

National Ethical Guidelines for Biomedical Research Involving Children



Indian Council of Medical Research
2017

Disclaimer:

Care has been taken to present the information accurately and inline with the latest government guidelines. However, in view of ongoing changes in government regulations and the constant flow of new information, the reader is urged to check the latest notifications/rules/ regulations provided by the Government of India from time to time.

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सचिव, भारत सरकार

स्वास्थ्य अनुसंधान विभाग

स्वास्थ्य एवं परिवार कल्याण मंत्रालय

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Message

It is important to include children in clinical research including clinical trials so that the benefit of new therapy can also be applied to children as soon as possible. Traditionally children are often the last to benefit from advances in medicine. However, because of their inherent vulnerability the potential risk from participation in research studies must be anticipated and adequate precautions taken. These guidelines have been developed specifically to address ethical issues of conducting research in children. We hope that these guidelines are put into practice in every institution conducting research in children and the scientific community, public at large get immensely benefited.



I am grateful to Prof. V.K.Paul and Dr. H.P.S.Sachdev under whose stewardship these guidelines were developed and all members of expert review committee who have contributed their time and ideas generously.

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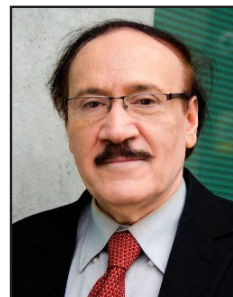
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Foreword

Children are unique biologically and in their interphase with the environment. This is true in fetal life and throughout childhood. The findings in adults cannot be automatically assumed to be true in children. This applies to the way therapeutics and preventive modalities are taken up and metabolised. Children are vulnerable and carry a greater risk of harm during research. Many new technologies that can provide cures for incurable disease also pose major ethical concerns. In countries where effective literacy is still not common, we have a far greater responsibility to ensure that the participants and their care givers understand, with utmost clarity, the research and procedures that researchers propose.



Practice of the right kind requires norms and guidelines that are articulated with sublime clarity. An institutional mechanism to administer and oversee research practice is critical at an institutional level. Monitoring of data safety and quality through data monitoring committees compliments the work of the ethics committees. In modern research privacy and confidentiality are important to preserve. Biological specimens must be obtained when the knowledge to be gained is likely to advance medical care, how these are used must have the explicit approval of the subjects of research. It is therefore, gratifying that the Indian Council of Medical Research, the nodal agency in the country has developed ethical guidelines for biomedical research involving children. These are written with clarity, based on scientific and ethical principles, and balanced in providing guiding principles and processes and practices for achieving compliance with these with the guidelines. As someone concerned with bringing the fruits of research to our children as well as to ensure their safety and security, I complement the council for this outstanding contribution. It is for us, researchers to ensure that the guidance becomes the practice in every institution of the country. We need research for children but only under the best ethical norms.

A handwritten signature in blue ink, appearing to read 'M.K. Bhan', with a horizontal line drawn underneath it.

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Foreword

In this era of evidence based medicine, it is imperative to conduct robust and ethical research in neonates, infants, children and adolescents to improve our understanding of disease and provide optimal healthcare. However, professionals and parents often feel apprehensive about asking this vulnerable population to take part in research because of greater potential risks or burdens. Furthermore, young children are not in a position to make autonomous decisions regarding their participation in research, which puts them at risk of coercion or undue influence.



It is therefore mandatory that biomedical research involving children zealously protects their interests, especially from an ethical perspective. Ethics could be considered as codified practices and procedures performed by the practitioners of the profession. Institutional Ethical Committees thus need to refer to consensus recommendations to arrive at meaningful decisions. Adult based guidelines are not ideal for this purpose because special concerns related to children are usually not addressed in detail. Realising this felt need, several developed countries have formulated their ethics guidelines for biomedical research involving children. However, there is a need to adapt these recommendations to the Indian context to overcome challenges of applying universal ethical principles in the multicultural Indian society with a diversity of health-care systems with varying standards.

In 2006, the Indian Council of Medical Research developed an updated, third version entitled "Ethical Guidelines for Biomedical Research on Human Participants". These guidelines contain only a small section pertaining to research in children, which does not address in detail several ethical perspectives of conducting biomedical research in neonates and children. This monograph is intended to accomplish this important task and serve as the reference manual for ethical committees in the national context. These consensus recommendations were formulated through a rigorous and robust methodology including review of pertinent national and international guidelines, multiple stakeholders' input and public scrutiny. It is hoped that this timely publication will fulfil the objectives with which it was conceived.

HP Sachdev

Prof. H.P.S. Sachdev,

Acknowledgement

For the first time The Indian Council of Medical Research has come out with the guidelines separately for Biomedical Research involving children. We acknowledge with gratitude the contributions made by ICMR Advance Center on Newborn Health Research at All India Institute of Medical Sciences under leadership of Professor Vinod Kumar Paul in creating the draft guidelines for biomedical research involving children.

We gratefully acknowledge contribution of Dr. Suvasini Sharma and Dr. Naveen Sankhyan for preparing the initial draft. We are indebted to all members of the core committee and members of expert group for their valuable contributions in finalizing the draft guidelines. Special thanks to Dr. Vasantha Muthuswamy and Dr. Roli Mathur for their constant guidance and final editing of the draft guidelines.

We are grateful to Secretary Department of Health Research and Director General ICMR – Dr. Soumya Swaminathan and Dr. V.M. Katoch (Former Secretary DHR & DG ICMR) for their continued support and guidance.

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Contents

Abbreviations

Section 1	10
1.1 Introduction	10
1.2 Needs and challenges of clinical research in children	11
1.2.1 Why is biomedical research necessary in children?	11
1.2.2 Challenges of biomedical research involving children	12
1.3 The process of developing ethics guidelines for research involving children	12
1.4 Scope of the guidelines	13
1.5 General guidelines for research in children	14
Section 2: Risk	13
2.1 Assessment of benefit and risk in research in children	15
2.2 Classification of Risks	16
Definitions:	16
2.2.1 Less than Minimal Risk	16
2.2.2 Minimal risk	16
2.2.3 Minor increase over minimal risk or Low risk	16
2.2.4 More than minimal risk or High risk	17
2.3 Concept of relative versus absolute interpretation of risk	17
2.4 Determinants of risk	17
2.5 Pain, distress, and fear minimization in children during research	17
2.6 Type of assays and sample collection	18
2.7 Paediatric formulations to be used in paediatric studies	18
2.8 Guidelines for ethical approval based on degree of risk	18
Section 3: Consent and Assent	19
3.1. Informed consent	19
3.1.1 General principles of informed consent	19
3.1.2 Waiver of consent	21
3.1.3. Concerns regarding informed consent	22
3.2 Children's assent	23

