CHAPTER 7

STUDY CONDUCT

7.1 Data and Safety Monitoring

One of the review criteria for DSRB approval at initial review is that there is an adequate data and safety monitoring plan. All research proposals should include adequate provisions for monitoring of data collected for scientific validity and safety of research subjects. 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.

Determination of Research Study Risk

Determination of risk should include a consideration of both the interventions being performed and the research study population. Risk assessments must also take into account special circumstances that are unique to the research study such as disclosures of HIV status or results of genetic studies.

MINIMAL RISK – A research study is said to be minimal risk when the probability and magnitude of harm and/or discomfort are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Minimal risk studies generally include research involving surveys, questionnaires, blood samples; MRI scans without contrast agents, exercise testing in low-risk populations, ECGs, and other such non-interventional studies.

MODERATE RISK – A moderate risk research study exceeds minimal risk but would be less risky to the subjects than high risk research studies. Moderate risk studies may include clinical trials and observational studies using procedures with well-established risk profiles, behavioural trials, studies involving endoscopy, glucose-tolerance tests, skin or muscle biopsy, imaging requiring sedation etc. For example, a Phase IV trial or research studying efficacy of drugs for their indicated use.

HIGH RISK – High risk research studies include clinical trials on new drugs, approved drugs for off-label use, new medical devices, new surgical procedures, etc.

In general, research involving not more than minimal risk does not require a data and safety monitoring plan.

7.1.1 Safety Monitoring

I. Who Should Perform Safety Monitoring

The data and safety monitoring plan should state who would assume monitoring responsibility. This will depend on the type and risk of the research study and may include the investigator, experts within the department or institution, independent consultants or a combination of the above. Some examples below:

- Principal Investigator (PI) – For a research study involving minimal risk to the subjects, it may be appropriate for the PI to manage the data and safety monitoring. Continuous close

monitoring by the PI may be an adequate and appropriate format for monitoring with prompt reporting of unanticipated problems involving subjects and others including serious adverse events to DSRB. For a minimal risk research study involving multiple sites, this function could be managed by the team PIs for each site or the lead / overall PI for the entire research study.

- INDEPENDENT EXPERT(s) or INDEPENDENT SAFETY MONITOR(s) (ISM) – For a moderate risk research study or investigator-initiated clinical trial involving single or multiple sites, or a study with endpoints that are not serious irreversible events, or the study's intervention effects are evaluated over periods of a few days to a few months or the study involves a smaller number of subjects whereby it can be completed quickly and the risk can be adequately assessed through simple comparisons. It is recommended that the data and safety monitoring be performed by an expert or group of experts in the disease and familiar with the agent being studied. Using an independent expert or team of experts is particularly helpful in monitoring of unblinded data for a double-blind research study, as this will help ensure a meaningful review by independent experts while maintaining study blinding amongst the research staff.

- DATA SAFETY MONITORING BOARD (DSMB) – DSMB is a committee that is established specifically to monitor participant safety and data throughout the life of a research study to determine if it is appropriate, from both scientific and ethical standpoints to continue the research study as planned. For high-risk studies and for sponsors or investigators- initiated large, blinded studies, involving multiple sites, it is recommended that a formal DSMB is appointed.

  When appropriate, the scope of the DSMB's review could also include continuously reviewing and evaluating the efficacy of the study intervention, scientific validity and merit of the study, and data quality and integrity. Items reviewed by a DSMB can include:

  i. Interim or cumulative data for evidence of study-related adverse events;

  ii. Interim or cumulative data for evidence of efficacy according to pre-established statistical guidelines;

  iii. Data quality, completeness and timeliness;

  iv. Adherence to the protocol;

  v. Adequacy of compliance with goals for recruitment and retention, including those related to the participation of minorities;

  vi. Factors that might affect the study outcome or compromise the confidentiality of the trial data such as protocol violations, unmasking, etc. and

  vii. Factors external to the study such as scientific and therapeutic developments that may raise ethical concerns and/or impact subject safety.

For high-risk studies and for sponsors or investigators-initiated large, blinded studies, involving multiple sites, it is recommended that a formal DSMB is appointed.

- COMPOSITION OF A DSMB – This is a multidisciplinary committee that is usually composed of 3 to 6 experts in at least two areas; medical issues (the disease, drug, device, procedure, or outcome measure) and method issues (clinical trials design, data management, and statistical analysis).

