ACTIVE MONITORING FOR HIGH RISK STUDIES: THE ROLE OF THE REC

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POST-APPROVAL REC RESPONSIBILITY: MONITORING

- What:
  - act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP & applicable regulatory requirements
- Why:
  - overarching ethical (primary) purpose – to verify rights & well-being of participants are protected
- How:
  - passive and / or active
- Current focus:
  - intrinsic emphasis on record keeping →can serve to obscure primary purpose
- Active Monitoring:
  - for participant protection in entirety, REC to visit study site where studies approved by them are ongoing

INTERNATIONAL GUIDELINES

- Declaration of Helsinki
  - *s23 The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events*
- CIOMS
  - *guideline23 Research ethics committees must be authorized to monitor ongoing studies. The researcher must provide relevant information to the committee to permit monitoring of research records, especially information about any serious adverse events*
- ICH GCP
  - *s3.1.4 The IRB/IEC1 should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year*
- None specify
  - onsite/offsite/both

SA GCP 2020

- **6.11 MONITORING**
  - 6.11.1 The purpose of trial monitoring is to verify that:
  - 6.11.1.1 The rights and well-being of human participants are protected;
  - 6.11.1.2 Reported trial data are accurate, complete and verifiable from source documents;
  - 6.11.1.3 The trial is conducted in compliance with the currently approved protocol (including any amendments), with SA GCP 2020 and with SAHPRA requirements.

- **6.11.2 Selection and Qualifications of Monitors**
  - Monitors should be
  - 6.11.2.1 Appointed by the Sponsor.
  - 6.11.2.2 Appropriately trained, with the scientific and/or clinical knowledge necessary to monitor the trial adequately. A monitor's qualifications should be documented.
  - 6.11.2.3 Thoroughly familiar with the IP, the protocol, the informed consent documents and other written information to be provided to participants, the Sponsor's SOPs, SA GCP 2020, and SAHPRA requirements

NHREC 2015

- s3.1.1.1
  - the REC must assess how the research will be conducted, whether the researchers are suitably qualified, that ***adequate monitoring and safety measures*** are in place and achievable, that the site is suitably resourced, and so forth.

- 3.2.1 Contextual Circumstances
  - In order to ensure optimal protection of vulnerable participants, the REC may impose additional protective measures for the informed consent process; or require ***increased monitoring and interim reporting*** on participants' welfare; or require post-recruitment reviews of the effectiveness of the protective measures imposed. Other measures may also be appropriate.

NHREC 2015

- ***4.5.1.10 Monitoring***
  - RECs ***have the right to monitor*** the research it approves (Declaration of Helsinki 2013 par 23). Researchers should provide appropriate information to the REC to facilitate monitoring, including alerts and investigator brochures. The frequency and type of monitoring should reflect the degree and extent of risk of harm to participants or animals.

  - RECs may recommend and adopt any additional appropriate mechanism for monitoring, ***including random inspection of research sites***, welfare monitoring sheets, data and signed consent forms, and records of interviews. Information and consent materials should indicate that such monitoring may take place.

- ***4.5.1.11 Suspension or discontinuation of projects***

  - Where circumstances indicate that a project is non-compliant with the approved protocol and the interests of participants are at risk of harm, the REC may withdraw approval, after due process has been followed

ACTIVE MONITORING: REC REALITIES

- Hurdles
  - Workload + lack of workforce in REC,
  - lack of administrative infrastructure,
  - lack of a clear framework for undertaking monitoring,
  - difficulty in getting members to conduct active monitoring,
  - lack of training of REC members on how to conduct monitoring,
  - inadequate funds – monitoring activities need to be adequately budgeted for
- Day-to-day REC activities
  - substantial time in reviewing and approving protocols
  - reserve some time for passive monitoring but almost none for site visits.

COMMON PROBLEMS

- Issues related to informed consent
- Protocol deviation
- Reporting of study progress to the REC
- Recruiting additional participants without REC approval
- Reporting of serious adverse events

Davis S Monitoring of approved studies: A difficult tightrope walk by Ethics Committees. Perspectives in Clinical Research (2018)

- Regulatory errors
- Fraud

Chantler T,Cheah PY, Miiro G, et al. International health research monitoring: exploring a Scientific and a cooperative approach using participatory action research. BMJ Open 2014;4:e004104. doi:10.1136/bmjopen-2013-004104

Table 1: On site monitoring checklist for Institutional Ethics Committees/institutional review boards

