Title: Initial Review of Submitted Protocol

SOP Code: SOP 06/V1 dated 18th February 2017

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1. Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe how the Institutional Ethics Committee (IEC) members will review an initially submitted protocol for approval using the Assessment Form for initial review. The Assessment Form *AX 02/SOP 06/V1* is designed to standardize the review process and to facilitate reporting, recommendations and comments given to each individual protocol.

2. Scope

This SOP applies to the review and assessment of all protocols submitted for initial review and approval from the IEC. The specific points in the guidelines attached to the Assessment Form for initial review must be adequately addressed in the protocol itself and/or protocol-related documents under review. Relevant queries/comments made during discussion and deliberation about a specific protocol should be recorded in the minutes of the meeting.
The decision reached by the IEC and the reasons for its decision is recorded on the IEC Decision Form *AX 03/SOP 06/V1*.

3. Responsibility

It is the responsibility of all the IEC members to fill the Assessment form along with decision and comments they might have after reviewing each study protocol. The IEC Secretariat is responsible for recording and filing the decision, relevant points and deliberation about a specific protocol, including the reasons for that decision. The Chairperson must sign and date to approve the decision in the IEC Decision Form *AX 02/SOP 06/V1*.

4. Flow chart

No.	Activity	Responsibility
1	Summarize the protocol in an Assessment Form and distribute the protocol package	Secretariat
2	Receive the distributed protocol Package	IEC members
3	Verify the contents of the package	IEC members
4	Review the Protocol	IEC members
5	Examine the qualification of investigators and of study sites	IEC members
6	Review study participation	IEC members
7	Examine community involvement and impact	IEC members
8	Make a decision	IEC members
9	Gather the assessment reports	Secretariat
10	At the IEC meeting record the IEC Decision	Secretariat

11	Final communication of the IEC Decision taken on the project to the Principal Investigator	Secretariat
12	Storage of documents	Secretariat

5. Detailed instructions

5.1 Distribute the protocol package.

The Secretariat will fill in the required details in the letter to the IEC Members requesting initial review *AX 01/SOP 06/V1* and the study assessment form *AX 02/SOP 06/V1* prior to circulation to the IEC members. The Secretariat will attach the letter to IEC Members requesting Initial Review with study assessment form *AX 01/SOP 06/V1* with the Project Submission Application Form *AX 01/SOP 05/V1*, Document Checklist *AX 02/SOP 05/V1*, the protocol and related documents and send the packet to the IEC members. The Study Assessment Form for Initial Review *AX 01/SOP 06/V1* will be included along with the letter to IEC Members requesting Initial Review with study assessment form *AX 01/SOP 06/V1*, the Project Submission Application Form -*AX 01/SOP 05/V1,* Document Checklist *AX 02/SOP 05/V1*, the protocol and related documents and will be sent to the respective primary reviewers.

5.2 Receive the distributed protocol Package:

The IEC member will receive the protocol package with the Project Application Form *AX 01/SOP 05/V1*, Checklist of all documents *AX 02/SOP 05/V1*. The primary reviewers will also receive the Study Assessment Form for Initial Review *AX 01/SOP 06/V1.*

5.3 Verify the contents of the package

- The IEC member will verify all the contents.
- The IEC member will check the meeting date to see if it is convenient to attend the meeting.
- The IEC member will notify the IEC Secretariat if there are documents missing in accordance to *AX 02/SOP 05/V1* or if the specified date of the IEC meeting is not convenient to attend.

5.4 Appointment of primary reviewers

- The Member Secretary/Chairperson will appoint one or more primary reviewers for each project on the basis of expertise in the related field and experience. The primary reviewer(s) will make his/her comments and fill the study assessment form *AX 02/SOP 06/V1*. They will present the summary of the project and the comments at the IEC board meeting.

5.5 Review by the IEC members

5.5.1 Review of the protocol

- The protocol will be reviewed by each member as per guidelines to review a study protocol described in *AX 05/SOP 06/V1*.

