being administered to human subjects for approved indications, are included and will require regulatory approval prior to their conduct.

The second key detail of interest would be the fact that the regulations require the PI of clinical trial to be a doctor or dentist. It is dictated in the Medicines Act that such a person should be registered under the Medical Registration Act or Dental Registration Act respectively (as applicable). While DSRB allows adequately-qualified nursing and allied health staff to be PIs for greater-than-minimal risk studies, caution should be exercised when such studies also fulfill clinical trial regulatory requirements. In such circumstances, it is imperative that an appropriately qualified medical doctor (or dentist) be appointed as the PI of the trial.

Consequently, for greater-than-minimal risk studies that are not clinical trials, DSRB may at their discretion approve the conduct of the study under the purview of a non-clinician PI. Where the PI is unable to determine if his/her study requires regulatory approval, he/she should write in directly to HSA to seek advice and clarification.

***References***


- Medicines Act and Medicines (Clinical Trials) Regulations
- Health Sciences Authority Website, Frequently Asked Questions on Clinical Trials (http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/clinical_trials/faqs.html#(A))
- NHG DSRB Investigator Manual (Chapter 1, Section 1.4)


# NON-COMPLIANCE REPORT: PLACING SUBJECTS' INTERESTS BEFORE RESEARCH PURSUITS

**Background**

The National Healthcare Group (NHG) Research Quality Management (RQM) team conducts regular and random study reviews on ongoing clinical research studies carried out in NHG and its partner institutions under the oversight of the NHG Domain Specific Review Board (DSRB).

The purpose of these study reviews is to increase awareness among investigators and their study staff on proper research practices and documentation techniques.

A recent study review performed by RQM unearthed a series of critical research-related non-conformities arising from a single study. While most of these breaches were unintentional, many valuable lessons could be gleaned from the study review findings.

Firstly, the Principal Investigator (PI) had failed to secure the investigational medical device supplies prior to study initiation, but had proceeded with subject enrolment for the purpose of reporting some progress in the study to the grant authorities.

The downstream consequence of this was that one of the main protocol-mandated procedures could not be performed and had to be deliberately omitted, resulting in a major protocol deviation. The data collected from the subjects had thus been incomplete, rendering it ineligible for per-protocol analysis.

Secondly, the Informed Consent Form (ICF) had been amended, in the absence of the Domain Specific Review Board's (DSRB's) approval, in an attempt to remove the procedures involving the use of the unavailable medical device. Consent from subjects had been taken using this unapproved ICF. Some subjects were approached for consent just prior to the study procedures being carried out.

On other occasions, informed consent had not been taken from subjects at all, prior to their enrolment in the study and before research-related activities was performed on them. Where consent was taken, the ICF dates written by some subjects had been intentionally amended by the study staff to reflect an erroneous date of consent.

The shortcomings in the informed consent process had been further compounded by the fact that consent for all enrolled subjects was taken by an inadequately trained study administrator.

The study administrator had not undergone any basic training for the role, such as attending the Collaborative Institutional Training Initiative (CITI) or Singapore Guideline for Good Clinical Practice (SGGCP) courses.

**Findings & Implications**

- The PI had wilfully deviated from the approved study design by recruiting subjects before ensuring that sufficient resources were available to initiate study procedures.

  `This had not only compromised the scientific validity of the study, but had also unnecessarily subjected patients to the risks of the research study, and from which the data collected could not be used for meaningful analysis.

- The questionable manner in which the informed consent process had been carried out surfaced doubts as to whether subjects had been adequately informed before agreeing to participate in the study.

- The study administrator's lack of SGGCP training exemplified the PI's comparable unfamiliarity with these guidelines. Furthermore, placing the scientific pursuits of the study and personal accountabilities above the interests of the subjects portended research misconduct on the part of the PI.

**Actions Taken by DSRB**

These ethical and procedural infringements were subsequently escalated to the DSRB, which resulted in a warning letter being meted out to the PI to suspend the study with immediate effect. The urgent need for the PI to attend the SGGCP course was resolutely enforced, being imposed as a mandatory requirement for which the PI had to fulfill before approval to the conduct of the study could be reinstated.

