National Ethics Guidelines for Bio-Medical Research involving Children
Section 1

1.1 Introduction

Biomedical and Health Research includes studies on basic, applied and operational research studies designed primarily to increase the scientific knowledge about diseases and conditions (physical or socio-behavioral), their detection, cause and strategies for health promotion, prevention, or amelioration of disease and rehabilitation.

Biomedical research involving children is needed for the benefit of the future generations of humanity. It leads to advances in medical care which can potentially improve the health and quality of life of children. As we complete the first decade of the 21st century, we have numerous opportunities to develop interventions to promote health, and prevent and treat diseases that affect children. This can only be achieved through experimentation. Research and innovation is therefore the core of the endeavor to generate and translate knowledge into clinical care. However, at the same time, we do not want to place children at risk of being harmed by participating in research studies.

As per the Helsinki declaration 2013, some research populations (such as children) are particularly vulnerable and have an increased likelihood of incurring additional and greater harm. Vulnerable means an individual or group of people who are not in a position to make autonomous decisions regarding participation in research, for example; children, students, prisoners, mentally challenged individuals and others. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence. All vulnerable groups need specifically considered protection. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and the research cannot be carried out in a non-vulnerable population. Additionally, if there is a reasonable likelihood that this population or community should stands to benefit from the knowledge, practices or interventions that result from the results of the research. Consideration should also be given to ensuring that the community receives a fair level of additional benefits.

Ethics are codified practices and/or procedures performed by the practitioners of the profession. The practice of biomedical research in children raises a number of ethical issues. The first issue is that children lack autonomy, i.e. the intellectual and emotional maturity to consent to research participation on their own behalf. Their vulnerability demands special consideration from researchers and policymakers and additional protections beyond those provided to mentally competent adult participants in research. Any research on children must consider the level of their physical, cognitive, emotional, and social development. The protection provided must be appropriate to the respective stage of development. Except when it is not feasible or reasonable, research with animals, and adults should precede studies with children to minimize research risks.1 These concepts underlie the basic ethical principles of beneficence and non-maleficence. However, any system for protecting children involved in research, should not unreasonably impede research that may potentially benefit them in the future. This goes against the basic ethical principle of justice. The concept of justice means that distribution of the potential harms and benefits of participating in research should be fairly distributed. For example, a vulnerable set of patients (e.g. children from poor socio-economic status being treated in a government hospital) should not be unduly exposed to research risks, just because they are available, and their parents are not fully aware of their rights.

There are also special challenges of research in developing countries. In our resource-constraint settings with parents having low levels of literacy, children are even more vulnerable. The concept of research is not well understood by most parents, and research is often confused with treatment (therapeutic misconception), or seen as a way of getting new therapies, or better clinical care. They may also be unduly susceptible to financial inducements to participate in research because of the poor socio-economic status of their families. Overuse of these vulnerable groups is a special concern when they are unlikely to benefit from the knowledge gained from research. Research in resource-poor countries has been particularly criticized as unjust when it is not responsive to the respective societies and countries. For instance, a study being conducted in children of a developing country with potential beneficiaries of the intervention being those from rich nations is bound to raise concerns. In India, we face the additional challenge of applying universal ethical principles to biomedical research in the multicultural Indian society with a wide diversity of health-care systems of considerably varying standards.

1.2 Needs and challenges of clinical research in children
Medical research involving children is essential for advancing child health. In most situations, research with adults cannot simply be generalized or extrapolated to infants, children, and adolescents and, research involving children is essential if children are to share fully in the benefits derived from advances in biomedical sciences.

1.2.1 Why is biomedical research necessary in children?

1) The disease may affect only children and newborns, e.g. hyaline membrane disease, birth asphyxia, neonatal hyperbilirubinemia, extrahepatic biliary atresia, infantile spasms, infantile tremor syndrome, Kawasaki disease, etc. Such diseases have no close parallels in adults, therefore it is necessary to carry out research with children to advance our knowledge in these diseases. Additionally, even if the same disease affects both children and adults, the pathophysiological processes and responses to treatment in children may differ from those in adults. Diseases such as nephrotic syndrome, hypertension and rheumatoid arthritis, for instance affect both adults and children, but the pathophysiological basis is very different in both.

2) The physiology of children is different from that of adults, and the pharmacokinetics of many drugs will vary with the age of the child. For example, children metabolize many drugs much more rapidly as compared to adults, hence the dose of the drug per kg of body weight that needs to be given, is much higher in children as compared to adults. The absorption of drugs also varies with age. Growth and maturation can alter the kinetics, end-organ responses, and toxicities of drugs used in infants, children, and adolescents compared with adults. Without proper drug studies in children, children may not benefit from and may even be harmed by drugs that are available to adults.

3) The adverse effects of many drugs may also be different in children as compared to adults. For instance, tetracyclines cause teeth discoloration in young children, aspirin use is associated with Reye's syndrome in children. Treatments designed specifically to meet the needs of children must ensure that age-related differences in drug handling and/or effects are recognized, that the doses needed for efficacy are elucidated, and that any adverse effects can be avoided.

4) There are requirements for age-appropriate formulations that allow the accurate, safe, and palatable administration of medicines to children of a wide range of weights and with a wide range of developmental characteristics. For the therapy to be effective, its delivery must suit their needs. Use of adult formulations is often not suitable; many children find it easier to swallow a liquid formulation than a tablet.

5) Many disorders can only be understood in the context of a child's growth and development. Examples include adaptive changes in the motor system following a perinatal stroke.

6) Research with children can also play a key part in increasing our understanding of some adult diseases that are thought to have their origins in early life. It enables the development of preventive intervention into the natural history of the disease. The findings of research involving children can therefore also be relevant for adults.

