Annex 14
Informed assent

In clinical research, informed consent refers to the state whereby a competent individual, of the legal age to consent, having been fully informed about the nature, benefits and risks of a clinical study, agrees to participate in the study voluntarily. Ethics guidelines define certain populations as vulnerable and therefore unable to provide informed consent, such as those without the necessary cognitive, psychological, or social maturity to understand the risks and benefits. In this context minors, that is individuals below the legal age to consent (which in many countries is below 18 years), are considered a vulnerable population and therefore may not autonomously provide informed consent. Yet it stands to logic that older children and adolescents are often quite capable of understanding the discomforts, risks and benefits associated with clinical activity, either as part of practice or research, and therefore should not always have the decisions of parents or legal guardians imposed upon them. Hence, the concept of pediatric assent, as opposed to consent, has come into existence. The term informed assent describes the process whereby minors may agree to participate in clinical research, independent of the views of their legally acceptable representatives, after having been explained about the potential discomforts, risks and benefits that participation entails.

Investigators wishing to conduct clinical research with children in India are required to seek the permission of both the child and a parent or a legally acceptable representative. The mere failure to object to participate cannot, without affirmative agreement, be taken as assent. The latter must be documented in a manner similar to informed consent. Although guidelines do not clearly specify a cut-off age for assent, in practice this is usually taken as 7 years. Before 7 years of age, children are held to lack the cognitive development necessary for autonomous decision-making. At age 7 years, most children are considered to be able to distinguish right from wrong and what is harmful (at least physically) from what is beneficial. Also, it has been found that most children from age 7 can understand basic information if it is given at their level. Some countries place the onus of deciding at what age assent should be required on the independent ethics committees reviewing the proposal or on individual institutions. Experience shows that the 7-years cut-off is accepted in most such instances.

Clinical research with children above 7 years age in India requires both informed assent from the minor subject as well as informed consent from his / her legally acceptable representative. Separate forms must be used for documenting consent and assent. Child-focused forms should include all the elements and considerations generally required for seeking informed consent from competent adults but in very simple language. Additionally, it should conform to their intellectual capacity to understand the risks and discomforts involved, and the family should be given sufficient time and information to consider the pros and cons. A child should also be aware that he / she can withdraw from the study at any time without fear of punishment for himself / herself or reprisal for the family.

Although the premise of informed assent is now being widely used and recognized as a practicable and ethical solution, controversies still abound. For instance:

- Should a child below 7 years who is vehemently uncooperative with a procedure (such as blood collection or a painful injection) be removed from the trial by the investigator?
- Should a child below 7 years who declines treatment for a serious illness, have his/her dissent overridden and made to undergo treatment, when the treatment is available only in a trial setting?
- Children over 14 years may be able to provide their own informed consent, independent of their parents. This is accepted in some countries. Therefore, should these minor subjects provide informed consent or only assent?
- There may be instances where children assent, solely to win favors with parents or the physician, without understanding the consequences of assenting.

Notwithstanding these controversies, the tenets of bioethics demands that children should also have a say in what happens to them. If they ask questions these should be answered at their level. When children are asked if they want to join a study, it shows respect for them, and they will feel good about being in the study and possibly more committed to doing what the study requires. In addition, the sustained dissent of all children, including those who are unable to provide assent, should be respected, since expression of dissent is evidence that a child is experiencing distress. While the assent requirement may be waived when research participation offers the potential for important and direct medical benefit that is unavailable outside of the research context, children's sustained dissent should be respected in all cases. Finally, children should not be required to participate in research not directly beneficial to them if it is more than minimally distressing.

We have provided a template for informed assent based on the Informed Assent Form Template for Children/Minors made available publicly by the World Health Organization Research Ethics Review Committee (WHO ERC) [Available from www.who.int/rpc/research_ethics/InformedAssent.doc; Accessed on Jun 15, 2014].

