murdoch children's research institute

Clinical Monitoring Plan Template for Investigator-initiated Trials

Notes to users

Why do you need a Clinical Monitoring Plan?	In accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18.7 (that was formerly adopted by the TGA with annotations on 8 February 2018), the Sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. For investigator-initiated trials, the Sponsor is the lead Principal Investigator/Coordinating Principal Investigator, also referred to as the Sponsor-Investigator. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.
Why use this template?	This template is appropriate for clinical trials of investigational products but may be adapted for all clinical research. The information requested by this template will help to ensure that the Sponsor-Investigator meets their Sponsor responsibilities for monitoring their trial in accordance with the Integrated Addendum to ICH E6 (R1) Guideline for Good Clinical Practice E6 (R2) Section 5.18 Monitoring.
How to use this template?	*Purple italics* under each section heading and within each section is used to indicate what information that should be contained in that section. *Green italics* is used for suggested or example wording in standard sections. You will need to input your study specific information under each heading and remove explanatory information. It is not necessary to include text under a major numbered heading (e.g., 1, 2) that is immediately followed by numbered subheadings, (e.g., 2.1, 2.2). That is because certain numbered headings are used only for organisational purposes. Text should be entered under all numbered subheadings. As this is a template, users are reminded that not all sections or examples may be applicable to their study. Please delete any sections that are not relevant to your study. A glossary has not been included in this document. Please refer to CRDO SOP, "Monitoring Visit Activities for Clinical Trials of Investigational Products" for a full glossary of terms.

Does the Clinical Monitoring Plan require ethics approval?	No but it is recommended you contact the Research Ethics Governance Office to seek guidance on whether the HREC would like to review the CMP prior to providing ethics approval for your trial. This is most likely if your trial is using an investigational product and is deemed high risk in terms of participant safety and/or data integrity.
Version	Clinical Monitoring Plan Template for Investigator-Initiated Trials Version 1.0, Dated 01 MAY 2018 This template has been developed by the Clinical Research Development Office (CRDO) for the Melbourne Children's Trials Centre.

Clinical Monitoring Plan
Protocol Number: *[insert protocol number]*

[Insert Full Study Title]

Document History:

Version No.	Version date	Major changes
V1 (Initial)	<insert>	

By signing below, I acknowledge my agreement to this plan.

Sponsor-Investigator

[Use Coordinating Principal Investigator if a multi-centre study. Use Principal Investigator if a single centre study.]

Name: _____

Signature: _____ Date: _____

Site Name: _____


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Table of Contents

1.0 LIST OF ABBREVIATIONS

All abbreviations used in the document, including appendices. Accepted international medical abbreviations should be used. All abbreviations should be spelled out when first used in the text, followed by the abbreviation in parentheses. Common units of measure like mg or mL don't need to be defined in the text or this list.

The following list is an example only. Add and delete abbreviations as appropriate for your clinical monitoring plan.

AE	*Adverse Event*
COV	*Close-Out Visit*
CMP	*Clinical Monitoring Plan*
CPI	*Coordinating/Lead Site Principal Investigator*
CRF	*Case Report Form – paper and electronic*
CRO	*Clinical Research Organisation*
CTN	*Clinical Trial Notification*
CTX	*Clinical Trial Exemption*
ED	*Essential Documents*
GCP	*Good Clinical Practice*
HREC	*Human Research Ethics Committee*
ICH	*International Conference on Harmonisation*
ISF	*Investigator Site File*
MCTC	*Melbourne Children's Trials Centre*
MCRI	*Melbourne Childrens Research Institute*
PI	*Principal Investigator*
PICF	*Participant Information and Consent Form*
RCH	*Royal Children's Hospital*
SAE	*Serious Adverse Event*
SC	*Study Coordinator*
SIV	*Site Initiation Visit*
SOP	*Standard Operating Procedure*
SSI	*Significant Safety Issue*
SUSAR	*Suspected Unexpected Serious Adverse Reaction*
TMF	*Trial Master File*

USM *Urgent Safety Measure*

2.0 ROLES & RESPONSIBILITIES

Indicate who will be responsible for monitoring the coordinating lead site and participating sites (if applicable). Note the Melbourne Children's Trials Centre has limited capacity to assist with monitoring sites. Sponsor-Investigators are strongly encouraged to include monitoring costs in any grant applications and consider using Monitors from a Clinical Research Organisation (CRO) but this may not always be feasible and other options may be investigated, including using staff from the Coordinating Lead Site to monitor participating sites. Indicate qualifications of monitors.

