Monitoring Clinical Trials

SOP Reference: JRCO/SOP/015

Version Number: 7.0

Effective Date: 25 Oct 2017

Review by: 25 Oct 2020

Author: Ana Arbeloa del Moral, Clinical Trials Monitor

Approved by: Gary Roper

Date: 24 Oct 2017

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Version 1.0</td>
<td>31 May 2007</td>
<td>1st Edition</td>
</tr>
<tr>
<td>Version 2.0</td>
<td>19 Jun 2008</td>
<td>Annual review</td>
</tr>
<tr>
<td>Version 3.0</td>
<td>08 Feb 2010</td>
<td>Formation of Joint Research Office</td>
</tr>
<tr>
<td>Version 4.0</td>
<td>14 Jul 2011</td>
<td>Annual review</td>
</tr>
<tr>
<td>Version 5.0</td>
<td>30 Nov 2012</td>
<td>Annual Review</td>
</tr>
<tr>
<td>Version 6.0</td>
<td>18 Feb 2015</td>
<td>Scheduled Review</td>
</tr>
<tr>
<td>Version 7.0</td>
<td>25 Oct 2017</td>
<td>Scheduled Review</td>
</tr>
</tbody>
</table>
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Purpose</td>
<td>Page 3</td>
</tr>
<tr>
<td>2. Introduction</td>
<td>Page 3</td>
</tr>
<tr>
<td>3. Responsibilities</td>
<td>Page 4</td>
</tr>
<tr>
<td>4. Procedure</td>
<td>Page 4</td>
</tr>
<tr>
<td>4.1 Qualification of monitors</td>
<td>Page 4</td>
</tr>
<tr>
<td>4.2 Types of monitoring</td>
<td>Page 5</td>
</tr>
<tr>
<td>4.3 Extent of monitoring</td>
<td>Page 8</td>
</tr>
<tr>
<td>4.4 Monitor’s responsibilities</td>
<td>Page 9</td>
</tr>
<tr>
<td>4.5 Monitoring report</td>
<td>Page 9</td>
</tr>
<tr>
<td>4.6 Trial Oversight Committees</td>
<td>Page 9</td>
</tr>
<tr>
<td>5. References</td>
<td>Page 10</td>
</tr>
<tr>
<td>6. Appendices</td>
<td>Page 11</td>
</tr>
<tr>
<td>Appendix 1 Monitoring risk assessment</td>
<td>Page 11</td>
</tr>
<tr>
<td>Appendix 2 Monitor’s responsibilities under ICH GCP (full details)</td>
<td>Page 15</td>
</tr>
</tbody>
</table>
1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to describe the monitoring procedures for clinical trials sponsored by Imperial College Academic Health Science Centre (AHSC).

2. INTRODUCTION

Monitoring is defined in The International Conference on Harmonisation of Good Clinical Practice (ICH GCP) guidelines as:

“The 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, and the applicable regulatory requirement(s)”, ICH GCP, section 1.38

Section 5.18 of ICH GCP states in detail the minimum requirements for monitoring of clinical trials.

The purpose of monitoring is to verify that:
- The rights and well-being of the human subjects are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.

Monitoring is an integral role in the Quality Control (QC) of a clinical trial and is designed to verify the quality of the study. Audits are designed to assess and assure the reliability and integrity of a trial’s quality control systems and are a way of measuring performance against recognised standards (Quality Assurance or QA). For further information on audits, consult JRCO/SOP/018.

Monitoring is usually performed by the JRCO monitors, an appropriately trained member of the study team/trial coordinating centre or by a contracted external monitor and should be designated on the study delegation log.

The involvement of Contracted External Monitor(s), the JRCO monitors, and the CI or PI in monitoring the Imperial College AHSC sponsored CTIMP studies will depend on whether the study is taking place in the AHSC hospitals, the College associated NHS Trusts or outside both the AHSC sites and the College associated NHS Trusts.

The Imperial College AHSC sites comprise of:
- Charing Cross Hospital;
- Hammersmith Hospital;
- Queen Charlotte’s and Chelsea Hospital;
- St Mary’s Hospital and
- Western Eye Hospital.

While the College associated NHS Trusts are:
- Royal Brompton and Harefield NHS Trust;
• Chelsea and Westminster Hospital NHS Foundation Trust and
• North West London Hospitals NHS Trust.

A Contracted External Monitor is defined in this context as any individual qualified by training and experience and who is not employed by the JRCO, Imperial College AHSC but is contracted to carry out clinical research monitoring in accordance with the GCP principles [see monitoring definition above].