1.2.2 Challenges of biomedical research in children

1) Diseases in children may be rare, and there may not be sufficient numbers of affected patients to answer the research questions. This may lead to difficulties in gaining statistical power to evaluate an effective treatment. For this purpose, large multi-centric trials lasting many years are needed.

2) It is usually difficult to find funding for above-mentioned pediatric research. The market for pediatric drugs and treatments is quite small compared to the adult ones, so pharmaceutical companies do not find it remunerative enough to fund pediatric research.

3) The ethical concerns with pediatric research, which include lack of autonomy and inherent vulnerability make it all the more difficult to perform research in children.

4) Research in children is not just performing research on individual patients. As parents and families are involved, we need to take the familial and socio-cultural concerns in view while planning research in children.
5) Research procedures and settings need to consider children’s physical, cognitive, and emotional development. Developmentally appropriate outcomes need to be studied. Follow up studies (which may take years) are often needed to see the long term outcomes of high risk neonates.

1.3 The process of developing ethics guidelines for research involving neonates and children

The Indian Council of Medical Research brought out the ‘Policy Statement on Ethical Considerations involved in Research on Human Subjects’ in 1980 and revised these guidelines in 2000 as the ‘Ethical guidelines for Biomedical Research on Human Subjects’. The third version was developed in 2006. ‘These guidelines do have a small section pertaining to research in children, however, a need was felt to develop more comprehensive detailed guidelines which pertain to the specifics of ethics in biomedical research in neonates and children. This endeavor was undertaken under the ‘AIIMS-ICMR collaborative project on center for excellence in newborn care’

As a first step, the existing national and international guidelines for biomedical research in children were reviewed. Separate guidelines available for pediatric biomedical research in other countries include the Institute of Medicine guidelines in the USA, the Medical Research Council guidelines in the United Kingdom, and the European union guidelines. These guidelines have been reviewed for a better understanding of the ethical principles of biomedical research in children. Also there have been meetings with experts in the field of bioethics to develop consensus guidelines in the Indian context. The guidelines have been developed after the expert group discussions and consensus development.

1.4 Scope of the guidelines

This document covers the ethical and legal issues that researchers need to consider when carrying out biomedical research in neonates and children. The aim has been to set out general principles that can be applied in most situations rather than to cover each and every situation. We have aimed to make the guidelines easy-to-read and pragmatic. These guidelines need to be used in conjunction with the other existing ICMR guidelines. These guidelines are meant for use by researchers, ethical committees and other involved stakeholders.

These guidelines cover general biomedical research involving children. The age limit for definition of ‘child’ has been variable according to various legal and social contexts.

As per the Ministry of Women and Child Health, a child ‘means every human being below the age of eighteen years’ (CRC document). A neonate is defined as a child who is less than 28 days old.

These guidelines are sub-serving to the constitution of India and our legislature. If the research is a regulatory clinical trial falling under the Drugs and Cosmetics Act, and its rules and amendments therein, the researchers should follow the requirements as stated under the act.

For regulatory purposes, ‘Clinical trial’ means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.

Definition of new drug: For the purpose of this part, new drug shall mean and include- 2(f)(a) A drug, as defined in the Act including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognized as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims:

Provided that the limited use, if any, has been with the permission of the licensing authority.

(b) A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

(c) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form)
form) and route of administration. (See items (b) and (c) of 3[Appendix VI] to Schedule Y) and Schedule-Y to the Drug and Cosmetics Rules, 1945.

[As per Rule 122DA: no clinical trial for a new drug whether for clinical investigation or any clinical experiment by any Institution shall be conducted without approval of DCG(I).]

Three amendments in the Drugs and Cosmetics Rules, 1945, have been made for safeguarding the rights, safety and well-being of trials subjects and registration of Ethics Committees for regulating the clinical trials in the country.

For details regarding clinical trials and regulations, please refer appendix (www.cdsco.nic.in/).

1.5 General guidelines for research involving children

Research proposals involving children should be scientifically sound, with benefit to children in general and, in most cases, to the individual child subject. The need for the study should be justified by a thorough review of literature. The research should be conducted by investigators who have the requisite expertise, and one or more members of the team should be a paediatrician and/or have prior experience of conducting research in children. Research involving children should take into consideration the unique physiology, anatomy, psychology, pharmacology, social situation, and special needs of children and their families. Research involving children must be conducted in a child-friendly environment.

In general, drugs should be tested for safety, pharmacokinetics, and at least initial indications of efficacy in adults before being tested in children. It may often be appropriate to defer pediatric testing until adult testing has reached phase 3 or beyond, when substantial data are available on the safety and efficacy of a drug in adults.3
Section 2: Risk

2.1 Assessment of risk and benefit in pediatric research

During the journey in the quest of new knowledge and science, every study entails some risk to the participant which should be balanced by the likelihood of anticipated benefit. The relationship between the risk the participant is likely to face and the anticipated benefit is a very important consideration in the ethical conduct of biomedical research. The equation between the potential risk and the risk or potential harm should be at least as favorable for the proposed research procedure as for the alternatives available to the children. A research equipoise between risk and benefit must be reached when considering biomedical research.

Risk or harm is a very important consideration in pediatric research. Risk refers to a potential harm that can occur to the child as a direct or indirect consequence of the research procedure. Research procedures include any procedure the participant undergoes for the purpose of research which include questionnaire, investigations such as blood sampling, bone marrow aspiration, liver biopsy etc or therapeutic intervention such as medication or surgery. The risk for the research procedures need to be considered when they are over and above the routine care of the participant.

Harms occurring from participating in research may be physical (e.g., pain, disability, discomfort, or death), or psychological (e.g., fear, anxiety, or depression), or social (missing school etc). For research that includes children, investigators and reviewers of research must consider potential harms such as fear and separation from parents that are usually not considered in studies involving adults. Harms related to the violation of privacy or confidentiality must also be considered.

