UTS IMPACCT Trials Coordination Centre

Guidance 5

Monitoring Guidelines for Monitors

The monitoring process in as on-going and intensive programme initiated by the IMPACCT Trials Coordination Centre (ITCC) and involves all sites. Monitoring is an important internal mechanism for ensuring compliance with Good Clinical Practice (GCP) and ITCC's own internal procedures, maintaining the quality of participant data for each of the studies undertaken by ITCC, and provides an excellent way ensuring quality across the Collaborative.

While there is a Standard Operating Procedure for monitoring (*refer* SOP 5.18 Monitoring), a few tips and guidelines have been collated to assist all sites in a more practical sense. These guidelines have been developed out of learnings so far, and during a period of the Collaborative being partway through an intensive period of monitoring.

1. Preparation

Adequate preparation by both the ITCC and the site being monitored enables the monitoring visit to proceed in a smooth manner with fewer disruptions to the daily work of the site team.

The ITCC monitoring team attempt to give sites at least two (2) weeks' notice of an on-site or telephone (remote) monitoring visit (14 calendar days), and in many cases the negotiation of a suitable visit date means that there is often four (4) weeks or more notice of the date along with the ID numbers of the participants (PID) to be monitored.

- Email site coordinator and Principal Investigator (PI) to discuss the need to monitor, specify the study(ies) and provide some suggested dates. Finalise the dates via email and send the PID numbers for participants to be monitored.
    - Select appropriate number participants to review per the Study Monitoring Plan.
    - Select participants based on early through to late recruitment, or if specific participants are known to have been a problem; or as defined in the monitoring plan (such as every second or third participants) or for a single study if recruitment has closed.
- Email the site coordinator and PI to confirm the date of the visit, and the PIDs to be reviewed.
    - <u>For on-site visit:</u> Include a summary of the local requirements such as availability and review of participant study files, medical records, and Investigator Site File (ISF).

- For telephone visit: Request a copy of the most current Staff Signatures and Delegation Log (SSDL), Training Log/Records and Monitoring Visit Log to be returned by email prior to the scheduled visit.
- Save the confirmation email in the study Trial Master File (TMF).

Start local preparation for the visit.

- Prepare the Study Monitoring documents excel workbook:
  - Complete the 'Monitor Preparation Checklist' tab
  - Customise the corrective action sheet, amended for each participant to be reviewed at the site.
  - Insert the PID onto the 'Timeline' tab
  - For on-site visits, customise the 'Site Periodic Review' tab, amended for the site.
  - Customise any other study specific checklist developed
  - Compile for each participant:
    - Timeline
    - Individual worksheet checklist
    - Randomisation fax/notification/email
    - Other notices as required
- Review the Study 'Tracking' and 'Forms and Documents' projects in REDCap and the TMF to check the following:
  - HREC approvals and/or the approval letters for the site/study
  - If first periodic monitoring visit, check CTN copy and TGA listing
  - Any other essential documents as part of the ISF

Additional preparation for Telephone (Remote) Monitoring Visits:

- Check the eCRF database to ensure that all data collection worksheets for the participants to be monitored have been uploaded and that all the eCRF data has been entered. Request site staff to provide copies of any missing worksheets and complete data entry prior to the scheduled visit.
- Review the data collection worksheets for participants to be monitored for compliance with the ALCOACCEA principles of GCP good documentation practice. Discrepancies within the source documents (e.g. inconsistent dates or data) should be noted in the corrective action sheet for discussion during the visit.
- Review site staff completing the data collection worksheets and performing study assessments are appropriately trained and delegated by the PI by checking against current SSDL and training records.
- At subsequent telephone monitoring visits, check previous corrective action sheet(s) for:

- Any unresolved issues
- Notable issues that may recur at this visit, such as but not limited to:
    - Issues related to consent or documentation
    - Issues related to delegation of duties
    - Issues related to organisation, access to information or source data
    - Any other issues

2. During the visit

2.1 For On-Site Monitoring Visits:

The monitors attempt to disrupt the working day of the study staff as little as possible, but some situations arise during the review that require assistance from the team to progress the review. For example:

- Documents cannot be located, without which the review of that participant cannot progress.
- Documentation is not consistent with other documents and requires clarification in order to continue the review without unnecessary file notes or corrective actions.

