Title: Reviewing Proposals Involving Vulnerable Populations

1. Purpose

This Standard Operating Procedure (SOP) describes the requirements and process of review of research that involves vulnerable participants.

2. Scope

This SOP covers the policies and procedures applied to all research dealing with vulnerable participants submitted to the IEC.

3. Responsibility

- It is the responsibility of the Member Secretary with Secretariat to maintain up-to-date tools, like checklists, for reviewing research concerning vulnerable groups based on new and evolving applicable regulations and guidelines.
- IEC Chairperson / Member Secretary are responsible for ensuring that IEC members are well-versed in new and evolving regulations and guidelines pertaining to vulnerable populations, through regular training programmes.
- The Member Secretary/ Chairperson is responsible for selecting primary reviewers with appropriate expertise to conduct the reviews of such research and for securing consulting expertise as and when required for selected reviews.
- IEC member is responsible for conducting review of research planned for vulnerable populations, including an assessment of potential for coercion.

4. Detailed instructions

Definition and Mandate

4.1 Definition

Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such

as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

[http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6 /E6_ R1_Guideline.pdf accessed on 23rd Nov 2015]

As per ICMR 2017 guidelines:

Following are some examples of vulnerable populations or groups:

• economically and socially disadvantaged (unemployed individuals, orphans, abandoned individuals, persons below the poverty line, ethnic minorities, sexual minorities – lesbian/ gay/bisexual and transgender (LGBT), etc.);

• unduly influenced either by the expectation of benefits or fear of retaliation in case of refusal to participate which may lead them to give consent;

• children (up to 18 years);

• women in special situations (pregnant or lactating women, or those who have poor decision-making powers/poor access to healthcare);

• tribals and marginalized communities;

• refugees, migrants, homeless, persons or populations in conflict zones,riot areas or disaster situations;

• afflicted with mental illness and cognitively impaired individuals, differently abled – mentally and physically disabled;

• terminally ill or are in search of new interventions having exhausted all therapies;

• suffering from stigmatizing or rare diseases; or

• have diminished autonomy due to dependency or being under a hierarchical system (students, employees, subordinates, defence services personnel, healthcare workers, institutionalized individuals, under trials and prisoners)

4.2 Mandate

Gazette notification dated 31st July 2015, [G.S.R. 611(E)] has mandated audio-visual recording of informed consent process in case of vulnerable participants in clinical trials of

new chemical entity/ new molecular entity.[**http://www.ferci.org/wp-content/uploads/2014/07/Gazette-Notification-31-July-2015-AV-consent.pdf]**

4.3. Reviewing protocols with vulnerable participants

- The protocol should be reviewed as per SOP 7A/V4. Additionally, the protocol should be reviewed to assess if the following points are addressed:
  - Can the research be performed in any other non-vulnerable participants?
  - Is there justification to use vulnerable population
  - Do the benefits justify the risks
  - Are the participants selected equitably
  - Have the measures to protect Autonomy of the vulnerable population been described
- IEC members dealing with such protocols should be well versed with the potential harm or risk of such population participating in the study.
- The review must address all points in the checklists for different vulnerable populations (Annexures 1 to 5- SOP 19).

As per ICMR 2017 guidelines: Categories of Risk

Type of risk	Definition/description
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.
Minimal risk	Probability of harm or discomfort anticipated in the research is not greater than that ordinarily encountered in routine daily life activities of an average healthy individual or general population or during the performance of routine tests where occurrence of serious harm or an adverse event (AE) is unlikely. Examples include research involving routine questioning or history taking, observing, physical examination, chest X-ray, obtaining body fluids without invasive intervention, such as hair, saliva or urine samples, etc.

Minor increase over minimal risk or Low risk	Increment in probability of harm or discomfort is only a little more than the minimal risk threshold. This may present in situations such as routine research on children and adolescents; research on persons incapable of giving consent; delaying or withholding a proven intervention or standard of care in a control or placebo group during randomized trials; use of minimally invasive procedures that might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress, such as drawing a small sample of blood for testing; trying a new diagnostic technique in pregnant and breastfeeding women, etc. Such research should have a social value. Use of personal identifiable data in research also imposes indirect risks. Social risks, psychological harm and discomfort may also fall in this category.
More than minimal risk or High risk	Probability of harm or discomfort anticipated in the research is invasive and greater than minimal risk. Examples include research involving any interventional study using a drug, device or invasive procedure such as lumbar puncture, lung or liver biopsy, endoscopic procedure, intravenous sedation for diagnostic procedures, etc.