- The IEC member will consider the following criteria when performing the review of the study protocol:
  - ✓ minimize risks to participants;
  - ✓ risks must be reasonable in relation to anticipated benefits;
  - ✓ participants are selected equitably;
  - ✓ informed consent is adequate, easy to understand and properly documented;
  - ✓ the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants, where appropriate;
  - ✓ there are adequate provisions to protect the privacy of participants and to maintain the confidentiality of data, where appropriate; and
  - ✓ Appropriate safeguards are included to protect vulnerable participants.

5.5.2 Examine the qualification of investigators and assess adequacy of study sites

The IEC members must consider whether the qualifications of the participating investigators relate to the study by reviewing their CVs.

- The IEC members must examine disclosure or declaration of potential conflicts of interest
- The IEC members must assess / ascertain, if required by reviewing the study site whether the facilities and infrastructure at study sites can accommodate the study.

5.5.3 Review study participation

The IEC member will examine for the presence of the following points while reviewing the patient information sheet/Informed Consent Form as per guidelines to review protocol and Informed Consent Document/Patient Information Sheet in *AX 05/SOP 06/V1.*

- Voluntary, non-coercive recruitment, participation/ withdrawal
- Procedures for obtaining informed consent
- Contents of the patient information sheet - title, objective, study design and procedures
- Contents and language of the informed consent document
- Translation of the informed consent document in the local languages
- Language used – plain and easy to understand by general public
- Contact persons with address and phone numbers for questions about research participants rights and study or injury
- Privacy and confidentiality
- Risks and discomforts – physical / mental / social
- Alternative treatments
- Benefits – to participants, community, institution and society

- Compensation for participation: (Whether it will act as undue inducement)
- Involvement of vulnerable participants
- Provisions for medical/ psychosocial support
- Treatment for study related injuries
- Compensation for study-related injuries: Reasonable
- Use of biological materials
- Check for provision for signatures with dates of participant, person conducting informed consent discussion, investigator and witness

5.5.4 Examine community involvement and impact

The IEC members will also consider the following points in the protocol, Informed Consent Form/ Patient Information Sheet

- Community consultation
- Benefit to local communities
- Contribution to development of local capacity for research and treatment
- Availability of study results

5.6 Provisional decision by the IEC members.

- The IEC members will write comments and suggestions after complete review of protocol and related documents in the space provided in Annexure 1 *AX 01/SOP 06/V1*. The IEC members will record the provisional decision by marking in the desired block on any of the following: "*Approved, Suggested recommendations, to be discussed at IEC meeting, Disapproved(with reasons) or Any other*

5.7 Gather the assessment reports.

The IEC Secretariat will collect the Assessment Forms *AX 01/SOP 06/V1,* the comments from each reviewer and file in the original set of the study file.

5.8 At the IEC meeting

During the discussion at the meeting, the primary reviewer shall brief the members about summary of the study protocol and read out the comments and evaluation provided on the assessment form. The comments of an independent consultant (if applicable) will be discussed by the member secretary. The other IEC members shall give their comments right after the presentation.

- The investigator/sub-investigator may be called in to provide clarifications on the study protocol that he/she has submitted for review to the IEC.
- The IEC members will discuss and clarify the comments and suggestions. The Member secretary (assisted by the Secretarial staff) shall record the discussions
- The final decision on the project as: "Approved/ Disapproved/ Suggested recommendations or any other----" in the meeting shall be by voting and will be recorded in the IEC Decision Form *AX 03/SOP 06/V1 by the Member Secretary*.

- A majority vote for approval, disapproval, request for modifications of a study suspension or termination of an ongoing study is defined as 2/3rd of the members (who have reviewed the project), present at the meeting and voting.
- Member(s) of the committee who is/are listed as investigator(s) on a research proposal will opt out from all deliberations on the proposal and will not vote on the proposal.
- An investigator or study team member invited for the meeting will not vote or participate in the decision making procedures of the committee.
- An independent consultant invited for the meeting to provide opinion will not vote or participate in the decision making procedures of the committee.
- Specific patient groups invited for the meeting will not vote or participate in the decision making procedures of the committee.