For the purpose of this study, the Coordinating Lead Site (MCRI/RCH) will be monitored by staff from Neuroscience Trials Australia, a Melbourne-based Clinical Research Organisation (CRO). Participating sites (WCH, PCH) will be monitored by staff from the Coordinating Lead Site. All monitors are qualified by education and experience to monitor the conduct of clinical research study sites according to applicable SOPs, including the CRDO SOP, Monitoring Visit Activities for Clinical Trials of Investigational Products, ICH GCP and local requirements.

3.0 INTRODUCTION

Briefly describe the purpose of the Clinical Monitoring Plan (CMP). The Sponsor-Investigator should be listed as a collaborator and involved in the process of CMP creation. The sentence listing "monitoring tasks performed in accordance with" should be modified to reflect a regulated [conducted under a Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX)] or non-regulated study. Current language reflects a regulated study.

This Clinical Monitoring Plan (CMP) establishes the guidelines for conducting monitoring visits and related tasks for monitoring Murdoch Children's Research Institute (MCRI) Protocol <Insert Protocol Number>, <Insert Full protocol title> and is a requirement of the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2).

The CMP was developed by MCRI's Melbourne Children's Trials Centre (MCTC) in collaboration with the Principal Investigator, <Insert Name>. Monitoring tasks will be performed in accordance with the protocol-specific requirements, the CRDO SOP Monitoring Visit Activities for Clinical Trials of Investigational Products, the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) – annotated with TGA comments (Current Step 4 version, dated 9 November 2016) and other applicable requirements.

4.0 MONITORING COMMUNICATION PLAN

Describe the process for distributing monitoring communication. Ensure that all stakeholders are reflected in the plan (Sponsor-Investigator, PI, CRO, HREC, TGA).

The Monitor will send monitoring communication including site visit confirmation emails, agendas, follow-up emails etc, to the following:

Coordinating Lead Site Contacts

Role	*Representative*
Coordinating Site Lead PI (CPI)	*<Insert Name>*
Study Contact	*<Insert Name>*

Participating Sites Contacts

Role	*Representative*
<Insert Site Name>	
Participating Site PI (PI)	*<Insert Name>*
Participating Site Contact	*<Insert Name>*
<Insert Site Name>	
Participating Site PI (PI)	*<Insert Name>*
Participating Site Contact	*<Insert Name>*

5.0 TYPES OF VISITS AND MONITORING ACTIVITIES

Describe the types of monitoring visits for the study, including onsite and remote monitoring. Indicate what activities will be conducted and the monitoring method to be used, i.e onsite (in person) or remote (centralised) monitoring. The latter involves the Monitor having regular contact with the site by phone and email and reviewing automated reports generated from electronic CRF database. Provide the rationale for the monitoring methods chosen. Amend list below to only include the types of visits planned for the study. If the study is single centre, modify text below to remove reference to CPI.

Note: Site Initiation is not considered a monitoring activity. The Sponsor-Investigator will be responsible for activities that occur during the SIV. These activities will be delegated to members of the research team at both the Coordinating Lead Site and Participating Sites.

There will be three types of monitoring visits for this study.

1. *Interim Monitoring Visits (hereafter referred to as Monitoring Visits) will be conducted to verify that, 1) the Investigator is conducting the study in accordance with the protocol, applicable SOPs, Good Clinical Practice (GCP) and applicable regulatory requirements; 2) participants' safety, rights and well-being are being protected; and 3) data recorded on the case report forms are accurate, complete and verifiable from source documentation. These activities will be performed using both on-site and remote (centralised) monitoring.*
2. *For-cause visits will be conducted to address any unanticipated issues that arise which require training, remediation or other situations in which the site requires assistance. For-cause visits can be mandated by the Sponsor-Investigator, or can be requested by the site. These visits may involve either on-site monitoring or remote monitoring.*
3. *A Close-Out Visit (COV) will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. The*

COV for the Coordinating Lead Site will be conducted on site. The COV for participating sites will be conducted on-site or via phone, depending on individual site circumstances.

