NABH Accreditation Standards for Clinical Trials and application form

Indian Society for Clinical Research

Recommendations/Suggestions on NABH Accreditation Standards for Clinical Trials (Ethics Committee, Investigator and Clinical Trial Site) and application form

Date: 31st March 2015

The recommendations and suggestions below have been collected by ISCR from various stakeholders like Sponsors, CROs, Ethics committees, Investigators and clinical trial site representatives.

General Comments and Recommendations:

- This is **an important initiative to ensure good quality and ethical conduct of clinical trials** in a consistent manner in India and should be done in a well planned and phased manner.
- **Adequate time** should be given to the sites to apply for this accreditation. **Ongoing trials should not get impacted** adversely by the outcome of NABH accreditation. Similarly, for new studies, the sites should be given time to prepare for accreditation and apply to NABH.
- First phase should be to train **adequate number of assessors** who will carry out this accreditation and ensure their time and availability to conduct assessments. In parallel, it is important to **offer training to the sites, investigators and ethics committees** to help them prepare the documentation and processes towards accreditation. They also need to be **given time to prepare these documents.**
- Accreditation procedure as we understand means having standards in place and ability to demonstrate that they are applied consistently in day to day conduct of the work – thus accreditation would be done in the sites that are already doing at least some trials. **For the new (first time) sites,** sometime needs to be given before they become fully compliant. It is hence recommended that a **"provisional accreditation"** or other such mechanism be in place for these new sites. Similar provisions should be there for accrediting new investigators.

General questions and clarifications requested on the accreditation process:

1. **Process for accreditation** needs to be provided along with:
   1) Timelines: From application to accreditation.
   2) Applicability to studies: The accreditation process should not affect studies already approved by CDSCO office.

2. Once the site is assessed for accreditation and a site has any deficiency, what is the **timeline by when the site can come up with the systems and processes** to comply with the requirements? Ongoing trials should not get impacted.

3. In case the Ethics Committee/Clinical Trial Site/Investigator **fails to qualify the first time, what are the options**? Ongoing trials should not get impacted.

4. There should be a plan in place to **handle an ongoing trial when the NABH certificate expires or is not renewed by the authority or is temporarily suspended.**

5. **Will NABH support Ethics committees / sites them after the audit** - with regards to generation of documents, additional information and so forth. If so, will these be additional expenses or will the same be covered by the audit.

6. Following areas **must be elaborated further in the standards/objective elements**:
   - Serious Adverse Events notification and EC opinion timelines. Section 1 (Accreditation of Ethics committees) talks about SAE receipt and determination of compensation but nothing about AE monitoring and other AE related tasks done by EC.
   - As there is a mandate for clinical trial liability insurance policy that a sponsor should have for a trial, is there any provision to protect the indemnity of site/PI especially for professional negligence while taking part in Clinical trial?
   - Regarding ICH-GCP training to investigators and EC Members – Will QCI/NABH enlist the qualifying body or personnel whose certification be accepted as a part of this process?

Following are comments for specific sections and objective elements:

Page No.	Standard & Element	Comment and Rationale	Proposed change to language (if applicable)
Section1: Accreditation of Ethics Committee			
1	Section 1:	- The change has been suggested in accordance with Indian GCP Guidelines Section 2.4.2.1 Basic Responsibilities of Ethics Committee	Outcome of Section 1 Ethics Committee competently assesses risk and scientific validity of trials ensures a competent review of all ethical aspects of the project proposals received and

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		- Also as per Indian GCP Guidelines Section 2.4.2.4. Review Procedures "It should ensure that a scientific evaluation has been completed before ethical review is taken up. The Committee should evaluate the possible risks to the subjects with proper justification, the expected benefits and adequacy of documentation for ensuring privacy, confidentiality and justice issues."	executes the same free from any bias and influence that could affect their objectivity.
2	1.2.1	Addition suggested for ease of understanding.	1.2.1 Procedures (SOP on SOPs) shall be in place and well defined for the development, review and revision of SOPs.
3	1.2.2	The document indicates that Ethics Committees are required to have separate SOPs for each of the procedures mentioned in the list of mandatory procedures for Ethics Committee. **It is recommended to clarify that the Ethics Committee may have one SOP or multiple SOPs covering the procedures listed in the section 1.2.2 List of mandatory procedures for Ethics Committee. i.e.** a. Terms of reference for Ethics Committees	It might be more practical for Ethics Committees to have one SOP covering all the mandatory procedures rather than have multiple SOPs, one for each of the procedures.

