



# Standard Operating Procedures

## 5.18 Monitoring ©2007

History			
Version	Date	Author	Reason
1.1	18 <sup>th</sup> July 2007	B Fazekas	New procedure
1.2	13 <sup>th</sup> August 2007	B Fazekas	Ratified by MAB
1.3	16 <sup>th</sup> October 2007	B Fazekas	Update following review by David Currow

Approval				
Version	Author	Signature	Approval Name	Approval Signature
1.3	B Fazekas	<i>B. Fazekas</i>	D Currow (CI)	<i>David Currow</i>

### Scheduled review

**Date** August 2009

**Responsible person** PaCCSC National Manager

## 5.18 Monitoring

### Purpose

The purpose of monitoring is to undertake a detailed review of the study documentation, protocol implementation and procedures, correct outstanding data queries, and to assess and provide support for site specific problems.

For PaCCSC, this will be to ensure that investigating sites comply with GCP, the protocol, and the Standard Operating Protocols (SOPs) relevant to the study.

Each study site can expect the monitor from the coordinating centre to examine all study documents, CRF's reports, correspondence etc as outlined in the attached templates. The site can expect problems identified during the visit to be discussed with the site team together with plans for correction, and can expect to have a written report from the monitor.

The study monitor can expect to be given access to all study related material, and adequate space and privacy in order to review the materials, including access to source documents as required.

Monitoring within PaCCSC will also involve training of other study site staff. This will be undertaken through a process of rotation. Each monitoring visit will be conducted by the coordinating site together with staff from a second study site.

The objectives of this SOP are to:

- define the role and responsibility of PaCCSC monitoring
- describe the monitoring process
- describe the process of reporting results and action that arises from those results
- ensure there is capacity building across the network by ensuring mutual monitoring at a site level in conjunction with the National Project Officer

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### Other related SOPs

KPI Compliance  
Auditing

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### Attachments

Monitoring plan.xls (Example)  
Protocol Violation

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### References

NHMRC National Statement on Ethical Conduct in Research Involving Humans 1999 (accessed 250207) <http://www.nhmrc.gov.au/publications/files/e35.pdf>

Guideline for Good Clinical Practice ICH Harmonised Tripartite 1996 (accessed 250207) <http://www.ich.org/LOB/media/MEDIA482.pdf>

'Guidelines for monitoring of clinical trials for cooperative groups, CCOP research bases, and clinical trials support unit (CTSU). National Cancer Institute. October 2006.

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Annotated with TGA comments 2000 (accessed 250207)  
<http://www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf>

Joint NHMRC/AVCC Statement and Guidelines on research practice 1997 (accessed 250207) <http://www.nhmrc.gov.au/funding/policy/researchprac.htm>

Liu MB, Davis K. Lessons from a horse named Jim. Duke Clinical Research Institute. 2001.

IUPUI/Clarian Standard operating procedure for Auditing of research involving human subjects. v04/05 (accessed 250207)  
[http://www.iupui.edu/~respoly/human-sop/SOP%20%20Auditing%20of%20Research%20Involving%20Human%20Subjects%20\(04-05\).pdf](http://www.iupui.edu/~respoly/human-sop/SOP%20%20Auditing%20of%20Research%20Involving%20Human%20Subjects%20(04-05).pdf)

Westat CTSU Work Procedures. CTSU 7.1, Auditing procedures, revised 03/31/2006.

## Definitions

### Monitoring

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, SOP's, Good Clinical Practice, and the applicable regulatory requirements.

Monitoring is a process internal to the clinical trial, where the trial management, investigators or other groups within the trial can monitor their own progress, and ensure that the trial complies with internal and external requirements.

This process differs from Audit which is a process conducted by personnel external to the trial. Monitoring enables problems and deficiencies to be detected and corrected at an early point, to be dealt with prior to auditing and to assist sites' ability to meet trial requirements. Monitoring enables the study team to be confident about undergoing an external audit process.

Monitoring is the responsibility of the sponsor (the Coordinating Agency).