- If the IEC decision is 'Approved', it implies the approval of the study as it is presented with no modifications and the study can be initiated.
- If the IEC decision is 'Suggested recommendations', it implies that the items noted at the convened meeting require modifications and project should be re-submitted to the IEC.
- If the changes requested are of minor nature, the IEC Chairperson may authorize the Secretary to determine if the response and changes are satisfactory and decide if letter of permission can be issued to the Principal Investigator.
- The Chairperson may send the response and amended protocol/ documents to one or more IEC members to recommend if letter of permission can be issued after satisfying himself/ herself/ themselves about satisfactoriness of the response and changes
- The response and changes carried out may be considered for discussion at a future IEC meeting.
- If the IEC decision is 'Disapproved' or any other, the decision should be made on the basis of specific reasons which are communicated by the IEC to the principal investigator in the letter of notification.

  The Secretariat will obtain the signature of all the members and of the Chairperson of the IEC on the IEC Decision Form *AX 03/SOP 06/V1*.
- If the study is approved, the Committee will determine the frequency of Continuing Review from each investigator.
- The Secretariat will list participating members in the meeting and summarize the guidance, advice and decision reached by the IEC members.
- With the study protocol, the Assessment Form from all members and IEC Decision Form will be filed in the project file by the Administrative Officer.
- The Administrative Officer will return the file and the protocol to the appropriate shelves.

5.9 Final communication of the IEC decision taken on the project to the Principal Investigator

- The Secretariat will prepare an approval letter as *AX 04/SOP 06/V1* to be sent to the Principal Investigator when the project is approved at an IEC meeting.
- The letter contains, at a minimum:
  - Project reference number
  - Project title
  - A listing of each document approved, the date set by the Committee for frequency of continuing review, and a review of other obligations and expectations from the investigator throughout the course of the study.
  - The approval is provided for the entire duration of the project.
  - List of IEC members present at the meeting when the project was approved.
  - The Chairperson / Member Secretary will sign the approval letter and the Secretariat will send it to the Principal Investigator within 14 days
- If the Committee disapproves a study, the Secretariat immediately notifies the investigator in writing about the decision and the reason/s for not approving the study within 7 working days. A notifying letter to the investigator should state the following:

  "If you wish to appeal to this decision, please contact the IEC and submit your appeal in writing within twelve (12) weeks of the receipt of the committee's decision, addressed to the IEC Chairperson with justification as to why the appeal should be granted. In absence of appeal, the project will be declared closed for the IEC office records."

  If the Committee requires modifications to any of the documents, the Secretariat will send a written request for carrying out specific changes to the investigator asking him or her to make the necessary changes and resubmit the documents to the IEC. The Principal Investigator will be asked to respond to the letter of comments/queries within 180 days of the receipt of the letter by the investigator. In the absence of any response, the project will be declared closed for the IEC office records.
- The Secretariat will verify the correctness of the wordings and spelling in all the letters and process all the above tasks within 14 days after the meeting.

5.10 Storage of Documents

- The Secretariat will keep a copy of the Approval letter/Query letter/Disapproval letter in the project file along with all the reviewed documents.
- The Administrative Officer will store the file on an appropriate shelf in the designated cabinet.

6. Glossary

Study Assessment Form	An official record that documents the protocol review process.

Document	Document may be of any forms, e.g., paper, electronic mail (e-mail), faxes, audio or video tape, etc.
Pre-clinical study	Animal and *in vitro* studies provide information on possible toxicities and mechanisms of action, and starting doses for human studies.
Vulnerable research participants	A vulnerable category of research participants includes children, prisoners, pregnant women, handicapped or mentally disabled persons, refugees, displaced persons and economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion or undue influence.
Initial Review	The first time review of that protocol made by two or three individual reviewers (IEC members or non-members) in advance of the full Committee meeting, and comments of the reviewers will be reported to the full Committee meeting.
Phase I studies	Initial introduction of an investigational new drug (IND) into humans, studies designed to determine the metabolism and pharmacological actions of drugs in humans, and studies designed to assess the side effects associated with increasing doses.
Phase II study	A Study of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.
Phase III study	A Study expands controlled and uncontrolled trials performed after preliminary evidence suggesting effectiveness of the drug has been obtained. They are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.
Phase IV study	A study that seeks to expand an approved medication's use into a new population, new indication, or new dose.