6.0 ON-SITE VISIT SCHEDULING

Describe the process for scheduling monitoring visits and expectations for the site study staff during the visits. If the study is single centre, modify text below to remove reference to CPI. Include language detailing the frequency of monitoring and the expectation of the site and monitor with respect to timeline for visit scheduling requests.

The Monitor will work with the Coordinating Site Lead Principal Investigator (CPI)/Participating Site Principal Investigator (PI) and Site Primary Contact to schedule monitoring visits. The CPI will be informed of visit scheduling at Participating Sites.

Prior to the visit, the PI will receive a visit confirmation email, agenda and a list of participant files to be monitored. Please see Section 8 for details on the selection of participant files for review. The Monitor will ensure that this information is communicated to the site personnel within a mutually agreed upon timeframe to allow sufficient time for record requests. The PI and research staff will be expected to secure a workspace for the Monitor and to be available during the visits to facilitate Monitoring activities. Depending on how many participants have been enrolled/randomised since the last monitoring visit, visits will take 1-2 days.

The Monitor will be available at the end of each monitoring visit day to discuss findings and answer questions from the study staff. The Site PI and Primary Site Contact are also expected to be available for a wrap-up meeting at the conclusion of the visit, as schedules allow. These expectations will be explained in the visit confirmation email.

Each site will have an on-site monitoring visit at least once per year during the active phase of the study. The first on-site monitoring visit should occur within 6-8 weeks of the first participant's first dose of investigational product. Thereafter, monitoring visits will be conducted annually until the last participant has completed the follow-up evaluations according to the protocol. Additional visits will only be scheduled if required.

The table below may be used when the Coordinating Lead site is responsible for monitoring participating sites and an independent Monitor is responsible for monitoring the lead site. Modify or delete as appropriate for your study.

Type of Visits and Monitor Responsible

	Undertaken by	
Type of Visit	*[Insert name of CRO] Monitor*	*Lead Coordinating Site Monitor*
Annual Monitoring Visits at <Insert Site Name>	*X*	
Annual Monitoring Visits at		*X*

<Insert Site Names>		

7.0 ESSENTIAL DOCUMENTS/TRIAL MASTER FILE

Describe required essential documents (ED), process for review, collection and submission of ED as it relates to monitoring. The list below is the minimum list identified by ICH GCP. Add additional documents if required to confirm the validity of the trial conduct and integrity of data collected. Identify owner of the study's Trial Master File (TMF). If the study is single centre, modify text below to remove reference to CPI and coordinating lead site.

7.1 Essential Documents to be filed by Participating Trial Sites

An electronic folder, which for purposes of this CMP will be defined as the Investigator Site File (ISF), will be maintained at each trial site and serve as the central source for essential document (ED) maintenance at the site. Documents with original signatures must also be maintained in a paper ISF. This includes study-level and participant-level documents (i.e. Clinical Trial Research Agreements and Participant Information and Consent Forms [PICFs]).

The following documents represent a complete site essential document packet and are to be maintained in the ISF:

- *The original HREC-approved protocol and any amendments to the protocol, Protocol Amendment(s) and Signature Pages, sample Case Report Form*
- *All versions of the informed consent, advertisements for participant recruitment, diaries and study documents provided to families.*
- *The original Investigator's Brochure / Product Information and any amendments*
- *Documented evidence of submission of Investigator's Brochure (IB)/Product Information to the RCH HREC and written acknowledgment from RCH HREC of receipt of the IB/Product Information.*
- *Annual Reports, Annual Safety Reports, expedited safety reports, serious breach reports, notification of changes to the study team, submitted to RCH HREC/local governance office/TGA/participating sites, as appropriate*
- *All correspondence between the CPI/Site PI and RCH HREC/local governance office, as appropriate. Includes submissions, approvals and responses to questions/comments.*
- *Documented evidence (e.g. Note to File) and reporting of non-compliance to GCP, SOPs, protocol to Investigator-Sponsor*
- *Principal Investigator's (PI) and Associate Investigator(s) [Sub-Investigator(s)] Curriculum Vitae (CV)*
- *Delegation Log – up-to-date, all tasks appropriately delegated*
- *Training Log – incudes trial-specific and GCP, valid for duration of involvement in study*

