**Institutional Ethics Committee,**

**Tata Memorial Centre (IEC, TMC)**

**Title: Continuing review of study protocols**

**SOP Code: SOP 07/ V6 Date: 28/04/2021 Pages: 1 to 23**

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| **7.1** | **Purpose** |

The purpose of continuing review is to monitor the progress of the study which was previously approved; not only for the changes but to ensure continued protection of the rights and welfare of research subjects.

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| **7.2** | **Scope** |

This SOP applies to conducting continuing review of studies involving human subjects at intervals appropriate to the degree of risk but not less than once a year. Depending upon the degree of risk to the participants, the nature of the study, the vulnerability of the study participants and duration of the study, IEC may choose to review the study more frequently.

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| **7.3** | **Responsibility** |

It is the responsibility of the IEC secretariat to send reminders to Principal Investigators regarding the submission of Continuing Review Application/Annual Status Report.

All IEC approved studies will be reviewed at least annually. IEC is responsible for determining the date of submission of continuing review application of the IEC approved projects including those that are reviewed more frequently in the year based on specific criteria. (e.g., an IEC may set a shorter approval period for high-risk protocols or protocols with a high risk: potential benefit ratio). This decision is taken during the IEC meeting wherein the project is finally approved.

IEC is primarily responsible for reviewing the study progress, the rate of accrual of participants, the occurrence of unexpected events or problems along with protocol deviation/violation and non compliance, any new information pertaining to the research and assess final reports of all research activities. The protocol, informed consent documents and assent documents are examined to ensure that the information remains accurate. The IEC has delegated this responsibility of initial detailed review of Continuing Review Application to DSMU.

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| **7.4** | **Detailed Instructions** |
| **7.4.1** | **Determine the date of continuing review** |

* The secretariat will identify the list of IEC approved projects that are due for continuing review on a regular basis.
* The Secretariat should receive the continuing review application well in advance i.e. 10 months after IEC final approval and atleast annually.

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| **7.4.2** | **Notify the Principal Investigator or the study team** |

* Reminder emails are sent from the IEC secretariat to the Principal Investigators for submission of continuing review applications for projects, 3 months prior to the expiry of study approval/CRA approval validity date. Principal Investigators are required to submit one signed hard copy of the CRA to the DSMU.
* First reminder will be sent 3 months in advance to the lapse in validity/annual review
* Failure to submit the CRA within the due date after the 1st reminder will result in issuance of warning letter and necessary action.
* IEC may close/suspend the study if PI fails to submit CRA on time and consider appropriate decision on publication and presentation of study data.

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| **7.4.3** | **Manage continuing review application upon receipt** |

* The Secretariat will receive the Continuing Review Application submitted by the Principal Investigator for each approved study.
* Upon receipt of the Continuing Review Application, the Secretariat of the IEC will review the application for its completeness and forward it to the DSMU Member Secretary for further scrutiny. However, IEC may verify from sources other than the investigators to ensure that no material changes had occurred since previous IEC review by conducting monitoring of the study. The projects for which this may be done includes complex projects involving unusual levels or types of risk to subjects; projects conducted by investigators who previously have failed to comply with the regulatory/IEC requirements, projects in which concern about possible material changes occurring without IEC approval have been raised based upon information provided in previous continuing review reports or from other sources.

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| **7.4.4** | **Verify the contents of the package** |

* The Secretariat will check for duly completed and signed application by Principal Investigator.

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| **7.4.5** | **Review of Continuing Review Application** |

* If IEC determines that a project needs verification from sources other than the investigators that no material changes have occurred since previous IEC review, including specific criteria used to make these determinations (e.g., such criteria could include some or all of the following: (a) randomly selected projects; (b) complex projects involving unusual levels or types of risk to subjects; (c) projects conducted by investigators who previously have failed to comply with the regulatory/IEC requirements ; and (d) projects where concern about possible material changes occurring without IEC approval have been raised based upon information provided in continuing review reports or from other sources.)
* The DSMU Secretary will review the Continuing Review Application and will record his/her comments on the application and the same will be forwarded to the IEC Secretary
* In case any clarifications or queries are raised by the Secretary DSMU the same will be intimated to PI and reply will be awaited. The IEC Secretary will decide whether to discuss the application along with the comments of the DSMU and Principal Investigator’s response in the next full board meeting or expedited review meeting.