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		b. Protocol Submission c. Ethical Review d. Decision making , minutes recording , post meeting activities including monitoring e. Documentation and archiving	
4	1.2.2 (d) And 1.8	It is recommended that the sections 1.2.2 (d) and 1.8 include the requirement for ECs to document a procedure on how they would monitor compliance to the regulation of video recordings of Informed Consents	Currently it is unclear who monitors compliance to the regulation video recordings of Informed Consents and how is it done. Ethics Committees in their procedures for periodic review and oversight should document this procedure. {Example. annual report by PI, format of report, visit to site for reviwing consent bprocess, compliance to protocol, Handling protocol deviation reported to EC}.
5	1.2.2 d. iv	Suggest adding the wording 'GCP' as the investigator is expected to conduct the study in accordance with the protocol and GCP.	1.2.2 d. iv. Procedure for handling issues related to non-compliance, protocol or GCP violation, Serious Breach of protocol and misconduct, negligence, complaints by the participants and other stake holders.
6	1.3.1	Suggest adding the wording 'GCP' as the investigator is expected to conduct the study in accordance with the protocol and GCP. Please clarify what would be the evidence for	Composition shall be multidisciplinary and multisectorial as per applicable rules and regulations and adequate for its functioning.

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		this element. Quorum needs to be defined. Example. Many ECs keep a quorum fixed at 5 even if the total no of EC members exceeds 9 There is a need to define who can serve as a lay person.	
7	1.3.2	The invitation to the subject matter expert or representative of vulnerable subjects could be allowed at the best discretion of Ethics Committee.	1.3.2 Subject experts and representatives of vulnerable subjects shall be invited as required with prior intimation, as deemed necessary by the committee.
8	1.3.5	- It is important to specify the training requirements on GCP guidelines along with applicable Indian regulations. - The regulations may undergo change over a period of time and hence it is important that the EC members undergo refresher training at least annually. - Training records should be documented by EC members. What evidence is required to document training? Whose certificate would be acceptable?	1.3.5 Ethics Committee members shall be trained (initial and ongoing) in applicable rules and regulations, GCP guidelines and Ethics Committee SOPs. The EC members shall undergo refresher training on Indian regulations and GCP guidelines at least annually.
9	1.3.6	Conflict of interests and confidentiality needs to	1.3.6 Conflict of interest and confidentiality shall be addressed at the time of composition as well as on an ongoing basis

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		be addressed on an ongoing basis. There is a need to define what would be considered conflict of interest for EC members.	
10	1.4	It is recommended that this section include the requirement for ECs to document a procedure on how they would ensure subject protection. For example: - Review of ICF to ensure that it contains the elements required by ICH GCP - Periodic monitoring of clinical trials by on-site monitoring.	The current objective elements described in the accreditation document does not provide details on how EC would ensure subject protection especially for vulnerable subjects.
11	1.4.1	- As per Schedule Y and Indian GCP guidelines the subject's rights and responsibilities will be provided to the potential subject in an informed consent form. - Apart from what is mentioned in the ICF, what additional information/documentation is required? - Responsibilities of the subject to a certain extent may vary depending on the type of study design, study drug, indication etc.	
12	1.4.2	ICH GCP does not require a subject to prior intimation before withdrawal. Trial participants could be requested and not	To align with ICH GCP