  The primary criterion for selecting DSMB members should be based on the respective member's expertise and experience. DSRB members could include:

  i. Expert(s) in research and biomedical ethics for trials with unusually high risks or with broad public health implications.

  ii. Epidemiologist(s), clinical pharmacologist(s), toxicologist(s) when such expertise appears important for informed interpretation of interim results.

  iii. Individuals (often non-scientists) who may help bring to the DSMB the perspectives of the population under study.

  iv. Representatives of the gender and ethnic groups, where appropriate.

  When appointing DSMB members, the member's prior conflict of interest, if any, as well as commitment level should be considered.

- ADDITIONAL CONSIDERATIONS WHEN DSMB IS REQUIRED – The DSMB should consider the following factors when determining if a DSMB is required:

  i. Study nature, design and procedures

  ii. Size / scale of the study

  iii. Study population

  iv. Whether the study is a planned emergency research that is required to comply with 21 CFR 50.24(a)(7)(a)(4)

  v. Practically of having a DSMB review

  vi. Whether a DSMB will help assure scientific validity of the study

  a. Examples of studies which may require DSMB include, but are not limited to the following:

     i. Phase III clinical trials involving interventions that entail potential risk to the participants

ii. Studies involving high-risk procedures and/or high expected rates of morbidity or mortality in the study population

iii. Studies involving randomization and/ or blinding

iv. Studies involving multi-sites which may or may not involve a large study population

v. Studies involving new therapies (including devices) or science

vi. Studies involving a high chance of early termination

vii. Studies involving a vulnerable population (e.g., pediatric population, geriatric population, cognitively impaired persons)

b. Examples of studies which may not require DSMB include, but are not limited to the following:

i. Clinical studies with non-critical indications where patients are treated for a relatively short time (practical constraints) patients and the drugs under investigation are well-characterized and known for not harming patients.

ii. Early studies which are often exploratory in nature; and they are frequently not randomized or controlled, therefore accumulating results are known to the investigators and sponsors. Hence, issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting.

II. Safety Monitoring Plan

Monitoring should be planned to occur at specific points in time, such as quarterly, every six months or annually or after a specific number of subjects have been enrolled, or upon recognition of harm. The monitoring plan should state how often monitoring will be performed, who will perform monitoring and what data will be reviewed for safety monitoring.

The safety monitoring plan should include:

a. Details of the assessments (laboratory tests, physical examinations, etc.) used to monitor for adverse events and the schedule of these evaluations.

b. Description of anticipated events including character and expected incidence.

c. Plan for grading the seriousness of events.

d. Plan for assessing the causal relationship of events to the study and/or agent(s) being investigated.

e. Persons responsible for assessing events.

f. Persons responsible for managing events – the plan should identify the PI, co-investigators and / or other key personnel who are medically trained to manage the disease under study, as well as the procedures that impart more than minimal risk to subjects. The plan should provide assurance that the PI will be on site to monitor the study subjects' safety on a daily basis.

g. Persons responsible for reporting events according to DSRB guidelines.

III. Stopping Criteria

An effective safety monitoring plan should be able to detect signals to decide when the research study should be stopped. Usually stopping criteria are based on one or more reasons such as:

- Efficacy – This occurs when there is high certainty that the research question has been answered. For example, when it is clear that one group is doing better than the others, or no group is likely to do better than any other.

- Futility – This occurs when it is evident that the research question will not be answered when the study is completed. For example, when too many subjects have withdrawn from the study, such that it is difficult to obtain conclusive data even though the study is continued.

- Safety – The risks of continued participation to subjects is too high.

IV. DSMB Reports

When a clinical trial is subject to oversight by a DSMB whose responsibilities include review of adverse events, interim findings and relevant literature, the DSRB conducting the renewal process may request for and rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the DSRB.

However, the DSRB must still receive and review reports of local, on-site UPIRTSOs and any other information needed to ensure that its continuing review is substantive and meaningful. Evaluation reports other than that of a DSMB may also be accepted provided the evaluation meets the criteria listed above.

7.1.2 Data Monitoring

I. Data Accuracy and Compliance

The PI should describe the measures that will be taken to ensure accuracy of data and compliance to protocol. The extent and nature of monitoring should be based on considerations such as objective, purpose, design, complexity, blinding, size, and endpoints of the research. In general, there should be monitoring before, during and after the research.

a. **Industry Sponsored Clinical Trials or Research Studies** – The PI is responsible for confirming with the Sponsor on the monitoring plan.

b. **Investigator Initiated Clinical Trials Regulated by Health Science Authority (HSA)** – The 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 at this site, appropriately trained and should have adequate scientific/clinical knowledge. The monitor's qualifications should also be documented.