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| **7.4.6** | **Prepare meeting agenda** |

The Secretariat will follow procedures on the preparation of meeting agenda and place the forwarded Annual Progress Report/Continuing Review Application on the agenda for the full board/expedited review meeting of the IEC

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| **7.4.7** | **Review Process** |

The IEC Chairperson/ Member Secretary/ members will use the Continuing Review Application Form (AX1-V6/SOP07/V6) to guide the review and deliberation process. The IEC members could arrive at any one of the following decisions at the IEC meeting:

1. Approval to continue the study
2. Revision with minor modifications- - Studies for which modifications have been suggested by the IEC may not proceed until the conditions set by the IEC have been met. Studies should be amended and submitted to the IEC within one month for re-review.
3. Query – The IEC and/or DSMU has raised queries against the continuing review application submitted. PI should respond to the IEC/DSMU queries at the earliest to maintain the study approval validity.
4. Deferred/On-hold-The IEC has postponed the decision on approval of continuing the study due to reasons such as awaiting expert opinion, awaiting site monitoring reports from the DSMU etc.
5. Not approved-The IEC feels that there are major concerns in the conduct of the study.

The decision will also include any significant findings that have arisen during review process and this will be communicated to Principal Investigator. It is the responsibility of Principal Investigator to provide this information to the participants and once done submit the report to IEC.

* The decision regarding the approval / recommended modifications / disapproval will be noted and documented in the minutes of the meeting by the Member Secretary and maintained as part of the official record of the review process.
* Continuing review of the study may not be conducted through an expedited review procedure, unless

1. The study was eligible for, and initially reviewed by, an expedited review procedure; or
2. The study has changed such that the only activities remaining are eligible for expedited review.
3. Continuing review of research previously approved by the convened IEC (e.g., not originally subject to expedited review) may be eligible for expedited review:
4. Where
5. the research is permanently closed to the enrollment of new subjects;
6. all subjects have completed all research-related interventions; and
7. the research remains active only for long-term follow-up of subjects; or
8. Where no subjects have been enrolled and no additional risks have been identified; or
9. Where the remaining research activities are limited to data analysis.

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| **7.4.8** | **Store original documents** |

The IEC secretariat will file the continuing review application in master file of the research study.

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| **7.4.9** | **Communicate the IEC decision to the Principal Investigator** |

The Secretariat will notify the Principal Investigator of the decision of the IEC. If IEC has recommended modifications, the decision will be notified to the Principal Investigator and he/she will be requested to comply to IEC recommendations/ respond to IEC queries within 1 week of receipt of the IEC decision letter. If the PI requires additional time to respond to queries raised against the CRA, he/she has to inform the IEC about the same and provide an approximate time frame for submission of data or information asked by IEC. In case the IEC decision is to put the study on-hold, then the subject recruitment or enrollment is suspended, however incase of safety concerns the project is completely suspended.

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| **7.4.10** | **Lapses in IEC Approval** |

Investigators must plan ahead to meet IEC determined dates of submission of continuing review application. If an investigator fails to submit continuing review application to the IEC or the IEC does not approve continuation of the research, the research must stop. All of the following research procedures must stop:

* + Subject recruitment or enrollment
  + Collection of data/information
  + All research-related interventions or interactions with currently enrolled subjects\*
  + Data analyses involving subject identifiable data

\*Exception: Research-related interventions or interactions with currently enrolled subjects can continue only if stopping the research would jeopardize the rights or welfare of current subjects. The IEC must make this determination and decide which subjects should continue with the intervention during the lapse. A request for such an exception must be made in the writing to the IEC by the PI.