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		insisted for "Prior intimation" of withdrawal. It is recommended to revise the sentence accordingly.	
13	1.4.3	There is no specific assessment for assuring comprehension by the subject. There is an affirmation obtained from patient in ICF (I have read an understood statement). Example. Can documentation of ICF process by PI be made mandatory for EC to check this requirement?	1.4.3 Subjects shall be informed and comprehend (initial and ongoing) of the associated risks and benefits of the trial.
14	1.4.6	The compensation should be clarified as “for travel or any other relevant logistic expenses” incurred for the participation to avoid any confusion with compensation for study related injury/death/.	1.4.6. Compensation for travel and other relevant expenses provided to subjects for participation in the trial shall be appropriate and as per the rules and regulation and is reflected in the contract.
15	1.4.8	Compensation should be for research related injury OR As per the Appendix XII of Schedule Y the	1.4.8 Compensation for research related Injury to the subject shall be as per Drugs and Compensation (First Amendment) rule 122 DAB and any amendments thereby and monitored for non compliance. OR Compensation for injury to the subject is paid by the sponsor within the framework of applicable regulations shall be as per

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		Independent Expert Committee constituted by the regulator and DCGI determine the causality of the SAE and quantum of compensation. Hence the rewording for 1.4.6 is suggested for appropriate interpretation.	the rules and regulations and monitored for noncompliance.
16	1.6.4	The informed consent process does not involve EC representation. It is the Investigator's responsibility. Hence the change in wording suggested.	1.6.4 Ethics Committee reviews the informed consent processes proposed to be followed at the site or PI and for a particular study to ensure that subject/LAR are provided appropriate information, adequate time is given and impartial witness used as applicable.
17	1.6.6	The change is suggested as per the terminology used in Schedule Y as 'Special population' instead of group. Currently the rules do not define how these populations should be protected by EC.	1.6.6 Proposals involving special group population and vulnerable population shall be evaluated as per rules and regulations.
18	1.6.7	- Site Contract (Clinical Trial Agreement) is a detailed and legal document. It would be important that ethics committee reviews the document in entirety. - Indian GCP guidelines and Schedule Y does not have the term 'indemnity'.	1.6.7 Contract and budget shall be reviewed evaluated, for the contents to ensure their compliance with indemnity, insurance, compensation, roles and responsibilities as per applicable rules and regulations.
19	1.6.8	- The change suggested hereby is in congruence with the section 1.6.2	1.6.8 Review of amendments to the originally approved protocol, consent forms and investigators brochure shall be

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			done in formal meetings to evaluate if any change in the risk Vs. benefit to trial subjects.
20	1.6.9	Periodic review of the trial should be done from overall "safety" perspective rather than just adverse events	1.6.9 Periodic review of trial shall be done for continuation, risk evaluation and safety monitoring Or 1.6.9 Periodic review of trial shall be done for continuation, risk evaluation and adverse event monitoring. EC conducting monitoring of site to ensure trial is conducted as per protocol, GCP and applicable regulations
21	1.7.3	EC members with conflict of interest should "abstain" from voting when the proposal is being evaluated	1.7.3 Conflict of interest shall be declared prior to the review and members with conflicts should abstain voluntarily during decision making process is documented
22	1.7.7	It should be clarified that ethics committee would employ the formulae laid down by Drugs and Compensation (First Amendment) rule 122 DAB and any amendments thereafter to derive compensation amount.	1.7.7 Serious adverse events shall be analysed and compensation amount assessed employing the formulae laid down by Drugs and Compensation (First Amendment) rule 122 DAB and any amendments thereby and reported to regulatory authority as per rules and regulations.
23	1.9 Self Assessment: The Ethics Committee has and follows documented procedures for self-assessment.	It is recommended that this section be clarified to explain what areas within the EC should be self-assessed. Clarity required how the self assessment will be done and who can do this. Can a third party audit EC?	To assist with practical implementation of the accreditation standards.