3.2.1 Age and method of obtaining assent	23
3.2.2 Waiver of assent	23
3.3.3 Content of assent forms	24
Section 4: Safeguard Systems	25
4.1 Ethics committee (EC)	25
4.2 Experience of investigator and research setting	26
4.3 Data and safety monitoring board (DSMB)	27
4.4 Data protection and confidentiality	28
4.5 Bio-banking of samples:	28
4.6 International collaboration and data sharing	28
Section 5: Compensation	28
5.1 Compensation for participation	28
5.2 Compensation for accidental injury	29
Section 6: Special situations	29
6.1 Research in neonates	29
6.2 Research in HIV positive children	30
6.3 Vaccine studies in children	30
6.4 Ethical issues in genetic research	30
6.5 Research involving children in an emergency situation	30
6.6 School-based research	31
6.7 Internet /Telephone based research in children	31
6.8 Community Based Research in Children	31
6.9 Research involving adolescents (12-18 years)	32
Section 7: Annexures	33
7.1 Glossary	28
7.2 Web Resources	34
Index	35
Bibliography	38
Members of the Expert Committee on Drafting and Reviewing of guidelines	40

Abbreviations

Acquired immunodeficiency syndrome	-	AIDS
All India Institute of Medical Sciences	-	AIIMS
Central Drugs Standard Control Organization	-	CDSCO
Data and Safety Monitoring Board (DSMB)	-	DSMB
Deoxyribonucleic acid	-	DNA
Department of Health Research	-	DHR
Drug Controller General of India	-	DCGI
Ethics committee	-	EC
Government of India	-	GOI
Health Ministry's Screening Committee	-	HMSC
Human immunodeficiency virus	-	HIV
Indian Council of Medical Research	-	ICMR
Legally acceptable/authorized representative	-	LAR
Participation information sheet	-	PIS
Principal investigator	-	PI
Ribonucleic acid	-	RNA

SECTION 1**1.1 Introduction**

Biomedical and health research includes basic, applied and operational research studies designed primarily to increase scientific knowledge about diseases and conditions (physical or socio-behavioural), 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 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 near the end of the second 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 endeavour to generate and translate knowledge into clinical care. However, at the same time, we cannot expose children to undue harm by participating in research studies

As per the Declaration of Helsinki, 2013, some research populations (such as children) are particularly vulnerable and have 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. This set of participants cannot give or refuse consent for themselves and they may be at risk of coercion or undue influence. All vulnerable groups need specifically considered protection. In vulnerable populations, biomedical research is justified only if it is based on the health priorities of that population.

Ethics are codified practices and/or procedures performed by the practitioners of the profession. The conduct of biomedical research involving children raises a number of ethical issues. The first issue is that children lack *autonomy* : that is, the cognitive and emotional level of maturity and the legal status to consent to research participation on their own behalf. Any research on children must consider the level of their physical, cognitive, emotional, and psychosocial development. Animal studies and research on adults should precede studies with children to minimize research risks except in situations where the disease occurs only in children. 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 on children that may potentially be beneficial to them in the future. This goes against the basic ethical principle of *justice*. The concept of justice means that distribution of the potential benefits and harm of participating in research should be fairly distributed. For example, a vulnerable set of patients (such as children from poor socio-economic strata being treated in government hospitals) 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 regarding research in developing countries. In resource-constraint settings where parents have 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 accessing new therapies or better clinical care. The parents may also be unduly susceptible to financial inducements to participate in research because of their poor socio-economic status. 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 found unjust when it does not consider the needs of those societies and countries. For instance, a study being conducted in children of a developing country with potential beneficiaries of the intervention being children from rich nations is bound to raise concerns. India faces additional challenges given the multicultural society and 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 many situations, research findings of studies in adults cannot simply be extrapolated to children and research involving children is essential if children are to benefit from advances in biomedical sciences and technology.

1.2.1 Why is biomedical research necessary in children?

Some of the reasons why biomedical research may be necessary in children are as follow:

1. The disease may affect only children, for example, hyaline membrane disease, birth asphyxia, neonatal hyperbilirubinemia, extrahepatic biliary atresia, infantile spasms, infantile tremor syndrome, Kawasaki disease, etc. Such diseases have no adult counterparts and therefore, it is necessary to carry out research in children to advance our knowledge of 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, hence, we cannot simply extrapolate the medications approved for adults to children. Some diseases such as nephrotic syndrome, hypertension and rheumatoid arthritis affect both adults and children, but the pathophysiological basis and clinical approach is very different in both.
2. The physiology of children is different from that of adults, and the pharmacokinetics of many drugs is age-dependent based on the maturation of the drug metabolism pathways. For example, children metabolize many drugs much more rapidly as compared to adults; hence, the dosage of the drug (per kg of body weight) that needs to be given is much higher in children. The absorption of drugs also varies with age. Pharmacokinetics and toxicity profile varies with growth and maturation from infancy to adulthood.
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 and aspirin use is associated with Reye's syndrome in children.

4. Age appropriate delivery vehicles and formulations (such as syrups) are needed for accurate, safe and palatable administration of medicines to infants and children.
5. The pathophysiology of many disorders is dependent on a child's growth, development and adaptive plasticity. Examples include adaptive changes in the motor system following a perinatal stroke.
6. Research in children is also one of the ways to understand some adult diseases that are thought to have their origins in early life. The natural history of the disease may be understood better and it may lead to potential preventive interventions in early life.

1.2. 2 Challenges of biomedical research involving 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 having adequately statistically powered studies to evaluate an effective treatment. For this reason, large multi-centric studies lasting many years may be needed, which are not always feasible. To overcome this difficulty studies in children often benefit from and require alternative and innovative study designs that incorporate multiple regions, high number of study sites relative to the number of patients to be enrolled, and realistic timelines to allow them to be feasible and to collect relevant data specific to the population being studied.
2. It is usually difficult to find funding for research in children. As the market for paediatric drugs and treatments is quite small compared to the adult ones, pharmaceutical companies do not find it sufficiently remunerative to fund research in children.
3. The ethical concerns regarding research involving children, which include lack of autonomy and inherent vulnerability, make it more difficult to perform research in children and obtain appropriate informed consent.
4. Research in children is not just about performing research on individual patients. As parents and families are involved, there is a need to take account of familial and socio-cultural concerns while planning the research.
5. Research procedures and settings need to consider children's physical, cognitive, and emotional development. Developmentally appropriate outcomes need to be studied. Followup 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 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 called the *Ethical Guidelines for Biomedical Research on Human Participants* was developed in 2006 and the latest version, developed in 2017, is called the *National Ethical Guidelines for Biomedical and Health*

Research Involving Human Participants. These guidelines have a section pertaining to research involving children, however, a need was felt to develop more comprehensive guidelines which pertain to the specifics of ethics in biomedical research involving children. This endeavour was undertaken under ICMR Advance Center for Newborn Health Research at All India Institute of Medical Sciences, New Delhi.