3. RESPONSABILITIES

All Clinical Trials Sponsored by the AHSC taking place at the AHSC sites and the College associated NHS Trusts will be monitored as described in this SOP. Monitoring will be conducted by the JRCO Clinical Trials Monitor and overseen by the JRCO Clinical Trials Manager or delegate.

For AHSC sponsored clinical trials which do not take place in any of the AHSC sites and/or College Associated NHS trust the Chief Investigator (CI) or Principle Investigator (PI) has the responsibility to make appropriate monitoring arrangements. This equally applies to all studies in the AHSC sites and the College associated NHS Trusts with Contracted External Monitors. The JRCO monitor must inform the CI of the JRMO monitoring requirements during a meeting or via email. The JRMO requirements include providing the monitor with the following information:

• Contact details of the external(s) Monitor at the site;
• Copy of the Monitor(s) contract for the study (if applicable) or job description;
• Copy of the Monitor(s) signed and dated CV;
• External/local Monitor monitoring plan
• Detailed report of all monitoring conducted

AHSC sponsored clinical trials conducted through the Imperial College Trials Unit (ICTU) will follow their monitoring and SOPs. ICTU will be responsible for assessing the suitability of trial monitors, conducting the risk assessment and compiling the monitoring plan. ICTU will provide the JRCO monitor with a copy of the monitoring plan prior the trial commencement and will provide the JRCO with copies of the monitoring reports as stipulated in the monitoring plan. The JRCO will carry out the study start and close out visit.

The JRCO will review all monitoring reports from external/local/ICTU Monitors to uphold Sponsor requirements and will advise if there are any queries. The CI or PI must ensure that all the above requirements are met.

4. PROCEDURE

4.1 Qualification of monitors
Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor’s qualifications should be documented. Training records, including relevant
qualifications, should be kept by the monitor and checked by the Chief Investigator. For further information on training records, see JRCO/SOP/024.

The monitor should be familiar with the Investigational Medicinal Product (IMP), the protocol, information sheet and consent form, as well as the Imperial College AHSC SOPs, GCP and applicable regulatory requirements.

4.2 Types of monitoring

4.2.1 Coordinating Centre day-to-day monitoring
Day-to-day monitoring should be carried out by those responsible for running the study. This would normally include the following checks:

- Data collected are consistent with the protocol
- The case report forms (CRFs) are only being completed by authorised staff
- No key data are missing
- Data appears to be valid (e.g. within range and is consistent)
- A review of recruitment rates, withdrawals and losses to follow-up

4.2.2 Central Monitoring
Centralised procedures can be used to confirm patient eligibility (usually through the collection of pathology reports to substantiate a diagnosis), to corroborate the existence of the patient (for example, through The Office for National Statistics (ONS) flagging or collection of an imaging investigation) and to determine the outcome (for example, ONS flagging for survival end-points or central assessment of the results of an investigation, such as a X-ray or scan).

In large, multi-centre trials, central monitoring of data using statistical techniques is particularly useful for the early identification of:

- Unusual patterns or trends
- Issues with plausibility or consistency
- Safety signals
- other deviation from the protocol/trial requirements such as poor/late completion of CRFs.

Where centralised monitoring indicates problems, it can be used to efficiently direct on-site monitoring activities to those sites requiring further investigation and/or additional training support. Although omissions (e.g. failure to report a serious adverse event (SAE)) or data entry errors cannot be detected directly, it may be possible to compare data from the different sites to identify sites that warrant investigation.

Examples of central statistical monitoring checks include:

1. Missing or invalid data
Range checks can be used to identify unlikely or implausible values, such as extreme values for weight, or diastolic greater than systolic blood
pressure. For trials using electronic data capture methods, these checks can usefully be built into the data collection form; any such automatic safeguards should be validated to ensure that they function correctly.

2. Calendar checks
Examining the day of the week that patients were randomised can be revealing (e.g. randomisation on Sunday in a trial of patients attending outpatient clinic). It is also helpful to compare the order of trial forms (particularly if they have an ordered numbering system) with the dates they were completed.

3. Unusual data patterns
Data from one site can be compared with data for the trial as a whole to identify patterns such as digit preference, rounding, or unusual frequency distribution (e.g. mean, variance, skewedness). Such checks can be applied both to a single variable (e.g. systolic blood pressure) and to the joint distribution of several variables (e.g. systolic blood pressure and weight).

