Title: Protocols involving vulnerable populations: Review and Management

SOP Code: SOP19/v3

Effective Date: 03/10/2019

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Notified by:

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Table of Contents:

1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the submission requirements, the process of review and monitoring mechanisms for research protocols involving vulnerable populations.

2. Scope

This SOP covers the procedures applied to all research dealing with vulnerable participants submitted to the YEC-1.

3. Definitions:

3.1. Vulnerable subjects:

3.1.1. Vulnerable subjects are those individuals who are relatively or absolutely incapable of protecting their own interests because of personal disability; environmental burdens, social justice, lack of power, understanding or ability to communicate or are in a situation that prevents them from doing so[1].

3.1.2. In addition - for the purpose of this SOP - vulnerable populations are defined as 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; of socio-economic disadvantage such that their exploitation potential is greater than that of other people; of a retaliatory response from senior members of a hierarchy in case of refusal to participate. in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent[2].

[1] ICMR National Ethical Guidelines for Biomedical Research Involving Human Participants, 2017

[2] Modified and adapted from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf accessed on 19 August 2019 at 1745 hours.

3.1.3. For the purpose of this SOP, following are examples of vulnerable population including but not limited to:

3.1.3.1. Economically and socially disadvantaged or marginalized sections of society (unemployed individuals, orphans, abandoned individuals, persons below the poverty line, ethnic minorities, sexual minorities – LGBTIQA+, etc.)

3.1.3.2. Legally defined minors (up to 18 years);

3.1.3.3. Women in special situations (pregnant or lactating women, or those who have poor decision-making powers/poor access to healthcare, or those who are victims of gender-based violence);

3.1.3.4. Tribals and other marginalized communities;

3.1.3.5. Refugees, migrants, homeless, persons or populations in conflict zones, riot areas or disaster situations, people kept in detention, people experiencing communicable diseases of epidemic proportions;

3.1.3.6. People afflicted with mental illness, or cognitively impaired individuals, differently abled – mentally and physically challenged;

3.1.3.7. Terminally ill or are in search of new interventions having exhausted all available therapies;

3.1.3.8. People with stigmatizing or rare diseases; or

3.1.3.9. Persons with diminished autonomy due to dependency or being within a hierarchical system (students - especially medical, pharmacy, dental and nursing students - employees especially subordinate hospital and laboratory personnel, defence services personnel, healthcare workers, institutionalized individuals, under trials and prisoners)

4. Mandate: Gazette notification (GoI) G.S.R. 611 (E) dated 31st July 2015 has mandated audio-visual recording of informed consent process in case of vulnerable

participants in clinical trials of new chemical entity/new molecular entity, and only audio IC process in the case of clinical trials involving people living with HIV and patients of leprosy[3].

5. Responsibility:

5.1. YEC-1 Chairperson will:

5.1.1. ensure that all protocols involving vulnerable populations are reviewed and monitored appropriately

5.1.2. ensure that all members present on the day of the meeting shall actively discuss the vulnerable research protocols.

5.2. YEC-1 Member-Secretary will:

5.2.1. determine/identify protocols involving vulnerable population

5.2.2. categorize protocols involving vulnerable population - even if the risk is minimal or less than minimal - for "full review' (as per SOP7A/v3)

5.2.3. oversee and confirm that each protocol involving vulnerable populations has the necessary checklist attached, duly filled and signed by the PI.

5.2.4. ensure that the monitoring mechanism for protocols involving vulnerable population is planned at the time of approval and in place during the conduct of the research

5.3. YEC-1 Member(s) will:

5.3.1. review the checklist for risk:benefit assessment

5.3.2. ensure adequate protection of vulnerable participants are strategized by the PI in the protocol

5.3.3. deliberate on the issues of vulnerable participants, the risk:benefit assessment and the protection provided - during the YEC-1 meeting

5.4. YEC-1 Secretarial staff will:

5.4.1. check whether every protocol involving vulnerable population includes the checklist for risk:benefit assessment and safeguards for the

[3] http://www.ferci.org/wp-content/uploads/2014/07/Gazette-Notification-31-July-2015-AV-consent.pdf accessed on 12 July 2016 at 1722 hours.

protection of vulnerable participants - duly filled and signed by the principal investigator

5.4.2. ensure that the checklist for risk:benefit assessment and safeguards for the protection of vulnerable participants is sent to the reviewers during the review of protocols

5.4.3. maintain a calendar for site monitoring (or audit) for protocols involving vulnerable populations, and remind the Member-Secretary of dates for due monitorings.