**AX1-V6/SOP 07/V6**

**Form A**

**Continuing Review Application**

SECTION A

1. TMC Study No:
2. CTRI No (if applicable):
3. Date of Registration:
4. Protocol title:
5. Principal Investigator:
6. Phone No:
7. Email Id:
8. Institute:
9. Source of funding: Please tick

**□** Intramural

**□** Extramural – Please specify and provide relevant documents (CTA/MoU/sanction letters from funding agencies )\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**□** Pharma – Please specify\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**□** Others- Please specify\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**□** Not applicable

1. Account No (If Applicable):
2. Date of IEC approval:
3. Date of Validity of IEC approval (for the full duration of the study):
4. Mention overall duration of study (in years/months) approved by IEC at the time of study approval:
5. Start Date of study:
6. If the start date is > 6 months from the IEC approval date kindly provide the reasons for the same
7. Date of approval of last CRA (if applicable):
8. CRA approval valid till date :
9. Period of report of the current CRA : \_\_\_\_\_/\_\_\_/\_\_\_\_\_\_\_ to \_\_\_\_\_\_\_\_/\_\_/\_\_\_\_\_
10. Study was initially reviewed by expedited review (Please tick) – **□** Yes **□** No
11. Is the study expected to extend beyond the projected duration: **□** Yes **□** No
12. If Yes- provide reasons for not being able to complete the work in stipulated time
13. Are you applying for extension for the same: **□** Yes **□** No
14. If yes- period of extension requested?\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
15. How many prior extensions sought? (in number) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Section B**

If the study pertains to retrospective case series / paraffin blocks / MRI or other radiological studies, etc. Please provide information on the status/progress of the study so far with regards to the final accrual/objective. Please mark what is not relevant as not applicable.

1. No of study arms (If Applicable):
2. Project Status (In case of studies on blocks/samples/retrospective case series please give the following information with respect to amount of work completed)

* Active enrollment  ongoing
* Active  accrual and intervention ongoing
* Accrual completed and intervention ongoing
* Accrual completed and follow-up ongoing
* Case review/sample review ongoing (audit studies)
* Data Analysis ongoing
* Publication activities ongoing
* Not started/Not initiated

If ‘Not started’ state reasons

The research is permanently closed to the enrollment of new subjects (Tick)

**□** Yes **□** No **□** NA

All subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; (Please tick)

**□** Yes **□** No **□** NA

The remaining research activities are limited to data analysis (Please tick)

**□** Yes **□** No **□** NA

1. Provide the date of last status review report submitted to IEC for this project

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (State NA if this is the first status report)

1. Summary of Protocol participants: (If the study does not deal with patient accrual, please provide a summary of the progress on the study so far)
   1. Target accrual of trial (entire study) including healthy volunteers, patients and biomedical samples/blocks) \_\_\_\_\_\_\_\_\_\_\_\_\_\_
   2. Total patients/samples to be recruited at TMC (IEC ceiling)\_\_\_\_\_\_\_\_\_\_
   3. Screened: \_\_\_\_\_\_\_\_\_\_
   4. Screen failures: \_\_\_\_\_\_\_\_\_\_
   5. Total participants/samples accrued since protocol began \_\_\_\_\_\_( should be equal to sum of i to n)
   6. Date of accrual of first subject/sample:
   7. New participants accrued since last review \_\_\_\_\_\_
   8. Date of accrual of last participant: \_\_\_\_\_\_\_\_\_\_
   9. Active on intervention- (exclude subjects who have completed intervention)05
   10. No of participants who have completed intervention and are on follow-up:02
   11. Patients lost to follow up: \_(includes subjects who have completed intervention)
   12. Consent Withdrawn: \_Reason and state at which phase of the study – before /during/after completion of intervention (Specify TMC case number/Sub Id)
   13. Withdrawn by PI: Reason and state at which phase of the study – before /during/after completion of intervention(Specify TMC case number/Sub Id)
   14. Deaths: State at which phase of the study – before /during/after completion of intervention (Specify TMC case number/Sub Id)

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| **Sub id** | **Phase- Before /during/after completion of intervention** | **Whether notified to IEC- Yes/No**  **If No- provide reasons** |
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* 1. Any other: \_\_\_\_\_\_\_\_\_\_
  2. Any Impaired participants
  + None\_\_\_\_\_
  + Physically \_\_\_\_\_
  + Cognitively \_\_\_\_\_
  + Both \_\_\_\_\_

1. a) Have any SAEs been noted since the last status report?