7. References

[1] World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000) - *www.who.int/tdr/publications/publications/* (last accessed 31st August 2013)

[2] International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996 - *http://www.ich.org/LOB/media/MEDIA482.pdf* (last accessed 31st August 2013).

[3] Cavazos N., Forster D., and Bowen A.J., Ethical Concerns in Placebo-controlled studies: An Analytical Approach, Drug Information Journal 36(2) 2002: pgs 249-259, via WIEC documents

8. Annexure

Annexure 1	*AX 01/SOP 06/V1*-	Letter to the IEC Members requesting Initial review with study assessment form
Annexure 2	*AX 02/SOP 06/V1*-	Study Assessment Form
Annexure 3	*AX 03/SOP 06/V1*-	IEC Decision Form
Annexure 4	*AX 04/SOP 06/V1* -	Format of Project Approval letter
Annexure 5	*AX 05/SOP 06/V1* -	Guidelines for reviewing a study protocol

Annexure 1

AX 01/SOP 06/V1

Letter to IEC Members requesting Initial Review with study assessment form

Dear member,

The next meeting of the IEC will be held on XXX at XXX in XXXX.

Please note that the package of research proposals is to be circulated in the following order. You are requested to review the same preferably within 5 working days of receiving the package. Please review the protocol and related documents as per the guidelines attached with Annex 1 and provide your comments below and fill the study assessment form (for primary reviewers only) provided with the package (*AX 02/SOP 06/V1*). Please also confirm your availability for the meeting.

Name of Member	Date of Receipt	Signature	Attending meeting Y/N

Protocol Number : (as per IEC records)	Date of receipt at IEC office after review by member (D/M/Y):
Protocol Title :	

Name of the Principal Investigator	Designation	Department
Name of the Reviewer:		

Comments:

_____

_____

_____

_____

_____

_____

_____

Signature of IEC member reviewing the project:		**Date:**

Annexure 2

AX 02/SOP 06/V1

Study Assessment Form to be used by the Primary Reviewer

IEC Protocol Number :		Date (D/M/Y):	
Protocol Title			
Principal Investigator:			
Department			
No. of Participants at the site:		No. of Study site(s):	

Mark and comment on whatever items applicable to the study.

1	Objectives of the Study ☐ clear ☐ unclear	What should be improved?
2	Need for Human Participants ☐ Yes ☐ No	Comment:
3	Methodology: ☐ clear ☐ unclear	

4a	What should be improved? Background Information and Data ☐ sufficient ☐ insufficient	Comment:
4b	Risks and Benefits Assessment ☐ acceptable ☐ unacceptable	
4c	Inclusion Criteria ☐ appropriate ☐ inappropriate	Comment:
4d	Exclusion Criteria ☐ appropriate ☐ inappropriate	Comment:
4e	Discontinuation and Withdrawal Criteria ☐ appropriate ☐ inappropriate	Comment:
5	Involvement of Vulnerable Participants: ☐ Yes ☐ No	Comment:
6	Voluntary, Non-Coercive Recruitment of Participants ☐ Yes ☐ No	Comment:
7	Sufficient number of participants? ☐ Yes ☐ No	Comment:
8	Control Arms (placebo, if any) ☐ Yes ☐ No	Comment:
9	Are Qualification and experience of the Participating Investigators appropriate? ☐ Yes ☐ No	Comment:
10	Disclosure or Declaration of Potential Conflicts of Interest ☐ Yes ☐ No	Comment:
11	Facilities and infrastructure of Participating Sites ☐ Appropriate ☐ Inappropriate	Comment:
12	Community Consultation: ☐ Yes ☐ No ☐ NA	Comment:
13	Benefit to Local Communities ☐ Yes ☐ No	Comment:
14	Contribution to development of local capacity for research and	Comment:

