Administrative Amendments such as a change in the address, contacts and correction of typographical and grammatical errors should be submitted to the DSRB for review. An acknowledgment letter by the DSRB will then be sent to the Investigator/ Sponsor. If the study is a HSA approved study, submission of administrative changes is not required. However, proper records of these changes should be maintained in the study site and sponsor files and made available to HSA upon request.

Minor Amendments are determined by DSRB if the changes to the protocol affect the risk-benefit assessment. Changes to the protocol that pose any increase in risk which is not more than minimal risk, or new procedures added that fit within the categories are eligible for expedited review. The Sponsor and/or PI should contact the HSA if they are unsure if the minor amendment(s) constitute a submission to HSA.

Major Amendments that significantly increase the overall risk or negatively alter the risk-benefit ratio to the subjects of the study will be reviewed at a DSRB Full Board Review meeting (e.g. a major change to the consent document or process that increases the overall risk to the subject involved in the study must be submitted to DSRB). HSA requires the Sponsor and/or PI to submit such major amendments as well as a copy of the amendment document.

The Sponsor and PI need to obtain approval from both DSRB and HSA before the amendment can be enforced.

PIs and Sponsors should to check with DSRB and HSA for further clarifications if unsure about their protocol amendment submission and/or procedures.

References:
SGGCP 6 Clinical Trial Protocol and Protocol Amendment(s)
NHG DSRB SOP 201-C11 & NHG Investigator Manual
Health Sciences Authority Frequently Asked Questions
Good Clinical Practice: A Question & Answer Reference Guide May 2011

UNDERSTANDING THE DIFFERENCES AND PREPARING FOR MONITORING, AUDIT AND INSPECTION

Well, you may ask, why is there a need to perform all these activities (i.e. Monitoring, Audit and Inspection) when a study has already been approved by the relevant Institutional Review Boards (IRB) or Regulatory Authorities?

Imagine if your loved one was asked to participate in a research study, what type of a mental checklist would you have before encouraging your loved one to participate in it?

- Your loved one is safe and his/her rights are protected
- The data obtained will be of good quality and integrity so that it will not be a waste of his/her effort
- Your loved one is under the protection of the available guidelines and regulatory requirements
- The operations of the study are well planned

These are very similar to the following points:

Purpose of Performing Monitoring, Audit and Inspection

- To safeguard the rights, safety and well-being of subjects participating in research studies;
- To verify the quality and integrity of the research data - to ensure that the data are accurate, complete and verifiable from source documents;
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), applicable Standard Operating Procedures (SOP), SG-GCP, and the applicable regulatory requirement(s). Some of these guidelines and requirements may include the respective institutional SOP and Institutional Review Board (IRB) SOP, SG-GCP, Medicines (Clinical Trial) Regulation, Guidelines for Clinical Trials provided by Health Sciences Authority (HSA) and Proper Conduct of Research SOP provided by National Healthcare Group (NHG).
- To assess whether the systems set up to conduct the research studies are suitably designed, controlled, maintained and documented to fulfill the objectives of the study; and
- To identify areas for quality improvement in conducting research

It may be difficult to ensure all of the above through a study application. Therefore, monitoring, audits and inspections are performed. The monitor/ auditor/inspector may look into all aspects of the research study, including the approval of the study application, subject recruitment methods, informed consent process, management of investigational products, documentation of study-related procedures and safety monitoring.

The Differences of Monitoring, Audit and Inspection

The distinction lies in the responsibilities of different parties and the different frequencies for the conduct of these activities.

MONITORING

Monitoring is carried out periodically and is applicable for all clinical trials. All clinical trials should include adequate provisions for the purpose of monitoring the conduct of a research study. The monitoring plan for a particular research study would depend on the complexity of the research study and the possibility of potential harm to subjects.

For Investigator-Initiated Clinical Trials, the Principal Investigator (PI) is responsible for having a written monitoring plan prior to study initiation. Clinical trials should be monitored regularly by a monitor who is independent of the research team. You may find the Monitoring Plan Template provided by (NHG-RDO) useful in drafting your respective monitoring plan. It can be found on National Healthcare Group – Research & Development Office's research portal (*www.research.nhg.com.sg*) (Resources -> Monitoring Plan Template).