### Monitor

An individual trained in research who has also undergone specific training on audit related activities. Within PaCCSC the monitors may be the site coordinators who, in conjunction with the Project Officer, will monitor other PaCCSC investigating sites.

The study monitor should be thoroughly familiar with the study protocol, investigational product, consent processes and related trial requirements.

The study monitor will undergo training at the coordinating site, where the first monitoring visit will take place under the supervision of the PI. Any adjustments to the monitoring plan or procedures will be reviewed at this time prior to other sites being monitored. All monitoring documents will be reviewed and revised prior to the first visit.

The monitor is responsible for

- Answering trial related questions
- Providing additional support to the site in order to successfully complete their recruitment and regulatory obligations
- On site data verification
- Resolution of outstanding data queries
- Documenting and reporting visits
- Completing a monitoring log for filing at the study site

### Monitoring Report

A written evaluation by the monitor of the results of the monitoring visit.

## Procedure

### Timeframe

Monitoring will be undertaken at least at the midway point of recruitment to the study and at study conclusion. Additional monitoring may be conducted at the request of the PaCCSC Trail Management Committee or Data Safety Monitoring Board.

All sites will be monitored within 6 weeks of each other at each proposed timepoint.

### Monitoring sites

The sites to be monitored will be each individual study site. The study sites are the participating sites for phase III studies for PaCCSC;

### Personnel involved

The study site monitor will be the Project Officer in conjunction with a site coordinator from another study site. All sites will be monitored by two clinical study staff. This will provide opportunity for training of study monitors across all sites and to enable validation and discussion of findings.

For example;

The SA site may be monitored by the Project Officer from the coordinating site, together with the site coordinator from the WA site. The WA site will then be monitored by the Project Officer from the coordinating site together with the site coordinator from the SA site. This mutual monitoring will achieve 2 aims;

1. to provide a level of monitoring the monitor through the involvement of others
2. build the capacity of other senior research staff to undertake monitoring for the future

All visits will be in the presence of the site investigator and/or the site coordinator of the site being monitored if they desire to be present.

### Scope

Each monitoring visit is designed to ensure that;

- The trial is conducted according to the protocol
- Deviations from the protocol are documented and reported
- Data on CRF's are accurate and complete
- Patients enrolled meet the eligibility criteria
- Personnel at each site are meeting GCP obligations
- Randomisation and allocation procedures are being followed.

The monitor may be able to discuss recruitment and retention issues, clarify protocol issues, and provide training and support, such as worksheets and tracking documents.

### Preparation for a visit

The investigator and study personnel can smooth the monitoring process by undertaking some prior preparation, including;

- Making a quiet space available, with adequate office access (telephone, fax, photocopier if possible)
- Completing and having available all CRF's
- Confirm that all SAE's have been submitted and are available
- Organise study file documents
- Have all consent forms available
- Have access to the source data
- Schedule time to be available to discuss study progress with the monitor.

## Visit

The visit will be conducted looking at specific components.

Study site:

1. Ethics and consent documentation will be assessed
2. Review of patient records for
  - a. Consent
  - b. Eligibility
  - c. Treatment
  - d. Evaluation of outcome
  - e. Adverse events
  - f. General data quality and completeness
3. Review of essential documents
  - a. Folders and files
  - b. Communications
  - c. Invoicing and accounting
  - d. Other documentation
    - File notes
    - Record of faxed requests
    - Training records
    - Invoicing and accounting

Each of the above components will be coded according to the level of deficiency

- a. None
- b. Minor
- c. Major

The deficiencies for each component at each location will be assigned an assessment of

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

A series of forms (see example Monitoring Plan.xls) will be developed for each study to ensure the major points for each study time point are monitored and assessment made regarding deficiency grading.

The coding schedule is summarised in the following table.