4. Rates of reporting
The frequency of reported adverse events and of missing data can be compared between centres.

5. Repeated measures
Where the same variable is measured on multiple occasions for each participant during the trial, it is possible to check that the variability and within individual changes of such repeated measurements is broadly consistent with the pattern seen for the trial as a whole.

6. Comparison with external sources
Checks with birth and death registries or with disease-specific registries (e.g. cancer registry) can be used to identify that particular patients exist and that particular events have (or have not) occurred.

In applying all these checks it is important to recognise that some variability is to be expected. Data that are too good should raise suspicion in the same way as data that are unusually poor.

4.2.3 On-site monitoring
On-site monitoring visits may be used in a variety of different ways:
- to educate staff about the trial; review understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents to conduct the trial;
- to ensure that the required pharmacy and laboratory resources are adequate;
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility,
- to verify all protocol required data (e.g. adverse event/concomitant medication) have been recorded on the
CRFs and compared with data in the clinical records to identify errors of omission as well as inaccuracies.

- To check trial procedures (e.g. informed consent procedures, data collection, CRF completion) to ensure quality and consistency and confirm all assessments are being made by appropriately qualified staff;
- To identify staff training needs.

4.2.3.1 On-site Visits

a) Site Initiation Visit

The JRCO Trial Monitor will perform the SIV at all Imperial College London/Imperial College Healthcare NHS Trust research sites. The SIV for all other research sites must be conducted by an external monitor or appropriate member of the lead research team. An SIV cannot be performed until there is assurance that site agreement(s) and all other relevant regulatory approvals are in place.

The SIV will be arranged so that the CI/PI and other key members of the study team can attend e.g. Study doctor, research nurse and pharmacist etc. A list of attendees will be collected.

A presentation will be given to the site to detail the responsibilities of the research team, as required by the sponsor. This will include at least the following:
- GCP and staff training
- The Informed Consent Process
- Safety Reporting
- Investigational Medicinal Product
- Protocol deviations and violations
- Trial Documentation
- Data Entry
- Laboratory
- Equipment calibration certificate or sop to demonstrate calibration is done
- Annual Reports
- Amendments
- End of Study
- Trial-specific procedures

The JRCO Monitor will check that all the documents required for the study to start the research are present. If the monitor is satisfied that all documents are present, the CI can sign the Study Start Approval form (SSA form), previous signed by the JRCO Clinical Trials Manager. Otherwise, the SSA for will be withheld pending a successful SIV.

b) Routine Monitoring Visit

The monitor will perform the following activities during each site monitoring visit:
- Review subject all informed consent forms
- Complete SDV as per requirements of the monitoring plan
Review data quality
Review the Trial Master File
   Review essential documents
   Ensure the SAE log is complete and filed
   Ensure that all Ethics reporting requirements have been met
   Ensure trial logs have been updated
Discussion with the site staff and principle investigator on new issues and unresolved issues from monitoring visit, patient recruitment, site’s compliance to protocol…Review pharmacy file and check temperature logs
Review Delegation of Duties and Site Signature Log

After the monitoring visit the JRCO Monitor will write the monitoring report including a list of all missing documents and issues raised that need to be resolved.

c) Site Close Out Visit
A COV will be performed after the trial has been completed (or if the study has terminated early). The Trial Monitor will arrange the visit at a convenient date and time with the site staff and notify them in writing. At sites which are not part of the Imperial College Healthcare Trust the delegated monitor will need to perform the close out visits.

The COV will comprise of full site file review and source data verification. It will also include ensuring that all listed actions from previous monitoring visits are resolved. The monitor will ensure data entry is complete and that all outstanding queries are resolved.
The pharmacy file will also be closed and a final accountability of IMP stock and returns will be conducted. Destruction of any remaining IMP will need to be approved by the CI/PI.
The trial monitor will discuss archiving requirements with the study team, and provide assistance where required. Final results reporting and upload to EudraCT will also be reviewed with the study team.

After the Close Out monitoring visit the JRCO Monitor will write the monitoring report including a list of all missing documents and issues raised that need to be resolved.

4.3 Extent of monitoring
The sponsor should ensure that the trials are adequately monitored and determine the appropriate extent and nature of monitoring. This should be based on the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial a CTIMP study is assessed as “high risk” or is First in Mankind which is automatically considered to be “high risk” the JRCO monitor will agree the frequency of routine monitoring visits with the CI of the study.
4.3.1 Risk Assessment

Appendix 1 contains an example Risk Assessment form that can be used by CI’s to suggest the appropriate level of monitoring for your study and to identify risks that may not have been considered in protocol development.