- *Laboratory Certifications*
- *Laboratory Reference Ranges*
- *Screen Log, listing all participants with a signed informed consent and, if the participant was randomised/treated. For any participant not randomised/treated, the reason they were not randomised/treated.*

7.2 Essential Documents to be Filed by Sponsor-Investigator in the Trial Master File (TMF) – excluding Site Information File subfolder

The Sponsor-Investigator is responsible for maintaining the Trial Master File (TMF). The Trial Master File is maintained in electronic and paper formats and owned by the Sponsor-Investigator. Documents cited in Section 7.1 and 7.2 with original signatures must be maintained in the ***paper*** *TMF/ISF. This includes study-level and participant-level documents. All other essential documents will be maintained in the electronic TMF only.*

Essential Documents that are common to all sites and essential documents specific to the Coordinating Lead Site must be filed in the TMF.

Need to decide if this needs to be expanded. E.g. Sponsor reporting of serious breaches may not be clear.

1. *For the lead site only – safety reporting to participating site Investigators/approving HREC/TGA*
    - *SSIs*
    - *USMs*
    - *SUSARs (TGA only)*
    - *Annual Safety Report (HREC only)*
    - *Updated Product Information/Investigator Brochure, if applicable (excluding TGA)*

7.3 Essential Documents to be Filed by Sponsor-Investigator in the TMF Site Information File subfolder (applicable for multi-centre studies ONLY)

Essential documents that are specific to a Participating Site must also be filed in a separate subfolder of the TMF called the Site Information File. The responsibility to hold and maintain an up-to-date TMF Site Information File, including all superseded documents, is with the Sponsor-Investigator.

Documentation that is site-specific includes the following:

1. *Study Contact List*
2. *Site-specific PICF (current and superseded)*
3. *Ethics and Governance*

- *Governance approval letter (current and superseded)*
- *Documentation of local governance submission*
- *Annual and final study reports*

4. *Re-identifiable Screening Log*
5. *Safety reporting to the Sponsor-Investigator:*
    - *All SAEs, except those identified in the protocol as not requiring immediate reporting*
    - *All SUSARs*
    - *All Urgent Safety Measures (USMs) instigated by the site*
    - *AEs and laboratory evaluations critical to safety (specified in the protocol)*
    - *All serious breaches*
6. *Safety reporting to the local research governance office*
    - *All SSIs*

      Note: The Sponsor-Investigator will report SSIs, including USMs, to Investigators for forwarding to their local RGO.
    - *All local SUSARs*
    - *All local serious breaches that have been confirmed by the Sponsor-Investigator*
    - *RGO acknowledgement of submitted reports (SSIs, local SUSARs)*
    - *Any other safety reporting required by the local governance authorisation.*
7. *Monitoring reports and associated correspondence*
8. *Local Lab(s)*
    - *Lab certification (Not required for labs undertaking exploratory testing)*
    - *Lab reference ranges*
    - *Tissue log (if applicable)*
9. *Study Team Documentation*
    - *Delegation and Signature Logs*
    - *Qualifications (CV) and Training Logs*
    - *Copy of SIV Presentation and any other study training materials used at site*
10. *Supplies / Shipping Records - Documentation relating to provision of study supplies (excluding investigational product)*
11. *Legal Documentation*

- *Copy of agreements as applicable (e.g. Clinical Trial Research Agreement, Material Transfer Agreement, Confidentiality Agreement)*
- *Correspondence with hospital lawyers*

12. *Finance Documentation*
13. *Correspondence – all correspondence pertinent to study conduct at site*
14. *Regulatory Documents – copies of all TGA correspondence, e.g. submission of CTN, CTN acknowledgement, CTN completion, submission of SSIs*
15. *Investigational Product – During the study this section to contain a file note stating location of documents in the site Pharmacy Folder. At end of study, a copy of documentation in site Pharmacy Folder is to be filed in this section, including:*
    - *Product delivery to site receipts*
    - *Product inventory including dispensing to and returns by participants, product expiry, product disposal*
    - *Product temperature logs*

7.4 Monitor's Role in Essential Document Maintenance

During the course of routine Monitoring visits, the Monitor will review the TMF/ISF for accuracy and completeness.