Points to note for the researcher:

1) This template is provided to assist you in designing your own informed assent document. It is important that investigators adapt the template to the requirements of their particular study.
2) An Informed Assent Form does NOT replace a consent form to be signed by parents or guardians. The assent is in addition to the consent and is meant to document the child's willing cooperation in the study.
3) The informed assent document consists of two parts: the information sheet and the assent form.
4) Do not be concerned by the length of this template. It is long because it contains guidance and explanations which are for you and which you do not have to include in the actual document that you develop and provide to participants in your research.
5) This template includes examples of key questions that may be asked at the end of each section, that could ensure the understanding of the information being provided, especially if the study is complex. These are just examples, and suggestions, and you will have to modify the sections in accordance with your own study.
6) In this template:
   - square brackets indicate where specific information is to be inserted
   - bold lettering indicates sections or wording which should be included
   - standard lettering is used for explanations to researchers only and must not be included in your assent form. The explanation is provided in black, and examples are provided in italics. Suggested questions to elucidate understanding are in italics and indented.

Informed Assent Document for
[Title of the study]

Version No. [_____] dated [_____]

Name the group of individuals for whom this assent is written. Because research for a single project is often carried out on a number of different groups of individuals - for example children with malaria, children without malaria, students - it is important that you identify which group particular assent is for.

(Example: This informed assent document is for children between the ages of 12 - 16 who attend clinic X and who we are inviting to participate in research Y.)

[Name of Principle Investigator]

[Name of Organization]

[Name of Sponsor]

This Informed Assent Form has two parts:

- **Information Sheet (gives you information about the study)**
- **Certificate of Assent (this is where you sign if you agree to participate)**

You will be given a copy of the full Informed Assent Form

Part I: Information Sheet

Introduction

This is a brief introduction to ensure the child knows who you are and that this is a research study. Give your name, say what you do and clearly state that you are doing research. Inform the child that you have spoken to their parents and that parental consent is also necessary. Let them know that they can speak to anyone they choose about the research before they make up their mind.

(Example: My name is _____ and my job is to research and test vaccines to see which work best to stop malaria before it makes someone sick .We want to know if this new vaccine will stop children from getting sick and we think this research could help tell us that.

I am going to give you information and invite you to be part of a research study. You can choose whether or not you want to participate. We have discussed this research with your parent(s)/guardian and they know that we are also asking you for your agreement. If you are going to participate in the research, your parent(s)/guardian also have to agree. But if you do not wish to take part in the research, you do not have to, even if your parents have agreed.

You may discuss anything in this form with your parents or friends or anyone else you feel comfortable talking to. You can decide whether to participate or not after you have talked it over. You do not have to decide immediately.

There may be some words you don't understand or things that you want me to explain more about because you are interested or concerned. Please ask me to stop at anytime and I will take time to explain).

Purpose: Why are you doing this research?
Explain the purpose of the research in clear simple terms.

(Example: We want to find better ways to prevent malaria before it makes children sick. We have a new vaccine to prevent malaria which we are hoping might be better than the one that is currently being used. In order to find out if it is better we have to test it.)

Choice of participants: Why are you asking me?
Children, like adults, like to know why they are being invited to be in the research. It is important to address any fears they may have about why they were chosen.

(Example: We are testing this vaccine on children who are your age - between 12 and 16 years old - who live in a place where there is malaria . We are only testing the vaccine on children who do not have malaria.)

Participation is voluntary: Do I have to do this?
State clearly and in child-friendly language that the choice to participate is theirs. If there is a possibility that their decision not to participate might be over-ridden by parental consent, this should be stated clearly and simply.

(Example: You don't have to be in this research if you don't want to be. It's up to you. If you decide not to be in the research, it's okay and nothing changes. This is still your clinic, everything stays the same as before. Even if you say "yes" now, you can change your mind later and it will still be okay.)

<u>If applicable:</u> If anything changes and we want you to stay in the research study even if you want to stop, we will talk to you first .)