Based on the Risk Assessment a Monitoring Plan will be put in place by the JRCO Team describing all monitoring activity for the Clinical Trial. The Monitoring Plan needs to be agreed with the CI. In general, for most studies there will be a need for on-site monitoring, however, in some academic clinical trials, the CI in conjunction with the JRCO, may decide that remote monitoring alongside relevant training and meetings with extensive written guidance can assure appropriate conduct of the trial. The JRCO will conduct a separate risk assessment as part of its study set-up process and will advise the CI on the recommended level of monitoring.

4.4 Monitor’s responsibilities

Monitors, in accordance with the Sponsor’s requirements, should ensure that the trial is conducted and documented properly by carrying out as a minimum the following activities:

- Ensuring that data collected is consistent with adherence to the protocol
- Case Report Forms (CRFs) are being completed by authorised personnel as designated by the delegation log
- No key data is missing
- Data appears to be valid (i.e. within range and consistent)
- Check adherence to protocol and GCP
- Verify selected items recorded on CRFs match data in participants’ health records
- Confirm that the participant has provided written consent

Full details of the monitor’s responsibilities as noted in section 5.18.4 of ICH GCP can be found in Appendix 2.

4.5 Monitoring report

Following the monitoring visit, the monitors should provide to the CI, pharmacy and the JRCO copies of all monitoring reports which should include:

- Date, site, name of monitor
- Name of CI/Principal Investigator or other site personnel in attendance

Summary of documents the monitor has reviewed, along with significant findings, deviations (if applicable), deficiencies, actions taken or recommended. When a protocol violation is identified the sponsor will advise on what action is required and may initiate a triggered audit. For IMP trials requiring MHRA approval, should the violation be identified as a serious breach, the Sponsor will inform the MRHA of the incident within seven days.

4.6 Trial Oversight committees

The funding body or sponsor may specify particular oversight arrangements. But even if they do not, some form of oversight is strongly recommended for all trials,
although the appropriate structures will vary according to the size, complexity and risks associated with the trial.

Commonly employed oversight committees for a phase III trial include:

4.6.1 Trial Management Group (TMG)
Most trials should have a TMG, although in simpler trials this may comprise only one individual: the CI. For larger studies, this normally includes individuals who are responsible for the day-to-day management of the trial (e.g. the CI, trial coordinator, statistician, research nurse, data manager). The group’s role is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

4.6.2 Data Monitoring Committee (DMC)
A DMC should be considered for all trials, although one may not be always necessary (e.g. non first in man phase I/II studies). DMCs should be set up for all phase III clinical trials. Its role is to review the accruing trial data and to assess whether there are any safety issues that should be brought to the attention of the TSC or any ethical reasons why the trial should not continue. The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH GCP 5.5.2) also to assess whether there are any safety issues that should be brought to participants’ attention.

The DMC should be the only body that has access to unblinded data.

DMCs might consider using the DAMOCLES Charter proposed in the Lancet 2005 as a model for the organisation of the IDMC.

4.6.3 Trial Steering Committee (TSC)
The role of a TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. It should agree the trial’s protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial.

The TSC will usually have members who are independent of the investigators, e.g. an independent chairperson. All documentation produced by the TSC will include key decisions made during the trial and should be archived in the Trial Master File (TMF).

Trial teams must send meeting minutes from TMG, TSC and DMC meetings to the JRCO for review. The JRCO should review the meeting minutes and confirm that there are no immediate actions arising from this meeting with regards to sponsor oversight.
5. REFERENCES

JRCO/SOP/018: Audit
JRCO/SOP/024: Training

http://www.ct-toolkit.ac.uk/routemap/trial-management-and-monitoring/


ICH GCP (1996), Section 1.8, 5.18 and 5.5.2

NHS R&D Forum. Distinguishing different types of Monitoring and Audit, November 2008

JRO UK regulations Compliance form (Part 2), version 1.0

6. APPENDICES

Appendix 1: Monitoring Risk Assessment

<table>
<thead>
<tr>
<th>Scoring Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Phase</td>
<td></td>
</tr>
<tr>
<td>2. Number of Participants</td>
<td></td>
</tr>
<tr>
<td>3. Number of Trial Arms</td>
<td></td>
</tr>
<tr>
<td>4. Number of IMPs</td>
<td></td>
</tr>
<tr>
<td>5. Type of Study</td>
<td></td>
</tr>
<tr>
<td>6. Vulnerable Groups</td>
<td></td>
</tr>
<tr>
<td>7. No of organisations/departments involved</td>
<td></td>
</tr>
<tr>
<td>8. Design</td>
<td></td>
</tr>
<tr>
<td>9. Study Team and their experience</td>
<td></td>
</tr>
<tr>
<td>10. Number of sites</td>
<td></td>
</tr>
<tr>
<td>11. Length of study</td>
<td></td>
</tr>
<tr>
<td>12. Complexity</td>
<td></td>
</tr>
<tr>
<td><strong>JRCO Monitoring Risk Score</strong></td>
<td></td>
</tr>
</tbody>
</table>
Risk Assessment Scoring