As a first step, the existing national and international guidelines for biomedical research in children were reviewed. Separate guidelines available for paediatric 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. All these guidelines were reviewed for a better understanding of the ethical principles of biomedical research in children. Meetings were also conducted with experts in the field of bioethics to develop a consensus on guidelines in the Indian context. These guidelines have been developed and finalized 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 is to set out general principles that can be applied in most situations rather than to cover every possible situation. These guidelines need to be used in conjunction with the current National Ethical Guidelines for Biomedical Research involving Human Participants, Indian Council of Medical Research (ICMR) Government of India and are meant for use by researchers, ethics committees and other involved stakeholders.

While these guidelines cover general biomedical research involving children, the definition of 'child' has been variable according to various legal and social contexts. As per the National Commission for Protection of Child Rights, a child is defined as a person from 0 to 18 years of age (<http://ncpcr.gov.in/>).

These guidelines are sub-serving to the Constitution of India and the legislature. If the research is a regulatory clinical trial under the Drugs and Cosmetics Act, 1940, 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 pharmacodynamics and pharmacokinetic) and /or adverse effects with the objective of determining safety and /or efficacy of the new drug (including drugs, biologicals, devices)

As per the Drugs and Cosmetics Rules, 1945:

Definition of new drug : For the purpose of this part, new drug shall mean and include- 2[(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) and route of administration (See items (b) and (c) of 3[Appendix VI] to 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 Drug Controller General of India (DCGI). The exception to the rule is for academic research as described below as per notification issued by Government of India)

Academic Research

The Government of India, vide GSR No.313 (E) dated 16.03.2016, stated that:

No permission for conduct of clinical trial intended for academic purposes in respect of approved drug formulation shall be required for any new indication or new route of administration or new dose or new dosage form where - (a) the trial is approved by the Ethics Committee; and (b) the data generated is not intended for submission to licensing authority. "The Ethics Committee shall however inform the licensing authority about the cases approved by it and also about cases where there could be an overlap between the clinical trial for academic and regulatory purposes and where the said authority does not convey its comments to the Ethics Committee within a period of thirty days from the date of receipt of communication from the Ethics Committee, it shall be presumed that no permission from the licensing authority is required.

Regulatory guidelines are dynamic and subject to frequent changes, hence researchers are advised to consult the latest guidelines from the Central Drugs Standard Control Organization (CDSCO) website (www.cdsc.co.nic.in/) at the time of planning and commencing their research. For details regarding clinical trials and regulations, please refer appendix.

1.5 General guidelines for research in children

The following guidelines should be followed when conducting research in children:

- Research proposals should be scientifically sound.
- The equation between the potential benefit and the risk or potential harm should be at least as favourable for the proposed research procedure as for the alternatives available to the children.

- There should be 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 a team of investigators who have the requisite expertise. One or more members of the team should be a paediatrician and/or have prior experience of conducting research involving 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, as far as possible.
- In general, drugs should be tested for safety, pharmacokinetics, and at least initial indications of efficacy in adults established before they are tested in children. It may often be appropriate to defer paediatric testing until adult testing has reached Phase III or beyond, when substantial data are available on the safety and efficacy of a drug in adults. However, there may be situations where studies involving children would be needed without prior adult studies, for example, surfactant use in premature babies with respiratory distress syndrome.

SECTION 2: Risk

2.1 Assessment of benefit and risk in research involving children

During the journey in quest of new knowledge and science, every study entails some risk to the participant which should be balanced against the likelihood of anticipated benefit. The relationship between the risk a participant is likely to face and the anticipated benefit is a very important consideration in the ethical conduct of biomedical research. A research “equipoise” between benefit and risk must be planned when considering biomedical research.

Risk or harm is a very important consideration in research involving children. Risk refers to a potential harm that can occur to the child as a direct or indirect consequence of the research procedure. Research may include any procedure the participant undergoes for research including questionnaires, investigations such as blood sampling, bone marrow aspiration, liver biopsy etc., or therapeutic interventions such as medication or surgery, *over and above the routine standard of care for the patient*. The risks entailed in research procedures need to be considered when they are over and above the routine care of the participant.

Harm occurring from participating in research may be physical (such as pain from a needle prick for blood sampling), psychological (such as fear of separation from parents) or social (such as missing school and friends etc). Risks must be assessed in relation to benefits. A benefit is a good

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 benefits include the possibility of recovery, reduction in pain, improvement in disease severity, etc. Indirect benefits include the opportunity to understand more about the disease, develop social relationship with other patients, etc. Payments for participation should not be considered in the benefit-risk- ratio. Also, patients and participants may consider other benefits such better access to doctors, access to investigations which are not otherwise freely available, being special patients as part of research, etc. These indirect benefits may be 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 for those procedures that are additional to the standard practice, which means they are 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 less than minimal, minimal, minor increase over minimal or low and more than minimal or high risk. These are however just broad guidelines. As explained later, the categorization of risk may vary from child to child even within the same research procedure, depending on the situation. It is therefore necessary to exercise individual judgement.

2.2.1 Less than minimal risk

Probability of harm or discomfort anticipated in the research is nil or not expected. For example, research on anonymous or non-identified data/samples, data available in the public domain, meta-analysis, etc.

2.2.2 Minimal Risk

Minimal risk is defined as those 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 the anthropometric parameters (such as height and weight) in children, provided that procedures are carried out in a child friendly way, respecting the child's wishes, and that consent has been given by appropriate persons. Procedures with minimal risk include history taking, physical examination, chest X-ray, obtaining bodily fluids without invasive intervention, for example, taking saliva or urine samples, etc. It is expected that the harm caused by the minimum risk level research would be very slight and temporary.

2.2.3 Minor increase over minimal risk or Low risk

Low risk is defined as a slight increase in the potential for harm or discomfort beyond or more than minimal risk (as defined in relation to the normal experiences of average, healthy, normal

children). These include procedures that might cause no more than transient pain or tenderness, small bruises or scars, or very slight, temporary distress, such as a blood test, oral sedation for diagnostic procedures, etc.