	treatment ☐ Yes ☐ No	
15	Availability of similar Study / Results: ☐ Yes ☐ No	Comment:
16	Are blood/tissue samples sent abroad? ☐ Yes ☐ No	Comment:
17	Are procedures for obtaining Informed Consent appropriate? ☐ Yes ☐ No	Comment:
18	Contents of the Informed Consent Document: ☐ clear ☐ unclear	Comment:
19	Language of the Informed Consent Document: ☐ clear ☐ unclear	Comment:
20	Contact Persons for Participants ☐ Yes ☐ No	Comment:
21	Privacy & Confidentiality ☐ Yes ☐ No	Comment:
22	Inducement for Participation ☐ Unlikely ☐ Likely	Comment:
23	Provision for Compensation for Participation ☐ appropriate ☐ inappropriate	Comment:
24	Provision for Treatment for Study-Related Injuries ☐ appropriate ☐ inappropriate	Comment:
25	Provision for Compensation for Study Related Injuries ☐ appropriate ☐ inappropriate	Comment:

Reviewer's Signature with date: _____

Annexure 3

AX 03/SOP 06/V1

IEC Decision Form

Date of IEC meeting: _____

Protocol number: _____

IEC Protocol No. and Title:	
Principal Investigator:	Department:
Final Decision at the meeting:	☐ Approved ☐ Approved with modifications ☐ Resubmission ☐ Disapproved ☐ Reviewed at the Full Board meeting ☐ Review by any 2 / more IEC members ☐ Monitoring required Reason:_____ **Disapproved, Reasons:**

No.	Names of Members present	AP	AM	RS	DA	Signature

Note: *AP: Approved; AM: Approved with modification [(either primary reviewer/full board) if reviewed by full board again a decision form has to be filled; RS: Resubmission; DA: Disapproved.*

Comments:

No. of members voting for the decision:

No. of members voting against the decision:

No. of members abstaining from voting:

_____

Signature of Chairperson **Date:** _____

Annexure 4

AX 04/SOP 06/V1

Format of Interventional Project Approval letter

Date XX/XX/XXXX

To,

Dr. xxxxxxxxxxxx,

Dept. of xxxxxxxxxxxxx.

Ref: The project no. EC/xxx/20xx entitled, "xxxxxxxxxx".

Sub: Letter no.

Dear Dr. XXXXx,

The meeting of the Institutional Ethics Committee (IEC) was held on xxxxx at xxxx, in the xxxxxxxxxxxxx with xxxxx as Chairperson.

xxxx members attended the meeting held on xxxx. The list of members who attended the meeting is as follows.

Name of Members	Position on IEC	Designation & Affiliation	Qualification	Gender

It is hereby confirmed that neither you nor any of the study team members have participated in the voting/decision making procedures of the committee.

The IEC reviewed the above mentioned clinical study and approved the following documents submitted for this clinical study at the meeting.

1. Xxx
2. Xxx
3. xxx

The IEC hereby approves the proposal entitled, "xxxxxxxxxxxx".

It is understood that the study will be conducted under your direction, in a total of xxxx research participants, at Dept. of xxxx, Institute of NephroUrology, Bengaluru-560002 as per the submitted protocol.

This approval is valid for the entire duration of the study.

It is the policy of IEC that, it be informed about any onsite serious adverse event or the unexpected adverse event report within 24 hours as per the format specified in AX 01/SOP 14/V1 (Appendix XI of Schedule Y) and AX 02/SOP 14/V1 to the IEC or by email if there is holiday. The report of SAE or death after due analysis shall be forwarded by the Investigator to chairman of the IEC and the head of the institution where the trial is been conducted within 10 calendar days of SAE or death.

The sponsor has to forward the report of SAE or death after due analysis to the chairman of the IEC and the head of the institution where the trial is been conducted within ten calendar days of occurrence of the SAE or death. The report of the SAE other than death after due analysis shall be forwarded to chairman of the IEC and the head of the institution.

In case of injury or death occurring trial subject the sponsor (whether a pharmaceutical company or an institution) or his representative, whosever had obtained permission from the Licensing Authority for conduct of the clinical trial shall make payments for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in the manner as prescribed in SOP 5 Annexure 6.