4.4. Appointing Reviewers

The Member Secretary/Chairperson will appoint two or more members of the IEC who have a thorough understanding of the ethical review process and experience in the field of research to review such type of protocols.

4.5. Duties of Secretariat

- Provide a suitable checklist to the investigator depending on the type of participants to be recruited for the study.
- Provide appropriate reference material or help reviewer locate the material relevant to vulnerable populations when specifically requested for, by a reviewing member.

4.6. Responsibilities of Reviewers

- IEC Members will review the protocol and the informed consent document or assent form as per this SOP and SOP 07A/V4.
- The IEC members will discuss the comments in the IEC meeting and letter regarding approval/modification/ disapproval will be sent to the principal investigator.
- The discussion will be documented in the minutes.
- The Member Secretary will ensure that the IEC recommendations have been incorporated in the revised protocol and protocol related documents.

4.7 Approval of the protocol

- The final version of the protocol will be approved at a full board meeting.
- Wherever necessary the IEC approval should state that if in future the vulnerability status of the participants changes, for e.g. unconscious patient gaining consciousness or a schizophrenic patient regains insight, the participant will be re-consented.

5. Reference to other applicable SOP: NIL

6. Annexure

NOTE: The following annexure apply to some sections of vulnerable participants. These checklists should be filled in by primary reviewer.

Annexure 1 *AX 01/SOP 19/V4* – Checklist: Requirements for Research Involving Children

Annexure 2 *AX 02/SOP 19/V4* - Checklist: Requirements for Research Involving Pregnant Women & Fetuses

Annexure 3 *AX 03/SOP 19/V4*- Checklist: Research Involving Cognitively Impaired Adults

Annexure 4 *AX 04/SOP 19/V4*- Checklist-Research Involving Students, Employees or Residents

Annexure 5 *AX 05/SOP 19/V4* – Checklist: Considerations for Genetic Research

[Adapted from http://www.kem.edu/wp-content/uploads/2014/04/SOP-24.pdf, Reviewing proposals involving vulnerable Populations http://www.kem.edu/wp- content/ uploads/ 2014/04/SOP-24.pdf]

Annexure 1: AX 01/SOP 19/V4

Checklist: Requirements for Research Involving Children

Study Title:

	Yes	No	NA
Does the research pose greater than minimal risk to children?			
If yes: Are convincing scientific and ethical justifications given?			
If yes: Are adequate safeguards in place to minimize these risks?			
Does the study involve healthy children?			
a) If yes: Is the inclusion of healthy children justified?			
Are the studies conducted on animals and adults appropriate and justified?			
Will older children be enrolled before younger ones?			
Is permission of both parents necessary?			
Are efforts being made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?			
Are provisions made to obtain the assent of children over 7 and, where appropriate, honoring their dissent?			
Are provisions made to protect participants' privacy and the confidentiality of information regarding procedures?			
Are there special problems that call for the presence of a monitor or IEC member during consent procedures?			
Are special needs of adolescents such as counseling and confidentiality accounted for in the research design?			
Are there any special problems such as confidentiality and reporting that might arise in sensitive research about child abuse or sexual practices of teenagers?			
Does the research involve possibility of findings which may have implications for other family members?(for eg. genetic risk, HIV infection, Hepatitis C)			

If Yes: Are there adequate mechanisms in place to deal with other members of the family?			
Are parents required to be present during the conduct of the research? (Are proposed participants' very young?)			

RISK DETERMINATION	BENEFIT ASSESSMENT	PRIMARY REVIEWER RECOMMENDATION
Minimal * ☐	Direct benefit	Approvable
☐	No direct benefit	
Greater than minimal risk ☐	Potential benefit to child	Approvable
Greater than minimal risk ☐	No direct benefit, offer knowledge about child's condition/disorder	Approvable on case –by- case basis**

* Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or occurring during the performance of routine physical or psychological examinations or tests.

** Consent of both parents may be needed as applicable.

Any other comments of Primary Reviewer:

Primary Reviewer Signature and Date

Annexure 2: AX 02/SOP 19/V4

Checklist: Requirements for Research Involving Pregnant Women and Fetuses

Study Title:

When research involves pregnant women or fetuses

	Yes	No	NA
Are scientifically appropriate preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been referenced in the proposal to provide data for accessing potential risks to pregnant women and fetuses?			
Are there risks and benefits clearly identified and explained in the proposal?			
Is the risks to the fetus not greater than minimal?			
Do the benefits justify the risks in the study?			
Are risks minimization strategies mentioned in the proposals?			
Are there provisions for obtaining informed consent from the pregnant women or her legally authorized representative			
Are there provisions for fully informing the woman or her legally authorized representative, regarding the reasonably foreseeable impact of the research on the fetus or resultant child?			