Risks have to be assessed in relation to benefits. A benefit is a positive outcome. The benefit is usually potential, which means positive but uncertain outcome. The benefit may be direct, as in a direct benefit to the participant; or indirect. Examples of direct benefit include the possibility of cure, alleviation of pain, improvement in disease severity etc. Indirect benefits include the opportunity to learn more about the disease, develop social relationship with other patients etc. Payments for participation should not be considered in the risk-benefit ratio. Also, patients and participants may consider other benefits such better access to the doctors, access to investigations which are not otherwise freely available, being special patients as part of research etc. These indirect benefits may be all the more misunderstood by illiterate patients from poor socioeconomic strata.

It needs to be emphasised that these research risks should be over and above the risks constituted by the standard of care. Risk assessment needs to be done only for those procedures that are additional to the standard practice, i.e. over and above those procedures that the child would anyway undergo during normal care.

2.2 Classification of Risks

Definitions:
Risks may be classified as minimal, low and high risk. These are however just broad guidelines. As explained later, the categorization of risk may vary from child to child even with the same research procedure depending on the situation, so individual judgement has to be exercised.

2.2.1 Minimal Risk

Minimal risk is defined as one which may be anticipated as harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. This includes procedures such as questioning, observing, and measuring children, provided that procedures are carried out in a sensitive way, respecting the child's autonomy, and that consent has been given. Procedures with minimal risk include history taking, physical examination, chest X-ray, obtaining bodily fluids without invasive intervention, e.g., taking saliva or urine samples etc. It is expected that research of minimal risk would not result in more than a very slight and temporary negative impact on the health of the person concerned.
2.2.2 Low risk

Low risk is defined as a slight increase in the potential for harms or discomfort beyond minimal risk (as defined in relation to the normal experiences of average, healthy, normal children). These include procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress; e.g., a blood test, oral sedation for diagnostic procedures etc.

2.2.3 High risk

All research procedures which have a risk over and above the low risk are classified as high risk. These include procedures such as lumbar puncture, lung or liver biopsy, intravenous sedation for diagnostic procedures etc.

2.3 Concept of relative versus absolute interpretation of risk

The relative interpretation takes into account the child’s underlying condition, and the treatment and risks he or she undergoes in daily life. For instance, a child with leukemia routinely undergoes bone marrow aspirations and chemotherapy. Therefore, the relative interpretation may claim that bone marrow aspirations and chemotherapy (otherwise high risk interventions) may be within ‘minimal risk’ for such a child. E.g. Bone marrow aspirations in this situation for the purpose of research may be considered ‘minimal risk’ in such children. A relative interpretation theoretically allows high-risk studies to be approved as ‘minimal-risk’ studies if members of target research populations experience high risks in their daily lives, because of their underlying medical or socioeconomic conditions. Such children may experience substantial everyday risks, distress, and uncomfortable medical examinations that are, for them, routine but not minimal in burden or discomfort. A relative interpretation of minimal risk would permit comparably high risks in research for these already high-risk children. In contrast, more fortunate research populations that experience low levels of risk in daily life would have a correspondingly low risk threshold for assessing whether a study presented minimal risk.

The relative interpretation of the minimal-risk standard may interfere with the objective of providing special protections to child participants in research. It misinterprets the purpose behind the minimal-risk standard; namely, to guide judgments about when risks are low enough to safely and ethically enrol children in studies that are not designed to benefit them. Furthermore, allowing a relative interpretation of minimal risk would violate the ethical principle of justice, which requires that the burdens and benefits of research be distributed equitably. Therefore, in children, an absolute interpretation of the ‘minimal risk’ may be better. The threshold of minimal risk should thus be the same for healthy and ill children.

2.4 Determinants of risk

1) Age and developmental status: Risk assessment in children must take into account their age, developmental status and maturity. For example, taking 10 ml blood sample may be low risk for a 10 year old, but high risk for a preterm neonate.

2) Underlying medical condition: In some cases, a procedure that is judged to involve minimal risk to healthy children may present more than minimal risk to children with certain medical conditions. For example, intramuscular injections that are safe for healthy children but would be risky for children with hemophilia. The eligibility and screening criteria described in research protocols should be sufficient to exclude such vulnerable children from studies that otherwise present minimal risk.

3) Cumulative characteristics of risk during a research: Determinations about risk should consider the duration and cumulative characteristics of research interventions or procedures, for example, the number of procedures included in a protocol or the number of times that an individual procedure is repeated in a given period of time. Certain studies may include several different procedures that involve minimal risk or burden individually but that taken together present more than minimal risk. Although a single blood sampling normally involves low risk but repeated blood sampling over a short period could, depending on the child’s age and other circumstances, present a higher degree of risk.

2.5 Pain, distress, and fear minimization in research in children

Both pain and emotional discomfort should be prevented as much as possible. When unavoidable it should be adequately managed and reduced as far as possible. As much as possible, non-invasive procedures should be
preferred. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples in each child.

The parents/LAR (Legally acceptable representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure as per research protocol) should be informed (IEC to ensure that this information appears in the parent information sheet) of which procedure is part of the usual care and which is performed in relation to the trial. In addition, 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 (therefore causing emotional pain) of the child (such as undressing) should be either avoided or explained. In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedure(s) should be maintained.

It is important that any studies that have the potential for participant discomfort are conducted in facilities appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. Children in a study should be hosted in a familiar environment, including appropriate furniture, toys, activities, and where appropriate, school attendance, and their concerns should be addressed by skilled personnel. 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. Separation of the child from parents or familiar persons should be avoided whenever possible. 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.

2.6 Type of assays and sample collection

In research involving children due consideration should be placed the number and type of body fluid assays and investigations.