6. Detailed instruction:

6.1. Completion of protocol submission:

6.1.1. The Member-Secretary should identify the protocols involving vulnerable populations (as listed in 4.3 of this SOP).

6.1.2. The Secretarial staff must provide the appropriate checklists to the principal investigators, depending on the type of vulnerable populations involved in the research.

6.1.3. The Member-Secretary and/Secretarial staff must make sure that all checklists pertaining to the specific vulnerable population involved in the research are duly filled and signed by the principal investigator.

6.2. Categorization of the protocols: The member-Secretary should categorize the protocols as follows:

6.2.1. Protocols involving vulnerable populations, should be categorized as full review, even if the risk is minimal as per the ICMR guidelines and reviewed as per SOP7A/v3.

6.2.2. The protocols involving vulnerable populations, may be categorized as expedited review if the risk is 'less than minimal' and reviewed as per SOP7B/v3.

6.3. Selection of reviewers and review support:

6.3.1. The Member-Secretary should appoint two or more members of the YEC-1 who have a thorough understanding of the ethical issues pertaining to those vulnerable populations.

6.3.2. The Member-Secretary must provide appropriate reference material and /or help reviewer locate the material relevant to review protocols involving vulnerable populations when specifically requested by a reviewer.

6.3.3. A representative from the vulnerable population may be consulted and invited to take part in the discussion during the Full review meeting as per SOP

6.4. Review of the protocols:

6.4.1. YEC-1 members reviewing such protocols should be well versed with the potential harm or risk of such population participating in the study.

6.4.2. Additionally, the reviewers should assess the following in the protocol and address all points in the checklists for different vulnerable populations (Annexures 1-5 of SOP19/v3):

6.5. Discussion in the full review meetings:

6.5.1. While discussing full review protocols involving vulnerable populations, YEC-1 members should deliberate on the following issues, but not limited to these :

6.5.1.1. Is there adequate justification for involvement of vulnerable population in the research?

6.5.1.2. Can the research be performed in any other non-vulnerable participants?

6.5.1.3. Are there additional safeguards for the protection of the vulnerable participants from harm?

6.5.1.4. Are there direct benefits to the population under study? Do the benefits justify the risks?

6.5.1.5. Are the participants selected equitably?

6.5.1.6. Have measures to protect the autonomy of the vulnerable population been described?

6.5.1.7. Has the informed consent been appropriately described?

6.5.1.8. Have issues about audio-visual recording of informed consent

been adequately addressed?

6.5.2. The YEC-1 members may consider a representative from the vulnerable population to attend the meeting, deliberate on the issues, but not take part in the decision making and voting. This will be done as per SOP05/v3.

6.5.3. The minutes will be prepared in detail as per SOP08/v3

6.6. Decision making:

6.6.1. Decision making for protocols will be done as per SOP7A/v3 for full review protocols and SOP7B/v3 for expedited review protocols

6.6.2. Post-approval plan should be incorporated in the final approval and should include the details and frequency of the following, whenever deemed essential:

6.6.2.1. Continuing review plan

6.6.2.2. Audit plan of the protocol documents

6.6.2.3. Site monitoring plan

6.6.3. YEC-1 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, wherever deemed necessary.

6.7. Post-approval:

6.7.1. The continuing review, audit and site monitoring plans should be conducted as per the decision at the time of approval of the protocols.