The JRCO monitor should use the following scoring in order to determine the frequency of monitoring visits for a study.

Please note that any studies which are First in Mankind are automatically considered to be “high risk” studies and will follow the monitoring plan outlined below.

**Phase.**
This question refers to what phase the study is. The earlier phases, by their nature, have more potential for adverse events and should be scored as follows:

- Phase 1 – 4
- Phase 2 – 3
- Phase 3 – 2
- Phase 4 – 1

**Number of participants**
This question refers to the number of participants in the study. The greater the number of patients, the more potential there is for something to be done in error:

- 1-10 – 1
- 11-50 – 2
- 50-100 – 3
- 101+ – 4

**Number of Trial Arms**
This question refers to the number of arms in the study. There is greater potential for more errors to be made if there are a large number of arms in the study:

- 0-2 – 1
- 3-4 – 2
- 5+ – 3

**Number of IMPs**
This question refers to the number of IMPs. If there are placebos in the study, these should also be counted individually for this question. This question should be scored as follows:

- 0-2 – 1
- 3-4 – 2
- 5+ – 3

**Type of Study**
This question refers to what type of study it is. IMPs being used within their licensed indication will be a lower risk than an IMP that is not licensed. If multiple IMPs are used, then the IMP that has the highest risk should be used to score this question.

- CTIMP licensed for use – 1
- CTIMP licensed, new use – 2
CTIMP not licensed – 3
Gene Therapy – 4

**Vulnerable Groups**
This question relates to whether the research will involve any vulnerable groups. If there are multiple vulnerable groups in the study, then the most vulnerable group should be used to score this question.
None involved – 0
Children – 1
Children under 5 – 2
Mental Capacity – 1
Prisoners – 1
Young Offenders – 1

**No of organisations/departments involved**
This question relates to the number of different departments or organisations that will be involved. Imaging, Pharmacy and Pathology should be considered as individual departments
0-1 – 1
2-3 – 2
3-5 – 3
5+ – 4

**Design**
This question relates to the design of the study. If more than one is applicable to the study, then the JRCO monitor should add up the scores to give a total figure.
RCT – 1
Open label – 1
Single Blinded – 1
Double Blinded – 1

**Study Team and their experience**
A more experienced and qualified research team is less likely to make errors than a team conducting their first research project. Qualifications and experience of the main members of the team should be considered when answering this question.
Low – 3
Moderate – 2
High – 1

**Number of sites**
The more sites that a study is conducted in, the higher the chance of errors occurring. If there are international sites, then these should be included in the scoring of this question.
0-1 – 1
2-5 – 2
6-10 – 3
10+ – 4

**Length of study**
If a study is conducted for a longer period of time, there may be for example, staff changes and therefore a greater risk of errors occurring. This question should be scored as follows:
< 1 year – 1
1-3 years – 2
4+ years – 3

**Complexity**
The more complicated or complex, the study, the greater the risk. This question should be scored as:
Simple – 1
Moderate – 2
Complex – 3

**Scoring Explained:**
A score of 11 -15 is considered a low risk study.
A score of 16- 20 is considered a study similar to usual care.
A score of 21- 26 is considered to be a study with substantial risk.
A score of 27-37 or a first in mankind study is considered to be a study with high risk.
Appendix 2: Monitor's responsibilities under ICH GCP (full details)

The monitor(s) in accordance with the Sponsor’s requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a. Acting as the main line of communication between the Sponsor and the investigator.

b. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

c. Verifying, for the investigational product(s):
   (i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
   (ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
   (iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
   (iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
   (v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

d. Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

e. Verifying that written informed consent was obtained before each subject's participation in the trial.

f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

g. Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

h. Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

i. Verifying that the investigator is enrolling only eligible subjects.

j. Reporting the subject recruitment rate.

k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
   (i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
   (ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
(iii) Adverse events, concomitant medications and inter-current illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

p. Determining whether the investigator is maintaining the essential documents.

q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.