- The blood samples should be the age and/or bodyweight appropriate
- The samples should be obtained using appropriate facilities and material
- Alternative sampling (e.g. urine or saliva sampling) for pharmacokinetic studies should be preferred when possible.
- For blood and tissue assays, microvolumes and micro-assays should be used, whenever possible.
- For painful and/or invasive procedures standard pain relief methods should be employed
- Timing of sampling should be co-ordinated to avoid repeated sampling procedures
- 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, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure.

2.7 Volume of blood

Preterm and term neonates have very limited blood volume. They are often anemic due to age and frequent sampling related to pathological conditions. Hence, monitoring of actual blood loss is routinely required in preterm and term neonates. Any research involving blood sampling should detail expected blood loss in the study protocol. This should also be detailed in the parent information sheet.

2.8 Pediatric formulations to be used in pediatric studies

Formulations used in a trial should be described in the protocol. 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. 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.
2.9 **Guidelines for ethical approval based on degree of risk**

Interventions intended to provide direct diagnostic, therapeutic or preventive benefit for the individual child participant must be justified in relation to anticipated risks involved in the study and anticipated benefits to society. Interventions that are intended to provide therapeutic benefit should be at least likely to be at least as advantageous to the individual child participant as any available alternative interventions. The risk presented by interventions not intended to benefit the individual child participant should be low when compared to the importance of the knowledge that is to be gained.

Section 3: Consent and Assent

3.1. **Informed consent**

In research involving children, the traditional method of informed consent which means that decisions about research participation are made by those with the legal and intellectual capacity to make such choices in their own right is difficult to execute. Children usually lack such capacity. Instead, the authority to allow a child’s participation in research rests with parents or guardians, who must provide their permission. However, with respect for children’s emerging maturity and independence and investigators must seek to involve children in discussions about research and obtain their *assent* to participation. The parental permission for the child’s participation in the research is termed as *consent* whereas the child’s agreement to participate is termed as *assent*.

3.1.1 **General principles of informed consent**

These principles hold true for all biomedical research, as per the ICMR guidelines. For all biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant or in the case of an individual who is not capable of giving informed consent, the consent of a legally acceptable representative. Legally acceptable representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure as per research protocol.

Informed consent protects the individual’s freedom of choice and respect for individual’s autonomy and is given voluntarily to participate in research or not. Adequate information about the research is given in a simple and easily understandable unambiguous language in a document known as the Informed Consent Form with Participant/ Information Sheet.

The latter should have following components as may be applicable:

1. Nature and purpose of study stating it as research
2. Duration of participation with number of participants
3. Procedures to be followed
4. Investigations, if any, to be performed
5. Foreseeable risks and discomforts adequately described and whether project involves more than minimal risk
6. Benefits to participant, community or medical profession as may be applicable
7. Policy on compensation
8. Availability of medical treatment for such injuries or risk management
9. Alternative treatments if available
10. Steps taken for ensuring confidentiality
11. No loss of benefits on withdrawal
12. Benefit sharing in the event of commercialization

13. Contact details of PI or local PI/Co-PI in multicentric studies for asking more information related to the research or in case of injury

14. Contact details of Chairman of the IEC for appeal against violation of rights

15. Voluntary participation

16. If test for genetics and HIV is to be done, counselling for consent for testing must be given as per national guidelines

17. Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipt of its results

A copy of the participant/information sheet should be given to the participant for her/his record. The informed consent should be brief in content highlighting that it is given of free will or voluntarily after understanding the implications of risks and benefits and s/he could withdraw without loss of routine care benefits. Assurance is given that confidentiality would be maintained and all the investigations/interventions would be carried out only after consent is obtained.

**Verbal Consent**

When the written consent is not possible because the parent/legal guardian is illiterate, verbal consent can be taken after ensuring its documentation by an unrelated witness. Audio-visual methods may be needed for vulnerable subjects in case of clinical trials.

Fresh or re-consent is taken in following conditions:

1. Availability of new information which would necessitate deviation of protocol.

2. When a research participant regains consciousness from unconscious state or is mentally competent to understand the study. If such an event is expected, then procedures to address it should be spelt out in the informed consent form.

3. When long term follow-up or study extension is planned later.

4. When there is change in treatment modality, procedures, site visits.

5. If the child is now above 18 years of age, or the LAR has changed.

6. Before publication if there is possibility of disclosure of identity through data presentation or photographs (which should be camouflaged adequately).

7. For use of stored biological samples if not anonymized.

**Stored samples:** For research on stored samples, the ICMR 2006 guidelines need to be followed.

**3.1.2 Waiver of consent**

Voluntary informed consent is always a requirement for every research proposal. However, this can be waived if it is justified that the research involves not more than minimal risk or when the participant and the researcher do not come into contact or when it is necessitated in emergency situations. If such studies have protections in place for both privacy and confidentiality, and do not violate the rights of the participants then IECs may waive off the requirement for informed consent in following instances:
i. When it is impractical to conduct research since confidentiality of personally identifiable information has to be maintained throughout research as may be required by the sensitivity of the research objective, eg., study on disease burden of HIV/AIDS.

ii. Research on publicly available information, documents, records, works, performances, reviews, quality assurance studies, archival materials or third-party interviews, service programs for benefit of public having a bearing on public health programs, and consumer acceptance studies.

iii. Research on anonymised biological samples, left over samples after clinical investigation, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognised institutions or qualified investigators, samples or data from repositories or registries etc.

iv. In emergency situations when no surrogate consent can be taken. Examples include research involving neonatal resuscitation, life threatening emergencies etc. In such situations, the parents/care givers may not be in a situation to give consent. However, once the child has been stabilized, a deferred consent must be taken.

v. Retrospective data analysis: For research on patient data already available in the hospital setting, the consent need not be taken if the patient’s data is anonymized. However, the protocols in the above mentioned studies need to be submitted to the IEC, and the decision for waiver of consent will lie with the IEC.