6.7.2. Continuing review should be conducted as per SOP

6.7.3. Audit and Site monitoring should be conducted as per SOP.

7. Annexures

7.1. Ann01/SOP19/v3: Checklist for research involving children <18 years

7.2. Ann02/SOP19/v3: Checklist for research involving pregnant women, neonates & fetuses

7.3. Ann03/SOP19/v3: Checklist for research involving cognitively impaired adults

7.4. Ann04/SOP19/v3: Checklist for research involving students, employees or residents

7.5. Ann05/SOP19/v3 - Checklist for involving populations for genetic research

Ann01/SOP19/v3

Checklist: Research Involving Children <18 years

Children (minors) have reduced capacity to understand and give informed consent. Such participants have decreased autonomy, and increased exploitative potential and are considered as vulnerable participants. Current regulations and guidelines require ethics committees to ensure that researchers provide ample safeguards in the research protocol for the protection of vulnerable populations. Filling out this checklist will help researchers in strengthening the research protocol, and ethics committees in reviewing this study more systematically. Principal Investigators are requested to provide their responses in this checklist in an honest and forthright manner.

Study Title:

Name of the Principal Investigator:

No.	Checklist item for the PI to fill before submission (information provided here should also clearly and unambiguously reflect in the methodology, participant information sheet and informed consent form)	Y	N	NA
1	Does the research pose greater than minimal risk to children?			
2	If yes: Are there convincing scientific and ethical justifications to carry out the research as designed?			
3	If yes: Are adequate safeguards in place (and described in the protocol) to minimize these risks?			
4	Is there an alternate study design that can achieve the same objectives without involving such vulnerable participants?			
5	Does the study involve healthy children?			
5A. If yes:				

5Ai	Is the inclusion of healthy children justified?			
5Aii	Have scientifically appropriate preclinical studies, including studies on animals, and clinical studies, including studies on children and/or adults, been conducted and do these provide data for assessing potential risks to children/minors?			
5Aiii	Do the results of those studies justify this study?			
	5B. If no:			
5Bi	Is the lack of studies conducted on animals and/or adults justified?			
5Bii	Would this study still be justified despite the lack of animal studies?			
6	Will older children be enrolled before younger ones?			
7	Is permission of both parents necessary?			
	If yes:			
7A	Are conditions under which one of the parents may be considered: "not reasonably available" described?			
7B	Are the conditions acceptable?			
8	Will efforts be made to ensure that parents' permission to involve their children in research studies is free from coercion, exploitation, and/or unrealistic promises?			
9	Are provisions made to obtain the written assent of children over 12 years, and oral assent of children between 7 and 12 years, and where appropriate, honor their dissent?			

10	Are provisions made to protect participants' privacy and the confidentiality of information gathered in the course of the research?			
11	Are there special problems that call for the presence of an external monitor during consent procedures?			
12	Are special needs of adolescents such as counseling and confidentiality accounted for in the research design?			
13	Are there any special problems such as confidentiality and reporting that might arise in sensitive research about child abuse or sexual practices of teenagers?			
14	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:				
14Ai	Are there adequate mechanisms in place to deal with other members of the family, should there be a risk to such bystanders?			
14Aii	Are parents required to be present during the conduct of the research?			

For the Principal Investigator *(tick whichever is applicable in the risk-benefit columns)*		**For the YEC-1 Secretariat** *(this column for YEC-1; circle whatever is applicable)*
Risk determination	**Benefit assessment**	**YEC-1 Action**
Minimal risk*	Direct benefit	Approvable

	No direct benefit	Approvable
Greater than minimal risk	Potential benefit to participant	Approvable
	No direct benefit; or offers new knowledge about the condition being investigated	Case-based approval on merits

* *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*

*** Consent of both parents (and assent) may be needed as applicable*

Signature of the Principal Investigator:

Date:

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Comments of Primary Reviewer:	
Primary Reviewer Signature and Date:	

Ann02/SOP19/v3

Checklist: Requirements for Research Involving Pregnant Women & Fetuses

Pregnant women and their unborn or just born fetuses are considered as vulnerable participants in research and therefore subject to increased harm. Current regulations and guidelines require ethics committees to ensure that researchers provide ample safeguards in the research protocol for the protection of vulnerable populations. Filling out this checklist will help researchers in strengthening the research protocol, and ethics committees in reviewing this study more systematically. Principal Investigators are requested to provide their responses in this checklist in an honest and forthright manner.