In addition, the monitors require a short period of time towards the end of the visit to summarise the findings, with both the site coordinator/study nurse and the PI, so that the report that follows is as expected. This gives the opportunity to discuss any study wide issues of problems and well as specific participant problems.

- Using the checklists, review the ISF and participant files and complete the Corrective Action Sheet (Template 15) to record any errors or issues found during the monitoring visit.
    - Refer to the attachment for completing the ‘corrective action sheet’.
    - The first few columns should be completed in order to identify which document is referred to. In addition, the ‘Findings’ should clearly identify the problem or deficiency, and the ‘Required action’ should detail what is required to correct the deficiency (or give guidance to the site team about correction). Any finding that may necessitate an amendment to eCRF data will require a corresponding data query to be raised in the eCRF database. This must be indicated in the column headed ‘REDCap data query raised’ to prompt the site staff to review and respond to these data queries.

The Monitoring Log must be signed at the end of the visit and will be left out so that site staff can also sign it.

A. Site periodic review

a. Review all HREC documents, or those since the last monitoring visit.

i. Check the site file to ensure that all protocol amendments and other relevant documents have been submitted and approved

ii. All SAEs have been reported as required and acknowledged

iii. All other correspondence appears to be complete

1. Compare the ISF against the ITCC listing to ensure that both lists reflect the full correspondence

2. Obtain or leave copies of documents to ensure the file is complete

b. Review the TGA listing is on file (if first monitoring visit to that site).

c. Check the remaining ISF for completeness and organisation.

d. Check and hold aside the monitoring log:

i. Check that it was signed after the previous visit

ii. Ensure the log is signed by the monitors during this visit and left out for signing by staff

e. Locate and hold aside the SSDL:

i. Check that all people listed on the log have been signed on completely

ii. Check that the delegation seems appropriate

iii. Check that the relevant documents (current CV) and training (GCP, protocol etc.) is on file for all site staff listed on the SSDL.

iv. Check against each participant during the patient file review, particularly if the appropriate signature is on the SSDL for:

1. Consent signature

2. Medical assessment

3. Order of study medication

4. Collection of CRF data (completion of data collection worksheets and data entry)

B. Patient review

The monitor must verify and check that informed consent has been adequately obtained (i.e a signed consent form is present) for each participant prior to accessing and reviewing their medical records and other study related documents.

a. Timeline check

i. This provides a summary of how the patient proceeded through the study and can provide useful information when the report is written.

ii. The dates of each visit should be filled in along with other pertinent information which may vary between studies, for example:

5. Risperidone study: it is important to track delirium resolution, which can be easier to track on this page rather than flicking through numerous pages.

6. Sertraline study: where there are numerous visits and phone calls, it is important to tract the actual date against the expected date.

iii. The timeline check can also give room for comments specific to this patient, such as protocol violation or other information that may become important when the data is being examined later

b. Individual worksheet checklist

i. This form guides through each eCRF and its corresponding data collection worksheet for each participant.

ii. Each checkpoint should be checked; the trigger column can give guidance on where or how to locate specific information to verify eCRF data.

iii. All lines for each worksheet and corresponding eCRF for that participant should be completed.

b. Other study-specific checklist (if used)

2.2 For Telephone (Remote) Monitoring Visits:

The focus of the telephone visits is to review and obtain verbal confirmation that the following data elements are documented in the participant's medical records/clinical notes:

- Informed consent process and documentation
- Eligibility including confirmation of admission details, confirmation that all assessments/measures required to confirm eligibility criteria were completed, review of concomitant medications for potentially exclusionary treatments, review of medical assessment for potentially exclusionary co-morbidities/health conditions
- Primary endpoints including completion of all required measures and assessments at each visit, and checking the accuracy of calculated scores for clinician assessments
- Consistency of dates and compliance with visit schedule
- Compliance with administration of study drug
- Safety and adverse events including review of medical assessments such as vital signs/ physical examination and concomitant medications that may indicate unreported adverse events
- Study termination: reviewing reason for cessation/withdrawal/completion and verification of the daily assessments in the days prior to that event

Using the available checklists (if applicable), review the data collection worksheets/eCRF and obtain verbal confirmation from the site staff of the key data elements listed above. Complete the Corrective Action Sheet (Template 15) to record any errors or issues identified during the preparatory activities and telephone discussion:

- Refer to the attachment for completing the 'Corrective Action Sheet'.