3.1.3. Concerns with the informed consent

1) The process of obtaining consent and assent should not be a mere formality and limited to the forms. Instead this should be a process, where-in the onus is on the investigator that he/she makes sure the parents and the children (as far as their developmental level and maturity) permits understand what is going on in the research.1 This process should include the opportunity for parents and children to ask questions and investigators to make assessments of the extent to which a decision about participation in research is made freely and with understanding of all the risks and benefits involved. The consent process also is not a one-time process but should be an ongoing interaction between the researcher and the participant, to help resolve the queries which may arise in the participant’s mind during the course of the study.

2) The language of the participant information sheet should be simple, and easily understood by the parents. Many times, in order to protect themselves from any future litigation, investigators make the patient information sheet full of technical terms (medical and legal) which the parents find difficult to understand.

3) When checking that parents understand all the aspects of research participation, a particular concern is whether they understand that they will be participating in research and that the purpose of research differs from the purpose of normal clinical care. The purpose of research is to generate knowledge, usually for the benefit of patients or individuals in the future. The belief that the purpose of research is treatment is termed the therapeutic misconception.5

3.2 Children’s assent

Assent is defined as a child’s affirmative agreement to participate in research. Mere failure to object should not be construed as assent. The assent process should take into account the child’s level of understanding and their general independence. Children first develop sensory and motor skills (from approximately birth to age 2 years) and then begin to use language and images (to approximately ages 6 or 7 years), develop certain concrete reasoning and problem-solving abilities (to approximately age 11 or 12 years), and, lastly, acquire more advanced capacities to think and reason about complex, abstract concepts, relationships, and processes (adolescence). Cultural and social factors also play an important role. Children vary considerably in the ability to understand abstract concepts depending on their age and maturity. Therefore, the same assent forms may not be uniformly applicable to all children in a particular age group. Children with chronic illness may have been challenged to develop increased capacity to make independent judgments based on previous life experience.

The other important issue here is the child’s general level of independence and autonomy.
Content of the assent process has to be in accordance with the developmental level and maturity of the child. For example, a child aged 8 years, would be told what exactly he/she is going to undergo. They may not understand the concept of research. Whereas, for a 15 year old, the assent process should be similar to the informed consent process. Children under age 9 or 10 years have a limited ability to understand the purposes, risks, and potential benefits of research, especially more complex research. These younger children are better able to grasp the more practical aspects of research (e.g., what they are expected to do) than they are to understand the more abstract dimensions (e.g., randomization). If the study is a long duration study, the researchers may have to repeat the assent process with more information, as the child grows older.

3.2.1 Age and method of obtaining assent

In children between 7 (84 months and above) to 12 years of age, oral assent must be obtained in the presence of parent/ legally acceptable representative. In children between 13 to 18 years of age, written assent must be obtained. If a child becomes 13 years old during the course of the study, then written assent must be obtained. In cases of verbal assent, the parent's counter-signature must be obtained that the child's verbal assent has been taken. Re-assent must be taken in all the same situations as re-consent as mentioned above.

3.2.2 Waiver of assent

Waiver of assent may be provided by the ethics committees in the following situations:

1) If the research has the prospect of directly benefiting the child and that potential benefit is available only in the research context. In such situations, the child's dissent may be overruled.

2) Waiver of assent may also be considered if the research involves children with mental retardation and other developmental disabilities, where the children may not have the developmental level and intellectual capability of giving assent.

3) Waiver of assent may be considered in community-based research if in socio-cultural-educational context, the children are considered to be immature and not capable of giving assent.

4) Assent may also be waived under the same conditions in which adult's informed consent maybe waived.

Refusal of child to participate must always be respected. The child must also be explained that he/she may withdraw his/her assent any time during the study.

3.3.3 Content of assent forms

The type and amount of information presented should be adapted to the child's cognitive and emotional status and experiences. The information should be simple, and age-appropriate. The basic information which needs to be provided includes:

1) What the study is about and whether it might help?

“We want to see whether a new medicine will or won’t help children like you who have headaches.”

“We want to understand your illness better”

2) What will happen and when?

“You will have to come to the hospital in the morning with an empty stomach. We will insert a needle and take a small amount of blood”

3) What discomfort there might be and what will be done to minimize it?

“It will hurt as much as a pin prick, but the pain will last only 5 minutes”

4) Who will answer the child's questions during the study?

5) Whether an option to say "no" exists?
“You do not have to be in this study and no one will be angry with you.”

“If you say “yes” and then change your mind, that is okay.”
Section 4: Safeguard Systems

4.1 Institutional ethics committee (IEC)

The ICMR provides clear guidelines for the requirement of IEC for institutes conducting bio-medical research. IECs when providing opinion on a study involving children should have experts with pediatric expertise. The experts may be permanent members of the IEC, or invited to provide advice and consulted on an ad-hoc basis.

Pediatric experts should be independent of the sponsor, the investigator and the research proposed. Experts should be available during the review of the initial protocol as well as any subsequent significant changes. The basic framework for review of research proposals by IECs remains the same as for research in adults.

4.2 Experience of investigator and research setting

The investigator’s competence and ethical conduct are the most important safeguards for protection of children involved in research. The experience of the investigator should be reviewed by the IEC. The IEC should seek the details of investigator’s publication and research experience along with the research proposal. The research team should have investigator(s) with expertise in sciences (health / social / behaviour etc.) related to childhood. If the investigator is less experienced, then IEC should ascertain appropriate mentorship, or oversight by a senior researcher / oversight committee.

It is desirable that research involving children is conducted in a child friendly environment. This however is not applicable to community based research. It is further desirable that individuals involved in interacting with children during the course of study are trained / experienced in dealing with children.