As noted in section 7.2, the CPI is tasked with maintenance of the TMF. The Monitor will support this endeavour by reviewing the essential documents for completeness and accuracy. No original documents will be collected. The Monitor will alert the study staff to discrepancies and upcoming expiration dates.

8.0 REVIEW OF SOURCE DOCUMENTS AND CASE REPORT FORMS (CRFs)

Modify text as appropriate for the study. Keep in mind the purpose of reviewing the source documents and CRF is to confirm the study is being conducted according to the protocol and applicable regulations, including GCP, and confirm accurate reporting of participant safety data and study endpoints. List the critical data that will be monitored, the percentage of source data verification to be undertaken and the percentage of participants. Generally for a risk-based monitoring approach, this will be 100% SDV for all critical data for all participants.

The process for source data verification will be the same for the Coordinating Lead Site and all Participating Sites. This study will use a risk-based monitoring approach, with ***100% source data verification for critical data and processes for 100% of patients randomised at each site****, with the exception of the first participant randomised where 100% source data verification will be performed for all data and processes.*

Monitoring will include both on-site and remote monitoring.

At each on-site monitoring visit, the Monitor will verify the following critical data/processes:

1. *Informed consent was obtained appropriately*
    - *Verify each participant entered into the study has a properly signed and dated HREC - approved informed consent and there is documentation confirming that the study was explained to the participant and that consent was obtained before conducting any study-related procedures. In cases where the person giving consent (i.e. the participant or the parent/legal guardian) cannot read, the Monitor must verify that an impartial witness has signed the form.*
    - *Verify the correct version of the informed consent was signed and revised versions of the consent form are signed, if applicable. Deviations to the informed consent process are documented and all applicable parties are informed.*
2. *The investigator is following the HREC-approved protocol and all approved amendment(s), if any.*
3. *The participants enrolled in the study meet the protocol criteria for eligibility.*
    - *If the Sponsor-Investigator has provided a waiver for the enrolment of an ineligible participant, the signed waiver must be filed in the participant's shadow file.*
    - *A serious breach is deemed to have occurred if an ineligible participant is enrolled without a waiver by the Sponsor-Investigator. In such cases, the PI must report the serious breach to the Sponsor-Investigator within 72 hours of becoming aware of the breach.*

      Note: The Sponsor-Investigator must report the serious breach to the reviewing HREC without delay and no later than 7 calendar days of confirming the serious breach occurred.
    - *If any Corrective and Preventative Action plans have been developed to address serious breaches related to enrolment, verify that these are being actioned by relevant site staff.*
4. *For participants that are randomised/receive the investigational product/intervention, their medical record references the study and indicates that the participant is receiving an investigational product/intervention. The medical record should contain progress notes, laboratory reports, concomitant therapies and adverse medical experiences.*
5. *Conduct and documentation (in medical records, CRFs, shadow charts (if used), TMF) are complete, accurate, consistent and adhere to the protocol for procedures and assessments related to:*
    - *Study endpoints*
    - *Protocol-required safety assessments*
    - *Evaluation, documentation and reporting of serious adverse events, SUSARs, Significant Safety Issues, participant deaths and withdrawals related to adverse events)*

6. *Conduct and documentation (in medical records, CRFs, participant shadow files (if used), TMF) are complete, accurate, consistent and adhere to the protocol for procedures related to trial integrity, such as:*
    - *The study blind is maintained (Delete if not applicable)*
    - *Any dose modifications (and the reason for the dose modification) for the investigational product are documented for each participant in both the medical record and the CRF.*
7. *Documentation and reporting of serious breaches meet the principles of ALCOA (attributable, legible, contemporaneous, original, accurate), plus complete and traceable.*
8. *Discrepancies between the source documents and the CRFs should be brought to the attention of the site staff and corrections made to the CRFs by the investigational site staff.*

Remote monitoring will be used to:

