Clinical Site Monitoring
DMID Protocols

Version 2.0 11-Aug-2006
Clinical Monitoring of DMID Sponsored Clinical Trials

• Contracted to PPD, Inc.
  Wilmington, North Carolina

• PPD Clinical Monitoring Group is staffed by Clinical Research Associates (CRAs) with a background in the health sciences and training in monitoring of clinical trials and all applicable regulations
Monitoring Objectives

• Ensure timelines are maintained
• Ensure compliance of all Essential Regulatory Documents per regulations (i.e., DMID, ICH/GCP, Federal)
• Ensure Protocol compliance
• Ensure Clinical Monitoring is completed per current version of Clinical Monitoring Plan
Monitoring Objectives

• Ensure Proper Initiation/Documentation of the Informed Consent Process
• Ensure protocol enrollment eligibility criteria.
• Ensure database entry is complete and consistent between Case Report Forms and Source Documents
• Ensure Test Article Accountability is handled and accurately documented per DMID IP procedural guidelines.
Monitoring Objectives

• Ensure Laboratory procedures are documented per current SOP’s and QA policies
• Ensure specimen storage per protocol
• Ensure the rights and well-being of human subjects are being protected
• Ensure that any safety issues have been identified
Types of Monitoring Visits/Activities

- Pre-Site Visit Questionnaire
- Site Assessment Visit
- Study Initiation Visit
- Interim Monitoring Visit
- Close Out Visit
- Sponsor Directed Visit (Ad Hoc)
- Site Management Call
- Central Monitoring
- Specialized Lab Audits
Site Assessment Visit

• Completed when a site is identified for participation in a DMID-sponsored clinical trial
• Purpose is to assess:
  – Site resources – facility, staffing, clinical trials experience, and population demographics
  – Feasibility – ability to accrue subjects and conduct DMID-sponsored studies
  – Site needs for training, support and monitoring
Study Initiation Visit

• A meeting prior to the official start of a clinical trial to discuss all aspects of the protocol, the day-to-day conduct of the protocol and the related clinical trial documents

• To review the site allocation of personnel responsibilities

• An opportunity to establish the groundwork for a successful clinical trial
Interim Monitoring Visits

Visit Scheduling

- First monitoring visit will be scheduled (enter protocol specific information here)
- Subsequent monitoring visits will then take place (enter protocol specific information here)
- The CRA will contact the appropriate site personnel to identify tentative visit dates
Interim Monitoring Visits Pre-Visit Letter

• Once the visit dates have been confirmed, a pre-visit letter will be sent to the site.

• The pre-visit letter will include:
  – Visit dates
  – Items required by the CRA for the visit
  – Activities to be completed during the visit
  – Contact information for the CRA
Interim Monitoring Visits

- Tasks to be performed during the visit:
  - Regulatory File Review
  - Test Article Accountability Review
  - Subject Record Review
  - Research Laboratory Review
  - Observation of Clinical Operations (as applicable)
  - Follow-up on issues identified at the previous site visits
  - Training
  - Debriefing
Interim Monitoring Visits

- The CRA will need access to:
  - A telephone and space to work
  - Subject records/source documents (medical records, research records, etc.)
  - Subject case report forms
  - The CRA will schedule time daily with the Study Coordinator or designee to review findings.
Subject Record Review

• Informed Consent Document
• Eligibility criteria met (inclusion/exclusion)
• Source verification of data
• Reporting of all safety events (non-serious and serious adverse events)
• Reporting of Protocol Deviations
Subject Record Review

• Applicable Guidelines for Subject Record Review
  – Clinical Protocol
  – Manual of Procedures (MOP)
  – Clinical Monitoring Plan (CMP)
  – DMID Source Documentation Standards
DMID Source Documentation Standards

• All Source Documents must be comprehensive and complete prior to the CRA’s review
  – Laboratory Reports must be labeled with the study subject identifier and have official headers or be on institutional letterhead
  – Records must be filed chronologically
  – Entries must be legible, signed, dated, and credentialed/certified
DMID Source Documentation Standards

• All Source Documents must be comprehensive and complete prior to the CRA’s review
  – Corrections should be made using only appropriate error correction techniques
  – Do not alter past dated notes; use addenda
  – Never destroy original documents even if they require error correction
  – Keep records secure yet accessible
Essential Regulatory Document Review and Retrieval