4.3 Data monitoring committees (DMC)

The need for DMC may be determined as an additional safeguard by the IEC depending on the anticipated risks to the children involved in the research. DMCs evaluating research performed in children should have members with appropriate expertise in the evaluation of clinical studies in children.
4.3 Data monitoring committees (DMC)

The fundamental reason to establish a DMC is to enhance the safety of trial participants in situations in which safety concerns may be unusually high. The need for DMC may be determined as an additional safeguard by the IEC depending on the anticipated risks to the participants of a study. (Clinical trials - European Commission, n.d.) The establishment of DMC is based on the fact that interim monitoring of accumulating study data may be essential to ensure the ongoing safety of trial participants. Those involved in the trial design and conduct of a trial may not be fully objective in reviewing the interim data for any emerging concerns. So there is a need for a group of expert advisors to ensure that such concerns would be addressed in an unbiased way. (ICMR, 2006)

DMCs have traditionally been established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome. DMCs add administrative complexity to a trial and require additional resources. DMCs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes.

Factors to consider when determining whether to establish a DMC for a particular trial;

The study endpoints are such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion.

There are a priori reasons for a particular safety concern [for example, if the procedure for administering the treatment is particularly invasive, or the treatment is potentially toxic]

The study is being performed in a potentially fragile population such as children, especially neonates or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity.

The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint.

The study is large, of long duration, and multi-centeric.

[Current FDA regulations, however, impose no requirements for the use of DMCs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted].

In studies with one or more of these characteristics, the additional oversight provided by a DMC can further protect study participants.

If the trial is likely to be completed quickly, the DMC may not have an opportunity to have a meaningful impact. In such cases, the DMC should be informed and convened quickly in the event of unexpected results that raise concerns, special mechanisms would have to be developed to permit DMC evaluation and input. Alternatively, the trial could build in “pauses” so that interim data could be reviewed by a DMC before an additional cohort of participants would be enrolled.

Another consideration in the decision of whether to have a DMC for a trial is whether a DMC can help assure scientific validity (and perception of such) of the trial. Sometimes accumulating data from within the trial (e.g., overall event rates) may suggest the need for modifications. Recommendations to change the inclusion criteria, the trial endpoints, or the size of the trial are best made by those without knowledge of the accumulating data.

Finally, the independent DMC evaluating trials performed in children should have members with appropriate expertise in the evaluation of clinical studies in children.

4.4 Data protection and confidentiality

Children are less likely to challenge records about themselves. Therefore, there is an additional duty of the investigator and the IEC to protect data of children and ensure confidentiality. IECs should review the issue of data protection and confidentiality in all research protocols. All documents of a research done involving children should be archived for a duration that takes into account the potential need for long-term review of data. This primarily pertains to long-term safety. When studies are performed in schools, parents or other individual may desire to know the responses of a child. This is particularly important when trials include adolescents and address issues of sexuality, illicit drug use or violence. It should be made amply clear in the protocol, in the
4.5 Bio-banking of samples:
Please refer to ICMR guidelines

4.6 International collaboration and data sharing
Please refer to ICMR guidelines and HMSC guidelines.

5.1 Compensation for participation

Parents and children should not be asked to bear the expenses of research participation. It is advised that IECs allow reimbursement of reasonable expenses incurred by child or caregivers to participate in research (e.g. travel, wage loss). Children involved in research may also receive free medical services. The IECs must ensure that payments do not act as inducements. Payments should not influence parents’ or children’s decisions to participate in research when such participation is not in child’s best interest. For example, providing a small payment at the end of the study may encourage completion, but making the entire payment contingent on completing a study could distort a parent’s or a child’s decision about continued participation in a study. IECs should assess this potential for undue influence, especially if such payments are proposed for studies that focus on low-income populations. When a guardian is asked to give consent on behalf of an incompetent person, no remuneration should be offered except a refund of out of pocket expenses.

Protocols should provide IECs with details about the type, level, and timing of payments to participants at the time of initial review and the details should also be included in the informed consent form. IECs should approve the type, level, and timing of payments made by the researchers. Full details of payments to be given to parents/child and other benefits of participation (e.g. free medical care) should be clearly mentioned in the protocol and parent/patient information sheet.

When children are enrolled into drug trials which come under the ambit of DCGI, all rules/guidelines pertaining to regulatory trials apply.

5.2 Compensation for Accidental Injury
Children are entitled for financial or other assistance to compensate them for any temporary or permanent impairment or disability resulting from participation in research. In case of death, their parents are entitled to compensation.

For research not under the DCGI purview, claims of compensation are to be submitted to the local IECs. IECs have the duty to assess the causality on case-to-case basis. The IECs decide on the amount of compensation by following the guidelines provided by GOI. While for research under the ambit of DCGI, the respective guidelines for compensation given by DCGI need to be followed.
Section 6: Special situations

6.1 Research in neonates

Neonates, represent the most vulnerable group within the pediatric population. Trial protocols in this population should take into account this and the potential for long-term effects of interventions, including developmental effects. Hence, a very careful scrutiny of protocols is required from the IECs. IECs reviewing any research proposed in neonates should have an advisory member with expertise in neonatal research/care.

IECs should carefully scrutinize all research proposed in neonates for the potential risks. Risks if any should be carefully weighed against possible benefits in this fragile population. IECs should ensure a proper scientific review of the protocol by a competent person to remove any risks resulting from poor methodology. Neonates should be researched only when the findings of the study will have direct implications on their future care. All measures to reduce risks should be undertaken. When possible, older children should be studied before work with younger children and infants. Within the neonates, those who are critically ill should be considered for research even more carefully. Parents or caretakers of these babies are facing stressors that may interfere with their ability to make an informed decision on behalf of the child. This problem can be reduced to some extent through strategies such as continuous consent. The consent of one parent is required for studies involving neonates with research exposing them to no or minimal risk or in studies that offer the prospect of direct benefit to the participant. However, studies that do not offer the prospect of direct benefit or are high risk, consent from both parents is required unless only one parent has legal responsibility for the care and custody of the child or 1 parent is deceased, unknown, incompetent, or not reasonably available.

