1. INTRODUCTION

This guidance provides recommendations on various ethical aspects of clinical trials performed in children from birth up to the legal age of adulthood. These recommendations will contribute to the protection of all children who are the subject of clinical trials. Protecting the pediatric population (signifies the population up to 18 years of age. This term is used to refer to all pediatric age groups) against the risks of research is paramount whilst this should not lead to denying them the benefits of research.In general children are unable to consent, but their assent should be taken using information appropriate for their age. Ethics Committees should consult with pediatric experts to balance the benefits and risks of research in children, and their decision must incorporate the favorable opinion and signature of a pediatric expert in respect of this. Studies in children should be conducted solely by well-trained investigators with pediatric experience.Pain, distress, fear, and parental separation should be prevented and minimized when unavoidable. The neonates of all the pediatric age groups require exercising the highest level of care during review.

2. OBJECTIVE

Clinical trials are necessary and should aim at progressing the well-being and treatment of bad health conditions, prevention and diagnosis of illnesses including in children. The same ethical principles apply across age ranges, from children to the elderly.The need for conducting trials on children is recognized in the specific provisions and conditions stated in the relevant legislation for protecting children. In order to improve the treatment opportunities of children, clinical trials involving children need to be performed. Children represent a population with developmental, physiological and psychological differences from adults, which make age- and development-related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the volunteers. Criteria for the protection of children in clinical trials therefore need to be laid down. Specific protection conditions should be defined for research performed in children, at all stages and ages.
The reasons why medicinal products need to be studied in children have been detailed in various publications. Differences in pharmacokinetics and pharmacodynamics and in adverse reactions are common in children compared to adults. Growth and maturation processes, as well as certain specific diseases are unique to children. Specific consequences of medical interventions may be seen in children, some of which may only appear long after exposure.
Because of the special protection they deserve, children should not be the volunteer of clinical trials if the clinical trial can be done in adult volunteers and it is not required for children.
If research with children proves necessary, the least vulnerable among them should usually be included (i.e. older children). If there is a necessity to subject children to a clinical trial, the choice of subsets of the pediatric population to be included should be made on the basis of the likely target population for the medicine being tested, the possibility of extrapolation, and the scientific validity of such an approach.

The recommendations in this guidance aim to bring together ethical principles in accordance with the applicable legislation.

3. SCOPE

This guidance is intended to provide recommendations on various ethical approaches of the performance of clinical trials falling under the provisions of applicable legislation.This guidance is without prejudice to the obligations under the Turkish Penal Code, Turkish Civil Code and the need to meet other applicable regulatory requirements. In addition, these recommendations do not distinguish between non-commercial and commercial research.This guidance focuses on the specificities of pediatric clinical trials.The recommendations in this guidance aim to contribute to the promotion and protection of the dignity, the well-being and the rights of children all of whom are vulnerable and unable to give informed consent. The clinical trials performed in children should be carried out under conditions providing the best possible protection for this vulnerable population whilst recognizing the children's right to benefit from research.

4. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS

Ethical principles referred to in this document are those expressed, for example, in the Declaration of Helsinki published by the World Medical Association, 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, and the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine and in the Guideline on current Good Clinical Practice. During research, three ethical principles should be adhered to: respect for persons, beneficence and justice. These are fully applicable for the clinical trials involving children.

5. THE PROCESS OF INFORMED CONSENT

5.1 When giving informed consent the legal representative must take into account the following issues:

5.1.1. As the child is unable to provide legally binding consent, informed consent must be taken from the parents or a legal representative on the child's behalf. The applicable regulations require that the specific and written informed consent of parent/legal representative must be taken prior to enrolling a child in a trial. Information should be given to the parents, or the legal representative, on the purpose of the trial, the potential benefits and risks, and the name of investigators who are responsible for conducting the trial with background professional information (such as education, work experience) and a 24-hour accessible telephone number for further information regarding the trial. The parent/legal representative should be given sufficient time and necessary information to consider the benefits and risks of involving the child in the clinical trial. When providing such information, it is important to take into consideration the fear and uncertainty of parents, especially when they are inexperienced with respect to the child's condition. However, the parents/legal representative might need more detailed and explicit information, and hence more time, to also reflect on the implications of consenting, especially since they bear the full responsibility for the child, unlike in adult trial where one takes the responsibility for oneself.

5.1.2. The investigator or sub-investigator who is physician or dentist when taking informed consent should not put undue pressure on the parent/legal representative. For example:

5.1.2.1. There must not be financial inducement to enroll the child in the trial; no financial incentive should be offered except compensation and expenses.

5.1.2.2. Parent/legal representative should be informed of the possibility to revoke informed consent even though it was made in writing.

5.1.2.3. Parent/legal representative should be reassured that the child's treatment will not be prejudiced by declining to participate, or by withdrawing from the trial.

5.1.2.4. Consent should be obtained from the parent/legal representative at the same time as assent is taken from the child.

5.1.3. In the relationship between parents and physician(s), especially in case of chronic diseases and of rare diseases, but also in acute serious illnesses, or in the situation of less educated parents, there is a risk of unrealized obligations and emotional subordination on the side of the parents. Moreover, this may not be perceived by either party. The investigator or sub-investigator who is physician or dentist should not take part in the decision making, but should ensure that the information has been understood and that there has been enough time allowed to come to a decision. Provision of information is also a continuous process.