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24	**1.9.1** Periodic self-assessments are conducted.	One of the objective element for clinical trial site oversight under 3.6.1 requires the clinical trial site to ensure regulatory compliance of ethics committee functioning	1.9.1 Periodic self-assessments are conducted in collaboration with the clinical trial site or management.
Section2: Accreditation of Investigator			
25	Section 2	- An investigator should be familiar with the GCP guidelines for conduct of clinical trials. - As per Schedule Y; 'Responsibilities of the Investigator(s):' The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII." - Many specialists have their MBBS degree registered with MCI but not their PG qualification registered.	Objective of Section 2: Investigators are adequately qualified, experienced and knowledgeable in procedures of conduct of clinical trials processes, ethical issues and applicable rules and regulations, GCP guidelines for conduct of clinical trials ensuring data integrity and protection of subject rights, safety and wellbeing Outcome of Section 2: - Clinical trial conduct is ethical and in compliance with the applicable rules and regulations and the GCP guidelines.
26	2.1.1 e	In case of new Principle Investigator's their past experience as a research coordinator/sub investigator in the past 2 years should be considered	2.1.1 e) Have knowledge and expertise in the area being studied in a particular trial. Should have experience of minimum two years in clinical trial/research as either an Investigator/co- investigator.

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27	2.1.1 (e)	It is recommended to limit this requirement to 'Should have knowledge and expertise in the area being studied in a particular trial', to allow new investigators to apply for accreditation It is recommended that this section includes what documents will need to be submitted by the investigator to the accreditation body to assess their qualifications and experience. It is recommended that this section includes the requirement of investigator training in local regulations, in addition to the ICH GCP and Indian GCP.	
28	2.1.3	1. Rewording because - The staff might be employed by the institution or by PI for the particular study. - the requirement of number of staff may vary depending on the tasks or functions to be performed. 2. The term "Qualified staff" is subjective and hence requesting to specify the definition of the staff and qualification benchmark.	2.1.3 Investigator has adequate number of qualified staff allocated in adequate number for proper conduct of trial.
29	2.2.1, 2.2.2 and 2.2.3	It is recommended that these sections include	

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		the documents required to be submitted by the investigator to the accreditation body to assess their compliance to sections 2.2.1, 2.2.2 and 2.2.3 of this accreditation standard. - It is also recommended to include provision for new investigators seeking accreditation, who does not have any prior experience of conducting clinical trials	
30	2.3 to 2.7	It is recommended that documents required to be submitted by the investigator to the accreditation body to assess their compliance to sections 2.3 to 2.7 of this standard, be included in the accreditation document.	
31	2.7.1	It is recommended that this section is revised to reflect that investigator should have procedures in place to check that the EC associated with the institution has been accredited. It is not clear what is meant by 'Approval of the accredited Ethics Committee **and regulatory authority** shall be obtained before initiation of the study at the site'. It is recommended to revise the sentence as deemed appropriate.	

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32	2.3.8	- This additional text is suggested to be added in accordance with the requirements stated in Office orders issued dated 3 Jul 2014 by the CDSCO and Ranjit Roy Chaudhury committee report.	2.3.8 Investigator shall provide adequate medical care and safety management of trial subjects and reports and analyses serious adverse events as per applicable rules and regulations.
33	2.4.2	For being more specific.	2.4.2 Investigator shall obtain ethics committee approval for the Patient Information Sheet and Informed Consent Document to be used in the clinical trial provided to subject/LAR.
34	2.4.3	As per Schedule Y; Informed Consent (ii)-If the Subject or his/her legally acceptable representative is unable to read/ write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form. Need to define who can be considered LAR/IW	2.4.3 The Subject/Legally Acceptable Representative/Impartial witness shall be adequately informed to understand the information given in the informed consent document.
35	2.5.3 and 2.5.4	- We believe the contents in 2.5.3 and 2.5.4 is repetitive except the death event outcome. Irrespective of outcome of SAE, the investigator will have to follow the reporting requirements. Hence we can combine the 2 points. - The Schedule Y requires PI to report the SAE to sponsor/representative, EC and DCGI (& independent expert committee	2.5.3 Investigator reports all serious adverse events as per the regulatory requirements to the Ethics Committee and regulatory authorities and 2.5.4 Investigator follows ethics committee recommendation to terminate or suspend a trial (as applicable).