Study Title:

Name of the Principal Investigator :

If the research involves pregnant women and/or their fetuses, please fill this form and submit along with the research protocol:

Sl.No.	**Checklist item**	**Yes**	**No**	**NA**
1	Have scientifically appropriate preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, been conducted and do these provide data for assessing potential risks to pregnant women and fetuses?			
2	Is the risk to the pregnant woman or the fetus “not greater than minimal”, or, any risk to the woman or the fetus, which is greater than minimal, is caused solely by the research intervention/procedure and this holds out the prospect of direct benefit for the woman or the fetus?			
3	Is any risk that is likely to occur, the least possible for achieving the objectives of this study?			

4	Is the woman's consent or the consent of her legally authorized representative (if the participant herself is unable to give consent) obtained in accordance with the informed consent provisions (as described in the ICMR National Ethical Guidelines for Biomedical Research involving Human Participants - 2017)?			
5	Is the woman or her legally authorized representative (as appropriate), fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child?			
6	Do individuals engaged in the research have a part in determining the viability of the fetus?			
7	Do individuals engaged in the research have a part in any decisions as to the timing, method, or procedures used to terminate the pregnancy?			
8	Will any inducements, monetary or otherwise, be offered to terminate the pregnancy?			

If the response to items 1-7 is **NO**, the research should not be approved by YEC-1. Response to item no. 8 will be assessed on a case-to-case basis.

Please fill this section of the checklist if the research involves neonates:

Sl No	Checklist item	Y	N	NA
1	Can this research be performed in any other non-vulnerable participants?			
2	Is there adequate justification for involvement of vulnerable population in the research?			
3	Are scientifically appropriate, preclinical and clinical studies, conducted and provide data for assessing potential risks to neonates?			

4	Is the individual providing consent, fully informed regarding the reasonably foreseeable impact of the research on neonate?			
5	Will any inducements, monetary or otherwise, be offered to terminate the pregnancy?			
6	Do individuals engaged in the research have a part in any decisions as to the timing, method or procedures used to terminate pregnancy?			
7	Do individuals engaged in the research have a part in determining the viability of a fetus?			

If the response to item no. 1 is **YES** and to item no. 2-7 is **NO**, the research should not be approved by YEC-1.

Fetus of uncertain viability:

Sl No	**Checklist item**	**Y**	**N**	**NA**
1	Is the purpose of the research the development of important biomedical knowledge which cannot be obtained by other means?			
2	Is any risk the fetus is exposed to, the least possible for achieving the objectives of the research?			
3	Does the research hold out the prospect of enhancing the probability of survival of the enrolled fetus to the point of viability?			
4	Will the legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative be obtained?			

If the response for any of the items no. 1-4 is **NO**, then YEC-1 should not approve the research

Non-viable fetus:

Sl No	**Checklist item**	**Y**	**N**	**NA**

1	Will vital functions of the neonate be artificially maintained in the course of the research, despite clinically being pronounced "non-viable"?			
2	Will the research-related risk to the neonate be less than minimal?			
3	Is the purpose of the research the development of important biomedical knowledge that cannot be obtained by other means?			
4	Will the legally effective informed consent of both parents of the neonate be obtained? Please note: If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable fetus will suffice to meet the requirements of this paragraph. (The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice to meet the requirements of this paragraph.)			

If the response to any of above is **NO,** the research should not be approved by the YEC-1.

<u>This type of research can be conducted only after YEC-1 determines that</u>

(a) The research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of pregnant women and/or fetuses**.**

(b) The research will be conducted in accordance with applicable regulatory and ethical guidelines.

Signature of the Principal Investigator: Date:

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Comments of Primary Reviewer:	
Primary Reviewer's Signature and Date:	

Ann03/SOP19/v3

Checklist: Research Involving Cognitively Impaired Adults

Cognitively impaired adults have reduced capacity to understand and give informed consent. Such participants have decreased autonomy, and increased exploitative potential and are considered as vulnerable participants. Current regulations and guidelines require ethics committees to ensure that researchers provide ample safeguards in the research protocol for the protection of vulnerable populations. Filling out this checklist will help researchers in strengthening the research protocol, and ethics committees to review this study more systematically. Principal Investigators are requested to provide their responses in this checklist in an honest and forthright manner.