No deviations from, or changes of the protocol and Informed Consent Document should be initiated without prior written approval by the IEC of an appropriate amendment. The IEC expects that the investigator should promptly report to the IEC any deviations from, or changes of, the protocol to eliminate immediate hazards to the research participants and about any new information that may affect adversely the safety of the research participants or the conduct of the trial.

For studies which will continue for more than a year, a continuing review report needs to be submitted (within 1 month of the due date i.e. 11 months from the date of approval) on or before XXXXXXXXXXX.

A copy of the final report should be submitted to the IEC for review.

The IEC functions in accordance with ICH GCP, Schedule Y, ICMR guidelines and other applicable regulatory requirements.

Sincerely yours

Member Secretary/ Chairperson,
IEC
(Signed and dated by the IEC Chairperson or Member Secretary)

Date of approval of the study: XX/XX/20XX

Annexure 5

AX 05/SOP 06/V1

Format of Observational Project Approval letter

Date XX/XX/XXXX

To,

Dr. xxxxxxxxxxxx,

Dept. of xxxxxxxxxxxxx.

Ref: The project no. EC/xxx/20xx entitled, "xxxxxxxxxx".

Sub: Letter no.

Dear Dr. XXXXx,

The meeting of the Institutional Ethics Committee (IEC) was held on xxxxx at xxxx, in the xxxxxxxxxxxxx with xxxxx as Chairperson.

xxxx members attended the meeting held on xxxx. The list of members who attended the meeting is as follows.

Name of Members	Position on IEC	Designation & Affiliation	Qualification	Gender

It is hereby confirmed that neither you nor any of the study team members have participated in the voting/decision making procedures of the committee.

The IEC has reviewed and approved the following documents submitted for the above – mentioned clinical study.

1. Xxx
2. Xxx
3. xxx

The IEC hereby approves the proposal entitled, "xxxxxxxxxxxxx".

It is understood that the study will be conducted under your direction, in a total of xxxx research participants, at Dept. of xxxx, Institute of NephroUrology, Bengaluru-560002 as per the submitted protocol.

This approval is valid for the entire duration of the study.

No deviations from, or changes of the protocol and Informed Consent Document should be initiated without prior written approval by the IEC of an appropriate amendment. The IEC expects that the investigator should promptly report to the IEC any deviations from, or changes of, the protocol to

eliminate immediate hazards to the research participants and about any new information that may affect adversely the safety of the research participants or the conduct of the trial.

For studies which will continue for more than a year, a continuing review report needs to be submitted (within 1 month of the due date i.e. 11 months from the date of approval) on or before XXXXXXXXXXX.

A copy of the final report should be submitted to the IEC for review.
The IEC functions in accordance with ICH GCP, Schedule Y, ICMR guidelines and other applicable regulatory requirements.

Sincerely yours

Member Secretary/ Chairperson,
IEC
(Signed and dated by the IEC Chairperson or Member Secretary)

Date of approval of the study: XX/XX/20XX

Annexure 6

AX 06/SOP 06/V1

Guidelines for reviewing a study protocol

Reviewers should think about and try to find answers to the following questions:

1. How will the knowledge, result or outcome of the study contribute to human well-being?
   - ❑ Knowledge from the basic research may possibly benefit.
   - ❑ A new choice of method, drug or device that benefits the research participants during the study and others in the future.
   - ❑ Provide safety data or more competitive choices.
2. Does the study design will be able to give answers to the objectives? Whether
   - ❑ The endpoints are appropriately selected.
   - ❑ The participating duration of a study participant is adequate to allow sufficient change in the endpoints.
   - ❑ The control arm is appropriately selected for best comparison.
   - ❑ The placebo is justified.
   - ❑ The number of study participants in non-treatment (or placebo) arm is minimized.
   - ❑ Unbiased assignment (e.g. randomization, etc.) is in practice.
   - ❑ Inclusion and exclusion criteria are carefully selected to eliminate confounding factors as much as possible.
   - ❑ The sample group size appropriate with the given statistical assumptions.