Location	Component	Level of deficiency		
		None	Minor	Major
Study site	Ethics and consent process	<ul style="list-style-type: none"> <li>▪ All approvals recorded and filed, annual reports submitted on time and re-approved</li> </ul>	<ul style="list-style-type: none"> <li>▪ Protocol re-approval delayed 30 days or less</li> <li>▪ Superseded consent form used for 90 days after new updated consent form available</li> </ul>	<ul style="list-style-type: none"> <li>▪ Protocol never approved</li> <li>▪ Approval documents missing</li> <li>▪ Patient recruitment prior to approval</li> <li>▪ Missing or expired re-approval</li> <li>▪ Reportable adverse events reported late or not reported</li> <li>▪ Failure to submit externally required SAE's</li> <li>▪ Failure to submit protocol amendments</li> <li>▪ Ethics committee does not meet national guidelines (not appropriate to provide approval)</li> <li>▪ Omission of required elements in the informed consent form</li> <li>▪ Use of non approved consent form</li> </ul>
	Patient records		<ul style="list-style-type: none"> <li>▪ &lt;6 month data delay</li> </ul>	<ul style="list-style-type: none"> <li>▪ Consent form not signed by all appropriate people/ missing/ signed after treatment commenced</li> <li>▪ Non approved version used, does not contain updates</li> <li>▪ Consent not protocol specific</li> <li>▪ Did not meet eligibility, could not be confirmed at visit</li> <li>▪ Patient existence could not be confirmed</li> <li>▪ Incorrect treatment used</li> </ul>

				<ul style="list-style-type: none"> <li>▪ Treatment outcome not measured on completion</li> <li>▪ Unjustified delay in treatment</li> <li>▪ Failure to assess and report adverse events</li> <li>▪ Follow up to SEA's not conducted</li> <li>▪ Failure to report AE or SAE</li> <li>▪ Recurrent missing documents</li> <li>▪ Frequent data inaccuracies</li> <li>▪ Altered data without explanation</li> <li>▪ &gt;6 month data delay</li> </ul>
	Essential documents	<ul style="list-style-type: none"> <li>▪ All essential documents files either within Investigator folder, project officer folder, or suitable filing cabinet</li> <li>▪ Current and previous versions of documents available</li> <li>▪ All invoicing and accounting documents available, clear and demonstrate compliance with agreed procedures and expenditure</li> </ul>	<ul style="list-style-type: none"> <li>▪ Previous versions not filed to demonstrate history of study</li> <li>▪ Communications filed sporadically, some missing</li> <li>▪ Invoicing documents available but are poorly filed and are unclear at times</li> </ul>	<ul style="list-style-type: none"> <li>▪ No access to essential study documents</li> <li>▪ Current versions not available</li> <li>▪ Many missing documents demonstrating poor site management of study</li> <li>▪ Invoicing and accounting does not demonstrate compliance with agreed expenditure</li> </ul>
Randomisation centre	Maintenance records		<ul style="list-style-type: none"> <li>▪ Poor record of maintenance schedule, not comprehensive</li> </ul>	<ul style="list-style-type: none"> <li>▪ No record of maintenance of equipment related to the study</li> <li>▪ Records cannot be clearly linked to a specific study machine</li> </ul>

			enough to demonstrate high level of achievement	<ul style="list-style-type: none"> <li>▪ Record shows that equipment faults have not been rectified</li> </ul>
	Blinding checks			<ul style="list-style-type: none"> <li>▪ Systematic failure to record of each machine being checked for gas emission prior to supply on each occasion</li> <li>▪ Checking process cannot be verified</li> </ul>
	Allocation		<ul style="list-style-type: none"> <li>▪ Allocation record has been altered, file notes provide full explanation of alteration, and new value can be confirmed</li> <li>▪ Notification of allocation to Central Registry is frequently late</li> </ul>	<ul style="list-style-type: none"> <li>▪ Alteration to record of allocation and no explanation is given (file notes absent)</li> <li>▪ Patient IDs do not exist in study site records</li> <li>▪ Patient ID repeated within tables</li> <li>▪ Non compliance with notification to Central Registry</li> </ul>
	Other documents		<ul style="list-style-type: none"> <li>▪ Related documents are filed but with no particular order</li> </ul>	<ul style="list-style-type: none"> <li>▪ Documents related to randomisation requests and/or confirmation missing</li> </ul>

The coding procedure has been adapted from 'Guidelines for monitoring of clinical trials for cooperative groups, CCOP research bases, and clinical trials support unit (CTSU). National Cancer Institute. October 2006.