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		in case of death). The language in the proposed accreditation standards document appears incomplete and hence broader text is recommended. - The recommendation of EC for termination or suspension of trial should be a separate point to avoid it linking it only with SAEs.	
36	2.5.6	The deviations from protocol or GCP guidelines should be analysed and corrective action taken to prevent them in future.	2.5.6 Protocol deviations or any transgression of the principles embodied in GCP affecting safety of subjects and integrity of data shall be reported to the ethics committee, analyzed and accordingly appropriate action be taken, if need arises, without prior intimation.
37	2.7.1	There may be a time difference in the issuance of accreditation to ethics committee, site and investigator at a particular hospital. Moreover the current regulation does not state have the approval of the study to be from only accredited ethics committee. Hence we suggest removing the word 'accredited' in this section.	2.7.1 Approval of the study from accredited Ethics Committee registered with the DCGI and regulatory authority shall be obtained before initiation of the study at the site.
38	2.7.9	Suggested to add the minimum frequency as annual considering the Indian GCP guidelines - section 2.4.2.6. Decision Making Process and Point no. 38 of Appendix V – Essential Documents for the conduct of clinical trial.	2.7.9 Periodic status report (annually at the minimum) of clinical trial shall be submitted to the Ethics Committee and recommendations shall be followed accordingly.
Section3: Accreditation of Clinical Trial Sites			
39	3.1 to 3.6	- It is recommended that documents required to be submitted by the clinical	To assist with practical implementation of the accreditation standards.

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		trial site to the accreditation body to assess their compliance to sections 3.1 to 3.6 of this standard, be included in the accreditation document.	
40	3.3.1c	- This additional text is suggested to be added in accordance with the requirements stated in Office orders issued dated 03 Jul 2014 by the CDSCO and Ranjit Roy Chaudhury committee report. - It is the investigator/institution that can provide the ancillary care to the subject directly.	3.3.1 c) Medical management of adverse events and provision for ancillary care to the subject for brief illness
41	3.3.1d	The Schedule Y and subsequent guidelines issued by the DCGI has detailed process, responsibilities for compensation to be paid in the event of study related injury. Hence it is important for institute to have well defined responsibilities in the process of payment of compensation.	3.3.1 d) Adverse events and serious adverse events reporting (including emergency care) and roles, responsibilities in payment of compensation for trial injury
42	3.3.1p (new clause)	We suggest that site should have the SOP in place so as to ensure there is a consistency in handling contracts (clinical trial agreements) in a timely manner.	3.3.1 p) Regarding payments/financial support/honoraria related to clinical trials
43	Section 3, 3.3.1q (new clause)	It is important that site have a SOP for scheduled maintenance and protection of hardware, computer/electronic systems, internet in the institution.	3.3.1 q) Maintenance of computerised systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.
44	3.4.1	- As per Schedule Y and Indian GCP guidelines the subject's rights and responsibilities will be provided to the	3.4.1 Rights and responsibilities of subject shall be documented.

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		potential subject in an informed consent form. - Responsibilities of the subject to a certain extent may vary depending on the type of study design, study drug, indication etc	
45	3.4.8	- This additional text is suggested to be added in accordance with the requirements stated in Office orders dated 03 Jul 2014 issued by the CDSCO and Ranjit Roy Chaudhury committee report. - It is the investigator/institution that can provide the ancillary care to the subject directly.	3.4.8 Adequate medical emergency care, ancillary care to the subject for brief illness and safety shall be provided for trial subject.
46	3.5.2	It is important that site have a SOP for scheduled maintenance and protection of hardware, computer/electronic systems, internet in the institution.	3.5.2 Subject files and clinical trial related information/documentation (paper and/or electronic) shall be well maintained. Maintenance of computerised systems – hardware as well as software - should be validated and a detailed description of their use be produced and kept up-to-date.
47	3.6.2 There shall be a plan for monitoring the conduct of study and addressing deviations and improvements are made as required	Monitoring of clinical trials is a Sponsor Responsibility according to ICH GCP. It is recommended that this section be revised to clarify that site should have a procedure in place for addressing deviations and implementation of corrective and preventive actions by the site to ensure compliance to SOPs and applicable rules and regulations To assist with practical	