   The PI may seek the assistance from their institution's Clinical Research Unit (CRU) / research office on finding a suitable monitor for their study. Some of the mechanisms by which monitoring can be achieved are:

   i. Cross monitoring by research coordinators working with different trials.

   ii. Research coordinators for same trial in different institutions cross monitor.

   iii. CRU may assign a senior coordinator as 'monitor' for PI-initiated studies conducted in the institution.

   iv. Research coordinators who usually coordinate industry sponsored studies may be assigned PI initiated studies to monitor.

   v. Engage an external vendor for monitoring services.

c. **Studies Regulated by Human Biomedical Research Act (HBRA)** - For studies that fall under the scope of the HBRA, it is the responsibility of the Research Institution (RI) to supervise, review and proactively monitor these studies. The PI should contact their respective CRU to find out more about the proactive monitoring programme within their institution.

II. Monitoring Plan

The monitoring plan should consist of a description of the monitoring strategy, the monitoring responsibilities of all parties involved, the monitoring methods and monitoring of the critical data and processes. The plan should be tailored to human subject protection and data integrity risks of the study. The monitoring plan should also reference the applicable policies and procedures.

Sponsor or PI should determine how the outcome of data and safety monitoring are communicated to other participating study sites, as well as to the DSRB (where applicable).

The Monitoring Plan Template is available for download from the NHG Health Research Website**.**

7.2 Privacy and Confidentiality

Personal information is any identifiable information about an individual. It not only includes personal particulars, but also details of medical conditions, as well as information disclosed or derived in the process of healthcare management. In the research context, it will include any information collected, used or generated as part of the research process.

Protecting the privacy of research participants and the confidentiality of their personal information obtained or derived from research is based on the principle of respect for persons. Thus, personal information should be stored and managed in ways that provide proper security and confidentiality.

Researchers should also ensure all necessary approvals (as per institution requirements) are obtained before accessing and using personal information for research. The patient must also give prior written consent for such access, unless the IRB has granted a waiver of consent.

7.2.1 Determining if Data is Identifiable

When determining if data is considered identifiable, researchers should consider if the data itself or from that data and other information to which the researcher or organisation has or is likely to have access to can lead to the identification of an individual.

Individually-identifiable in relation to human biological material or health information pertaining to an individual, means that the individual can be identified:

i. From the human biological material or health information; or

ii. From that human biological material or health information and other information to which the person, research institution, tissue bank or other organisation has or is likely to have access.

De-identified data refers to data that is lightly processed and coupled with appropriate data safeguard measure to reduce the risk of re-identification of data subjects.

For more information on:

- *HealthTech Instruction Manual (HIM), please refer to the MOH website*
- *PDPC Guide to Basic Data Anonymisation Techniques, please refer to the PDPC website*

7.2.2 Use of Subject Identification Codes

Data collection forms (DCFs) and Case Report Forms (CRFs) should not contain information directly identifiable to a subject (such as name, identity card number, address, etc.) unless it is to be used as a source document.

Each subject should be assigned a unique subject identification code to be used on DCFs, CRFs, serious adverse event reports, UPIRTSOs and any other research-related data. In

addition to the subject identification code, subject initials may also be entered. The link between the subject identification code and the subject identifiers should be stored in a separate document.

In some instances, a combination of data elements collected on DCFs or CRFs may potentially identify a subject. Care should be taken to ensure that the information collected is appropriately coded such that it cannot be traced back to the individual without the linking code unless it is to be used as source records*.

**Source records are original or data (which includes relevant ^metadata) or certified copies of the original documents or data, irrespective of the media used. This may include research subjects' medical health/health records/notes/charts; data provided/ entered by research subjects (e.g., electronic patient-reported outcomes (ePROs)); healthcare professionals' records from pharmacies, laboratories and other facilities involved in the research; and data from automated instruments, such as wearables and sensors.*

^metadata - The contextual information required to understand a given data element. Metadata is structured information that describes, explains or otherwise makes it easier to retrieve, use or manage data. For research, relevant metadata are those needed to allow the appropriate evaluation of the research conduct.