- ❑ Predictable risks are minimized.
- ❑ The tests and procedures that are more than minimal risk are cautiously used.
- ❑ Research participants deception is avoid.
- ❑ Instruction and counseling for study participants are included (if needed) when deception is integral to the study design.
- ❑ The study participants are adequately assessed and provided follow-up care, if needed.

3. Who will be the participants in the study? Whether
   - ❑ The described population is appropriate for the study.
   - ❑ Predictable vulnerabilities are considered.
   - ❑ It is completely necessary to conduct the study in a vulnerable population. If not, is there any other way to get the study answers?
   - ❑ There will be secondary participants.
4. Do the inclusion and exclusion criteria
   - ❑ Selectively include participants most likely to serve the objective of the study?
   - ❑ Equitably include participants?
   - ❑ Properly exclude participants who can predictably confound the results?
   - ❑ Properly exclude participants who may predictably be at increased risk in the study due to coexisting conditions or circumstances?
5. Does the study design have adequate built-in safeguards for risks?
   - ❑ Appropriate screening of potential participants?
   - ❑ Use of a stepwise dose escalation with analysis of the results before proceeding?
   - ❑ Does the frequency of visits and biological samplings reasonably monitor the expected effects?
   - ❑ Are there defined stopping (discontinuation) / withdrawal criteria for participants with worsening condition?
   - ❑ Is there minimized use of medication withdrawal and placebo whenever possible?
   - ❑ Will rescue medications and procedures be allowed when appropriate?
   - ❑ Is there a defined safety committee to perform interim assessments, when appropriate?
   - ❑ Is appropriate follow-up designed into the study? For instance, gene transfer research may require following the participants for years or for their entire lifetime after they receive the gene transfer agent.
6. Is pre-clinical and/or early clinical studies sufficiently performed before this study?
   - ❑ The animal study and *in vitro* testing results?
   - ❑ Previous clinical results, if done?

- Whether the proposed study is appropriately built on the pre-clinical and/or early clinical results.
  - The selected dose based on adequate prior results?
  - Monitoring tests designed to detect expected possible risks and side effects?

7. Do the study and the informed consent process include issues of special concern, such as:
   - Waiver or alteration of consent?
   - Delayed consent (e.g., emergency treatment, etc.)?
   - Deception?
   - Sensitive information of participants that may require a confidentiality statement?

Guidelines to review Informed Consent Document/Patient Information Sheet

The actual process of informed consent should:

- Give the participants significant information about the study.
- Make sure the participants have enough time to carefully read and consider all options.
- Answer all questions of the participants before making decision to participate.
- Explain risks or concerns to the participants.
- Make sure that all information is understood and satisfied by the participants.
- Make sure the participants understand the study and the consent process.
- Obtain voluntary informed consent to participate.
- Make sure the participants can freely consent without coercion, pressure or other undue influences.
- Consent should be informally verified on a continuing basis.
- Continue to inform the participants throughout the study.
- Continue to re-affirm the consent to participate throughout the study.

Procedures or methods used in the informed consent process if recruitment of study participants include:

- A consent form
- Brochures, Pamphlets or other reading materials (i.e., letters to participants, phone pre-screening questionnaires, phone hold messages)
- Internet information
- Instruction sheets
- Audio-visual presentations
- Charts, diagrams or posters
- Discussions

- Consultation with others

Techniques to improve the readability of consent forms:

- Use short sentences and paragraphs
- Limit to one thought or topic in a sentence, avoid run-on sentence
- Use simple words, less syllables in a word.
- Use common words; remove technical jargon and medical terms.
- Try to use correct basic grammar and form.
- Use "gene transfer" instead of "gene therapy" (less implied effectiveness).
- Use "agent" instead of "drug" or "medicine" (less implied effectiveness).
- Try to avoid the use of "treatment", "therapy" or "therapeutic" in studies involving gene transfer (because these words imply effectiveness)

Guidelines to Placebo Justification

Background conditions, such as benefits of standard treatment, risk of using placebo, risk management and disclosure should be considered. The followings are some guides to ease Board decision.