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	to ensure compliance to SOPs and applicable rules and regulations.	implementation of the accreditation standards.	

Comments on Format for Application for Accreditation:

Sr.	Section, Standard	Suggestion/ Comment	Rationale for suggestion
1	**Activities and Fee Structure** Fee structure	We suggest to bring clarity around the fees structure and recommendations for the same so as to bring in efficiency in the process Will the fee include EC accreditation for the site? In application form, the table mentions about Annual fee however the comment mentions below about the validity to be for 3 years. Need to clarify if the sites have to pay annual fee every year even if the validity is provided for 3 years.	At bigger institutes there would be many number of investigators, sites, however it would be prudent to have the assessment visit for accreditation of all of them simultaneously.
2	Service Tax on Fees	Remove the specific figure of 12.36% Service tax and instead use 'Service tax as applicable'.	The service tax provisions have undergone a change and are subject to change and hence we suggest to remove the figure 12.36%
3	**Guidance Notes:** Expenses on travel, lodging/ boarding of	- There are no specifics or limits stated for these expenses and lacs clarity.	There may differences, payment issues and current requirement lacks clarity.

	assessors	- Suggest there should fixed amount for these expenses	
4	The surveillance visit will be planned during the 2nd year of accreditation which is usually between 15-18 months.	- Will there be an additional visit for Reaccreditation/renewal of accreditation? If yes, when?? - Is site/Investigator/EC expected to bear the expenses of this visit??	Need clarity
5	NABH may call for an un-announced visit, which could be a Surprise Assessment or based on any concern/ feedback/ complaint reported by any individual or organization or media.	Clarity required is site/Investigator/EC expected to bear the expenses of this visit??	Need clarity.
6	**General Information** **1. b.** Reaccreditation cycle number	The term needs explanatory note for the applicant to choose correct number and details	
7	**Name and other details of the applicant** **3. a. Ethics Committee** Accreditation Number or Application acknowledgement Number	- Suggest to revise and state: Accreditation Number (if the application is for reaccreditation) - Add the explanation of what details/which number is expected to be provided for heading 'Application acknowledgement Number'	Need clarity
8	**3.c. Clinical Site** Number of (operational) beds in the hospital/institution	Need clarity whether the number of beds in the "whole hospital" or the number of beds in particular unit (site) within the hospital" are required?	Need clarity
9	**5. Ethics Committee Chairperson (For Independent Ethics Committee)**	Add the wording 'Institutional'	The requirement is applicable to institutional EC as well.
10	**6. Accreditation Coordinator**	- Are there any specific requirements for this person to be a coordinator? - Can there be separate person for accreditation of EC, sites, investigator??	Need clarity
11	**List of Attached Reference documents** List of Trials	- Clarity required whether the list of currently ongoing trials reviewed by EC is required?	Need clarity

		- Are only the titles of the ongoing trials needed to be provided here??	
12	**Annexure 2 - Investigator Declaration Form** Degrees/ years	Suggest to use the term "Qualification/Years"	Suggestion for the term
13	**Annexure 1, 2 and 3** "Access will be provided to NABH assessors to areas necessary for conducting assessment of clinical trial at the site."	We suggest the rewording "Access will be provided to NABH assessors to areas necessary for conducting assessment of conduct of clinical trial at the site."	Access to the trial documents and records is provided to Regulatory authorities, ethics committees other than sponsor/CRO. The access to a particular site would not be provided to assessor by the site.