5.1.4. In the case of adolescents aged 16 to 18, as well as the consent given by the parents/legal representatives, written informed consent is required as for any adult capable of giving consent.

5.2 Consent at the beginning of a trial and continued consent and assent during the trial should take into account the following matters:

5.2.1. Sufficient time should be dedicated to provide information and take the legal representative(s)' consent as well as the child's assent, in accordance with the relevant legislation.

5.2.2. It is important to understand that consent is a dynamic, continuous process, and should therefore not only be obtained prior to enrolling a child in a trial but should be maintained during the trial on a continuous basis. This could be done for example, by a brief discussion during each repeat visit. It is recommended to document this process in the medical records or equivalent systems. The discussion is part of the ongoing dialogue between children, parents and investigators or sub-investigator who is physician or dentist and should focus on all aspects of the trial but in particular on any new information that arises in relation to the trial and that might affect the willingness of the parent and child to continue.

5.2.3. Especially in long-term trials, the investigator should check the progressing maturation of the child and its ability for assent.

5.2.4. In the rare event of a change in legal representative during the trial, informed consent should be taken again as soon as possible.

5.3. In case withdrawal of the consent, the following matters should be taken into due account:

5.3.1. In all circumstances, parent/legal representative should be made aware of the rights to refuse participation in a clinical trial and to freely withdraw their informed consent, without giving reasons. Parent/legal representatives should be reassured that the withdrawal from the trial will not prejudice the child, will not result in any detriment and will not affect treatment. In addition, refusal to give consent or withdrawal of consent to participation in research must not lead to any liability or discrimination against the person concerned.

5.3.2. Legal representatives who gave informed consent for a child to participate in clinical trials should be given the opportunity to follow research as it proceeds (unless clinically inappropriate, e.g., during an operation under general anesthesia), so as to be able to decide whether to withdraw the child from the research at any time. In the event of withdrawal from a blinded trial, if the parents/legal representative wishes to continue to follow the progress of the trial, information should be given that the actual data will not be available until the trial has ended.

5.3.3. When consent is withdrawn during a procedure, for example, during anesthesia, it may not always be possible to stop the procedure immediately, as this might jeopardize the health of the child.

5.3.4. It must be emphasized that after a child withdraws from a trial, the investigator or sub-investigator who is physician or dentist is still responsible for reporting trial-related events. In addition, the investigator or sub-investigator who is physician or dentist needs to assure appropriate treatment and follow-up.

5.4 When obtaining assent/consent from children, the following matters should be taken into due account:

5.4.1. Whenever appropriate, the child should participate in the informed consent process together with the parents. Involving children in discussions and the decision-making process respects their emerging maturity. This process should be conducted with enough time and at the same time as obtaining consent from the parents or the legal representative, so that the informed consent reflects the presumed will of the minor, in accordance with the applicable legislation. The central role of parents in the protection of their child should be recognized. The parents might also wish to discuss with the child on their own, after having been informed on the trial, and before meeting with the investigator or sub-investigator who is physician or dentist.

5.4.2. The evaluation of whether or not a child can give assent should not solely be based on chronological age, but should also depend on other factors such as developmental stage, intellectual capacities (especially in children with special needs and/or learning difficulties), life / disease experience, etc. This needs to be made after discussion of the parents / legal representative with the physician, but the parents will normally know the child best and hence are usually in a position to determine the degree to which the child has understood the information.

5.4.3. It is recommended that the assent is obtained in addition to informed consent of the legal representative. If the child's assent is not obtained, it is recommended that this be documented with justification in the consent form which is signed by the parents/legal representative and investigator.

5.4.4 The child's assent alone is not sufficient to allow participation in research unless supplemented by informed consent of the legal representative.

5.4.5. Separate information sheets for adults and children, and separate consent and assent forms should be used in order to provide age appropriate information, in language and wording appropriate to age, psychological and intellectual maturity. The assent information sheets and assent forms should be age appropriate and should include provision of information on the purpose of the trial, and potential benefits and harms, in terms that are honest, but not frightening. See also the annex to this guidance for recommended contents.

5.4.6. As discussed above, assent, like consent, is a continuous process and should be taken during the trial as well, e.g. during repeat trial visits. Objections raised by a child at any time during a trial should be considered. Will of the child should be respected. The child should not be forced to provide reasons. The child should be informed of the possibility to freely withdraw from the trial, at any time for any reason, without any disadvantage or prejudice.

5.4.7. The processes for informing the child and taking assent should be clearly defined in advance of the research and documented for each child. In age groups where obtaining assent may not be possible (e.g., neonates) or in certain research conditions (e.g., research in emergency situations), the information process provided to the child and the child's response should be documented.

5.4.8. Assenting/consenting procedure according to age groups and level of maturity should meet at least the following conditions:

5.4.8.1. *Children from birth to 3 years of age*: In this age group, it is not possible to obtain assent/consent, and understanding of research is not expected.

5.4.8.2. *Children from 3 years of age*: Within this age group there is the emergent capacity to agree. Where the child has some capacity of understanding (pre-school children), age- and maturity-appropriate information is still needed even if after giving information, assent is evaluated not to be obtainable.