2.2.4 More than minimal risk or High risk

All research procedures which have a risk over and above 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 she or he undergoes in daily life. For instance, a child with leukaemia 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. Bone marrow aspirations for research in this situation may be considered minimal risk' in such children. A relative interpretation theoretically allows high-risk studies to be approved as minimal-risk studies in children who undergo high-risk interventions in their routine life. In contrast, healthy children who experience low levels of risk in daily life would have a correspondingly low risk threshold for assessing whether a study presented minimal risk. Therefore, in children, an absolute interpretation of the minimal risk may be better.

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 research procedure that may be of minimal or low risk to a healthy child could be of high risk to a child with underlying medical condition. For example, intramuscular injections that may be safe for healthy children are risky for children with clotting disorders. Ethics committees should ensure that children with underlying medical conditions that place them at risk due to research procedures are excluded from the study.
- 3. Cumulative characteristics of risk during research:** Determinations about risk should consider the cumulative characteristics of research interventions or procedures and the time period for which they are done. For example, a single chest X-ray is a minimal risk procedure, but if the child has to undergo multiple chest X-rays over a short duration of time, the risk category should be higher.

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

Both pain and emotional discomfort should be prevented as much as possible. When unavoidable, it should be adequately managed and reduced. To do this, non-invasive procedures should be

preferred. The environment of the study should be as child-friendly; and the child should not be separated from his/her parents as far as possible.

2.6 Type of assays and sample collection

In research in children, due consideration should be given to the number and type of body fluid assays and investigations.

- Blood samples should be age and/or bodyweight appropriate. Depending on the nature of the study the ethics committee may obtain an independent opinion from a paediatrician regarding the safety of blood volumes proposed to be drawn for the purpose of the study.
- The samples should be obtained using appropriate facilities and materials.
- Alternative sampling (for example, urine or saliva sampling) for pharmacokinetic studies should be preferred when possible. However, the ability to use alternative samples may depend on the validation of the analytical methodology and clinical utility of measurements made in these matrices.
- For blood and tissue assays, micro volumes 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 coordinated with the routine standard of care sampling of the patients to avoid repeated needle pricks.
- 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 should take over the procedure.

2.7 Paediatric formulations to be used in paediatric studies

Formulations used in a study 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. Whenever available, paediatric formulations should be used. Excipients used for the formulation should take into consideration the age of the children included in the study (for example, benzyl alcohol is contraindicated in neonates). Conditions to avoid bacterial contamination and degradation of the medicinal product should be specified in the protocol.

2.8 Guidelines for ethical approval based on degree of risk

For research procedures that are intended to provide potential direct diagnostic, therapeutic or preventive benefit for the individual child participant, a risk category higher than minimal risk may be justified. For studies having interventions not intended to directly benefit the individual child participant, the risk-levels should be minimum risk or low risk.

SECTION 3: Consent and Assent**3.1. Informed consent**

In research involving children, the traditional method of informed consent where decisions about research participation are made by those with the legal and intellectual capacity to make such choices for themselves cannot be implemented, as children usually lack this capacity. Instead, the authority to allow a child's participation in research rests with parents or a legally acceptable/ authorized representative (LAR), as the case may be. A LAR is 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. However, investigators must seek to involve children in discussions about research and obtain their assent to participation as in accordance with their developmental level and decision making capacity. The parental/LARs' 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

Informed consent protects the individual's freedom of choice and respect for the individual's autonomy and is given voluntarily to participate in research or not. Adequate information about the research is given in simple and unambiguous language in a document known as the informed consent form with participant/ parent /LAR information sheet. A copy of this information sheet should be given to the parents /LAR as well as children from whom assent is being taken. A signed copy of the informed consent/assent form must be kept by the investigator.

The participant information sheet should have following components as may be applicable:

Essential Elements of an Informed Consent Document

1. Statement mentioning that it is research.
2. Purpose and methods of the research in simple language.
3. Expected duration of the participation and frequency of contact with estimated number of participants to be enrolled, types of data collection and methods.
4. Benefits that might reasonably be expected as an outcome of research to the participant or community or to others.
5. Any foreseeable risks, discomfort or inconvenience to the participant resulting from participation in the study.
6. Extent to which confidentiality of records could be maintained i.e. the limits to which the researcher would be able to safeguard confidentiality and the anticipated consequences of breach of confidentiality.

7. Freedom of individual to participate and to withdraw from research any time without penalty or loss of benefits which the participant would otherwise be entitled to.
8. Free treatment and/or compensation of participants for research-related injury and harms.
9. The identity of the research teams and contact persons with address and phone numbers (PI/ Co-PI for queries related to the research and Chairperson/Member Secretary or helpline for appeal against violations of ethical principles and human rights)

In addition, the following elements may also be required depending on the type of study:

1. Any alternative procedures or courses of treatment that might be as advantageous to the participant as the ones to which she/he is going to be subjected to.
2. Payment/reimbursement for participation and incidental expenses depending on the type of study.
3. If the research could lead to any stigma, e.g. HIV and genetic disorders, provision for pre-test- and post-test counselling.
4. Insurance coverage if any, for research-related or other adverse events.
5. Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research. Other specifics are as follows -
 - a) Period of storage of the sample/data
 - b) If the material would be or is likely to be used for secondary purposes
 - c) If material is to be shared with others, this should be clearly mentioned
 - d) Risk of discovery of biologically sensitive information and provision to safeguard confidentiality
 - e) Right to prevent use of her/his biological sample (DNA, cell-line, etc. and related data at any time during or after the conduct of the research
 - f) Benefit sharing, if research on biological material and/or data may lead to commercialisation.
6. Publication plan, if any, including photographs and pedigree charts.

A copy of the participant/ information sheet should be given to the participant for her/ his record. Content on the informed consent form should be brief and written in simple local language highlighting that it is given of free will or voluntarily after understanding the implications of benefits and risks that the participant 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.

Consent process for illiterate parents /LARs

When a participant is willing to participate but not willing to sign or give thumb impression or cannot do so, then verbal/oral consent may be taken on approval of the EC, in the presence of

an impartial witness who should sign and date the document. This can be documented through audio or video recording of the participant, the PI and the impartial witness, all of whom should be captured in the frame. However, verbal consent should be an exception for specific reasons carried out with the approval of EC and not to be followed routinely.