- The first few columns should be completed in order to identify which document is referred to. In addition, the 'Findings' should clearly identify the problem or deficiency, and the 'Required action' should detail what is required to correct the deficiency (or give guidance to the site team about correction). Any finding that may necessitate an amendment to eCRF data will require a corresponding data query to be raised in the eCRF database. This must be indicated in the column headed 'REDCap data query raised' to prompt the site staff to review and respond to these data queries.

In addition, the following other items may also be reviewed during the call to assess overall site health and compliance. Other items discussed during the telephone visit are to be documented in the 'Other items discussed' tab of the Study Monitoring Documents excel workbook. Any findings related to these items should also be documented in the corrective action sheet for the telephone visit:

- Protocol deviations and violations
- Recruitment activities, eCRF data entry and completion of participant data collection worksheets
- Discussion of issues identified during data verification activities
- Site staff changes and resources at the site
- Assessment of requirement for additional site staff training
- Unresolved corrective action items or site issues
- Recurring issues such as those related to consent, documentation, delegation of duties, and issues related to organisation, access to information or source data
- Availability of important regulatory and essential documents in the ISF such as CVs, training records, HREC/RGO documentation, Serious Adverse Event Reports etc.

The review prompts outlined in the 'Site Periodic Review' and 'Patient Review' sections for On-Site Monitoring Visits are also applicable to Telephone Monitoring Visits and should be considered when preparing for and conducting these remote monitoring visits. The only exception applies to the physical review of ISF quality and completeness. Whilst this cannot be directly verified, certain discussions and confirmations related to the filing of important key regulatory and essential documents, including study-specific logs, can be used to monitor ISF maintenance and filing compliance remotely. The monitor should also utilise the Study 'Forms and Documents' and 'Tracking' projects in REDCap to assist with central monitoring of ISF filing and completeness.

Print and sign the copy of the most current version of the Monitoring Log received prior to the telephone visit. Return a copy by email so the site staff can countersign and file it in the ISF.

3. Monitoring Visit assessment

An overall assessment is made of the on-site or telephone visit based on the levels of deficiencies recorded in the Corrective Action Sheet (Template 15) subsequent to the review.

These are:

- None
    - Complete
    - Error-free, or corrected appropriately
    - Filed and accessible
    - Clear documentation of procedures
- Minor
    - Source data does not support worksheet and eCRF entry
    - Late approvals
    - Poor filing and documentation
    - Difficult to follow errors
- Major
    - Approvals absent
    - Violation
    - Critical documents not available
    - Errors not accounted for

The overall assessment recorded in the Monitoring Report Email will be one of the following:

- Acceptable
    - No deficiencies
    - Few minor deficiencies
    - Major deficiencies were identified and/or corrected prior to the monitoring visit, and no further action is required
- Acceptable needs follow-up
    - Any major deficiency identified during the monitoring visit, not identified, or corrected prior to the visit
    - Multiple minor deficiencies identified
- Unacceptable
    - Multiple major deficiencies identified
    - A single major blatant deficiency (total disregard for protocol)
    - Excessive number of minor deficiencies

NOTE: Any on-site or remote monitoring visit with a final assessment of ‘Unacceptable’ must be referred to the CPI who will convene an out of session meeting of the relevant committee

(Scientific Advisory Committee or Data Safety Monitoring Committee) such that a decision can be made regarding ongoing recruitment at that site.

4. Follow-up to Monitoring Visits

1. Log any protocol violations identified during on-site or remote monitoring activities on the Protocol Deviation/Violation Log and report to the CPI using a Protocol Violation Form (Template 8) per ITCC SOP 4.5 Protocol Deviations and Violations.

2. Complete an email report of the on-site or telephone visit findings:

- Use the checklists, site review and Corrective Action Sheet to formulate specific and general comments for the Monitoring Report

The site will be sent the report within 14 calendar days following the on-site or telephone visit. This email will include:

- A summary of the visit outlining:
  - Date(s) of monitoring visit
  - Name of site and site personnel in attendance
  - Name of monitor(s)
  - A summary of the review process
  - A summary of the findings, for the site and the organisation
- An electronic copy of the corrective action sheet
- The Principal Investigator is requested to confirm by reply email to acknowledge receipt and review of the monitoring report and the findings summarised therein.