Research on cognition shows that younger children have significant ability to provide assent. It is recognized that children from the age of 3-4 years can understand some expression of altruism. From the age of 9, children may be able to understand benefits and risks of research but are less able to understand conflicting or abstract information. This should be taken into consideration when writing information forms aimed at children. Most children are unlikely to understand randomization, as indeed are some parents. However, it has been shown that children with chronic illness may develop increased capacity to make independent judgments based on previous life experience.

In any case, it is of major importance to inform the child and obtain assent as described above, preferably in writing, when the child is of school age (6 or 7 years old), i.e. able to read and write, and to then keep track of such assent.

5.4.8.3. *Adolescents*: The ability to conduct research in this group remains difficult as many threats to adolescent health continue to be evident. Adolescents belong to the pediatric age group, although they have the capacity to make adult decisions in many other areas of life. Taking assent should put in balance the emerging capacity of an adolescent for independent decision-making with the need for continued special protection as provided by parents or legal representatives. Numerous publications recognize that adolescents are, under certain circumstances, able to make independent judgments, and this should be respected within the confines of the applicable regulatory provisions. As in the younger age groups, the individual capacity is also linked to developing cognition and previous life/disease experiences.

The information about the clinical trial needs to be provided to the adolescent according to their level of understanding and maturity.

An additional issue of trials in adolescents is the protection of confidentiality, especially for research on socially sensitive issues such as illicit drugs, sexuality, and violence.

The specific aspects of disclosure to parents of information concerning adolescents should be taken into consideration for clinical trials in this age group.

When an adolescent is legally emancipated, i.e. ceases to be a minor, informed consent must be taken directly from the individual and as soon as possible. Precautions should be taken to ensure that information provided is sufficiently understood.

5.4.9. Every effort should be made to understand and respect differences of opinion between the child and his/her parents or legal representative. Strong and definitive objections from the child should be respected.

6. ETHICS COMMITTEE'S COMPOSITION IN RESPECT OF PEDIATRIC TRIALS

6.1. These studies should be reviewed by an Ethics Committee assembled in line with the applicable regulatory provisions.

6.2. The Turkish Penal Code and applicable legislation requires seating of members with appropriate expertise at the Ethics Committee when providing an opinion on a clinical trial to be performed in children of any age group. The experts may be

permanent members of the Ethics Committee, or experts providing advice and consulted on an *ad-hoc* basis, and in this condition, they should provide a signed opinion stating their decision in addition to the decision of the ethics committee.

6.3. If a pediatric expert isn't available in the ethics committee or the existing pediatric expert is related to the trial (e.g. being principal investigator), opinion of the pediatric expert must certainly be added to the decision of the ethics committee.

6.4. Ethics committee is informed by a physician expert on child's health and diseases regarding the clinical, ethic, psychological and social problems related to trial, and Ethics Committee is informed in trials related to dentistry by a dentist with doctorate or specialty degree in pediatric dentistry and the protocol is assessed in this regard.

6.5. All members of the Ethics Committee including pediatric experts consulted on an ad hoc basis should be independent of the sponsor, the investigator and the research proposed.

6.6. The qualifications and expertise of the experts consulted and the members of the Ethics Committee should be documented and annexed to its opinion.

6.7. Ethics Committees should use pediatric experts when reviewing the initial protocol as well as any subsequent substantial amendments.

6.8. Examples of consulting expert opinion for clinical trials in the pediatric population are as follows.

6.8.1. Pediatric experts, pediatric ethicists, pediatric pharmacologists who are doctors of medicine, pharmacologist, qualified pediatric nurses or psychologists may be used as consultants for these studies. In addition to their qualifications, it is recommended that the experts demonstrate at least some years of experience in pediatric care and direct experience of clinical trials with children in similar age groups, for example as an investigator who is principal investigator or physician or dentist in trials performed in children of similar age groups.

6.8.2. If an expert with these qualities cannot be found, pediatric experts could contribute to the expertise needed. Expertise used should be documented and recorded by the Ethics Committee.

6.9. Considering the need for additional protection of children involved in trials and with a view to providing an opinion on the protocol, the Ethics Committee should also check the content of the protocol with respect to pediatric protection. Scientific validity of the study should be verified.

6.9.1. Whether or not the trial replicates trials conducted previously with the same objective (which should be avoided) must be examined;

6.9.2. Protection and safety of children is ensured (including minimization of risks, fear, pain and distress) and appropriate pediatric expertise is available at all trial sites.

6.9.3. A justification is provided for the inclusion of children to achieve the trial objectives and for the choice of age groups. Depending on age groups, inclusion/exclusion criteria may need to include a pregnancy test.

6.9.4. Appropriate non-clinical data are available before the use of the product in children.

6.9.5. Extensive and comprehensive review of available evidence (including relevant publications) and experimental work on the investigational medicinal product should be available and reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit, and the age ranges of children to be included.

6.9.6. The quality of the performance of the trial is such that it ensures that the results will be interpretable; monitoring, audit and quality assurance should be described.

6.9.7. The trial uses age-appropriate formulations of the medicinal product(s).

6.9.8. An Independent Data Monitoring Committee involved in the conduct of clinical trials in children is specified, unless provided otherwise in the protocol. If it is not available, the ethics committee or the Turkish Pharmaceuticals and Medical Device Agency may require assembling of this committee.

6.9.9. There should be provisions in the protocol for systematic independent publication of results, within a reasonable timeframe, including when results are unfavorable.