• PPD is now responsible for the collection and tracking of all essential regulatory documents. They will be reviewed at every visit.
  – During the first interim visit and the close out visit the review will be comprehensive
  – During routine interim visits the review will be limited to any new submissions/approvals/IRB correspondence
  – Any issues identified will be followed at each subsequent visit until resolved
Essential Regulatory Document Review and Retrieval

• The CRA will:
  
  – Verify regulatory document files are in compliance with the Regulatory Document Guidelines for DMID Clinical Studies, Version 5.10, dated 10/Feb/04, and any other applicable regulatory requirements
  
  – Retrieve photocopies of essential regulatory documents filed at the site that have not yet been sent to PPD for the central files
Test Article Accountability Review

• Review of Accountability includes:
  – Accountability Logs
  – Received, used, remaining, discrepancies
  – Amount ordered = amount dispensed/administered
  – Monthly inventories conducted on active studies, regularly thereafter
  – Test article storage area, accessibility
Test Article Accountability Review

- Storage and Handling
  - Test article temperature maintained per protocol
  - Log Record of temperature readings maintained
  - Cold chain maintained

As per the DMID Clinical Agents Repository (CAR) Investigational Agents Accountability Guidelines and Instructions for DMID-Sponsored Studies (11/Oct/05) and the Regulatory Document Guidelines for DMID Clinical Studies (version 5.10 Feb 10, 2004)
Research Laboratory Review

• Samples
  – What samples are collected
  – Who collects samples
  – How are samples collected
  – How are samples transferred
  – Are samples clearly labeled, legible, easily retrievable, and stored appropriately
  – Are laboratory SOPs in place for equipment maintenance
Protocol Deviation Reporting

• A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice, or protocol-specific Manual of Procedures

• The noncompliance may be on the part of the subject, the investigator, or the study site staff
Reporting Deviations

• DMID Deviation Reporting Requirements:
  – ALL protocol deviations must be reported within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity
  – If study data is captured via EMMES Internet Data Entry System (IDES), protocol deviations will be submitted via IDES
  – No other reporting is required as the IDES system will notify DMID of the deviation automatically
Deviations from Protocol

• All deviations from the Protocol must be addressed in study Subject Source Documentation

• The documentation should include the reasons for the deviation and all attempts to prevent or correct them

  - For example, documentation of a missed visit would properly consist of a note explaining the missed visit and the site’s attempt to locate the Subject to request that the Subject comes in to make up that visit
Debriefing

• The PI and Study Coordinator should be present for the debriefing, which consists of a synopsis of the site visit findings and activities conducted during the visit. Topics to be covered include:
  – All key items to be entered into the monitoring visit report
  – Any identified trends
  – Resolution of follow-up issues from previous site visits and identification of any follow-up issues from the current visit
Debriefing

• The CRA will attempt to resolve all identified issues prior to the conclusion of the current site visit.
Post Visit Activities

• PPD will issue the Monitoring Visit Report and the follow-up Cover Letter
• Site staff should review the Cover Letter and Monitoring Visit Report carefully
• All issues identified as “follow-up required” should be resolved prior to the next planned monitoring visit
• Draft monitoring report is reviewed by the PPD Monitoring Manager and DMID
Site Responsibilities

• Review the previous report and letter for outstanding items to be addressed before the monitor arrives

• Make sure all departments with the action items from the previous reports have provided follow-up information to you before the monitor arrives

• Keep the monitor informed of any changes in plans that may impact the visit
Site Responsibilities

• Assist the CRA in scheduling the visit (provide directions to the site, parking information, etc.)
• Assist with scheduling visits to the pharmacy and research laboratory as necessary
Site Responsibilities

• Assure space for monitoring activities
• Have subjects records available (if necessary)
• Dedicate time to work with the CRA each day to discuss findings, communicate/answer questions, resolve identified “action” items
Site Responsibilities

• Site Post Visit Activities
  – Review the findings with the research team
  – Thoroughly review the Cover Letter and the Monitoring Visit Report for “follow-up/ action required” items
Site Responsibilities

- A site “Response Letter” is not a DMID requirement; however, if a response letter is sent, please address to the PPD CRA who completed the visit with a copy to the DMID Protocol Champion and the Clinical Monitoring Coordinator
- Consider the need for staff re-training or additional training based on monitoring findings
- Prepare for next visit