- ***Examples of question to elucidate understanding:*** *If you decide not to take part in this research study, do you know what your options are? Do you know that you do not have to take part in this research study, if you do not wish to? Do you have any questions?*

<u>Include the following section only if the protocol is for a clinical trial:</u>
Information on the Trial Drug [Name of Drug]: What is this drug and what do you know about it?
1) give the phase of the trial and explain what that means. Explain to the participant why you are comparing or testing the drugs.
2) provide as much information as is appropriate and understandable about the drug such as its manufacturer or location of manufacture and the reason for its development.
3) explain the known experience with this drug
4) explain comprehensively all the known side-effects/toxicity of this drug, as well as the adverse effects of all the other medicines that are being used in the trial

(Example: The vaccine we are testing in this research is called ABX. It has been tested twice before with adults who do not have malaria but who live in areas where malaria is common. We now want to test the vaccine on teenagers who do not have malaria. This second research is called a "phase 2" trial.

The vaccine ABX is made by Company C. It has very few side effects. It can make you feel tired for the first 24 hours after being given the drug. Also, 20% of the people who tried the drug in previous research experienced temporary swelling where the injection entered the skin. We know of no greater risk or other side effects. Some participants in the research will not be given the drug which we are testing. Instead, they will be given the drug XYZ, the drug which is most commonly used in this region to treat malaria. There is no risk associated with that drug and no known side effects.)

Procedures: What is going to happen to me?
Explain the procedures and any medical terminology in simple language. Focus on what is expected of the child. Describe which part of the research is experimental.

(Example: We are going to test the vaccine by giving some of the children in the research study the new vaccine and the others are going to get the vaccine that is already being used to prevent malaria. Neither you nor the researchers will know which vaccine you were given until after the study is over. By doing the research like this, we can compare which of the vaccines is better without being influenced by what we think or hope the research will show.

If you decide that you want to do this, there will be three things that happen.

1. In about ten days, you will come to the clinic with your parents and you will get an injection/shot in your arm. This is either the vaccine that we are testing or the vaccine that is usually used to prevent malaria.

2. At the clinic we will also give you a mosquito net to take home and sleep under. Maybe you have seen these before. They stop mosquitoes from biting you during the night when you sleep.

3. Once a month for six months after that, you will come to the clinic and the nurse will take your temperature. She will also take a little bit of your blood, about three or four drops, from your finger with a finger prick. This might hurt a little but the hurt will go away before very long.

Altogether you will come to the clinic 7 times over 7 months. I have a picture here to show you what will happen. You can ask me to stop and explain again at any time and I will explain more about the process).

- ***Examples of question to elucidate understanding:*** *Can you tell me if you remember the number of times that we are asking you to come to the hospital to complete the treatment? How many times extra will you have to come if you decide to take part in the research study? How many injections will you be given? How many tablets? How much blood will be taken from your veins, using a syringe and needle? Over how many weeks? Do you have any other questions? Do you want me to go through the procedures again?*

Risks: Is this bad or dangerous for me?
Explain any risks using simple, clear language.

(Example: The vaccine is considered safe. It has already been tested on adults and on other children. There has been nothing that has worried us at all. If anything unusual happens to you, however, we need to know and you should feel free you to call us anytime with your concerns or questions. Another way of us knowing how you are is by having you come to the clinic every month for a check-up. If you get sick or have concerns or questions in-between the scheduled visits to clinic, you should let me or the staff nurse know. You don't have to wait for a scheduled visit.)

Discomforts: Will it hurt?
If there will be any discomforts state these clearly and simply. State that they should tell you and/or their parents if they are sick, experience discomfort or pain. Address what may be some of the child's worries, for example, missing school or extra expense to parents.

(Example: There are a few other things that I want you to know. The injection might hurt for just a second when it goes into your arm. It might get a little bit red and hard around the place where the injection/needle goes in. That should go away in a day. If it hurts longer than that, or if it stays hard for longer or swells up, tell your parents or me. If you feel bad or strange, tell us. Sleeping under a mosquito net can be uncomfortable because it can be stuffy.

Sometimes you may not want to come to the clinic to get your blood checked or have your temperature taken. It's important that you try to come. It won't take very long. You will miss a little bit of school - about an hour every month - and we will tell your teacher about that so that she knows it's okay.)