6.9.10.

The Ethics Committee and the Turkish Pharmaceuticals and Medical Device Agency should ensure that the sponsor regularly monitors and reviews the balance of risk and benefit of the research so that the health and wellbeing of the children enrolled are safeguarded.

6.9.11. For randomized trials there should be equipoise at the beginning of the trial and no participants should receive care known to be inferior to existing treatments.

7. DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE PEDIATRIC POPULATION

7.1. The clinical trial design depends on the objectives of the trial and the scientific questions to be asked.

7.2. To ensure validity of trials to be performed, it is recommended that the trial design be set up following consultation of the patients from the age groups to be involved in the trial (in older children or adolescents) or from patient representatives.

7.3. In addition to the selection of the age groups of children to be included in the trial, particular attention should be paid to the inclusion (and possibly detection) of certain subgroups with certain genetic characteristics (e.g. G6PDH deficiency). Genetic diversity may produce significant differences in drug metabolism, in clinical response to drugs, and in adverse reactions that are to be expected.

7.4. As is the case for trials in adults, all measures to avoid bias should be included in trials performed in children. For example, unblinded or uncontrolled trials for the demonstration of efficacy are subject to increased bias and should be avoided whenever possible.

7.5. Whenever possible (e.g., when differences in the mode of administration of the product precludes masking), open trials should include provisions for blinding of assessment. Assessment, i.e., a systematic evaluation and documentation, in many cases will be based on the assessment by parents, or other caregivers. Whenever possible, the evaluation by the child should additionally be obtained.

7.6. Uncontrolled trials for demonstration of efficacy should be avoided in principle. They have limited usefulness for the demonstration of safety, unless they are used prospectively or in predefined subgroups. Trials performed in children affected by rare diseases should follow the same methodological standards as those performed in more common diseases. Alternative designs and analyses should be justified; it is recommended that they should be agreed with the Turkish Pharmaceuticals and Medical Device Agency when used with a view to provide data for regulatory purposes.

7.7. The size of the trial conducted in children should be as small as possible but large enough to demonstrate the appropriate efficacy with sufficient statistical power. In conjunction with the analysis of risks and benefit, trials involving fewer children should be weighed against trials involving more children but using less invasive procedures. Adaptive or other designs may be used to minimize the size of the clinical trial.

7.8. The use of control groups and placebo should be based on equipoise, should be appropriate to the conditions under investigation in the trial, and should be justified scientifically.

7.8.1. Use of placebo: Use of placebo in children is more restricted than in adults, because children cannot consent. Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions. The use of placebo is often needed for scientific reasons, including in pediatric trials. The use of placebo may be warranted in children as in adults when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain, hay fever). As the level of evidence in favor of an effective treatment increases, the ethical justification for placebo use decreases.

Placebo use is not equivalent to absence of treatment, for example placebo could be used on top of standard care. In all cases, its use should be associated with measures to minimize exposure and avoid irreversible harm, especially in serious or rapidly

evolving diseases. As appropriate, rescue treatment (treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level) and escape procedures (prompt removal of volunteers whose clinical status worsens or fails to improve to a defined level in a trial) should be set up. Other situations where the use of placebo should be scrutinized and challenged include run-in periods where a protocol requires active treatment to be withheld.

Situations in which placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the investigational medicinal product is the first one that may modify the course of the disease process, or, when the commonly used therapy for the condition is of questionable efficacy or carries with it a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.

Other trial designs should be considered if appropriate. Active-control trials may be more difficult to interpret than placebo-controlled ones but may provide useful information on comparative benefit/risk balance.

Therefore it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for pediatric clinical trials.

7.8.2. Superiority versus non-inferiority trials: Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins in relation to sample sizes feasible in the pediatric population, raise several issues, and should be fully justified when used instead of superiority trials. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non–inferiority trials. Existing guidelines on methodology issues and/or specific guidelines on relevant therapeutic areas should be consulted.

7.8.3. Controlled trials with (reference) medicinal products without a marketing registration in children in our Country: As many medicines used in children have not been fully assessed and authorized, the choice of active control products should be weighed thoroughly. Medicinal products not having a marketing authorization in our country may be considered suitable as controls if they represent evidence-based standard of care. Definitions of standard of care may vary.

7.8.4. Clinical trials in children using medicinal products containing radioisotopes: Except when radio-isotopes are required for therapy, stable isotopes should be used to avoid irradiation.

8. PAIN, DISTRESS, AND FEAR MINIMIZATION

8.1. Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and distress intensity is assessed and regularly monitored according to guidelines and age and condition-appropriate validated scales, particularly in preterm, newborn and other children who cannot express it. Effective treatment appropriate for the intensity of pain should be administered and reviewed regularly on the basis of the assessments performed. Patient-controlled analgesia may be used where appropriate, i.e., in children of sufficient understanding. Pain may be due to the disease or condition itself, and directly or indirectly to the medical interventions. Painful procedures should be minimized. Validated, non-invasive procedures should be preferred. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples in each child.

8.2. The parents and legal representatives should be informed of which procedure is part of the usual care and which is performed in relation to the trial. Age-appropriate explanation should be given to the child prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might also lead to humiliation of the child and therefore causing emotional pain should be avoided or explained. Examples of painful procedures include but are not limited to physical discomfort (exposure to cold, heat or light, noise), positioning and immobilization, invasive procedures such as blood sampling (capillary, venous and especially arterial) and vascular access, biopsies, lumbar puncture, sampling, repeat examination of injured or traumatized limbs or part of the body, endotracheal intubations and airways clearance, oral or nasal tubing. In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedures should be maintained.