7.2.3 Use of Anonymised Data

Anonymised Data refers to data that is heavily processed to the extent that it is very unlikely a unique individual can be re-identified evidently (spontaneous re-identification), or through attempts to match with other identifiable datasets or publicly available information.

Researchers should seek to use anonymised data for their research or for datasets to be processed for statistical outputs to safeguard patient or participant confidentiality from exposure or loss as far as possible. De-identified data could be used for data analysis purpose with consent from research subjects. The use of anonymised data is outside the scope of the PDPA.

Researchers can obtain anonymised data from their institution's information management team or equivalent (e.g., Trusted Third Party). Data would not be considered anonymised if there are serious possibility that an individual could be re-identified, taking into consideration both:

a. The data itself, or the data combined with other information to which the institution has or is likely to have access; and

b. The measures and safeguards (or lack thereof) implemented by the institution to mitigate the risk of identification.

The reversibility of the specific process used would be a relevant consideration for institutions when managing the risk of identification.

For more information on:

- *HealthTech Instruction Manual (HIM), please refer to the MOH website*

- *PDPC Guide to Basic Data Anonymisation Techniques, please refer to the PDPC website*

7.2.4 Data Protection

Individuals conducting research should take all reasonable steps and safeguards to protect personal information against accidental or unlawful loss, modification or destruction, or unauthorised access, disclosure, copying, use or modification.

Individuals should not attempt to re-identify anonymised information or biological material, or disclose any individually-identifiable information of a research subject except:

a. With the consent of the research subject or the person authorised to give consent on the research subject's behalf

b. When it is necessary to do so in connection with the administration or execution of anything under the HBRA;

c. When ordered to do so by a court;

d. Where the information on the identity is publicly available;

e. For the purposes of providing the identity/information to any person or class of persons to whom, in the opinion of the Ministry of Health (MOH), it is in the public interest that the information is disclosed;

f. Where it is permitted or provided for under the HBRA or any other written law or rule of law; or

g. In such other circumstances and to such persons as may be prescribed.

Individual receiving individually-identifiable information of human biological material of a research subject should not disclose any individually-identifiable information of the research subject, if at the time when the individuals receiving the information or material, they know or had reasonable grounds to believe that it had been communicated or supplied to them in a manner which breaches the HBRA or any other applicable law.

7.2.5 Data Management

The Principal Investigator should ensure the following:

a. The Study Responsibility Log clearly states who in the research team is responsible for data management activities such as transcription of data to CRFs, data entry, and analysis (where applicable).

b. The research data is recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

c. The databases (for data analysis) should not contain subject identifiers. The data linking subject identifiers and the subject identification codes should be stored separately.

d. All personal data files (containing patients' name, NRIC etc.) must be protected with strong passwords as per Healthtech Instruction Manual-Data Management (HIM-DM), e.g., minimally 12 alphabets, includes upper and lower case, mixture of numbers and symbols and cannot include the personal information (e.g., name, NRIC).

Use of Research Data Capturing Tools and Application

a. The Research Electronic Data Capture system (e.g., REDCap) is recommended as a data capture tool.

b. FormSG may also be used as a data capturing tool.

c. Researchers should check their institution policies to ensure that the data capture tool used in all research (including industry sponsored studies) is acceptable and meets institution requirements, e.g., comply with Synapxe or equivalent security recommendation, obtain approval to use alternative platforms.

d. Private and public Cloud & Google Drive should not be used to capture Patients' Personal Data. Only corporate approved Cloud services (i.e., H-Cloud) is allowed. Please refer to the HIM for the latest regulations on the use of public Clouds.

e. The access to shared drive folders containing research data files must be restricted to authorised personnel only.

For more information on HealthTech Instruction Manual (HIM), please refer to the MOH website.

Storage of Research Data

a. Corporate approved secure data storage facilities managed by Synapxe, Storage Area Network (SAN), Sharepoint or equivalent and institution endorsed systems should be used for the storage of research data.

b. Research data stored in hardcopy form (e.g., study documents, data collection form, etc.), should minimally be locked in storage units within institution's premises and only accessible by authorized study team member.

c. Users should consider the following storage options for storage of research data and research documents.
    i. Only authorised corporate devices should be used, and these should be for specific circumstances. For example, to transfer data between computers and when sharing data with collaborators or individuals beyond the institution network.

ii. Corporate issued storage devices should only be accessed and used by authorized persons. Personal hard disks or thumb drives are unauthorised and should not be utilized.

iii. Institutions are strongly recommended to track the issuance and use of corporate issued devices (external hard disk and thumb drives). Issuing institutions are accountable for any loss of these devices.

iv. When the data is stored in an external device (corporate issued hard disk or thumb drive), subjects' identifiers should never be stored in the same device.

d. Users are to abide and follow the on-site and off-site requirements in the HIM-DM and all other relevant regulations and guidelines.

e. Individual issued with corporate devices are accountable for the proper usage and will need to report to the institution for any loss and non-compliances.

