADVERSE REACTIONS AND REPORTING THEREOF

18.1. The rules and obligations regarding the reporting of adverse reactions in pediatric trials are the same as those in trials involving adults, including the reporting of serious adverse reactions observed in clinical trials, and must be carried out in accordance with the applicable legislation.

18.2. Since data from adults have insufficient predictive value for the safety of children, target organs, types of reactions different from those expected in adults, and reaction severities may be included in reports. The Development Safety Update Report (DSUR) should include a specific adverse reaction assessment regarding the use of the investigational medicinal product in children.

18.3. Parents or legal representatives and caregivers should be clearly informed that they are required to report these adverse reactions and events to investigators in a timely manner. This requirement is particularly prominent for young children who are not in a position to recognize adverse reactions.

19. PERSUASIVE INCENTIVES OR FINANCIAL OFFERS TO CHILDREN

19.1. The sponsor shall not make any persuasive incentive or financial offer to parents, legal representatives, or children in order to ensure their participation in or continuation of the trial.

19.2. However, expenses arising from the volunteers' participation in the trial and the loss of income resulting from the loss of working days by healthy volunteers shall be specified in the trial budget and covered from that budget.

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

20. INSURANCE

20.1. Situations in which insurance is mandatory are set forth in the applicable legislation. In clinical trials involving children, obtaining insurance, particularly for newborns, may be difficult due to insurance companies having issues with long-term financial liability. In insurance policies, financial obligations related to long-term effects should be valid, the duration of the obligation should not be limited, and although this period generally varies depending on the nature of the trial, it covers at least 5 (five) years following the completion of the trial. Ethics committees should pay particular attention in this regard,

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

especially to insurance policies regarding long-term effects on the child's development.

20.2. Unrecognized hereditary disorders are generally excluded from coverage. Suspected, unexpected, serious adverse reactions attributable to unrecognized hereditary disorders should be included in insurance policies.

20.3. In order to prevent the risk of insurance companies labeling persons based on their existing conditions, medical records should be protected by the confidentiality provisions of the applicable legislation.

21. ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GOOD CLINICAL PRACTICE

21.1. Compliance with good clinical practice (GCP) and applicable legislation in clinical trials is mandatory. Although not specific to pediatric trials, since children constitute a vulnerable population, ethical violations and non-compliance with good clinical practice gain particular importance in this field.

21.2. In cases of ethical violations and non-compliance with good clinical practice, ethics committees and the Turkish Medicines and Medical Devices Agency (TİTCK) have duties to assume. Violations are classified as critical, major, and minor, depending on whether patient safety and scientific value have been jeopardized and, if so, to what extent. The preferred option in preventing these violations is education, training, and advisory support. When ethics committees receive information about such a violation or non-compliance with good clinical practice, they should inform the Turkish Medicines and Medical Devices Agency.

21.3. Compliance with GCP should be explicitly stated in publications. The results of trials conducted through unethical means should be explained with clear warnings identifying the unethical aspects. Information about such trials is necessary in order to prevent unnecessary repetition of trials and to protect volunteers in the future.

21.4. If data not compliant with GCP are found in a marketing authorization application, the quality of the data, the findings of the trial, and the validity of the authorization should be subjected to review. A sensitivity analysis should be performed on the entire GCP-compliant data set and, in certain cases, in comparison with non-GCP-compliant data. The overall reliability of the trial should be questioned.

22. MATTERS TO BE CONSIDERED IN THE PLANNING OF CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION

Some of the matters that should be considered in the planning of clinical trials conducted in the pediatric population are listed below:

22.1. Definition and scientific validity of the question to be answered by the trial,

22.2. Justification for conducting the trial with children and with the proposed age groups,

22.3. Evidence of direct benefit to the individual or benefit to the group,

22.4. Competency level of the investigator responsible for the trial and the team,

22.5. Infrastructure of the institution or trial site, which should be qualified and experienced specifically in the field of the implemented project and, in general, in pediatric research,

22.6. Non-clinical safety and efficacy data, which are a prerequisite in pediatric clinical trials (such as the investigator's brochure, available literature),

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

22.7. Clinical findings of trials conducted with adults, if any (such as literature, investigator's brochure),

22.8. Type and phase of the trial,

22.9. Use of placebo or active control,

22.10. Age-appropriate formulations of medicinal products,

22.11. Age-appropriate scales or measurements of endpoints (such as a pain scale),

22.12. Trial design and biometric planning in connection with the trial question,

22.13. Applicability of designs reviewed by child/patient representatives and information forms,

22.14. Inclusion and exclusion criteria for the trial,

22.15. Statistical methods,

22.16. Criteria for termination of the trial,

22.17. Safety measures, including the establishment of an independent data monitoring committee,

22.18. Appropriate pharmacovigilance methods to be implemented by the sponsor,

22.19. Risks of the trial, pain, fear, and distress,

22.20. Assessment of potential risks (actual and theoretical) to children enrolled in the clinical trial against the expected benefits,

22.21. A positive expected benefit/risk balance in the clinical trial,

22.22. A comprehensive and understandable informed consent form and information forms for the legal representative,

22.23. Age-specific, understandable informed consent forms and information forms for children,

22.24. Anonymization of data and confidentiality of personal information regarding the child and family participating in the trial,

22.25. Insurance for child participants,

22.26. Opinions of other ethics committees, if any, regarding international multicenter trials,

22.27. Publication of trial results,

22.28. Continued use of the drugs used in the trial if the volunteer benefits from them.

23. INFORMATION REGARDING THE INFORMED CONSENT FORM TO BE USED IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION

23.1. The information forms to be provided to parents and to children should be separate.

23.2. The language of the forms should be understandable (technical terms should not be used) and age-appropriate (abstract concepts and multiple options should be avoided).