## Reports

At the conclusion of a site visit an exit interview will be held with the site investigator and project staff highlighting the main summary findings of the visit and the likely content of the report. A report will be produced, in writing, and presented to the study site within 14 days, after having been reviewed by the study Coordinating Investigator. The report will contain;

- Date/s of monitoring visit
- Name of site and site personnel
- Name of monitor
- A summary of the review process
- A summary of the findings, for the site and the company (will contain a description of all major deficiencies in the 2 locations and 7 components under review)
- Conclusions and recommendations (a general assessment of the review)

The report may require a response by the study site to specific issues raised during the monitoring visit. This response should be provided, in writing, within 30 days of receipt.

The study monitor will provide a study wide report on conclusion of all visits, this will be reviewed by the Coordinating Investigator and used for reporting to;

- The DSMB
- the funding organisations
- each site investigator
- Research ethics committees (IRB's) at each site

This report will be written within 60 days of the last response to a site visit report, and will be endorsed for circulation within 30 days of submission.

1 <sup>st</sup> Visit	Last visit	Site report	Report response	Submission of summative report	Endorsed for circulation	Total timeframe
0	6 weeks	14 days	30 days	60 days	30 days	11 weeks

**Protocol violation.**

**Principal investigator** \_\_\_\_\_ **Participant ID** \_\_\_\_\_

**Date of event** \_\_\_\_\_

**Date became known** \_\_\_\_\_

**Date form completed** \_\_\_\_\_

**Type of violation**

<input type="checkbox"/>	Randomisation of ineligible patient
<input type="checkbox"/>	Enrolled outside prescribed time periods
<input type="checkbox"/>	Incomplete data for enrolled patient
<input type="checkbox"/>	Treatment cannot be verified
<input type="checkbox"/>	SAE not reported
<input type="checkbox"/>	

**Description**

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**Action taken**

<input type="checkbox"/>	Patient withdrawn
<input type="checkbox"/>	Data inclusion to be modified
<input type="checkbox"/>	DSMB notified
<input type="checkbox"/>	Ethics committee notified
<input type="checkbox"/>	
<input type="checkbox"/>	

**Signatures**

Monitor \_\_\_\_\_ Date \_\_\_\_\_

Site investigator \_\_\_\_\_ Date \_\_\_\_\_

Sample Only

Start up visit

Site \_\_\_\_\_

Date \_\_\_\_\_

Trial area	Specific check	Completed	NA	Trigger	Comments
Training and set-up	Copy of investigator CV's				
	Start up document signed				
	Provision of protocol			Check for protocol questions	
	All participant documents and CRF's				
	SOP's				
	Adverse event reporting				
	Authorship				
	Data management				
	Randomisation - at site				
	Unblinding				
	Ethics committee				
Administration	Authorisation document to company			Signed and completed	
	Ethics clearance			Letter of approval	
	Invoice and account procedures			Account set up, invoicing arranged	
	Study folders			Investigator and PO folders	
	Secure filing			Lockable, secure	
	Data base access			Paasword, internet access	
	Prepared patient folders			Nurse folder, patient diaries	
	Equipment			BP, ox sats	
Recruitment	Recruitment base discussed and identified				
	Information to likely referral base				
	Master list prepared				
	Approved PIS and Consent				

Trial area	Specific check	Completed	NA	Trigger	Comments
Randomisation centre	SOP's				
	Randomisation - at company				
	Unblinding				
	File notes				
	Randomisation folder				
	Strata logs				
	Maintenance schedule and record sheets				
	Testing record for each delivery				
	Fax sheets				
	Concentrators			Look and sound identical	
	Communication strategy clear			Who and how to contact	

Summary assessment

Acceptable

Acceptable, needs follow-up

Not acceptable

Monitor signature \_\_\_\_\_

Date \_\_\_\_\_