8.3. In order to minimize pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained in the care of children. Staff should be trained to communicate with the both parents (or the legal representative) and children. Children in a trial should be hosted in a familiar environment, including appropriate furniture, toys, activities, and where appropriate, school attendance, and their concerns should be addressed by specialty personnel.

8.4. Fear should be prevented if possible, or if not, minimized; the need of the child for comfort and reassurance should always be kept in mind. Changes in the procedures should be announced to the child. Separation of the child from parents or familiar persons should be avoided whenever possible. If unavoidable, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent the procedure should be stopped; a short pause to allow the child to feel in control, further explanation and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure.

8.5. The variability of response to pain, distress and fear between children should be taken into consideration. Different reactions may be expected, when children are affected by a chronic or acute disease. Tolerance of pain increases with age and maturation when medical procedures are not considered any more as punitive.

8.6. In all situations, investigations/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.

9. RISK ASSESSMENT AND MONITORING

9.1. The child's interest should always prevail over that of science and society. This is paramount when assessing and monitoring risks. Risks are to be viewed in balance to the benefit.

9.2. Risk assessment is the most crucial step in evaluating a protocol and conducting the trial. Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. It may vary according to age groups. Risk should be assessed in terms of probability, magnitude and duration. Pediatric trials should be analyzed for potential risks, including those that may not usually be of concern in adults because medicines or procedures may cause adverse events in children who are not defined as adults. It is the responsibility of the principal investigator to make a thorough analysis of the risks in the trial and to describe this in the protocol in order for the ethics committee to be able to conclude on the approvability.

9.3. Risk assessment includes the evaluation of the risk of the medicinal product tested or the control, the risk of withholding active treatment in some cases, the risk of the disease itself. Potential harms would include prevalence and intrusiveness of research, the severity as well as seriousness of potential harms, the reversibility of adverse events and reactions, and their preventability. The accumulation of research projects in the same population (over-studied population) is another potential harm. Multiple clinical trials in an individual should be discouraged.

9.4. The timing of pediatric studies in relation to the information obtained from preclinical data and in adults may also be related to the levels of risk, either when studies are performed too early or when a delay to study potentially effective medicinal products in children is linked to obtaining adult data.

9.5. The unavailability of age-appropriate pediatric formulations may also incur a risk. Disclosure of a risk for an incurable disease following a pre-symptomatic diagnosis (e.g., genetic diagnosis) might also incur a risk, such as decrease in opportunities and freedom of choice. Similarly, violation of privacy is considered as potential harm.

9.6. In case of emerging issues during a trial with potential conflict between the children's interest and research interest, the protocol should envisage the management of such issues, e.g., harm in giving versus harm in withholding treatment. In addition to the risk inherent to the trial, there is a need for evaluation of external risks, for example linked to the variable level of expertise or experience of the centers involved.

9.7. Risk assessment is difficult in practice as probabilities are unknown; the elements that influence the risks should be identified in the protocol. Finally, any identified risk should be associated to measures to prevent, minimize and monitor such risks as much as possible.

9.8. The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. The following distinct risk levels are proposed as a means to decide on the ethical acceptability of trials:

> **9.8.1.** Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

9.8.2. Minor increase over minimal risk.

9.8.3. Greater than minor increase over minimal risk.

9.9. The level of risk may rise over time, during the trial and with emerging knowledge. Risk should be continuously monitored and specified in the protocol. Stopping rules should be included in the protocol, especially for unscheduled or scheduled analyses in relation to safety or non-compliance. The use of an independent data monitoring committee is recommended. The board should include pediatric experts. If an independent data monitoring committee is not used, for example in certain pharmacokinetic studies, this should be justified.

9.10. The sponsor of the clinical trial should identify and assess the risks (real and theoretical) and harms induced by the investigational medicinal products in the safety report submitted once a year throughout the clinical trial, or on request, to the Turkish Pharmaceuticals and Medical Device Agency and the ethics committee. In this report the sponsor should perform a specific analysis of the volunteers' safety in the pediatric population enrolled in the clinical trial, and provide an update of the risk/benefit evaluation for the pediatric population, in the light of scientific developments or events arising in the course of the research.

10. BENEFIT AND MEASURES OF BENEFIT

10.1. Direct benefit refers to benefit of the individual or benefit of the group.

10.2. Benefit can be defined as progress in treatment, diagnosis, or prevention for the child or the group of children affected. It is a tangible outcome that may be experienced by the volunteer. It may be obtained through either increased efficacy or safety resulting in a better risk/benefit balance, or through the provision of an alternative to existing treatment with at least similar expected benefit/risk balance. Benefit can also be obtained through contribution to patient care (for example, better route of administration, decreased frequency of dosing, improvement in relation to potential medication errors or compliance, reduced treatment duration, or a clinically relevant age-appropriate formulation).

10.3. Benefit for a group of children affected by the same disease, or a disease which shares similar features and for which the medicinal product could be of benefit, could be defined by increased knowledge of the condition or treatment, which would possibly result in better diagnosis, treatment or prevention. Measures of such benefit would include the importance of knowledge gained, seriousness and the commonality of the issue to be addressed, likelihood of obtaining results from the proposed research, and usefulness of benefits obtained.