- ***Examples of question to elucidate understanding:*** *Do you understand that, while the research study is on-going, no-one may know which medicine you are receiving? Do you know that the medicine that we are testing is a new medicine, and we do not know everything about it? Do you understand that you may have some unwanted side-effects from the medicines? Do you understand that these side-effects can happen whether or not you are in the research study? Do you have any other questions?*

Benefits: Is there anything good that happens to me?
Describe any benefits to the child.

(Example: Nothing really good might happen to you. The vaccine may not stop you from getting malaria. But this research might help us to find a vaccine now or later that could help other children. There are a couple of good things if you do decide that you want to do this. You do get regular check-ups with the nurse so that if you are sick, we will know very soon and this can be important. And you will keep the mosquito net which will help keep mosquitoes away from you. Because mosquitoes cause malaria, this is important.)

Reimbursement: Do I get anything for being in the research?
Mention any reimbursements or forms of appreciation that will be provided. Any gifts given to children should be small enough to not be an inducement or reason for participating. We do not encourage incentives beyond reimbursements for expenses incurred as a result of participation in the research. These expenses may include, for example, travel expenses and reimbursement for time lost. The amount should be determined within the host country context.

(Example: Because you live quite far from the clinic, we will give your parents enough money to pay for the trip here and (whatever other expense is reasonable).

- ***Examples of question to elucidate understanding:*** *Can you tell me if you have understood correctly the benefits that you will have if you take part in the study? Do you know if the study will pay for your travel costs and time lost, and do you know how much you will be reimbursed? Do you have any other questions?*

Confidentiality: Is everybody going to know about this?
Explain what confidentiality means in simple terms. State any limits to confidentiality. Indicate what their parents will or will not be told.

(Example: We will not tell other people that you are in this research and we won't share information about you to anyone who does not work in the research study. After the research is over, you and your parents will be told which of the two injections you received and the results.

Information about you that will be collected from the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone not authorized.)

- ***Example of question to elucidate understanding:*** *Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?*

Compensation: What happens if I get hurt?
Describe to the ability of the child to understand and explain that parents have been given more information.

(Example: If you become sick during the research, we will look after you. We have given your parents information about what to do if you are hurt or get sick during the research.)

Sharing the findings: Will you tell me the results?
Describe to the ability of the child to understand that the research findings will be shared in a timely fashion but that confidential information will remain confidential. If you have a plan and a timeline for the sharing of information, include the details. Also tell the child that the research will be shared more broadly, i.e. in a book, journal, conferences, etc.

(Example: When we are finished the research, I will sit down with you and your parent and I will tell you about what we learnt. I will also give you a paper with the results written down. Afterwards, we will be telling more people, scientists and others, about the research and what we found. We will do this by writing and sharing reports and by going to meetings with people who are interested in the work we do.)

Right to refuse or withdraw: Can I choose not to be in the research? Can I change my mind?
You may want to re-emphasize that participation is voluntary and any limits to this.

(Example: You do not have to be in this research. No one will be mad or disappointed with you if you say no. It's your choice. You can think about it and tell us later if you want. You can say "yes" now and change your mind later and it will still be okay.)

Who to Contact: Who can I talk to or ask questions to?
List and give contact information for those people who the child can contact easily (a local person who can actually be contacted). Tell the child that they can also talk to anyone they want to about this (their own doctor, a family friend, a teacher).

(Example: You can ask me questions now or later. You can ask the nurse questions. I have written a number and address where you can reach us or, if you are nearby, you can come and see us. If you want to talk to someone else that you know like your teacher or doctor or auntie, that's okay too.)

If you choose to be part of this research I will also give you a copy of this paper to keep for yourself. You can ask your parents to look after it if you want.

- ***Example of question to elucidate understanding:*** *Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study?*

You can ask me any more questions about any part of the research study, if you wish to. Do you have any more questions right now?

PART 2: Assent Form

This section would be similar to the template for the informed consent form. Although the child's name must be recorded he/she should not be made to sign if below 14 years. However, the investigator and a legally acceptable representative going over the informed assent with the child must sign. If the child or the legally acceptable representative is illiterate, the signing must be witnessed by a literate person who also signs at the same time.