For industry sponsored research, data management at the site is usually restricted to transcribing information on case report forms, whether paper based or electronic and answering data clarification queries.

a. The PI should endorse any changes or corrections made in the CRFs by sponsor's designated representatives. The PI should retain records of the changes and corrections.

b. The PI must ensure the accuracy, completeness, legibility and timeliness of data reported to the sponsor in the CRF and data queries are replied to in a timely manner.

NHG Health researchers are strongly encouraged to use REDCap (E.g. NHG Health REDCap) for data capturing. Alternatives could be explored, but they must comply with Synapxe security recommendation.

7.2.5 Transferring or Releasing or Sharing of Research Data

The organisation transferring data must take appropriate steps to ensure its own compliance with the data protection requirements in the PDPA while the personal data to be transferred remains in its possession or under its control. The orgnaisation should also comply with its own requirements on data transfer (e.g., seek approval from institution Data Exchange Office (DXO) prior to any data transferring or sharing).

The transferring organization must also ensure that it has taken appropriate steps to ascertain whether, and ensure that, the overseas recipient is bound by legally enforceable obligations to protect the personal data to a standard comparable to the PDPA. Legally enforceable obligations include those imposed under:

a. Any law;

b. Any contract that imposes an obligation on the overseas recipient to protect the personal data to a standard comparable to the PDPA, and which specifies the countries to which the personal data may be transferred; or

c. In the case of data transfers between related organisations, any binding corporate rules imposing an obligation on the overseas recipient to accord the personal data protection to a standard comparable to the PDPA and specifies the recipient, the countries to which the personal data may be transferred and the rights and obligations under the corporate rules.

d. Any other legally binding instrument.

Alternatively, the transferring organisation can be considered to have taken such appropriate steps if-

a. The individual gives consent.

However, this is provided that:

(i) The individual has been given a reasonable written summary of the extent to which the personal data will enjoy protection comparable to that under the PDPA;
(ii) The transfer of personal data is reasonably necessary to provide a product or service to the individual; and
(iii) The transferring organisation did not give the individual false or misleading information about the transfer;

b. The transfer is necessary to perform a contract between the individual and the transferring organisation; or

c. The transfer is necessary to conclude or perform a contract between the transferring organisation and a third party if -

(i) The contract is entered into at the individual's request or
(ii) If a reasonable person would consider the contract to be in the individual's interest.

Research Agreements should be in place to capture the sharing of research data. Each institution may determine the form of documentation to record the sharing of research data. Institutions could take guidance from PDPC's Guide on Data Protection Clauses for Agreements relating to the Processing of Personal Data.

Where the research data arise from joint collaboration and are not owned solely by one institution, the sharing of such research data should be with the express consent and agreement from the other data co-owner(s).

The sharing of research data should take into consideration the funding terms and conditions and any other rights or restrictions on the ownership, use and disclosure of such research data, where applicable.

Researchers who intend to share research data with journals or public data repositories must ensure:

a) They obtain the approval from the institution prior to each submission;
b) Data shared is anonymized and only data that is used to derive the conclusions in the publication is shared; and

c) Comply with the relevant institution policy and guidelines.

7.2.6 Management of Research Data Upon Study Completion

Study teams must retain research data for a minimum retention period. At present, the minimum retention period of research data is 6 years. Study teams may retain research data for a longer period, where it is specifically indicated. For example, within the institution policy, Research Collaboration Agreement (RCA) or Clinical Trial arrangements.

If there is a potential use of the data for future research, the study team should register it as a standing database in accordance with institutional requirements.

If the research data is no longer required at the end of the stipulated minimal archival period, the research data should be destroyed according to institutional disposal policies. A documentation of destruction should be maintained.

7.2.7 Research Data Breach Management

A data breach generally refers to the accidental and/or intentional unauthorized access and retrieval of information that may include corporate and personal data.