10.4. The determination of the levels of risk and the associated benefits are the basis for ethical approvability. The risk levels should be presented by the sponsor and assessed by the ethics committee. As the assessment of the risk and the benefit may be based on probabilities and assumptions, this should also be balanced with the seriousness of the condition or diseases to be studied and the risk and benefit of alternative treatments.

10.5. In the following examples, levels of risk are considered to be in balance with the benefit for a trial with the pediatric population:

10.5.1. Minimal risk with benefit for the individual or benefit for the group

10.5.2. Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favorable as that of available alternative approaches

10.5.3. Greater than minor increase over minimal risk with benefit for the individual that is especially favorable in relation to available alternative approaches for the individual's condition.

11. TRIALS WITH ASSAYS IN RELATION TO AGE/BODYWEIGHT AND BLOOD SAMPLING

11.1. The type of assays, investigations and blood sampling volumes related to the trial should be described and justified in the protocol.

11.2. The number and type of assays and investigations should take into consideration the age and/or bodyweight (body surface area if appropriate) of the children to be included in the trial: appropriate tools and material should be used. Alternative sampling (e.g. urine or salvia sampling) for pharmacokinetic studies should be preferred when possible. For blood and tissue assays, micro-volumes

and micro-assays should be used, whenever possible. In principle, general or local anesthesia should be used as appropriate for painful or invasive procedures.

11.3. Timing of sampling should be coordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimize pain and distress, and the risk of iatrogenic complications. Sampling should be performed by trained staff. The number of attempts for sampling should be limited. Timing of sampling and number of sampling attempts should be defined in the protocol. For example, after one unsuccessful attempt, another experienced person should take over the procedure.

11.4. Preterm and term neonates have very limited blood volume, are often anemic due to age and frequent sampling related to pathological conditions. The fact that children, especially in this age group, receive blood transfusions (or iron or erythropoietin supplementation) should not be used as a convenience for increased volume or frequency for blood sampling.

11.5. The following blood volume limits for sampling are recommended. If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including during preventive interventions) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 ml/kg of body weight, i.e. 3% is 2.4 ml blood per kg of body weight.

11.6. Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected blood loss should be detailed in any trial protocol, and should be detailed also in the patient information sheet.

12. TRIALS WITH NEONATES (TERM AND PRETERM)

12.1. Neonates, be they preterm or term, represent the most vulnerable group of the pediatric populations. When affected by a serious disease, a neonate is transformed into a multi-drug user with potential interactions to be taken into consideration. This pediatric subset may also differ pharmacologically from older ones. Trial protocols in this population should take into account the complexity of the situation and potential for long-term, including developmental effects. Comprehensive scrutiny from ethics committees and investigators is therefore required.

13. TRIALS WITH HEALTHY CHILDREN

13.1. In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable like children with a disease or condition. Studies should not be performed in children when they can be performed in adults. Exceptions could be where healthy children participate in palatability testing such as swill and spit taste testing for a new flavored medicine.

13.2. In some situations, studies need to be performed in children who are healthy at the time of the trial. Prevention trials or pediatric vaccine trials, including immunogenicity studies, will fall into this category, and the likelihood of the target population to benefit from them is high. Clinical trials in children with intermittent diseases (e.g., flare-ups or seizures) are acceptable because even in the healthy phase the children are in fact affected. Whenever possible the older age groups should be considered for inclusion in the study before the younger ones.

13.3. Proof of concept should first be obtained in relevant animal models and/or in adults. Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible, i.e., the one affected by the disease, although it is recognized that data obtained in affected children may have variability.

14. VACCINES

14.1. Immune response should be studied in the target population taking into consideration immune system maturation.

15. PEDIATRIC FORMULATIONS TO BE USED IN PEDIATRIC TRIALS

15.1. Formulations used in a trial should be described in the protocol in accordance with the applicable legislation. Additionally, formulations used in pediatric clinical trials should be reported in publications.

15.2. Age-appropriate formulations should be used to avoid the risk of adverse reactions (for example, young children choking on tablets), the risk of dosing errors or inaccuracy. When they exist, pediatric formulations should be used. If extemporaneous preparations are used as a consequence of a lack of appropriate formulation, the conditions for preparing them and the dose should be indicated and should follow good manufacturing principles.

15.3. Excipients used for the formulation should take into consideration the age of the children included in the trial (e.g., benzyl alcohol is contraindicated in neonates). Conditions to avoid bacterial contamination and degradation of the medicinal product should be specified in the protocol.

16. INDIVIDUAL DATA PROTECTION

16.1. The specificity of data protection in children also relates to future (unknown) use of data obtained in children. Biobank samples retention and the need for consenting to such use should be discussed in the protocol. The trial documents should be archived for a duration that takes into consideration the potential need for longer-term review of trials performed in children (long-term safety).

16.2. Instances are rare of children challenging the records about themselves. Therefore there is the additional duty of researchers to protect confidentiality and access to data. Protocols should specify the level of protection of educational performance records contained in trial documents when studies are performed in schools (access, amendments and disclosure), and the information given to parents or legal representative. This is particularly important when trials include adolescents and address issues of sexuality, illicit drug use, or violence.