1. *Verify the correct version of the informed consent was signed and revised versions of the consent form are signed, if applicable.*
    - *The participating site to send redacted scanned signed PICF to the Monitor. The participants name should be redacted so that only the initials are visible. Frequency of review will depend on rate of recruitment and will be determined by the Monitor.*
    - *Monitor to compare date of signed PICF with documentation of informed consent in CRF*

    Note: Onsite monitoring of signed consent forms is still required to confirm the participant's full name, original signature, that the participant was consented prior to study procedures, and that proper consent processes were followed by the site.
2. *Review Screening Logs monthly – verify number of patients screened and screen failure rates as expected*
3. *Review Delegation and Training Logs monthly – verify they are current and tasks delegated appropriately*
4. *Review Investigational product Temperature Logs bimonthly (if applicable)*
5. *Once electronic CRFs are available, check entries/ REDCap reports for completeness of data, sites with a higher frequency of protocol deviations and screen failures.*
6. *Review maintenance of the TMF Site Information File for each participating site..*
7. *Maintain relationship with site staff with regular discussions via telephone or e-mail to follow-up on study progress or to answer questions.*
8. *Review safety reports in accordance with safety monitoring requirements outlined in protocol and report to stakeholders in accordance with NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods (November 2016), the protocol, approving HREC and local governance office.*

9.0 REVIEW OF INVESTIGATIONAL PRODUCT ACCOUNTABILITY RECORDS

Delete this section if not applicable.

If investigational product is being used, describe process for verifying the following:

1. *That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.*
2. *That the investigational product(s) are supplied only to participants who are eligible to receive it and at the protocol specified dose(s).*
3. *That participants are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).*
4. *That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.*
5. *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-Investigator's requirements (e.g. protocol, SOPs describing process for Investigational Product Accountability).*

Include frequency of monitoring, what must be done on-site and what can be done remotely.

For blinded studies, explain how the blind will be maintained during product accountability activities. If there is a risk that handling the investigational product or viewing the product accountability records will unblind the Monitor, a separate unblinded Monitor must undertake these activities. In such cases, contact CRDO to request the CRDO template, "Plan for Unblinded Monitoring of Investigational Product - a Template for Investigator-Initiated Trials".

10.0 REVIEW OF INVESTIGATOR AND SITE STAFF SUITABILITY

In accordance with ICH GCP Section 5.18.4, the Monitor should verify that the Investigator has adequate qualifications and resources throughout the trial period and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.

At each monitoring visit, the Monitor should confirm the continued ability and commitment of the Investigator and site staff to conduct the study. This includes the following tasks:

16. *Verify that the PI and site personnel are adhering to the protocol and conducting the study according to regulatory requirements, GCP and study-specific standard operating procedures (SOPs).*
17. *Verify that the PI is providing adequate supervision to any individual or party to whom they have delegated trial-related duties and functions. Evidence of supervision may include email correspondence, meeting minutes with attendees listed etc.*
18. *Review the Delegations Log and Training Log to ensure it is complete, current and delegation is in accordance with qualifications and training.*
19. *Ascertain the participant recruitment rate and determine if enrolment is adequate.*

11.0 MONITORING REPORTS / ACTION ITEMS

The monitor should provide a written Monitoring Visit Report to the Coordinating Principal Investigator after each on-site visit and after centralised monitoring activities in a timely manner for review and follow up. The report should provide sufficient detail to allow verification with the Clinical Monitoring Plan. Note it is recommended Monitors use a Monitoring Visit Report template such as the template developed by CRDO and available on the CRDO website.

Monitoring visit findings and resulting action items will be documented in Monitoring Visit Reports. The Monitor will complete a written Monitoring Visit Report and provide a follow up letter to identified study team members as noted in Section 4.0 within 10 business days of the visit. The follow-up letter should be signed and filed in the ISF and TMF. The Monitoring Visit Report is not for distribution to the site and should be filed in the TMF only.

The Monitor will work with designated site staff to resolve any outstanding action items as communicated in the follow-up letter. At a mutually agreed upon time, or 4 to 6 weeks post visit, whichever is earlier, the Monitor and site research staff designee will discuss via telephone conference or email all resolved, in process, and pending action Items. At this time the need for, and frequency of subsequent meetings will be discussed.