Study title:

Name of the Principal Investigator:

1. **Research Involving Cognitively Impaired Adults in which there is anticipated direct benefit to the participant**

Sl No	**Checklist item** *All items should be answered and the substantiation for the same should be evident in the protocol (methodology) as well as in the participant information sheet and informed consent form)*			
1	Is recruitment of participants justified considering the rationale and objectives of the study?			
2	Is the risk justified by the anticipated benefit?			
3	Is the relation of the anticipated benefit to the risk at least as favorable to the participants as that presented by available alternative approaches?			
4	Will the participants be withdrawn if they appear to be unduly distressed?			
5	Is the proposed plan for the assessment of the capacity to consent adequate?			
6	Will consent be taken from participants capable of being consulted?			

7	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

Sl No	Checklist item	Y	N	NA
1	Is the recruitment of participants justified considering the rationale and objectives of the study?			
2	Are the foreseeable risks to the participants low?			
3	Is the negative impact on the participant's well-being minimized and low?			
4	Will the participants be closely monitored?			
5	Will the participants be withdrawn if they appear to be unduly distressed?			
6	Is the proposed plan for the assessment of the capacity to consent adequate?			
7	Will consent be taken from participants capable of being consulted?			
8	Does the consent document include provision for a legally authorized representative in case participants are not capable of being consulted?			

Signature of the Principal Investigator: Date:

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Comments of Primary Reviewer	
Primary Reviewer Signature and Date	

Ann04/SOP19/v3

Checklist-Research Involving Students, Employees or Residents

Research participants drawn from institutions with hierarchical cultures, have reduced capacity to understand and give informed consent. Such participants have decreased autonomy, and increased exploitative potential and are considered as vulnerable participants. Current regulations and guidelines require ethics committees to ensure that researchers provide ample safeguards in the research protocol for the protection of vulnerable populations. Filling out this checklist will help researchers in strengthening the research protocol, and ethics committees to review this study more systematically. Principal Investigators are requested to provide their responses in this checklist in an honest and forthright manner.

Name of the Principal Investigator:

Study title:

l No	Checklist item	Y	N	NA
1	Have the participants been assured that their status (education, employment and/or promotion) will not be affected by any decision to participate or not?			
2	Have the risks to participants been minimized and are such strategies described in the protocol?			
3	Have participants been assured that participation is voluntary (no signs of coercion)?			
4	Have participants been assured that privacy and confidentiality will be protected?			

All items must be marked 'yes' and the same should reflect in the

Signature of Principal Investigator Date:

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Comments of Primary Reviewer	
Primary Reviewer Signature and Date	

Ann05/SOP19/v3

Checklist: Considerations for Genetic Research

Genetic research is still poorly understood and there is much to be learned by the scientific community, for a fuller and more comprehensive understanding of the genetic functions of the human body. Potential participants may have difficulty in understanding the research details and thus give informed consent on less-than-optimal understanding. Such participants have decreased autonomy, and increased exploitative potential and are considered as vulnerable participants. Current regulations and guidelines require ethics committees to ensure that researchers provide ample safeguards in the research protocol for the protection of vulnerable populations. Filling out this checklist will help researchers in strengthening the research protocol, and ethics committees to review this study more systematically. Principal Investigators are requested to provide their responses in this checklist in an honest and forthright manner.

Name of the Principal Investigator

Study Title:

Sl No	Checklist item	Y	N	NA
1	Will the samples be made anonymous to maintain confidentiality?			
2	Will the results be disclosed to the participant or legally authorized representative? a. If yes, has the investigator established clear guidelin 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 withou consent?			
6	Will the samples be destroyed in the future?			
7	Will the samples be used for future research			
8	Will the human biological sample or the data associated with it, be shared with other researchers?			
9	Will genetic counseling be offered?			