In non-regulatory, observational studies, sometimes literate or illiterate, parents /LARs may verbally agree to participate but refuse to give their thumb impression. In such cases, again, the documentation of the consent process needs to be done by a literate impartial witness.

In some cases, fresh or re-consent may need to be taken, such as when:

1. New information becomes available which would necessitate amendment/deviation of protocol (excluding any new safety related information which can harm the participant if not immediately implemented by the investigator);
2. A research participant regains consciousness from an unconscious state or becomes mentally competent to understand the study (procedures to address such a possibility should be spelt out in the informed consent form);
3. Long term follow-up or study extension is planned at a later stage;
4. There is change in treatment modality, procedures, site visits;
5. Attains 18 years of age, or the legally acceptable representative has changed;
6. There is possibility of disclosure of identity through data presentation or photographs (which should be camouflaged adequately) in an upcoming publication; or
7. Future research may be carried out on stored biological samples if not anonymized

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 ECs may waive the requirement for informed consent in the 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, for example, study on disease burden of HIV/AIDS
- ii. Research is carried out on publicly available information, documents, records, works, performances, reviews, quality assurance studies, archival materials or third-party interviews, service programmes for public benefit, having a bearing on public health programmes, and consumer acceptance studies

- iii. Research on anonymized biological samples, left over samples after clinical investigation/ research, cell lines or cell free derivatives like viral isolates, DNA or RNA from recognized institutions or qualified investigators, samples or data from repositories or registries, etc. provided permission for future research on these samples has been taken in the previous consent form. For further details on research using stored samples, please refer to the section 11.0 Biological materials, Biobanking and Datasets for further details of the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017 ICMR.
- iv. In emergency situations when no surrogate consent can be taken. Examples include research in neonatal resuscitation, life threatening emergencies, etc. In such situations, the parents/ care givers / LAR may not be in a situation to give consent. However, once the child has been stabilized, a deferred/delayed consent must be taken. In case the parents refuse the deferred consent, the child should not be included in the research, and no further research related procedures /data collection must be done from the patient. Also, the data previously collected prior to the consent process should not be used without the authorised adult's permission.
- v. Retrospective studies, where the participants are de-identified or cannot be contacted.

The protocols in all the above studies need to be submitted to the EC, and the decision for waiver of consent will lie with the EC.

3.1.3. Concerns regarding informed consent

1. The process of obtaining consent and assent should not be a mere formality, limited to getting the participants' signatures on the forms. Instead this should be a process, wherein the onus is on the investigator to ensure that the parents and children (as far as their developmental level and maturity permits) understand what is going on in the research. This process should also include opportunities for the parents and children to ask questions. The consent process 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 patients/participant information sheet (PIS) should be simple and easily understood by the parents. Many times, in order to protect themselves from any future litigation, investigators fill PIS with technical terms (medical and legal) which the parents find difficult to understand. While translating to a local language difficult technical words must be avoided, and simple daily-use words that the participant is able to understand should be used.
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

misbelief that the purpose of research is treatment is termed as therapeutic misconception.

3.2 Children's assent

Assent is defined as a child's affirmative agreement to participate in research. A mere failure of the child to object should not be interpreted as assent. The assent process should take into account the children's developmental level and capability of understanding. 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. The assent form chosen should be appropriate for the child's age and reading ability. Children with chronic illness may have been challenged to develop increased capacity to make independent judgments based on previous experiences. The other important issue here is the child's general level of independence and autonomy.

Content of the assent form has to be in accordance with the developmental level and understanding capacity of the child. For example, a child aged 8 years should be told what exactly she/he is going to undergo, although they may not understand the concept of research. Younger children are better able to grasp the more practical aspects of research (e.g., what they are expected to do or what will happen) than they are to understand the abstract concepts such as randomization. For a 15-year-old, however, the assent process should be similar to the informed consent process. If the study is of 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

For children between 7 (84 months and above) and 11 years of age, oral assent must be obtained in the presence of parent/LAR. For children between 12 and 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 addition to parent/LAR consent. This is a joint decision-making process between the child and the concerned adult. In cases of verbal assent, the parent /LAR's counter-signature must be obtained confirming 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. For children less than 7 years of age, parental consent is sufficient. As assent is part of the informed consent process, the regulations as per the CDSCO guidelines for regulatory clinical trials apply for assent as well.

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 potential of directly benefiting the child and this 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.

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

Dissent or refusal of a child to participate must always be respected. Explanation must be given to ensure that the child understands that she/he may withdraw her/his assent at any time during the study.

3.3.3 Content of assent form

The type and amount of information given needs to be simplified as per the child's cognitive and developmental level. The information should be simple, and age-appropriate. The basic information that needs to be provided includes:

1. What the study is about and how it might help
"We want to see whether a new medicine will or won't help children like you who have skin rashes"
"We want to understand why children get tummy aches, like you do"
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 teaspoonful 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. The area may look red for sometime"
4. Who will answer the child's questions during the study
"If you have any questions at any time, you can ask Dr X."
5. Whether an option to say "no" exists
"You can say "no" if you don't wish to take part in the study. No one will be angry with you."
"If you say "yes" and then change your mind later, it will be fine. No one will scold you".

Table 2 : Consent of parent/LAR

1	Ethics committee (EC) should determine if consent of one or both parents would be required before a child could be enrolled.
2	Generally, consent from one parent/LAR may be considered sufficient for research involving no more than minimal risk or low risk.
3	Consent from both parents may have to be obtained when the research involves more than minimal risk or high risk to the child.
4	Only one parent's consent is acceptable, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child irrespective of the risk involved.
5	Whenever relevant, the protocol should include a parent/LAR information sheet that contains information about specific aspects relevant to children such as effects on growth and development, psychological well-being and school attendance, in addition to all the components described in the participant information sheet.
6	When the research involves sensitive issues related to neglect and abuse of a child, the EC may waive the requirement of obtaining parental/LAR consent and prescribe an appropriate mechanism to safeguard the interest of the child.
7	Cognitively impaired children or children with developmental disorders form one of the most vulnerable populations. In fact, their parents are also vulnerable and there is a high likelihood of therapeutic misconception. The potential benefits and risks must be explained carefully to parents so that they understand the proposed research.

SECTION 4: Safeguard Systems

4.1 Ethics committee (EC)

The current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants*, ICMR, provide clear guidelines for the requirement of EC for institutes conducting biomedical and health research. Ethics Committees when providing opinion in a study involving children should have member/s, with paediatric expertise¹. The expert or experts may be permanent members of the EC, or invited as subject experts to provide advice and consulted on an ad hoc basis.