16.3. Where personal information on a child is collected, stored, accessed, used, or disposed of, principal investigator and other investigators should ensure that the privacy, confidentiality and cultural sensitivities of the volunteer and the community are respected. Children participating in a trial are entitled to know any information collected on their health. Other personal information collected for a research project will need to be made accessible to them in conformity with the applicable legislation on the protection of individual data. Disclosure of genetic findings, which may be risks in clinical trials, requires expert counseling in an adequate setting.

17. UNNECESSARY REPLICATION OF TRIALS

17.1. It is considered unethical to unnecessarily replicate trials in children.

17.2. Systematic registration of pediatric clinical trials and publication of results including unfavorable ones, together with a thorough analysis of the literature should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in children.

17.3. Ethics committees should not accept pediatric protocols that prevent independent publication by investigators, and the timeline for publication should be specified in the respective protocols.

18. ADVERSE REACTIONS AND REPORTING

18.1. Rules and obligations for reporting adverse reactions in pediatric trials are identical to those in adults, and to the notification of serious adverse reactions observed in clinical trials, and these have to be conducted in full compliance with the relevant legislation in force.

18.2. As adult data are poorly predictive of children's safety, reporting may cover target organs and types or severity of reactions differing from that expected in adults. A specific assessment of the adverse reactions associated with the administration of the investigational medicinal product in children should be given in the annual safety report.

18.3. Parents/legal representatives and caregivers should be particularly instructed to report adverse reactions and events to the investigators in a timely manner. This is particularly important in young children, who are in no position to identify adverse reactions.

19. INDUCEMENTS/COMPENSATION FOR CHILDREN

19.1. There must be no inducement, or any promise for financial gain to enter and stay on a trial, either for the parents, legal representatives or children.

19.2. However, the costs associated with participation of the volunteers to the trial, and decrease of income associated with loss of workdays by the healthy volunteers will be designated in the trial budget and compensated from this budget.

20. INSURANCE

20.1. The applicable legislation requires insurance in certain circumstances. Obtaining insurance for trials performed in children, in particular those in neonates, may be difficult because insurance companies invoke issues of long-term liability. Insurance policies should not waive liabilities regarding long-term effects, or limit the liability period; this period usually covers at least 5 years following the completion of trial, and also varies according to the quality of the trial. Ethics committees should pay careful attention to the insurance policy regarding this issue, in particular with respect to long-term effects on the child's development.

20.2. Unrecognized congenital defects are generally excluded. Suspected unexpected serious adverse reactions that can be related to these unrecognized congenital defects should be covered in insurance contracts.

20.3. Medical records should be protected by the privacy requirements of the applicable legislations in order not to pose a risk of labeling individuals with pre-existing conditions by insurance companies.

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

21.1. Compliance of clinical trials with the good clinical practice (GCP) and relevant legislation is required. Although not specific to pediatric trials, ethical violations and non-compliance with good clinical practice is particularly important as children are a vulnerable population.

21.2. There are roles for Ethics Committees and the Turkish Pharmaceuticals and Medical Device Agency in case of violation and non-compliance with good clinical practice. Violations fall into categories of critical, major and minor issues according to whether and to which extent patient safety and scientific value are compromised. The preferred option to avoid such violations is education, training and counseling. Ethics committees should notify the Turkish Pharmaceuticals and Medical Devic Agency if they are informed of such violation or non-compliance with good clinical practice.

21.3. Compliance with GCP should be explicit in publications, and results of studies conducted unethically should be made public with a clear warning specifying the unethical aspects. Information on such trials is needed to avoid unnecessary repetition of the trials and to protect future trial volunteers.

21.4. If non GCP-compliant data are submitted as part of a marketing registration application, an inquiry should be launched into the quality of the data, the study results, and consequently the validity of the marketing registration application. Sensitivity analysis should be performed within the GCP-compliant full data set, and in some cases also in comparison with all GCP-non compliant data. The overall reliability of the trial should be questioned.

22. THE ISSUES TO BE TAKEN INTO CONSIDERATION FOR PLANNING A CLINICAL TRIAL TO BE CONDUCTED IN PEDIATRIC POPULATION

Some of the issues to be taken into consideration for planning a clinical trial to be conducted in pediatric population are listed below.

22.1. Identification and scientific validity of the study question to be answered

22.2. Justification of the study to be performed in children and in the proposed age groups

22.3. Evidence of direct benefit for the child, or benefit for the group

22.4. The competence of the responsible study investigator and his team

22.5. The infrastructure of the institution or primary care practice that should be qualified and experienced in pediatric research in general and in particular in the field of the applied project

22.6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a pediatric clinical trial

22.7. The clinical results of adult studies (literature, investigator's brochure), if any.

22.8. Type and phase of the study

22.9. Use of placebo or active control

22.10. Age-appropriate formulations of medicinal products

22.11. Age-appropriate scales or measures of endpoints (e.g., pain scale)

22.12. Study design and biometric planning in relation to the trial question

22.13. Design feasibility and information sheets checked with children / patient representatives

22.14. Inclusion and exclusion criteria

22.15. Statistical methods

22.16. Criteria for the termination of the study

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

22.18. Appropriate pharmacovigilance procedures put in place by the sponsor

22.19. Study risks, pain, fear and discomfort

22.20. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial

22.21. The balance of expected benefit versus risks should be positive for the clinical trial

22.22. Comprehensive, understandable volunteer informed consent form and information sheets for legal representatives

22.23. Understandable age specific volunteer informed consent form and information sheet for children

22.24. Anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his family

22.25. Insurance of child participants

22.26. If available, opinions of other ethics committees for international multi-center studies

22.27. Publication of trial results

22.28. Continuation of trial medication where appropriate

23. INFORMATION FOR VOLUNTEER INFORMED CONSENT FORM TO BE USED IN CLINICAL TRIALS TO BE CONDUCTED IN PEDIATRIC POPULATION