**□** Yes **□** No **□** NA

If ‘Yes’, attach in format below

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| TMC Case No/Sub Id | SAE Event | Report type | Arm | Date submitted to DSMU |
|  |  |  |  |  |

b) In case of multicentre trials state whether reports of offsite SAEs have been submitted to the IEC –

**□** Yes **□** No **□** NA

1. Have any Deviations/Violations/Waivers been noted since the last status report?

**□** Yes **□** No **□** NA

If ‘Yes’, attach in format below

|  |  |  |  |
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| TMC Case No/Sub Id | Type of Deviation | Study Arm | Date of submission |
|  |  |  |  |
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1. Have any unanticipated problems involving risks to participants or others (including but not limited to adverse events) been noted?

**□** Yes **□** No **□** NA

If Yes please provide a summary-

1. Were there any Complaints about the research?

**□** Yes **□** No

If Yes please provide a summary-

If this is your first CRA kindly mention about the changes which has been done in the period after final approval till the submission of this CRA.

1. Have there been any Protocol amendments since last status report?

**□** Yes **□** No **□** NA

If ‘YES’, please provide in format below

|  |  |  |
| --- | --- | --- |
| Amendment No. Version Dated | Date of submission | Date of IEC Approval |
|  |  |  |

1. Were any changes initiated in approved research without IEC approval to eliminate apparent immediate hazards to the participants:

**□** Yes **□** No **□** NA

If yes please provide in format below

|  |  |  |
| --- | --- | --- |
| Date Reported to the IEC. | Description of change | Date of IEC Approval |
|  |  |  |

1. Have any Informed Consent documents been amended since the last status report? **□** Yes **□** No **□** NA

If ‘YES’, fill in format below

|  |  |  |
| --- | --- | --- |
| Amendment No. Version Dated | Date of submission | Date of IEC Approval |
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1. If the amendments were approved by IEC then please state whether all the patients were reconsented on the amended ICF on the next scheduled visit

**□** Yes **□** No **□** NA

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| --- | --- | --- |
| Amendment No. Version Dated | Date of submission | Date of Approval |
|  |  |  |
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1. Is the recruitment on schedule?

**□** Yes **□** No **□** NA

(If ‘NO’, please attach a sheet giving reasons and your plans to improve accrual)

1. Have there been any changes in the participant population, recruitment or selection criteria since the last status report was submitted to IEC?

**□** Yes **□** No **□** NA

(If ‘YES’, Kindly attach a sheet explaining the changes)

1. Have any participating investigators been added or deleted since the last status report was submitted to IEC?

**□** Yes **□** No **□** NA

(If ‘YES’, Kindly attach a sheet with details regarding the changes)

1. Have any new collaborating sites (institutions) been added or deleted since the last status report was submitted to IEC?

**□** Yes **□** No **□** NA

(If ‘YES’, kindly give details in the attached sheet)

If ‘YES’, kindly confirm if MOU/CTA has been submitted to the IEC: **□** Yes **□** No**□** NA

1. Does the protocol have an inbuilt monitoring plan?

**□** Yes **□** No **□** NA

(Kindly mark the above as ‘No’ in case of an Investigator initiated study wherein there is no external DSMB to monitor the data generated. The study will be then monitored by DSMU, TMC)

1. Has the study been monitored?

**□** Yes **□** No **□** NA

(If ‘YES’, submit the monitoring report only in case of pharma-sponsored)

Date of monitoring \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Monitored by \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Number of subjects monitored \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Is the Data Safety and Monitoring Board report available?

**□** Yes **□** No **□** NA

( If ‘YES’, submit as an attachment)

1. Did the monitoring team have any adverse comments regarding the study?

**□** Yes **□** No **□** NA

(If, ‘YES’, please attach a copy of their comments)

1. Is the report on interim data analysis available?

**□** Yes **□** No **□** NA

( If ‘YES’, kindly submit as an attachment )

1. Has any information appeared in the literature, OR evolved from this OR similar research that might affect the IEC evaluation of the risk/benefit analysis of human subjects involved in this protocol?

**□** Yes **□** No **□** NA

(If ‘YES’ kindly attach a sheet providing the details)

1. Has there been any presentation/publication related to the data generated in this trial?

**□** Yes **□** No **□** NA

(If, ‘YES’, kindly attach a sheet enclosing the details)

If ‘YES’ then has this been intimated to the TRAC office?

**□** Yes **□** No **□** NA

Please provide summary of current risk-potential benefit assessment based on study results if any?