¹Paediatric expertise — "Expertise could be considered based on the education and experience on various aspects of child development, ethics, psychological and social aspects. It would include physicians with paediatric qualification; paediatric ethicists; qualified paediatric nurses or psychologists, among others. In addition to qualifications, it is recommended that the experts have at least some years of experience in child care/ health / research / advocacy. If the requisite experience cannot be found in one individual, two or more experts could be selected to provide the composite expertise needed. The expertise of invited experts should be documented and recorded by the ethics committee in its proceedings/minutes."

All experts reviewing the research proposal 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 ECs' remains the same as for research in adults. (Table 1)

Table 3: Considerations by ECs while evaluating research proposals

Scientific validity	Has the scientific evaluation of the proposal been completed before the ethics review? *
Risks [EC considers only additional interventions which are done as a part of research]	What is the level of risk? Have the risks been 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?
Safety	Are there adequate provisions to monitor the data and ensure participant safety
Autonomy	Is 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?
Confidentiality	Are adequate measures taken to ensure privacy of participants and maintain confidentiality of data?
Voluntariness	What is the influence of payments, if any? Are payments reasonable or can act as inducements? Are the selection, amount, and timing of payments appropriate? Are there additional safeguards for any vulnerable group prone to inducement?

*Examples include the following- thesis protocols reviewed by department faculty/committee, formal review by scientific expert committees/ peer group, etc.

4.2 Experience of investigator and research setting

For the protection of children involved in research, the investigator's competence and ethical conduct are the most important safeguards. The experience of investigators should be reviewed by the EC. The EC 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/ behavioural, etc.) related to childhood. If the investigator is less experienced, then EC should ascertain appropriate mentorship, or oversight by a senior researcher/ oversight committee.

It is desirable that research in children be 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 study be trained and experienced in dealing with children.

4.3 Data and Safety Monitoring Board (DSMB)

The need for a DSMB may be determined as an additional safeguard by the EC depending on the anticipated risks to the children involved in the research. Data and Safety Monitoring Board evaluating research performed in children should have members with appropriate *expertise* in reviewing clinical studies in children.

When studies have a significant safety concern, the establishment of a DSMB can enhance the safety of study participants. An independent review of research data may be essential to ensure the ongoing safety of study participants. Those involved in the study design and conduct of a study may be biased in reviewing the data. Hence, there is a need for a group of expert advisors to ensure that such concerns would be addressed in an unbiased way.

Data and Safety Monitoring Boards are traditionally established for large, multicentric, randomized, studies that evaluate interventions intended to prolong life or decrease an adverse health outcome. Though desirable, DSMBs add complexity to a study and need additional resources.

Factors to consider while establishing a DSMB for a particular study;

- The study endpoints are such that a highly favourable or unfavourable result, or even a finding of futility, during an interim review might make the continuation of the study unethical.
- The indicators for safety concern due to the intervention (for example, an invasive procedure, or potentially toxic drug).
- The study is being performed in a potentially vulnerable population such as neonates or other vulnerable individuals.
- The study involves a population at heightened risk of death or other serious adverse health outcomes.
- The study includes a large number of individuals, is of long duration, or is multi-centric.

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

If the study is likely to be completed in a short span, the DSMB may not be effective. In such situations, mechanisms should be in place a priori to expedite DSMB reviews and inputs. Alternatively, the study could build in periods of pauses to allow the DSMB to review interim data before any further enrolment of participants.

A DSMB can also enhance the scientific validity of a study by reviewing accumulating data of the study (for example, overall event rates) and suggest modifications in the protocol such as change in the inclusion criteria, the study endpoints, or the size of the study.

Finally, any independent DSMB evaluating studies 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 unlikely to challenge records about themselves. Therefore, there the investigator and the EC have an additional responsibility to protect data of children and ensure confidentiality. ECs should review the issue of data protection and confidentiality in all research protocols. All records must be archived for a period of at least 3 years after the completion/termination of the study. Documents related to regulatory clinical trials must be archived for 5 years after the completion /termination of the study or as per regulations. Preserving the data for a longer duration is suggested, keeping in mind the potential need for a long-term review of data. This primarily pertains to long term safety data of interventions.

When studies are performed in schools, parents or another individual may desire to know the responses of a child. This situation arises when studies include adolescents and address issues of sexuality, illicit drug use or violence. It should be made explicitly clear in the protocol, in the parent/LAR/PIS, and the consent and assent form, that information collected will not be disclosed to anyone.

4.5 Bio-banking of samples:

Please refer to the current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* ICMR for details.

4.6 International collaboration and data sharing

Please refer to the current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* (ICMR) for details. The International Health Division at ICMR is the secretariat for Health Ministry's Screening Committee (HMSC) and facilitates technical and administrative review of the collaborative proposals for placement before this Committee as a mandatory requirement.

SECTION 5: Compensation

5.1 Compensation for participation

Parents and children should not be asked to bear the expenses of research participation. It is advised that ECs allow reimbursement of reasonable expenses incurred by child or caregivers to participate in research (for example, travel, wage loss). Children involved in research may also receive free medical services. The ECs' have to ensure that payments do not act as inducements. Payments should not influence parents' or children's decisions on research participation, especially if such participation is not in the child's best interest. For example, providing a little payment at the completion of the study may encourage compliance, but making a large payment on completing

the study could act as an inducement for continued participation. Such issues become even more pertinent in research in low resource settings. When a LAR is consenting on behalf of the child, no remuneration should be offered. The only exception being a refund of out-of-pocket expenses.

Protocols should clearly mention the details about the type, level, and timing of payments to participants. The details should also be included in the informed consent form. EC's should approve the type, level, and timing of payments made by researchers. Full details of payments to be given to parents/LAR and other benefits of participation (such as, free medical care) should be explicitly mentioned in the parent/participant information sheet.

When children are enrolled in drug trials that come within the ambit of DCGI, all rules/guidelines of regulatory trials apply.

5.2 Compensation for Accidental Injury

Children are entitled to financial compensation and/or other assistance for any temporary or permanent impairment or disability resulting from participation in research. In the case of death, their parents are entitled to compensation.

Please refer to the current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* (ICMR) for more details on compensation.

SECTION 6: Special situation

6.1 Research in neonates

Neonates represent the most vulnerable group within the paediatric population. Study protocols in this population should take into account this, and the potential long-term effects of interventions, including developmental effects. ECs' reviewing any research proposed in neonates should have an advisory member with expertise in neonatal research/care.