Any other comments of Primary Reviewer:

Primary Reviewer Signature and Date

Annexure 3: AX 03/SOP 19/V4
Checklist- Research Involving Cognitively Impaired Adults

Study Title:

1. Research Involving Cognitively Impaired Adults in which there is Anticipated Direct Benefit to the participant (All items must be "Yes")		
Yes	No	Is the recruitment of participants justified considering the rationale and objectives of the study?
Yes	No	The risk is justified by the anticipated benefit to the participants.
Yes	No	The relation of anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches
Yes	No	Are there provisions to withdraw the participants, if they appear to be unduly distressed?
Yes	No	Is the proposed plan for the assessment of the capacity to consent adequate?
Yes	No	Will consent be taken from participants capable of being consulted?
Yes	No	Does the consent document include provision for a legally authorized representative in case participants are not capable of being consulted?

2. Research Involving Cognitively Impaired Adults in which there is No Anticipated Direct Benefit to the participant (All items must be "Yes")		
Yes	No	Is the recruitment of participants justified considering the rationale and objectives of the study?
Yes	No	Are the foreseeable risks to the participants low?
Yes	No	Is the negative impact on the participant's well-being minimized and low?
Yes	No	Are there provisions for close monitoring of the participants?
Yes	No	Are there provisions for withdrawal of the participants if they appear to be unduly distressed?
Yes	No	Is the proposed plan for the assessment of the capacity to consent adequate?
Yes	No	Will consent be taken from participants capable of being consulted?
Yes	No	Does the consent document include provision for a legally authorized representative in case participants are not capable of being consulted?

Any other comments of Primary Reviewer:

Primary Reviewer Signature and Date

Annexure 4: AX 04/SOP 19/V4

Checklist: Research Involving Students, Employees or Residents

Study Title:

Participants who are students, employees or residents require special considerations.

Are there provisions for informing the participants that their status (education, employment and/or promotion) will not be affected by any decision to participate or not?	No	Yes
Have the risks to participants been minimized?	No	Yes
Are there provisions to assure the participants that the participation is voluntary (no signs of coercion)?	No	Yes
Are there provisions to assure the participants that their privacy and confidentiality will be protected?	No	Yes

Answers to all the above points should be YES for approval

Any other comments of Primary Reviewer:

Primary Reviewer Signature and Date

Annexure 5: AX 05/SOP 19/V4

Checklist: Considerations for Genetic Research

Study Title:

	Yes	No
1. Will the samples be made anonymous to maintain confidentiality? If yes, then the following checklist points are not applicable		
2. Will the results be disclosed? a) If yes, has the investigator established clear guidelines for disclosure of information, including interim or inconclusive research result? b) Will the results be used in management of current condition of patient?		
3. Has the appropriateness of the various strategies for recruiting participants and their family members been considered?		
4. Does the proposed study population comprise family members?		
5. Will family members be implicated in the studies without consent?		
6. Will the samples be destroyed in the future?		
7. Will the samples be used for future research		
8. Is genetic counseling being offered?		

Any other comments of Primary Reviewer:

Primary Reviewer Signature and Date

7. Flow Chart

No.	Activity	Responsibility
1	Appoint reviewers	Chairperson/ Member Secretary
2	Review the protocol	IEC members
3	Discussion at IEC meeting	IEC member
4	Communicating the decisions to principal investigator	IEC Secretariat

8. References

1. Forum for Ethics review Committees in India (FERCI). Standard Operating Procedures of Institutional Ethics Committee (cited 22nd October 2018). Available from: http:// www.ferci.org/sops/
2. Ethical guidelines for biomedical research on human participants. (2017). Indian Council of Medical Research. Available from: http://www.icmr.nic.in/guidelines/ICMR_Ethical_Guidelines_2017.pdf
3. Ministry of Health and Family Welfare. New Drugs and Clinical Trials Rules, 2019. Available from: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

	Name	Designation	Signature
Prepared	Dr. Girija. S	Member	
	Dr. Nishanthi. A	Member	
Reviewed	Dr. Vimal. M	Member Secretary	
Approved	Dr. T. Thiagarajan	Chairman	
Issued	Dr. R. N. Kagne	Dean	