In the event of a research data breach, researchers should report the breach in the accordance to their institution policy (e.g., NHG Health Research Data Policy).

7.2.8 References and Further Reading

For NHG Health institutions: NHG Health researchers should adhere to the **NHG Health Research Data Policy** and other applicable institutional requirements to ensure that research data is appropriately managed.

For Non-NHG institutions: Please refer to your institution specific requirements and policies governing data.

7.3 Compensation for Research-Related Injuries

7.3.1 General Principles

a. The CIOMS International Ethical Guidelines for Biomedical Research Involving Human subjects states that investigators are responsible for ensuring that research subjects who suffer injury as a result of their participation should be entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap.

b. The DSRB's stand is that lack of compensation for medical care to individuals who are injured as a result of their involvement in a research study is indefensible because it is against the ethical principle of justice. Thus, in good faith, compensation (i.e. medical treatment of research-related injuries) should be provided for all research subjects who suffer a research-related injury. The investigator's institution may purchase clinical trial insurance and medical malpractice insurance to provide for such compensation.

7.3.2 Guidelines for Subject Compensation for Research-Related Injuries

In general, institutions (and/or sponsors) should pay for medical treatment of any injuries arising from participation in the research as long as the injury is related to participation in the research and the injury is not a consequence of an existing condition or standard clinical care and standard diagnostic procedures.

Several exclusions may be acceptable, depending on the nature of injury, study, subjects, etc. For example:

a. Compensation may be paid for only serious injury of an enduring and disabling character and not for exacerbation of an existing condition or temporary pain or discomfort, or less serious or curable complaints.

b. Compensation need not be paid for the failure of a medicinal product to have its intended effect or to provide any other benefit to the patient; or to patients receiving placebo in consideration of its failure to provide a therapeutic benefit.

c. Compensation need not be paid when injuries arise due to non-compliance with the trial protocol on the part of the subject.

The institution must remain responsible to compensate for injuries resulting from negligence / non-compliance by the research team.

For the avoidance of doubt, these recommendations are not intended to discourage or prevent investigators (and/or sponsors) from providing further or additional compensation to subjects if they feel that it is appropriate to do so.

For sponsor-initiated studies:

a. Sponsor-initiated studies often follow the ABPI guidelines for compensation of research-related injuries.

    i. ABPI's Guideline for Medical Experiments in Non-Patient Human Volunteers (for Phase I studies).

    ii. ABPI's Clinical Trial Compensation Guidelines (for Phase II and III studies).

b. The DSRB may accept alternative guidelines of compensation to research subjects, if the terms provide equal to or more protection than that provided by the ABPI guidelines.

    Research subjects should be adequately informed of compensation guidelines applicable to them and the limitations (if any). In addition, the PI is encouraged to actively provide a copy of the ABPI guidelines to the research subjects.

c. Depending on the nature of the study, risks and population involved, the DSRB may require additional provisions of compensation.

7.3.3 Informed Consent Process and ICF Language

Research subjects should be adequately informed of compensation guidelines applicable to them and the limitations of these (if any). This can be done via the inclusion of a compensation statement in the ICF.

The recommended wording for the compensation statement is provided in the NHG Health DSRB Informed Consent Form Template.

7.4 Audits and Inspections

7.4.1 Preparing for Audits and Inspections

Upon receiving notice that an audit or inspection is to be scheduled, the PI should inform the Director or designee of Research where appropriate, the purpose, time and date of the audit or inspection. If the research team receives a notice for an inspection, the PI should inform the sponsor and all individuals and groups involved in the conduct of the study, if any, as soon as possible.

The PI or designee should ensure that all documentation, including ICFs, source documents, DCFs or CRFs, and the investigator files for the study are accurate, complete and available for review by the auditor(s) or inspector(s).

The clinical research coordinator or study pharmacist should ensure that the investigational product accountability records are accurate, complete and available for review. If there had been any instances where an emergency breaking of the blind was required, the documentation would have to be made available.

The PI or designee should ensure that documentation on collection, shipment, receipt and storage of biological specimens is accurate, complete and available for review.

The PI or designee should ensure that all records of staff qualifications, research-related training and protocol-related SOPs are available for review by the auditor(s) or inspector(s).

The PI should ensure that key study team members are available for a meeting with the auditor(s) or inspector(s) on the day of the audit or inspection.