Monitoring domain	Methodology	Remarks
I. IC process and documentation		
a. IC form used	Inspect	• Site has used valid, contemporaneous and EC/IRB approved consent forms
b. AV recording documentation, storage/archival	Observe, inspect and interview investigator and other delegated personnel	• Process of audio video recording of IC process is appropriate • Documentation of AV recording of IC is adequate • Patient privacy and confidentiality is respected • Storage area is well protected
II. Site documentation		
a. Availability of site SOPs	Observe, inspect Interview site personnel	Site conducts research according to SOPs
III. SAE management		
a. Reporting of SAEs	Inspect and interview site personnel	• Site has reported SAEs as required by current regulatory requirements • No discrepancy between the SAEs reported to ECs and that known to the site
b. Any unanticipated increase in SAE?	Observe and interviews	No increase in SAEs in the study than initial baseline assumed
c. SAEs/SUSAR review	Ongoing review of documents submitted, interview investigator	No increase in SAEs at other sites; no increase in SUSARs in the study or any significant patient safety concerns
IV. Subject related		
a. Subject withdrawals after last EC site review	Review records, interview site personnel	Reasons for withdrawal are well documented
b. Protocol deviations and violations	Observe, interview investigator and site staff	• Site has SOP on how to manage protocol deviations and violations • Check if any of the protocol deviations violations are recurring in nature • Ascertain reasons for continued noncompliance with protocol and its impact on subject safety
c. Subject complaints received at site and how handled	Inspect, observe, interviews with Investigators/site staff and subject	Subject complaints are handled as per SOP and discussed in team meetings, escalated to EC, etc.,

IC=Informed consent, AV=Audio visual, SOP=Standard operating procedures, SAE=Serious adverse event, SUSAR=Suspected unexpected serious adverse reaction, EC=Ethics Committee, IRB=Institutional review boards

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Table 1. GCP discrepancies identified by on-site monitoring.

Areas of discrepancy	Type of discrepancy
Informed consent	1. Incomplete 2. Signature of witness not available to document consent for illiterate research participants. The signature is evidence that the contents of the participant information sheet were read out and explained to the illiterate participant. 3. Assent form for the involvement of children in research was not available. 4. Separate consent form for HIV testing was not used. 5. Consent form was not available in the language the participant had signed in. 6. The husband had signed a consent form instead of the participant herself. 7. The participant was not given a copy of the consent form to keep. 8. Audio visual consent recording was not kept in a secure place. 9. Consent forms were not updated with information about adverse events.
Adverse events	1. Failure to report a serious adverse event to the EC or delayed reporting when compared to regulatory requirements of India. 2. Failure to go into the details of a potential serious adverse event to investigate what caused it. 3. Failure to communicate adverse events from other sites of the same study to the EC. 4. Inability to recognize signals that could lead to adverse events. 5. Absent details of follow-up on abnormal lab or ECG findings.
Communication to EC	1. Failure to provide relevant forms to enable the committee for monitoring SAEs to detect any signals/concerns. 2. Failure to provide monitoring reports from sponsor to EC.
Case record form (CRF)	1. Overwriting not initialled by study staff making entries. It is essential that any correction in CRF made is initialled by the person making it. 2. Incomplete
Source document[3]	1. Improperly maintained source document. 2. Source documents not available at the site.
Insurance	1. Outdated insurance
Reimbursement and compensation	1. Failure to reimburse research participants for the management of SAEs

EC: Ethics Committee; SAEs: serious adverse events.

How does the monitoring of clinical trials by ECs work? Most ECs require the principal investigators to submit annual reports of their ongoing projects to the EC. These reports are then examined by ECs off-site. In addition to these annual reports, ECs also review protocol amendments and serious adverse event (SAE)reports and notifications. However, off-site monitoring may be inadequate as it may miss protocol violations, misreporting or discrepancies in consent administration and records thereof, to give some examples. At the same time, on-site monitoring by ECs does not seem to be a common practice and there are very little published data

Nusrat Shafiq *et al*. On-site monitoring of clinical trials by an Ethics Committee in India: a road less travelled. Research Ethics 2021, Vol. 17(1) 45–54

Figure 3 Elements of monitoring.

Our data suggest that while investigators appreciated the need for regulatory and ethics oversight, they want monitoring to be collaborative in nature and scientific in focus. Some investigators related how constructive interactions with monitors assuaged their initial fears and changed their perceptions about the value of monitoring. Others championed the need for cooperative monitoring as a result of encounters with monitors who questioned their intentions from the outset, or prioritised document verification and paperwork over observing critical research processes.

A monitor's personal and professional approach was viewed as crucial in promoting positive interactions and improving the quality of trials ….. educational process

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VALUE

- Important post-approval responsibility

- Can be instrumental in guiding researchers towards following ethical principles.
  - could allow for identification and management of ethical issues as early as possible
  - provide ethical guidance throughout entire research process, and mitigate negative effects, harms and wrongs

- Collaborative / Cooperative approach →'Communities of Practice': encourage situated learning & practical application of knowledge
  - COP: groups of people who share a concern, a set of problems, or a passion about a topic, and who deepen their knowledge and expertise in this area by interacting on an on-going basis

POINTS FOR DISCUSSION

- Is on-site monitoring conducted by the sponsor adequate?
- Is there a need for on-site monitoring by the REC?
- Who in the REC should participate in the on-site monitoring & how should they be trained?
- Are there ways to make on-site monitoring less resource consuming?
- Will this type of activity be feasible & sustainable?
- Collaborative / Cooperative approach: risks vs benefits?
- Is on-site monitoring another bureaucratic burden?
- Can on-site monitoring be seen as excessive policing that interferes with valuable research?

Thank you