Signature of the Principal Investigator: Date:

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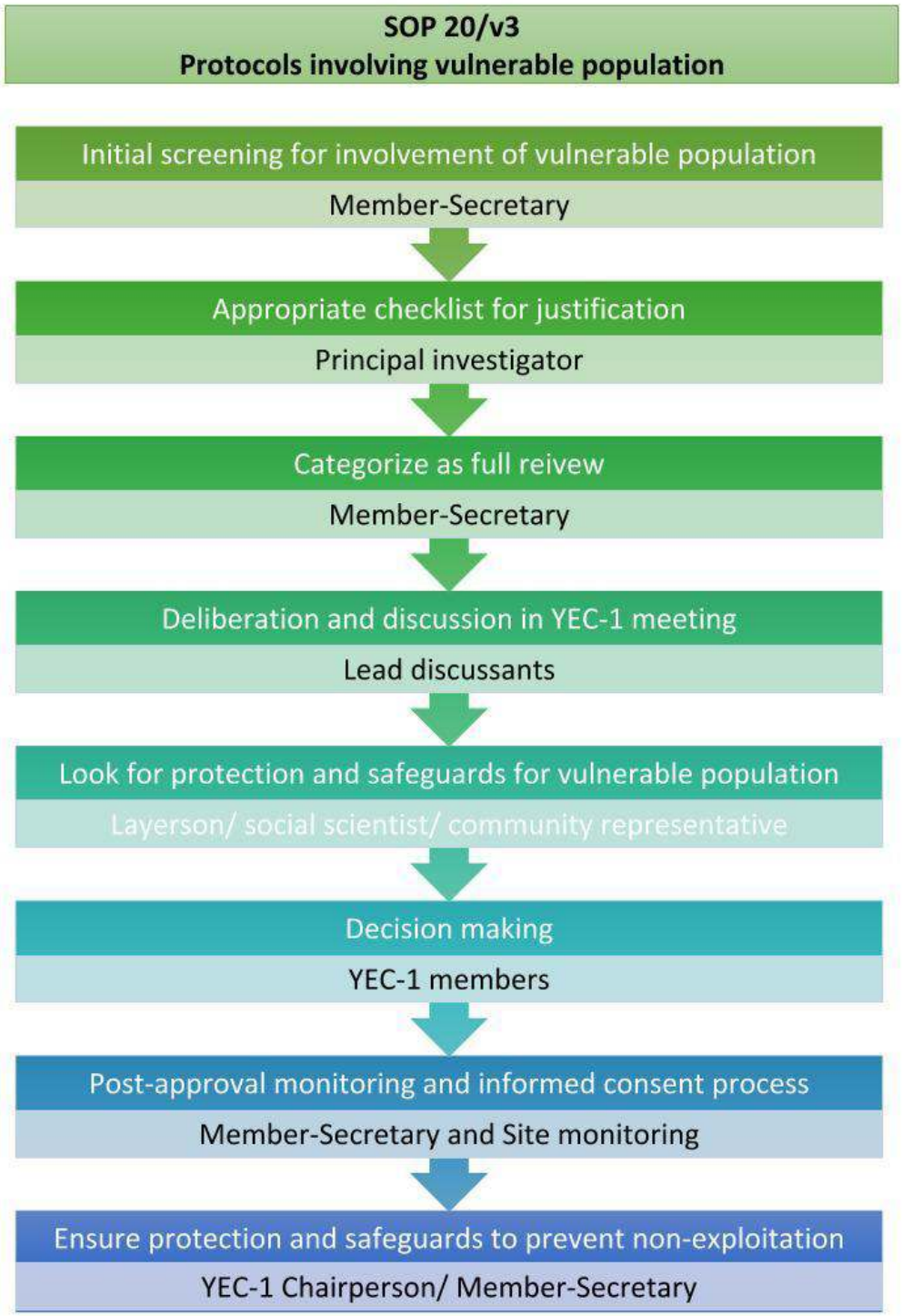
Primary Reviewer Signature and Date	

7. Flow Chart


SOP 20/v3
Protocols involving vulnerable population
Initial screening for involvement of vulnerable population
Member-Secretary
Appropriate checklist for justification
Principal investigator
Categorize as full reivew
Member-Secretary
Deliberation and discussion in YEC-1 meeting
Lead discussants
Look for protection and safeguards for vulnerable population
Layerson/ social scientist/ community representative
Decision making
YEC-1 members
Post-approval monitoring and informed consent process
Member-Secretary and Site monitoring
Ensure protection and safeguards to prevent non-exploitation
YEC-1 Chairperson/ Member-Secretary