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The program with a mission to ensure and enforce the responsible conduct of research meeting high ethical standards.

Standardising Research

Changes to the Proper Conduct of Research (PCR) Standard Operating Procedures (SOPs) which are effective from 31st July 2013.

The Research Quality Management (RQM) unit in the Office of Human Research Protection Programme (OHRPP) reviews its Proper Conduct of Research (PCR) standard operating procedures (SOPs) on a regular basis to keep abreast of developments within the industry, while maintaining their operational relevance to research staff on the ground.

Changes to PCR SOPs

The latest round of PCR SOP review has seen notable changes made to the informed consent process, data collection and handling, as well as the need for delegation of research-related responsibilities when the principal investigators (PI) are away for an extended period of time. These changes are effective from 31st July 2013.

Here is a summary of the PCR SOP changes:

PCR SOP 501-A02 – Responsibilities of the Research Team

The changes in this SOP will apply to PIs going away for a prolonged period of time and who will be unable to discharge his / her research-related responsibilities during the period of absence.

In such circumstances the PI will be required to either:

- Delegate his / her responsibilities as a PI to a suitably-qualified deputy (e.g. the co-investigator) and document this arrangement on the study delegation log; or
- Formally transfer the research study to another suitably-qualified PI. The Domain Specific Review Board (DSRB) should be informed of this change of PI, and the incoming PI should assume oversight of the study only upon obtaining DSRB approval.

The following guidelines for the period of absence will apply:

- More than minimal risk studies – The study should be formally transferred to another PI if the original PI will be away for more than three months.
- Minimal risk studies – Where there are subject recruitment and ongoing follow-up activities, the study should be formally transferred to another PI if the original PI will be away for more than six months.

PCR SOP 501-C01 – Informed Consent Form and Process

1. Study staff authorised to take informed consent

The informed consent discussion with subjects should be conducted by appropriately trained and qualified study staff, who have been listed in the DSRB application form as the designated person(s) to take consent. It is the responsibility of the PI to ensure that the study delegation log is updated to indicate study team members who are authorised to take consent.

2. Informed consent process for mentally competent subjects who are unable to sign and date the informed consent form

A formal process for obtaining consent from mentally competent subjects who are unable to sign and date the informed consent form has been established in the revised SOP. Examples of subjects for whom this informed consent process may be applicable to are illiterate subjects or persons with physical disabilities that prevent them from being able to write.

It should be ascertained that these subjects demonstrate mental competence and are able to understand the informed consent discussion. Subjects should also be able to indicate clearly whether they wish to participate in the study or not. An impartial witness is required to attend the informed consent discussion involving such subjects.

To document consent, the subject will be required to affix his / her thumbprint on the informed consent form. The impartial witness is allowed to fill in the subject's name and date of consent on the form, on the subject's behalf.

Importantly, the informed consent process should be clearly described and documented in the subject's medical records.

3. Consent requirements in emergency situations

The SOP has been revised to provide greater clarity on the consent requirements for clinical research studies and clinical trials conducted in emergency situations respectively. These are studies in which taking informed consent from subjects or their legal representatives prior to study enrolment is not possible.

For *clinical research studies* conducted in emergency situations, the PI and 2 independent specialists (who are not participating in the study) are required to make a written certification *prior to enrolling each subject*. This written certification should be retained on file for verification.

Additional procedures apply for clinical trials conducted in emergency situations. *Prior to initiating the study*, the PI and 2 independent specialists must provide a written certification attesting to specified criteria. Subsequently *at the point of enrolling each subject,* the PI and 2 independent specialists must provide another written certification attesting to another set of specified criteria relating to the subject being enrolled. It should be noted that both sets of written certifications must be promptly submitted to the Health Sciences Authority (HSA) at the time each the certification is made. In addition, copies of the written certifications should be retained on file for verification.

After enrolling the subject into the clinical research study or clinical trial, the following consent procedures must be followed through:

- At the earliest possible opportunity, consent from the subject or his / her legal representatives should be sought for continued participation.
- If the PI is made aware of any objection by the subject, his / her legal representative and / or any family member(s) for continued participation in the study, the subject should be immediately discontinued.

PCR SOP 501-B05 – Documentation

The minimum retention period for documents from completed clinical research studies (excluding clinical trials) has been extended from 3 years to 6 years. For clinical trials, there is no change to the current minimum retention period of 6 years after completion of the clinical trial, or alternative duration as otherwise specified in the Medicines (Clinical Trials) Regulations.

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Availability of New Study Templates

In keeping with the PCR SOP changes, several study document templates have been developed to aid investigator-initiated studies with creating essential documents. Concurrently, a significant number of existing study document templates has also been revised.

The new study document templates are listed below.