If one of the parents is a minor, then the consent should not be taken from him/her. If both parents are minors then enrolment of such a baby should be avoided as far as possible. To enrol such neonates for research the investigators should provide adequate justification to the IEC. Strong consideration should be given to involving an independent observer in these situations to assure that the conditions of a competent, voluntary, and fully informed consent have occurred.

6.2 Research in HIV positive children

Research in HIV positive children involves some special situations which need to be considered by the IEC. Informed consent is to be obtained from the parent of the child or a legally authorized representative. For children enrolled in long term trials, and who lose a surviving parent or guardian during the study period, a re-consenting needs to be done for continued participation. This consent can be given by another custodian appointed by the family.

6.3 Vaccine trials in children

Please refer to section on vaccine trials in the ICMR guidelines on biomedical research.

6.4 Ethical issues in genetic research

Please refer to section on genetic research in the ICMR guidelines on biomedical research.

One important aspect of genetic research pertains to stored samples in which patient identity is identifiable. In such situations periodic re-consent is needed once the child attains the age of assent or consent.

6.5 Research involving children in an emergency situation

Research involving children in emergency situations should be carried out only when its scientifically justified and cannot be carried out outside this setting. All principals of ethical research need to be followed and IECs need to carefully scrutinize and approve all research proposed in emergency situations. There are no exceptions for obtaining consent in research done in emergency situations. The time frame within which the consent would be obtained should be reviewed and approved by the IEC. If the parent is not available or unable to give consent another individual can give consent as a legal representative. This could be the doctor primarily responsible for the person’s treatment (if not involved in the research) or, a person nominated by the healthcare provider. The parents and child must be informed about the research as soon as possible afterwards and their consent for future involvement sought.

6.6 School-based research

Any research that is to be conducted in a school setting must be submitted and reviewed in accordance with the ICMR guidelines by an IEC. The researchers should submit the protocol to school authorities and obtain written approval to conduct research. A copy of the approval given by the school should be submitted to the IEC. Researchers should comply with a schools policies and procedures for all proposed research. All the guidelines for consent and assent apply to school-based research as well (see section 2). If justified, IEC may decide to waive individual consent depending on the context and the type of research (e.g. collecting data already with school authorities like number of disabled children, number availing mid day meal services).
6.7 Internet based/Tele research in children

All research planned in children including internet based/Tele research needs to be submitted to the IEC. Following the guidelines provided by ICMR, the IEC may choose to exempt some internet -based research from review ( e.g.working on data that is in the public domain). Even if the research is exempt from a full IEC review the researchers are required to keep an auditable record of the data.

The IEC may allow for internet based consent and tele consent(recordings to be stored) depending on the type and nature of research. All the guidelines for consent and assent apply for internet based/tele research as well (see section 2). There may be special precautions that are needed to ensure confidentiality and safe storage of data in this kind of research. IECs and researchers need to ensure that data confidentiality and privacy of participants needs to be maintained as per ICMR guidelines. [IT act provisions ?]

6.8 Community Based Research in Children

Community based epidemiological research encompasses basically two forms of research; observational and experimental. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health and the social milieu.(ICMR 2006) The general principals and guidelines of epidemiological research or community based studies detailed in the ICMR Research done in populations based in the community as opposed to hospital-based population are required in the following scenarios.

- when epidemiological studies have a tacit need to be based in population
- The research question may be such that the study can only be conducted in the community
- For policy-makers, data from effectiveness studies (real world studies) are imperative for providing evidence-based data so that an informed decision can be made.
- Identification and enrollment of participants is from the community directly and not from patients attending an OPD/hospital

The guiding Ethical Principles do not change at all except that they are more difficult to put in place. Also, in addition to ensuring rights and safety of the participating population, the rights and safety of the community at large need to be kept in mind. These studies are more challenging to operationalize and the study team needs to build systems (patient management, transportation for home visits, transportation systems for delivery of specimens to the laboratory, etc) that already exist or not needed in studies conducted in hospitals.

These studies are done after engaging the community leaders, the health workers and other organizations working in the area. The important issues are to gain trust of the community through open and transparent communication and address promptly any queries or issues that are raised at any time during the study implementation.

guidelines and need to be followed.

6.9 Research involving adolescents

Adolescents differ both from children and adults. The differences are not limited to psychological, social and behavioural aspects, but also in drug kinetics and therapeutic responses. Research involving adolescents can guide interventions and inform public policy in this area. Violence, sexually transmitted diseases including HIV, alcohol and drug use, high risk behaviours, unintended pregnancy are serious challenges to health of youth across the country. Many of the above mentioned behaviours and risks originate during adolescence. Research on cognition and capacity suggests that adolescents show significant ability to provide informed consent. By mid-to late adolescence, the ability to make decisions about research participation are similar to abilities of adults. This capacity is dependent on both cognition and previous life experiences. Lack of experience with decision making in real-world situations may reduce this capacity. On the other hand adolescents, who have chronic illnesses, may have been challenged to develop increased capacity.\textsuperscript{VIII} benefits of involvement in informed consent process for research include an increased sense of self control and increased decision making capacity. Any researcher attempting research in this population should be conversant with the unique aspects of adolescent\textsuperscript{c} cognitive, psychological and social development.