1. Details regarding the budget- : (kindly attach consolidated account summary duly signed by Accounts Officer)

Total budget proposed for the project \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Total budget sanctioned for the project \_\_\_\_\_\_\_\_\_\_\_\_\_\_

Total budget utilized for the project (entire budget utilized) \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. Total Budget utilized for patient reimbursement (entire budget)\_\_\_\_\_\_\_\_\_\_ (kindly attach details of reimbursement to participants e.g. investigations/scans/travel as per IEC approved budget)
2. Have any investigators developed an equity or consultative relationship with a source related to this protocol which might be considered as conflict of interest?

**□** Yes **□** No **□** NA

(If YES, kindly append a statement of disclosure for the same)

1. Any other information:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**SIGNATURES:**

**Principal Investigator:**

**Date:**

**AX2-V6/SOP 07/V6**

**Reminder letter to investigator**

Name of Principal Investigator:-

Address of Principal Investigator:-

Ref: - Project Title: XXXXXX

The above referenced project was approved by the IEC on (date) and CRA validity is up to (date) and is due for continuing annual review by the IEC.

Kindly submit the continuing review application on or before\_\_\_\_\_\_\_\_. In case the project have been completed / terminated, kindly complete the appropriate form and submit to IEC/DSMU on or before (date).

Thanking you for your co-operation,

Yours truly,

Signature with date

Secretary, DSMU

**AX3-V6/SOP 07/V6**

**IEC decision letter for Continuing Review of projects**

Date

Principal Investigator,

TMC

Ref: Project No./ Title

Dear Dr.

The continuing review application for the above referenced project was reviewed and discussed during the Institutional Ethics Committee (IEC) meeting held on (date) (place) (time)

The following members of the Institutional Ethics Committee were present:

IEC comments were as follows:

**Status**: IEC approved the continuation of the study till (valid date). The Principal Investigator should submit continuing review application/annual status report on or before \_\_\_\_. In order to ensure that there is no lapse in the IEC approval period, it is mandatory to submit study status report prior to lapse of study validity. Principal Investigator to ensure that data of participants recruited in the IEC approval lapse period of the study is removed from data analysis, as and when applicable.

**Status**: Revisions with minor/major modifications/ Query/Deferred/On-hold/Not approved. Kindly respond to IEC at the earliest.

This decision was taken by consensus/unanimously/voting.

Neither Principal Investigator nor any of the study team members participated during the decision making of the IEC.

Thanking you,

Yours faithfully,

Member Secretary,

Institutional Ethics Committee

**AX4-V6/SOP 07/V6**

**IEC warning letter for continuing Review of projects**

Date

Principal Investigator,

TMC

Ref: Project No./ Title

Dear Dr.

Sub: Warning letter for CRA non-compliance

Dear Dr.

The above referenced project was approved on (date)

The IEC has noticed that you had failed to submit the annual status report/continuing review application as is mandated by the IEC SOPs, in spite of reminders on (dates).

The committee expresses strong concerns about your non adherence to IEC policy and negligence of your duty as Principal Investigator.

You are hereby mandated to submit the continuing review application/study completion report as is applicable by (date)

Failure to comply with the final reminder of the IEC will result in immediate closure of the study by the IEC. You shall thereafter abstain from all research activities of the project except those that would jeopardize the safety, rights or welfare of current subjects.

Thanking you,

Yours faithfully,

Member Secretary,

Institutional Ethics Committee

**AX5-V6/SOP 07/V6**

**IEC closure letter for non compliance to submission of study status reports**

Date

Principal Investigator,

TMC

Ref: Project No./ Title

Dear Dr.

Sub:

Pursuant to the CRA non compliance warning letter sent to you on (date), kindly note that your study has been closed by the IEC due to failure in timely submission of Continuing Review Application (CRA) or study completion report / response to the IEC queries on CRA submitted to IEC resulting in lapse of IEC approval for the above referenced study.

Thanking you,

Yours faithfully,

Member Secretary,

Institutional Ethics Committee

Flow Chart

Determine the date of continuing review

Notify the Principal Investigator or study team

Include in meeting agenda

Verify the contents of the package

Manage continuing review package upon receipt

Communicate the IEC decision to the Principal Investigator

Store original documents

Review process

Full board/Expedited