New Template Available	Purpose of Template
Corrective Action & Preventive Action Plan (CAPA) Template	The CAPA template may be used to detail the corrective actions and preventive actions taken to address study findings detailed in study review reports. The study team should work together to complete the CAPA, which should be submitted to the study reviewer by the stipulated deadline.
Note to File Template	This template may be used to document explanations or supplement inadequate information in the study documentation. The completed note to file should be retained in the study file.
Template for Documentation of Adverse Event in Medical Records	This template format may be directly entered into the subject medical records by the investigator performing the documentation. The template serves as a guide on the necessary fields and details that should be documented pertaining to the adverse event(s) experienced by the subject.
Adverse Event / Serious Adverse Event Tracking Log	This template helps investigators track the adverse events (AEs) or serious adverse events (SAEs) that occur during the study, particularly for the purpose of determining whether these event(s) qualify for expedited reporting to the sponsor and / or regulatory authorities.
Investigational Product Dispensing & Accountability Log (Multiple Subjects)	This template is used to document the receipt, supply and return of the investigational product(s) used in a clinical trial. Two different formats of the same template are available to cater to different study requirements.
Investigational Product Dispensing & Accountability Log (Per Subject)	
Subject Identification Log	This template is used to document the personal particulars of all subjects participating in the study.
Temperature Log	This template is used to document the temperature monitoring records of the premises in which the investigational product is stored.
Study Initiation Meeting Attendance Log	This log serves as a record of the study staff who attended the study initiation meeting. This log also constitutes documentation of study-related training records.

Principal investigators and all research staff are advised to read the above-mentioned PCR SOPs in their entirety to obtain a better understanding of the SOP changes. The new and revised study document templates are also available for downloading from the NHG research website. Researchers may adapt and customise the various templates to suit the individual study requirements.

To access the full listing of PCR SOPs and study document templates, please refer to the following link: http://www.research.nhg.com.sg/wps/wcm/connect/romp/nhgromp/resources/research+sops

References

4. NHG Proper Conduct of Research Standard Operating Procedures (PCR SOP) 501-A02 – Responsibilities of the Research Team
5. NHG Proper Conduct of Research Standard Operating Procedures (PCR SOP) 501-C01 – Informed Consent Form and Process
6. NHG Proper Conduct of Research Standard Operating Procedures (PCR SOP) 501-B05 – Documentation

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GCP Frequently Asked Questions – How to Write a CAPA

In our last issue, we introduced readers to the scope and directives of the Research Quality Management unit under the Office of Human Research Protection Program (OHRPP). The attentive reader may recall one of the core functions of RQM introduced – that is, the conduct of study reviews on research studies that are currently ongoing in NHG and partner institutions. Principal investigators whose research studies have undergone study reviews would be issued a study review report by RQM. To address the findings in the study review report, the principal investigator would be tasked to submit a corrective action and preventive action plan (CAPA) by the stipulated deadline.

What is a CAPA?

Based on the ISO 9000 definition, corrective actions are steps taken to eliminate the causes of existing non-conformities in order to prevent recurrence of the deviation. Consequently, preventive actions are steps taken to prevent the occurrence of non-conformities or undesirable situations that do not yet exist. Occurrence is prevented by eliminating the potential causes of such situations. Originally a Good Manufacturing Practice (GMP) concept, the use of CAPAs has been adopted in the clinical research industry as a compliance and quality improvement strategy.

Creating a CAPA

As the CAPA can be an effective way to address non-compliances within a research study, it is typically requested for by the relevant authorities following an audit and / or inspection visit. In creating a CAPA, the following important steps should be considered:

1. **Determine the problem**
   Review the finding raised by the auditor / inspector, as well as the evidence cited to substantiate the finding, to pinpoint the nature of the non-compliance.

2. **Determine the corrective actions to be taken**
   Identify the action(s) that can be taken to rectify the problem, as well as the person(s) responsible for implementing the corrective actions proposed. In instances where the non-compliance has already occurred and cannot be corrected or reversed, the only action that can be taken is to document the problem by means of a file note or protocol deviation report.

3. **Conduct a root cause analysis**
   Determine the root cause of the finding, particularly to establish if it is a systematic or isolated problem. A systematic problem could mean that other studies may also be affected. Examples of systematic problems include lack of training, or inadequate standard operating procedures (SOPs).

4. **Determine the preventive measures that may be taken**
   Propose solutions to address the root cause of the problems, taking into account existing regulations, guidelines and resources that may be allocated for the study. Again, an accountable person should be appointed to oversee the implementation process.

5. **Set realistic deadlines**
   Consider the manpower and resources that can be assigned to implement the corrective and preventive measures proposed above. A reasonable time frame for achieving these measures should be proposed and documented on the CAPA.