23.3. Age-specific differences in the information forms should be kept to the minimum required, thus allowing room for significantly different expression or presentation. In addition, unnecessary distress should not be caused through the information forms.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

23.4. In multicenter trials, the information forms should be harmonized across all centers, and multinational trials should similarly be directed at equivalent age groups.

23.5. A list of topics recommended for inclusion in information forms and informed consent forms is provided below:

23.5.1. What is the purpose of the trial?

23.5.2. Why was I selected?

23.5.3. Am I required to participate?

23.5.4. What will happen to me if I participate?

23.5.5. What are the compensations?

23.5.6. What will I need to do?

23.5.7. What drug is the drug being tested?

23.5.8. What are the diagnostic or treatment alternatives?

23.5.9. What are the potential harms or risks of participation?

23.5.10. What side effects will the administered treatments have on participants?

23.5.11. Will ionizing radiation be administered, and which legislation applies?

23.5.12. Is there a possibility of harm to the unborn child?

23.5.13. What are the potential benefits of participation?

23.5.14. What happens if the trial is stopped?

23.5.15. What happens if a problem arises?

23.5.16. Will my participation in the trial be kept confidential?

23.5.17. What happens if I do not wish to continue the trial?

23.5.18. What are my options if I want to withdraw from the trial?

23.5.19. Does my private physician/family physician have a role in this matter?

23.5.20. What will be done with the samples taken from my body?

23.5.21. Will genetic testing be performed? If so, in which country and, if possible, in which laboratory will it be performed?

23.5.22. What will be done with the findings of the trial?

23.5.23. Who is organizing the trial and who is providing the funding?

23.5.24. Who reviewed the trial and what are the results?

23.5.25. What are the contact details for obtaining information or lodging complaints? The child and, if necessary, the parent or legal representative should be provided with trial alert and information cards containing the main principles of the trial and, in particular, the contact details.

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.

24. EXAMPLES OF RISK LEVELS

24.1. The appendix of this Guideline contains examples of risk assessments for measurements performed in a trial. This assessment is not definitive, since the conditions in which the child finds him/herself affect the assessment of risks. For example, the presence of a central venous access reduces both pain and the invasiveness of blood collection, but at the same time increases the risk of infection and excessive blood loss. In some measurements (including but not limited to those marked with *), the risk assessment is highly dependent on such conditions and the context in which they are used in the trial. Furthermore,

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

the risk level is also elevated by increased frequency of measurement and susceptibility to damage in the relevant organs. The categories recommended in the table apply to situations where the measurement is performed once or very frequently. In these examples, it is assumed that the measurements are performed according to the highest professional standards.

25. REPEALED PROVISIONS

The "Guideline on Ethical Approaches in Clinical Trials Conducted in the Pediatric Population", which was put into effect by the Approval of the Authority dated 17.04.2013 and numbered 43020, has been repealed.

26. ENTRY INTO FORCE

This Guideline enters into force on the date of its approval.

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

ANNEX-1: TABLE 1 No risk or minimal risk Minor increase over minimal risk More than a minor increase over minimal risk - Taking anamnesis - Clinical examination - Auxological measurements - Tanner stages - Behavioral testing - Psychological testing* - Quality of life assessment - Venipuncture* - Heel stick blood sampling - Finger prick blood sampling* - Subcutaneous injection - Urine collection into a bag* - Collection of exhaled breath moisture - Collection of saliva or sputum - Hair sample collection - Taking tissue samples from the body as part of medical treatment* - Topical analgesia* - Stool tests - Bioimpedance meter - Transcutaneous oxygen saturation monitoring (pulse oximetry)* - Blood pressure monitoring - Electroencephalography - Electrocardiography - Vision/hearing tests - Ophthalmoscopy - Tympanometry - Lung function tests (peak flow, exhaled NO, spirometry) - Oral glucose tolerance test - Ultrasound scanning - Chest or arm-leg X-ray with digital amplification* - Stable isotope examination - Urine collection by endoluminal or suprapubic catheter - Arterial puncture - Umbilical catheter - pH measurement - Insertion and use of a nasogastric tube - Transcutaneous oxygen or carbon dioxide pressure monitoring - Electrophysiological measurements (with stimulation) - Exercise tests (ergometry, spiroergometry) - High-volume pulmonary function test (in infants) - Peripheral vascular access - Polysomnography - Fasting conditions (≥ one meal) - Lumbar puncture (CSF) - Bone marrow aspiration − MRI scan - X-ray examinations other than chest or arm-leg X-rays with digital amplification − CT scan* - DEXA bone density measurement with X-ray - Use of contrast agents - Paracentesis - Skin punch biopsy - Airway or skin hyperreactivity challenge test - Cardiac catheterization - Endoscopy - Biopsy - Surgeries performed as part of medical treatment or modification of the standard surgical procedure - Sedation - Anesthesia - Systemic analgesia - Hypoglycemia test - Use of unstable isotopes - PET scan

GUIDELINE ON ETHICAL APPROACHES IN CLINICAL TRIALS CONDUCTED IN THE PEDIATRIC POPULATION 24 NOVEMBER 2015

Dates and Issue Numbers of the Publication of Amendments Made to the Guideline Date Issue No. 1. 12.11.2009 7219 2. 09.04.2010 2227 3. 24.12.2010 8066 4. 23.08.2011 7480 5. 17.04.2013 43020

Unofficial English translation for information purposes only. In the event of any discrepancy, the Turkish original text (mevzuat.gov.tr) shall prevail.