ECs' should carefully scrutinize all research proposed in neonates for potential risks. Risks if any should be carefully weighed against possible benefits in this fragile population. ECs' should ensure a proper scientific review of the protocol by a competent person/s to remove any risks resulting from poor methodology. Neonates should be researched when the findings of the study will have potential implications for neonatal healthcare. All measures to reduce risks should be undertaken. When possible, older children should be studied before conducting studies in younger children and infants. Within neonates, those who are critically ill should be considered for research even more carefully. Parents or caretakers of these babies face stresses that may interfere with their ability to make an informed decision on behalf of their baby. Strategies such as continuous consent can to some extent reduce such problems. The consent of one parent is required for studies in neonates with research exposing them to no or minimal risk or in studies that offer the prospect of direct benefit to the participant. However, for studies that do not offer the prospect of direct

benefit or are high risk, consent from both parents is required. The exception being when only one parent has legal responsibility for the care and custody of the child, one parent is deceased, unknown, incompetent, or not reasonably available. In such cases, it is the duty of the investigators to provide adequate justification.

If one of the parents is a minor, then consent should not be taken from her/him. 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 EC. A legally acceptable representative should provide an informed consent in such situations.

6.2 Research in HIV-positive children

Research in HIV-positive children involves some special situations that need to be considered by the EC. Issues of confidentiality and anonymity assume great significance in these children. For children enrolled in long term studies, and who lose a surviving parent or guardian during the study period, re-consenting needs to be done for continued participation. This consent can be given by another custodian appointed by the family.

6.3 Vaccine studies in children

Please refer to the section on vaccine studies in the current National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (ICMR)

6.4 Ethical issues in genetic research

Please refer to the section on genetic research in the current National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (ICMR)

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 it is scientifically justified and cannot be carried out outside this setting. All principles of ethical research need to be followed and ECs' 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. However, it may not be possible to take formal consent in some emergency or critical care research settings (for example, research on drugs used in resuscitation). In such situations, deferred consent is suggested (see section 3.1.2). In deferred consent the process is split to give minimum information verbally, followed by full details and formal consent later. Therefore, in extremely sick children where immediate informed consent is not possible the process of deferred consent, as described above, can be followed. The time-frame within which formal consent would be obtained should be reviewed and approved by the ECs. 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. Formation of a DSMB should be strongly considered for research studies in emergency settings in which the informed consent requirement is waived or is not possible.

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 national guidelines by an EC. 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 EC. Researchers should comply with a school's 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, the EC may decide to waive individual consent, depending on the context and the type of research (for example, collecting data already with school authorities like number of disabled children, number availing mid-day meal services, etc.).

6.7 Internet /Telephone-based research in children

All research planned in children including Internet-based/tele research needs to be submitted to the EC. Following the guidelines provided by ICMR, the EC may choose to exempt some Internet-based research from the review (such as working on data that is in the public domain). Even if the research is exempt from a full EC review, researchers are required to keep an auditable record of the data after the completion of research. All records must be archived for a period of at least 3 years after the completion/termination of the study. Documents related to regulatory clinical trials must be archived for 5 years after the completion/termination of the study or as per regulations.

The EC 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 to Internet-based/tele research as well (see section 2). Special precautions may be needed to ensure confidentiality and safe storage of data in this kind of research. ECs and researchers need to ensure that data confidentiality and privacy of participants needs to be maintained as per the current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* (ICMR).

6.8 Community-based Research in Children

Community-based epidemiological research encompasses two forms of research; observational and experimental. Ethics in epidemiological studies is multidimensional covering clinical medicine, public health, and the socio-cultural milieu of the population. The general principles and guidelines of epidemiological research or community-based studies are detailed in the current *National Ethical Guidelines for Biomedical and Health Research Involving Human Participants* (ICMR).

Research done in populations based in the community as opposed to hospital-based population is required in the following scenarios:

- a) When epidemiological studies have a tacit need to be based in a population;
- b) The research questions are such that the study can only be conducted in the community
- c) Data from effectiveness studies (real world studies) are imperative for providing evidence-based data for policy-makers, so that an informed decision can be made; or
- d) Identification and enrolment of participants is from the community directly and not from patients attending an outdoor clinic/hospital.

The guiding ethical principles do not change at all except that they are harder to put in place. Also, in addition to ensuring the rights and safety of the participating population, the rights and safety of the community as a whole needs 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 are 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 the 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.

6.9 Research involving adolescents (12-18 years)

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), high-risk behaviours, unintended pregnancy, alcohol and drug use, are serious challenges to the health of the youth. Any researcher attempting research in this population should be conversant with the unique aspects of adolescent's cognitive, psychological and social development.

Studies suggest that adolescents have the ability to provide an informed consent. It is suggested that by mid-to-late adolescence, their capacity to make decisions about research participation are similar to that of adults. However, this capability is dependent on both cognition and previous life experiences. Their capacity for independent decision making is reduced if they have not made decisions in the real-world situations. On the other hand, adolescents who have had chronic illnesses may develop this capacity earlier. Inclusion of adolescents in the informed consent process increases their sense of self-control, improves their decision-making capacity and possibly improves compliance too.

In community-based studies in adolescents, involvement of youth advisory committees can be an effective way of incorporating youth into the planning research. 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 ethical issues and advising on other aspects study planning and implementation.

Any research that is to be conducted in adolescents must be submitted and reviewed by an EC in agreement with the current national guidelines. While conducting sexual health research in adolescent's researchers need to pay utmost attention to issues of confidentiality and anonymity. EC's should ensure that research protocols are prepared to keep in mind the local beliefs and socio-cultural sensitivities. EC's may consider waiver of parental consent in certain studies where parental permission may interfere with the validity of study results. Examples include the collection of data as the use of contraception and psychotropic drug. Such waivers only apply to research of low risk (e.g., confidential or anonymous surveys). In all such situations, EC must take the final decision regarding waiver of the requirement of parental consent. Additionally, an informed assent should be obtained from the adolescent in such types of research. In all other forms of research in adolescents, the principles of assent and consent have to be followed. (see Section 2 for further details).

SECTION 7: Annexures

7.1 Glossary

Assent

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

Child

A person under the age of 18 years

Consent

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

Harm

That which negatively affects the interests or welfare of an individual. (for example, physical harm, discomfort, anxiety, pain, and psychological disturbance or social disadvantage).

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.

Legally acceptable/authorised representative

An individual or judicial or other body authorized under applicable law to give consent on behalf of a prospective participant to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure as per research protocol.