23.1. Information sheets should be separate for parents and children.

23.2. The information sheets should be concise in content, precise in language (use of technical terms should be avoided), and appropriate for the age of children (abstract concepts, multiple options should be avoided).

23.3. The number of age-specific variations in information forms should be kept in a minimum number in order to include different wording or presentation to a great extent. In addition, information sheets should not cause unnecessary distress.

23.4. Information sheets should be harmonized throughout sites in multi-center trials, and address similar age groups in multinational trials.

23.5 The list of items recommended to be included in information sheets and volunteer informed consent forms are provided below:

23.5.1. What is the purpose of the trial?

23.5.2. Why have I been chosen?

23.5.3. Do I have to take part?

23.5.4. What will happen to me if I take part?

23.5.5. What are the compensations?

23.5.6. What will I have to do?

23.5.7. What is the medicine that is being tested?

23.5.8. What are the alternatives for diagnosis or treatment?

23.5.9. What are the possible disadvantages and risks of taking part?

23.5.10. What are the side effects of any treatment received when taking part?

23.5.11. Is ionizing radiation to be received, and which regulations are applicable?

23.5.12. Is there possible harm to an unborn child?

23.5.13. What are the possible benefits of taking part?

23.5.14. What happens when the research study stops?

23.5.15. What if there is a problem?

23.5.16. Will my taking part in the trial be kept confidential?

23.5.17. What will happen if I don't want to carry on with the trial?

23.5.18. What are the options if I stop taking part in the trial?

23.5.19. Is there any role of my doctor/family doctor in this trial?

23.5.20. What will happen to any samples taken from my body?

23.5.21. Will any genetic tests be done? If it is to be performed in which country and in which laboratory, if possible, it will be done?

23.5.22. What will happen to the results of the research trial?

23.5.23. Who is organizing and funding the research?

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

23.5.25. What are the contact details for obtaining information or filing complaints? Trial alert and information cards, which includes the trial essentials and especially the contact information, should be handed to the child, and if appropriate, to the parents/legal representatives.

24. EXAMPLES FOR LEVELS OF RISKS

24.1. Table-1 provides examples of risk evaluation for measures carried out for the purpose of a trial. This evaluation is not definite because the circumstances of child influence evaluation of risks. For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling.

The risk evaluation of some of the measures (including, but not limited to those marked *) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the risk level increases with the increase in frequency of the measures and with the susceptibility to harm of involved organs. The categorization proposed in the table applies to single or very

infrequent use of the measure. The examples presuppose that the measures are carried out to the highest professional standards.

25. ANNULLED REGULATIONS

Guidance on Ethical Approaches for Clinical Trials Conducted with the Pediatric Population, which entered into force in accordance with the Authority Approval dated 23.08.2011 and numbered 7481 was abolished.

26. ENFORCEMENT

This guideline will enter into force on the date of approval.

Table 1

No or minimal riskrisk	Minor increase over minimal risk	Greater than minor increase over minimal risk
- History taking - Clinical examination - Auxological measurements - Tanner staging - Behavioral testing - Psychological testing* - Quality of Life assessment - Venipuncture* - Heel prick* - Finger prick* - Subcutaneous injection - Urine collection with bag* - Breath condensate collection - Collection of saliva or sputum - Collection of hair sample - Collection of tissue removed from body as part of medical treatment* - Topical analgesia* - Stool tests - Bioimpedancemetry - Transcutaneous oxygen saturation monitoring (pulse oxymetry)* - Blood pressure monitoring - Electroencephalography - Electrocardiography - Vision or hearing testing - Ophthalmoscopy - Tympanometry - Lung function tests (peak flow, exhaled NO, spirometry) - Oral glucose tolerance test - Ultrasound scan - Digitally amplified chest or limb X-ray* - Stable isotope examination	- Urine collection via endoluminal or suprapubic catheter - Arterial puncture - Umbilical catheter - pH measurement - Nasogastric tube insertion anduse - Transcutaneous oxygen or carbon dioxide tension monitoring - Electrophysiological measurements (using stimulation) - Exercise testing (ergometry, spiroergometry) - Raised volume pulmonary function testing (infants) - Peripheral venous lines - Polysomnography - Fasting (≥ meal) - Spinal CSF tap - Bone marrow aspiration - MRI scan - X-ray other than digitally amplified chest or limb X-ray - CT scan* - X-ray DEXA bone density measurement - Use of contrast media - Paracentesis - Skin punch biopsy - Airways or skin hyperreactivit y challenge test	- Heart catheterization - Endoscopy - Biopsy - Surgery or modification of standard surgical procedure carried out as part of medical treatment - Sedation - Anesthesia - Systemic analgesia - Hypoglycemia test - Unstable isotope usage - PET scanning