I. Benefits of standard treatment

1) Is there a standard treatment?
2) Is the standard treatment widely accepted?
3) Has efficacy of the treatment been consistently proven?
4) Are all newly diagnosed patients with this condition put in standard treatment (versus observed or other)?
5) Does the treatment act on the basic mechanism of the disease (vs. symptoms)?
6) Are most (≥85%) of the patients with this condition responsive to standard treatment alternatives (vs. resistant or refractory)?

   If the answers of (1) to (6) are "yes", placebo is not recommended.

   If any one or more answers are "no", placebo may be possible.

7) Are the side effects of the standard treatment severe?
8) Does standard treatment have many uncomfortable side effects?
9) Does standard treatment have contraindications that prevent some research participants from being treated?
10) Is there substantial (≤25%) placebo response in this disease or symptom?

    If the answer of (7) *to* (10) *are "no", placebo is not recommended.*

    If any one or more answers are "yes", placebo may be possible.

II. Risks of placebo

1) Is the risk of using placebo instead of treatment life threatening?

   If yes, placebo is not acceptable.

2) Is the use of placebo instead of treatment likely to lead to permanent damage?

   If yes, placebo is not acceptable.

3) Is the risk of using placebo instead of treatment likely to cause irreversible disease progression?

   If yes, placebo is not acceptable.

4) Can the use of placebo instead of treatment lead to an acute emergency?

5) Is the risk of using placebo instead of treatment the persistence of distressing symptoms?

6) Is the risk of using placebo instead of treatment severe physical discomfort or pain?

   If answers of (4) *to* (6) *are "yes", placebo is not acceptable unless risk management is adequate.*

III. Risk management

1) Is there benefit in the overall management of the research participants?

   ☐ *Yes, consider placebo*

   ☐ *No, placebo not recommended*.

2) Will the discontinuation of previous treatment put the participant in danger of acute relapse when transferred to placebo?

   ☐ *No, consider placebo*

   ☐ *Yes, placebo not recommended*.

3) Are research participants at high risk for the use of placebo excluded?

   ☐ *Yes, consider placebo*

   ☐ *No, placebo not recommended*.

4) Is the duration of the study the minimum necessary in relation to the action of the drug?

   ☐ *Yes, consider placebo*

   ☐ *No, placebo not recommended*.

5) Are there clearly defined stopping rules to withdraw the research participants in case he/she does not improve?

   ☐ *Yes, consider placebo*

   ☐ *No, placebo not recommended*.

6) Is risk monitoring adequate to identify progression of the disease before the research participants experience severe consequences?

   ☐ *Not applicable.*

☐ *Yes, consider placebo*

☐ *No, placebo not recommended*.

7) Are there clearly defined stopping rules to withdraw the research participants before the advent of severe disease progression?

☐ *Yes, consider placebo*

☐ *No, placebo not recommended*.

8) If the risk of placebo is an acute emergency, are rescue medication and emergency treatment available?

☐ *Not applicable.*

☐ *Yes, consider placebo*

☐ *No, placebo not recommended*.

9) If the risk of placebo is the persistence of distressing symptoms, is concurrent medication to control them allowed?

☐ *Not applicable.*

☐ *Yes, consider placebo.*

☐ *No, placebo not recommended*.

10) If the risk of placebo is severely physical discomfort or pain, is there rescue medication?

☐ *Not applicable.*

☐ *Yes, consider placebo.*

☐ *No, placebo not recommended*.

IV. Risk disclosure in the consent form

1) Are the risks of getting placebo instead of active treatment fully disclosed?

☐ *Yes, consider placebo.*

2) Are the risks of the test drug disclosed?

☐ *Yes, consider placebo.*

3) Are the advantages of alternative treatments explained?

☐ *Yes, consider placebo.*

Conclusions:

1. The use of placebo is ethically acceptable because:

   ☐ Research participants are not exposed to severe or permanent harm by the use of placebo.

   ☐ Research participants under placebo will benefit from the overall treatment of the disease.

   ☐ Risks of the use of placebo are minimized.

   ☐ Risks are adequately disclosed in the consent form.