Sexual health research in adolescents requires researchers to pay maximum attention to issues of confidentiality and anonymity. IECs should pay careful attention so that such research involving adolescents be conducted with the utmost sensitivity to ethical issues.\textsuperscript{XI} The setting of research and the local beliefs and cultural background of the participants of research need to be carefully taken into account for such a research. In community based studies involving adolescents, involvement of youth advisory committees can be an effective way of incorporating youth into the planning research that is ultimately meant to serve them. Youth members of these committees should ideally mirror the diversity of the study population in terms of ethnicity, caste, socioeconomic status, educational background and residence. Youth advisory committees can be helpful in exploring and attending to ethical issues and advising on all aspects of protocol development and implementation.\textsuperscript{XIV}

Any research that is to be conducted involving adolescents must be submitted and reviewed in accordance with the ICMR guidelines by an IEC. IECs may consider waiver of parental consent in certain studies where parental permission may not be
appropriate such as health care for contraception and drug abuse. Adolescents’ right to research participation may be compromised in situations where parental permission is required for research but not required for health care. In such settings, for research of low risk (e.g. confidential or anonymous surveys) capacity to give consent can be based on the reasonable expectation of capacity for the group of adolescents to be studied, and that the informed consent of adolescent can be substituted for parental permission. For research involving greater risk, and where circumstances merit waving parental permission, an individual assessment of capacity to consent needs to be taken into account. IEC has to take the final decision regarding exempting parental consent for research.[legal review] In all such situations an informed consent has to be obtained from the adolescent. In all other forms of research involving adolescents the principals of assent and consent have to be followed. (see Section 2)
Section 7: Annexures

7.1 Glossary

The definitions provided here apply as they are used in the above guidelines.

**Academic research**

New drug
Regulatory trial
Clinical trial

**Assent**

A child's affirmative agreement to participate. Failure to object should not be construed as assent.

**Burden of disease**

The impact of disease on the individual and on society due to loss of duration and quality of life. Measures include (i) 'morbidity burden', ie, the prevalence of a condition, the range of its severity and the age distribution of the population suffering from the condition, and (ii) the financial burden to society in meeting the obligation to support the individual; for example, in terms of net public expenditure on health services and on social services.

**Child**

A person under the age of 18. "Young person" is a term often used to describe older children in this age group.

**Consent**

The voluntary agreement of an adult or competent child, based on adequate knowledge and understanding of relevant information, to participate in research.

**Harm**

That which adversely affects the interests or welfare of an individual. This may be physical harm, discomfort, anxiety, pain, and psychological disturbance or social disadvantage.

**Investigational medicinal product**

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorised indication, or when used to gain further information about the authorized form.

**Minimal Risk**

Minimal risk is defined as one which may be anticipated as harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

**Therapeutic Misconception**

The belief that the purpose of research is treatment is termed the *therapeutic misconception*. 
### Table 1: Considerations for Institute Ethics Committees (IECs') while evaluating research proposals

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risks</strong></td>
<td>Are risks minimized? Are risks reasonable in relation to anticipated benefits? What are the potential benefits to participants? What is the importance of the knowledge likely to be gained from the study? Do the benefits justify the risks?</td>
</tr>
<tr>
<td>[IEC considers only additional interventions which are done as a part of research]</td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Are there adequate provisions to monitor the data and ensure participant safety</td>
</tr>
<tr>
<td><strong>Autonomy</strong></td>
<td>Are proper consent, assent procedures and documentation being followed? Is selection of participants equitable? Are any vulnerable groups being enrolled? Is there additional protection for vulnerable groups?</td>
</tr>
<tr>
<td><strong>Confidentiality</strong></td>
<td>Are adequate measures taken to ensure privacy of participants and maintain confidentiality of data?</td>
</tr>
<tr>
<td><strong>Voluntariness</strong></td>
<td>What is the influence of payments if any? Are payments reasonable or can act as inducements? Is the selection, amount, and timing of payments appropriate? Are there additional safeguards for any vulnerable group prone for inducement?</td>
</tr>
</tbody>
</table>

### Web Resources

- The Clinical Trials Registry- India (CTRI), hosted at the ICMR's National Institute of Medical Statistics [http://ctri.nic.in/Clinicaltrials/login.php](http://ctri.nic.in/Clinicaltrials/login.php)
- WHO - International Clinical Trials Registry Platform (ICTRP) [http://www.who.int/ictrp/en/](http://www.who.int/ictrp/en/)
- U.S. National Institutes of Health clinical trials registry [https://clinicaltrials.gov/](https://clinicaltrials.gov/)
- Indian Council of Medical Research (ICMR), New Delhi [http://icmr.nic.in/index.html](http://icmr.nic.in/index.html)
- Department of Science & Technology (DST) [http://www.dst.gov.in/index.htm](http://www.dst.gov.in/index.htm)
7.2. Guidelines for list of issues while approving pediatric trials should be provided to the ethics committee.

1. Ensure scientific validity of the study question to be answered
2. Justification of the study to be performed in children and in the proposed age groups
3. Evidence of direct benefit for the child, or benefit for the group
4. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial.
5. The competence of the responsible study investigator and his/her team and the infrastructure of the institution and experience in pediatric research in general and in particular in the field of the applied project.
6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) is to be reviewed in detail prior to the clinical trial
7. The clinical results of adult studies
8. Type and phase of the study
9. Use of placebo or active control
10. Is any money being given as a part of participation
11. Age-appropriate scales or measures of end-points (e.g., pain scale)
12. Study design and biometric planning in relation to the trial question
13. Inclusion and exclusion criteria
14. Statistical methods
15. Criteria for the termination of the study
16. Safety measures
17. Study risks, pain, fear and discomfort
18. Comprehensive, understandable Informed Consent and Information sheets for legal representatives
19. Understandable age specific Informed Assent and Information sheet for children
20. Anonymity of the data
21. Appropriate pharmacovigilance procedures are put in place by the sponsor
22. If available, opinions of other ethics committees for international multicentre studies
23. Plan for publication of study results
24. Continuation of trial medication where appropriate
References:


3 ICMR. Ethical guidelines for biomedical research on human participants. icmr.nic.in/ethical_guidelines. 2006.