In the event that recurring notable issues or serious breaches are identified at a monitoring visit, a follow-up telephone call will be scheduled with the Principal Investigator to discuss an appropriate corrective and preventative action plan.

3. File a copy of the email report and Principal Investigator acknowledgement in the TMF.

The completed Corrective Action Sheet should be returned to the monitors within four (4) weeks of receipt (30 calendar days). It should document the activities that have taken place in order to correct the findings of the visit.

- The column ‘Actual outcomes’ detailing the action taken should be completed for each issue; these might be:
  - A file note
  - Confirmation of training or a discussion/meeting
  - A correction to a specific data item within a data collection worksheet and/or eCRF
  - Location and confirmation of a document
- Examples of this might be:
  - File note confirming consent form written, attached
  - Data collection worksheet amended as requested, page attached
  - No worksheet/eCRF change required, rescue medications checked and are correct in the worksheet and eCRF

- Or other statements that address the finding by the monitors

- If a data query linked to the monitoring finding was raised in the eCRF database, this should be responded to and resolved.
- The ‘Date completed’ column should be completed.
- The completed corrective action sheet is sent back to the ITCC. Any relevant file notes, pages of corrected data collection worksheets, medication pages etc. should be uploaded to the eCRF database or emailed to the ITCC to confirm that the action was completed.
- The ITCC checks each completed outcome against any other supporting documents (such as worksheets, file notes, or comments of training or other outcomes). The monitor will enter their initials and a date in the column headed ‘ITCC resolution confirmation’ to confirm that the finding is resolved and closed. When all findings on the corrective action sheet are confirmed resolved, the line at the bottom of the corrective action sheet is then signed and dated by the monitor to confirm completion.
- The completed corrective action sheet is logged, and a copy is filed in the TMF.

5. Follow-up

- The ITCC National Project Officer (or ITCC monitor) should review each finding and outcome to ensure that the outcome has now resolved the issue; the ITCC National Project Officer/Monitor should initial and date the line as closure of that finding.
- File notes should be checked to:
    - ensure that the problem has been adequately explained,
    - outcome should indicate that the finding is now resolved, and
    - any changes to data collection worksheets should be attached so that the database can be amended following established procedures (the amended page is to be handed to the data checking team for confirmation that the eCRF and database has been updated accordingly).

6. Second and subsequent visits

After initial monitoring, subsequent monitoring visits will review only those sections of the ISF and participant files that required updating since the previous visit, such as:

- Ongoing HREC/RGO communications, approvals, and submissions
- Protocol amendments
- Staff Signatures and Delegation Logs
- Training records
- Monitoring logs
- The next list of enrolled participants
- Any corrective actions that are outstanding from the previous visit

7. Support monitors

Support monitors (co-monitors) assist the main ITCC monitor while undertaking file review, predominantly during on-site monitoring visits. They are not familiar with the study protocols or with the structure or content of the data collection worksheets and eCRFs. They are employed in a support capacity because of their clinical skills. The primary monitor is expected to lead the monitoring process and utilise the support monitor appropriately. The co-monitor can:

- Examine the medical record for each participant as the primary monitor reviews the data collection worksheets and eCRFs.
- Locate the informed consent form and confirm the documentation of the consent process.
- Locate and confirm the medications that form the inclusion or exclusion criteria for the study.
- Confirm diagnostic and medical conditions that are used to assess eligibility to the study.
- Locate and confirm laboratory, pathology, or radiology results.
- Confirm that certain timepoints were followed by notation of study progress within the medical record.
- Locate any other information within the medical record such as nursing plans, falls risk assessments, vital sign measures, infusion charts.
- Read and interpret medical, nursing, and allied health notes for general progress and for any change in condition that may constitute adverse events.

The primary monitor should instruct the co-monitor throughout the review for the information to be located and the two monitors should have a continuing discussion about findings from both the medical record and worksheets/eCRFs to compare notes and confirm the accuracy of the data.

A co-monitor may also assist with some of the above tasks, as appropriate during telephone monitoring visits.

The primary monitor is responsible for preparing the visit report and following up on the resolution of monitoring findings and corrective actions.