Low risk

Low risk is defined as a slight increase in the potential for harms or discomfort beyond or more than 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 (for example, a blood test, oral sedation for diagnostic procedures. etc.).

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 by appropriate persons. Procedures with minimal risk include history taking, physical examination, chest X-ray, obtaining bodily fluids without invasive intervention, (for example, taking saliva or urine samples, etc.). It is expected that the harm caused by the minimum risk level research would be very slight and temporary.

Therapeutic misconception

The belief that the purpose of research is treatment.

7.2: Web Resources

Clinical Trials Registry-India. Available from: <http://ctri.nic.in/Clinicaltrials/login.php>

Central Drugs Standard Control Organization. Available from: <http://www.cdsco.nic.in/forms/Default.aspx>

Indian Council of Medical Research. Available from: <http://icmr.nic.in/index.html>

Department of Science and Technology. Available from: <http://www.dst.gov.in/index.htm>

Department of Biotechnology. Available from: <http://dbtindia.nic.in/index.asp>

WHO-International Clinical Trials Registry Platform. Available from: <http://www.who.int/ictrp/en/>

US National Institutes of Health Clinical Trials Registry. Available from: <https://clinicaltrials.gov/>

FDA. Guidelines on good clinical practice. Available from: <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>.

Index

A

Adolescents, 28,32,33
 Adverse effects, 11,13
 Anatomy, 15
 Animal studies, 10
 Anonymized, 21,22
 Assent, 19,22,23,24,26,28,30,31,33
 Autonomy, 10, 12, 19, 23, 26,34

B

Beneficence, 10
 Benefit, 10,11,12,14,15,16,18,19,20,22,23,25,26,29,30
 Bio-banking, 28
 Biological, 13,20,21,22
 Biomedical, 10,11,12,13,15,22,25,28,29,30,31
 Birth asphyxia, 11
 Blood sample, 17,18

C

CDSCO, 14, 23
 Child, 11
 Child rights, 13
 Child-friendly environment, 15, 27
 Children's assent, 23
 Classification of Risks, 16
 Clinical care, 10,11,23
 Clinical research, 11,22
 Clinical trial, 13,14,23,28,31,34
 Coercion, 10
 Community Based Research, 27,31
 Compensation, 20,28,29

Compensation for Accidental Injury, 29
 Compensation for participation, 28
 Confidentiality, 19,20,21,26,28,30,21,33
 Consent, 10,12,16,19,20,21,22,23,24,25,26,29,30,31,32,33,34
 Consent Form, 19,20,21,29
 Consent process, 20,21,22,23,32
 Consumer acceptance studies, 21
 Content of assent forms, 23,24

D

DSMB, 27,28,31
 Data protection, 28
 Data sharing, 28
 DCGI, 14,29
 Declaration of Helsinki, 10
 Deferred consent, 22,30
 Department of Health Research, 6,9
 Determinants of risk, 17
 Developing countries, 11
 Developmentally appropriate, 12
 Devices, 13
 Disabled children, 31
 Drug and Cosmetics, 14
 Drugs, 11,12,13,14,15,30,34
 Drugs and Cosmetics Act, 13

E

Efficacy, 13,15
 Emergencies, 22
 Emergency, 21,22,30,31
 Ethical concerns, 12
 Ethics, 9,10,12,13,14,17,18,23,25,26,31

Ethics Committee, 13,14,17,18,23,25

European union guidelines, 13

Experience, 15,16,17,23,25,26,32,34

Experience of investigator, 26

Expertise, 15,25,26,27,28,29

F

Fixed dose combination, 14

Formulations, 12,18

G

Genetic research, 30

Government of India, 2,9,13,14

H

Harms, 20,34

Health, 10,11,12,13,21,22,25,26,27,28,29,30,31,32,33,34

Helsinki, 10

High risk, 12,16,17,25,30,32,33

HIV positive children, 30

HIV/AIDS, 21

Hyaline membrane disease, 11

Hypertension, 11

I

Illiterate parents, 20

Indian Council of Medical Research, 12,13,34

Infantile spasms, 11

Informed consent, 12,19,20,21,22,23,24,29,30,31,32

International collaboration, 28

Internet /Telephone based research, 31

Investigators, 19,22,26,30

J

Justice, 10

K

Kawasaki disease, 11

L

LAR, 19,20,21,22,23,25,28,29

Legally acceptable representative, 21,30,34

Legislature, 13

Licensing Authority, 13,14

Litigation,, 22

Low risk, 16,17,18,25,33,34

M

Marketed, 14

Maturity, 17,22,23

Medical Research Council, 13

Metabolism, 11

Minimal Risk, 16,17,18,21,25,29,34

Multi-centric studies, 12

N

National Commission, 13

National guidelines, 31,33

Neonatal healthcare, 29

Neonatal hyperbilirubinemia, 11

Nephrotic syndrome, 11

New drug, 13,14

Newborns, 13

Non-maleficence, 10

O

Observational studies, 21

P

Pain, distress, and fear, 17

Participant information sheet, 20,22,25,29

Pathophysiology, 12

- Paediatric ethicists, 25
- Paediatric expertise, 25
- Paediatric nurses, 25
- Paediatrician, 15,18,41
- Pharmacokinetic, 11,13,15,18
- Poor methodology, 29
- Poor socio-economic status, 11
- Powered, 12
- Premature, 15
- Procedures,10,12,15,16,17,18,20,21,22,26,31, 33,34
- Psychologists, 25
- Psychology, 15,39
- Public health programs, 21
- Q**
- Quality assurance studies, 21
- R**
- Re-consent, 21,23,30
- Regulatory, 13,14,21,23,28,29,31
- Regulatory guidelines, 14
- Relative versus absolute interpretation of risk, 17
- Repositories, 22
- Research in neonates, 29
- Resource-poor, 11
- Review of literature, 15
- Reye's syndrome, 11
- Rheumatoid arthritis, 11
- Risk, 15
- Route of administration, 14
- S**
- Safety, ,13,15,18,21,26,27,28,32
- Sampling, 15,18
- Schedule-Y, 14
- School-based research, 31
- Service programs, 21
- Special needs, 15
- Sponsor, 26
- Statistically, 12
- Study designs, 12
- Surfactant, 15
- Syrups, 12
- T**
- Testing, 15
- Therapeutic misconception, 11,23,25,34,39
- Toxicity, 11
- V**
- Vaccine studies, 30
- Voluntariness, 26
- Vulnerable,10,11,25,26,27,29
- W**
- Waiver of assent, 23
- Waiver of consent, 21
- Witness., 21

Bibliography

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