Where requested by the auditor or inspector, the PI should provide relevant documents for pre-audit review in a secure manner (e.g., password protected via corporate email).

The Investigator File Contents Template and Pre-Audit Checklist is available for download from the NHG Health Research Website to help you prepare for an audit or inspection.

7.4.2 During The Audit or Inspection

The PI should meet with the auditor(s) or inspector(s), provide orientation and access to the study records and files, as well as provide copies of requested study-related documents.

The PI should ensure that questions posed by the auditor or inspector are answered by the appropriate study personnel.

Possible questions that may be asked during the audit or inspection:

a. What is your research topic?

b. What are the inclusion and exclusion criteria?

c. Describe the screening method used to determine subjects' eligibility and who implements the screening process.

d. How are prospective subjects identified for the project, i.e., what are your recruitment strategies?

e. Describe the mechanisms you have in place to ensure that each subject meets the stated inclusion / exclusion criteria and that all study procedures are implemented as written. Do you document the eligibility assessment in the source documents (e.g., medical records)?

f. Once a prospective subject is identified, describe the procedures by which informed consent is obtained from a subject. Who is the person responsible for taking informed consent?

g. Who addresses questions presented by the subject or subject's family?

h. What is the time interval between the presentation of the research study information and the actual signing of the ICF?

i. Who are the study team members and what are their responsibilities in the study? Are the study team members trained and are trainings documented?

j. What are the study procedures and how are they performed? Are the study visits and procedures documented?

k. What is the procedure for the management of investigational product (IP)? Is there an IP management workflow or SOP and documentation of IP accountability?

l. What is the procedure for randomisation and unblinding?

m. How are the biological specimens managed? Is there a biological specimen management workflow or SOP and a biological specimen log to track collection or storage or transfer or use or disposal etc.?

n. Is refrigeration required for biological samples? If yes, is a temperature log and equipment maintenance or calibration log maintained?

o. How long will the samples be stored?

p. Do you maintain an investigator file for this study?

q. Do you have case report forms or data collection tools developed for this study?

r. How do you handle (e.g., store, monitor) the data collected?

s. Where are your research records stored?

t. What mechanisms do you have in place to protect the confidentiality of your subjects?

u. How frequently is the study data reviewed, i.e., per subject, per month etc.?

v. How would you handle an unexpected event such as the loss of research records or study data?

w. How do you deal with unanticipated problems involving risks to subject and others?

x. What additional mechanisms do you have in place to protect subjects in your research?

y. What do you do if you receive a complaint from a subject? If you are unable to resolve the issue – what do you do?

z. Describe your oversight of the study and the communications that occur regarding this study, i.e., do you have weekly meetings? Are the meetings documented?

At the end of the audit or inspection, the PI and key study team members should participate in the closing meeting with the auditor(s) or inspector(s).

The Study Review Checklist is available for download from the NHG Research Website to help you prepare for an audit or inspection.

7.4.3 After The Audit or Inspection

The audit or inspection report will be sent to the PI on a communicated date after the audit or inspection, detailing the findings. The PI, in collaboration with the study team members, will be required to formulate a CAPA in response to the audit or inspection report. The CAPA should detail the measures implemented or steps taken to address each finding. The completed CAPA should be sent back to the auditor or inspector by the stipulated deadline.

The Corrective Action & Preventive Action Plan (CAPA) is available for download from the NHG Health Research Website.

7.5 PI Self-Assessment Programme

The PI Self-Assessment Programme is a quality assurance component under the NHG Health OHRPP Research Quality framework. This programme familiarises investigators with the requirements of proper research conduct and identifies areas in their conduct of research that may require improvements.

The PI Self-Assessment Form (PISAF) is a tool used to facilitate self-monitoring and is an effective way for investigators to assess if the research study has been conducted in compliance with applicable regulations and guidelines.

The NHG Health Research Quality Management (RQM) unit would select PI(s) to complete the PISAF based on specific criteria such as experience of the PI and study risk level (e.g., expedited or full board review study). Selected PIs would be notified through email to complete the PISAF.

RQM will review the completed PISAF and make recommendations or issue queries on any aspect(s) of the study conduct that may require improvement. PI would be required to respond to queries issued by RQM within a stipulated timeline.

The Investigator File Contents Template and Pre-Audit Checklist are available for download from the NHG Health Research Website to help you prepare for an audit or inspection.