For Industry Sponsored Clinical Trials, the PI is responsible for ensuring that the sponsor provides a monitoring plan for the clinical trial.

On the other hand, audits and inspections are 2 forms of quality assurance for clinical research/trials.

AUDITS

Audits are usually carried out on an ad-hoc basis. It can be performed by the institution or the sponsor. Audits, conducted by the NHG Research Quality Management team, apply to all research studies conducted at institutions under the oversight of NHG Domain Specific Review Board (DSRB).

INSPECTIONS

Inspections are also carried out on an ad-hoc basis, but it is usually performed by the regulatory authority (i.e. Health Sciences Authority (HSA) in Singapore). They my be conducted on clinical trials involving medicinal products, where a clinical trial certificate has been issued. GCP Site inspections may be either protocol-specific or systems-oriented. Systems that may be inspected include Investigator site files, informed consent, investigational products, pharmacovigilance, biological samples, monitoring, data management, biostatistics and final reports.

Preparing for Audits and Inspections

As a principal investigator, you are responsible for ensuring that there is adequate preparation for the audit/inspection, cooperation with the auditor/inspector and appropriate follow-up actions.

You may wish to refer to NHG PCR SOP 501-B10 (Handling Audits) for more guidance on how to prepare for an audit/study review by NHG. Prior to that, you may also find the Investigator File Content Template and the Essential Document checklist, provided by NHG-RDO, useful to ensure all essential documents are in the investigator file.

For more details about the inspections by the HSA, you may refer to Guideline on GCP Compliance Inspection Framework, available on their website.

Helpful tools and resources

1. Proper Conduct of Research Standard Operating Procedures and Templates *www.research.nhg.com.sg/wps/wcm/connect/romp/nhgromp/resources/research+sops*
2. Guideline on GCP Compliance Inspection Framework *www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/guidelines/gcp_compliance_inspection.html*

Templates available from NHG-RDO (under the PCR SOP link mentioned above)

1. Investigator File Contents Template
2. Essential Documents Checklist
3. Monitoring Plan Template

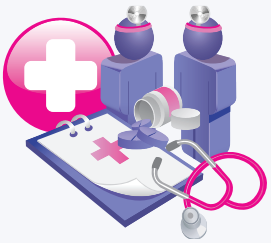
References:

Singapore Guideline for Good Clinical Practice (SGGCP)
NHG Proper Conduct of Research Standard Operating Procedures
Health Sciences Authority, Guideline on GCP Compliance Inspection Framework

PROTOCOL NON-COMPLIANCE

DSRB AND SUBJECTS

NOT UPDATED OF STUDY CHANGES



Background

In a recent study, the Principal Investigator (PI) was replaced by the Co-Investigator as the initial PI had left the institution. As the Co-Investigator had been an active member from the start of the study, subject enrolment and other study activities continued without informing the Domain Specific Review Board (DSRB) and research subjects.

In another study, study procedures were not performed due to lack of resources and the PI was in the midst of securing the necessary grant/resources to continue the study. These changes however were not communicated to the DSRB and subjects.

Findings & Implications

The PI had implemented changes to the study without ensuring that prior review and documented approval/ favourable opinion from the DSRB had been obtained. The PI also did not update the information in the Participant Information Sheet/Consent Form provided to the ongoing research subjects enrolled in the study.

By not providing the updated information to the DSRB and research subjects, the PI had compromised on the ethical review and the informed consent process of the study. The changes to the study may affect the subject's willingness to participate or continue participation in the study.

Tips and Recommendations

- It is advisable to always notify the DSRB and Health Sciences Authority (HSA) (if applicable) of changes made to the study. In general, major changes can be done via a protocol amendment, and minor/administrative changes may be made via a notification.
- To avoid making too many changes to the study, the PI may try as much as possible to finalise study details before submitting it for approval. The PI should also be prepared to implement changes only after receiving favorable approval and opinion from DSRB and HSA (when applicable).
- The PI should update the study protocol and Participant Information Sheet/Consent Form and/or create an addendum for research subjects who had given consent previously to document new information that may be relevant to the research subject's consent. Any new information communicated to the research subjects should be documented.

References:

Singapore Guideline for Good Clinical Practice (SGGCP) 4.4.1, 4.5.2, 4.8.2