8. Corrective actions

Findings	▪ Lists the problem or issue. ▪ Can be related to site documents, organisation, and participant review. Anything related to the visit that is not as it could or should be.
Required action	▪ Suggestion for how the finding can be rectified. Can be a single suggestion or a number of suggestions in order to rectify, correct or resolve the issue listed as a finding.
REDCap query raised	▪ Indicate if a data query linked to the finding has been raised in the eCRF database which needs to be reviewed, actioned and responded to by the site staff.
REDCap query resolved	▪ Site staff to confirm with Yes, No or N/A response that the data query has been resolved. If no, a reason should be provided.
Actual outcome	▪ The action taken by the site to rectify the finding. May be one or all of the suggestions made by the monitor/s, or may be another outcome as a result of the site reviewing the circumstances.
Date	▪ The date recorded by the site when the outcome was completed, and the finding has now been resolved

10.1 Examples of corrective actions

Findings	Required action	Actual outcome
General documents		
Missing documents	Regulatory documents, consent forms, data collection worksheets, source documents, eligibility documents	Locate document and confirm
		Reconstruct document from other sources and file note that source was used
		Cannot locate and file note to confirm document did exist and can be verified by person

Findings	Required action	Actual outcome
		Cannot locate and cannot be confirmed, file note. This may be a protocol violation.
HREC documents missing, approval for amendment 1.3 cannot be located	Locate approval and confirm File note lost document, obtain copy form HREC	Approval found in other folder, attached
Doctor is not listed on the SSDL, but has performed medical assessments	File note by PI: explained protocol, qualifications have been checked, appropriate delegated activities were assigned, delegated tasks were performed as per delegation	File note attached to the relevant worksheet and copy attached to the SSDL
Consent forms		
Consent form has not been dated by patient	File note that patient missed placing the date and was incorrectly inserted by study staff	File note attached (written by staff member who obtained or witnessed consent)
	Staff training that patient must sign and date the consent form	Discussed at team meeting on (date) and noted in meeting minutes
		Written procedures provided to nurses
Consent form not signed by patient	File note by person who obtained consent	Person no longer employed at site; file note attached. (if the file note cannot be written by person who obtained consent, this is a protocol violation)
		Refer to comprehensive clinical progress notes
Incorrect consent form in use	File note to explain difference in version of consent form	File note attached
		HREC informed that incorrect version has been approved, or not listed on approval letter, attached
Data Collection Worksheets		
Worksheet missing	Locate and confirm to ITCC, provide copy, and enter data	Worksheet found, data entered, and copy attached OR Not completed, CRF constructed from clinical record, withdrawal worksheet, file note written, worksheet and file note attached, data entered
Document is incorrect or conflicts with other documents	Worksheet against source, Eligibility against clinical record, Prescription not followed or incorrect, consent form problem	Correct the document if it can be confirmed by other documents, initial and date the correction
		File note the correction such as medical assessment, dosing can be

Findings	Required action	Actual outcome
		confirmed as correct, file note that date on consent form was correct (signed by person who took consent)
		File note to explain discrepancy, may be a protocol violation
Medical assessment indicated no previous adverse reaction to opioids, medical record records allergy to morphine	Review clinical record, amend medical assessment, file note eligibility, amend worksheet (initial and date correction)	Medical record records allergy, but actually reaction was dose related, assessed by investigator as no problem, medical assessment form has note added
Documents are incomplete	Consent form not fully filled in, signatures missing, missing data points, PID missing from pages, dates of review for confirmation for study	Complete if possible, initial and date
		File note to confirm that incomplete was correct at the time and can be confirmed
		File note that data is missing and cannot be traced as person has left, may be a protocol violation
[PID] 24 hours. NuDesc for 8am blank	Complete worksheet (initial and date correction); File note that score not done; Protocol violation	8am score located on source document in clinical record (archived in different place) worksheet amended; copy attached
Response assessment (or primary outcome) is inconsistent with other data or is incorrect (according to monitor calculations)	Reassess, correct worksheet, file note; Protocol violation	File note attached worksheet corrected and copy attached
PID, date, study nurse initials missing from the top of each page	The information is required on each page for identification purposes	All of the header information should be completed but does not need to send to ITCC (this is the only exception whereby ITCC do not need to be provided with evidence the action has been completed)
PI has not signed the eligibility (or cessation / withdrawal) worksheet	PI to sign and date worksheet, with appropriate notation of actual date of signature	Worksheet signed and dated by PI, dated dd/mm/yyyy
PI has not circled appropriateness to continue study	PI to circle worksheet with initial and date of change	Worksheet amended; copy attached