These findings were also escalated to the Research Ethics Committee in tandem, who responded by issuing an equally stern warning to the PI.

**Useful Tips and Recommendations**

- It is the PI's responsibility to commit sufficient time in acquiring manpower and procuring adequate resources for the foreseen duration of the study, prior to initiating any study activities.

- The PI is responsible for ensuring that the study staff members are appropriately qualified and trained on their delegated tasks before study initiation.

- Should any amendments to the study documents and/or procedures be necessary, the PI should ensure that written approval is received from the DSRB (and the regulatory authority, if applicable) before implementing these changes.

- Regular and open communication within the study team is encouraged.

- Protocol deviations and any other pertinent information should be promptly and accurately reported to the DSRB (and the regulatory authority, if applicable) for review.

## GCP FREQUENTLY ASKED QUESTIONS

# WHAT ARE THE PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES WITH REGARD TO THE MANAGEMENT OF A STUDY TEAM?

The Singapore Guideline for Good Clinical Practice (SGGCP) places much responsibility on the Principal Investigator (PI) to secure sufficient manpower and resources, to ensure that a study can be properly carried out. A crucial element to this end would be having appropriately trained and qualified study staff to assist with the delegated responsibilities.

Section 4.1.1 of the SGGCP states that investigators must be "qualified by education, training and experience to assume responsibility for the proper conduct of the trial". Section 4.2.3 further elaborates that "the investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely".

### The PI's Role

Listed below are some pointers that PIs should take into consideration prior to the commencement of a clinical research study:

- As a prerequisite, the PI must bear qualifications that satisfy the ethics committee's requirements (and the regulatory authority's requirements, where applicable) to lead the study. These may include having appropriate medical credentials, as well as completing the Collaborative Institutional Training Initiative (CITI) and Singapore Guideline for Good Clinical Practice (SGGCP) courses;

- When conducting clinical trials, the PI should be thoroughly familiar with the study protocol, and the appropriate use of the investigational product as described in the Investigator's Brochure, product information or any other information sources provided by the sponsor;

- The PI should maintain a list of appropriately qualified persons to whom he/she has delegated significant research-related responsibilities. Additionally, the PI will be required to train the study team on their respective roles in the study, based on the protocol requirements; and

- The PI should ensure that all persons assisting with the research are adequately informed about the protocol, investigational product(s) and their research-related duties.

### Change of PI

If it is anticipated that the PI will be going away for an extended period of time or resigning from his/her institution, the research project should be formally transferred to another PI to oversee. The incoming PI will then assume the same responsibilities as the outgoing PI as detailed above.

In the process of ensuring a smooth transition of duties, it should be noted that any change of PI must first be reviewed and approved by the ethics committee (and the regulatory authority, where applicable) prior to implementation. Once approval is received, the new PI's start date and delegated responsibilities should be updated accordingly on the delegation log.

### The Study Team

Each study staff plays a similarly crucial role in ensuring that the conduct of the study goes smoothly. Aside from accruing study team members with the necessary qualifications to discharge their study responsibilities, the PI needs to ensure the following:

- For any new additions to the study team after study initiation, the PI is responsible for providing protocol-related training for the new staff member(s). Such training should also be documented;

- The delegation log will need to be updated with the roles, responsibilities and signatures of the new study staff, endorsed by the PI ;

- For current staff exiting the study, the PI should ensure that there is a proper handover of responsibilities from the outgoing staff to another member of the study team; and

- The delegation log should be similarly updated with the end date of the outgoing study staff member.

Paying heed to these details will go a long way in ensuring that PIs are better equipped to manage changes in their study team, which will in turn translate into more efficiently-run research studies.

***References***


- *Singapore Guideline for Good Clinical Practice (SGGCP)*
- *NHG DSRB SOP 201-E01 Responsibilities of Investigators*
- *Good Clinical Practice: A Question & Answer Reference Guide. May 2011. Chapters 2.13 and 2.14*