JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 8, No. 2, February 2012 "Happy Trials to You"

Site Visit Follow-Up

By Amy Adams and Rosanne Petros

Introduction

One of the most important sponsor responsibilities is to monitor study conduct by the research sites.[1,2] Site monitoring, usually accomplished through site visits, is the best way for the sponsor to ensure regulatory and protocol compliance and to establish solid working relationships with the principal investigator (PI) and other site personnel. Effective site monitoring requires follow-up to ensure that any issues are properly addressed.

Site Visit Follow-Up Communications

Following a site visit, the monitor normally writes a "site visit" or "follow-up" letter to the site that clearly describes visit findings, including any items requiring follow up. Timeliness is important, so monitors normally transmit site visit letters within 10 to 20 business days after visits, and preferably sooner. (Site monitors normally communicate issues and required actions during visits so sites can get started on them before the follow-up letter arrives.)

Site visit follow-up letters should have the following characteristics:

- Provide adequate details and supporting information so sites know exactly what is expected of them.[3]
- Support requests with valid reasons, including specific references to the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP) guidelines, and regulations.[4]
- Promote a constructive relationship with the site, for example, by giving equal weight to what the site has done right and any actions required by the sponsor.
- Be consistent with the corresponding visit reports submitted to the project manager.
- Document compliance with site oversight regulations and guidelines.

The following sections provide more detail for the three main types of site visit letters during a clinical study.

Site Initiation Visit (SIV) Letter

The SIV may be the first time the site monitor meets the investigator and site personnel or the first time the team has worked together on a study. SIV follow-up letters should therefore set a positive tone, make the sponsor's expectations clear, and include the following information:

- Names, titles and roles for study personnel present during the visit
- Summary of training provided during the visit, including key sections of the protocol and other study documents reviewed, as well as any procedures and other study activities[5]
- Summary of discussions, with a detailed description of any decisions made regarding protocol procedures
- Description of the parties' agreement on visit follow-up expectations, including issue resolution and written communications

- List of action items for the site and sponsor personnel, with a focus on those required to begin enrolling subjects

Routine Monitoring Visit (RMV) Letter

Site monitors commonly identify multiple issues during RMVs that require follow up. Issues that are not resolved before the next visit require a reminder in the next letter and possibly more forceful action by the sponsor. Of course, sponsors cannot expect timely action by sites if the sponsor's follow-up letters, responses to clarification requests, or own actions are delinquent.

Many sponsors employ a visit summary form and/or discrepancy log to make sure issues are discussed in the end-of-visit meeting. These documents are essentially the first draft of the follow-up letter. The forms can be printed on NCR (no carbon paper required) paper, with the site taking the top copy and the monitor the bottom copy.

RMV follow-up letters should include the following information:

- Statement of the main purpose of the visit
- Detailed statement of documents reviewed during the visit (including document name and page number):
    - Source documents
    - Case report forms
    - Test article accountability records
    - Essential documents
    - Other documents
- Summary of data queries generated during the RMV
- Summary of enrollment activity
- Statement of protocol deviations
- Summary of discussions and statement of any resulting decisions
- Statement of new, open and resolved action items

Closeout Visit (COV) Letter

The COV follow-up letter should be comprehensive, especially with respect to any open action items required to complete study close-out. The monitor will also transmit one or more subsequent letters until all open issues are resolved.

COV follow-up letters should include the following information:

- Statement that the site has completed the study, subject to items listed below
- Post–study obligations and responsibilities of the PI
- Statement of new, open and resolved action items
- Disposition of test articles and study materials
- Record retention requirements, including Sponsor contact information for issues like destruction
- Summary of site enrollment and data entry to demonstrate that the appropriate level of monitoring was performed (as applicable)
- Thank you to the site, with special attention to positive elements
- An attachment with instructions, in case the FDA notifies the site about an inspection of the study[3]
- An attachment with instructions, in case the PI leaves the site.

Visit Follow-Up for the Site

Research sites share responsibility for following up on site visits. They should therefore take the following actions:

- Establish procedures and forms to manage and resolve issues per the site's commitments to the sponsor.
- Prior to or at the beginning of a visit, respond in writing to the monitor's follow-up letter, describing actions taken, questions to clarify, and plans to resolve open issues.
- Make sure appropriate personnel are available to meet with the monitor at appropriate times during each visit.
- Communicate the site's issues to the monitor and follow-up appropriately.

Site Visit Documentation: Notes to File

A Note to File (NTF) is a memorandum, usually placed in the regulatory binder, that explains something about a study that might otherwise be unclear, confusing or misunderstood by study personnel, sponsor personnel, FDA inspectors, or others. However, an NTF cannot resolve an issue like a protocol deviations unless it explains the issue, describes a plan to resolve the issue (and how to determine it has been resolved), and, later, how it was actually resolved. Proper NTFs often include a brief plan to prevent similar issues from occurring again and, later, how the plan was actually implemented.

Study visits can generate NTFs when a visit follow-up letter does not provide adequate documentation. Consider the following points when writing an NTF:

- Write as simply and concisely as possible.
- Cite the applicable regulations, guidelines and guidances.
- Consider whether a progress note in a subject's medical record would be more appropriate.[6]
- Do not duplicate documentation that already exists in the study records.
- Proofread carefully and have someone else review the contents, especially to make sure the correct subject and protocol are identified.

Site Visit Documentation: Corrective and Preventive Action Plans

Corrective and Preventative Action (CAPA) plans are like action-oriented NTFs but are typically used for larger-scale activities, often as an element of a quality system. As a result, they tend to be longer and more formal than NTFs. For example, if a monitor determines at an SIV that a site requires a major training program, then the monitor and the site might create a CAPA plan to develop and implement the program. However, if a study coordinator just needs a training session on a study procedure, an NTF might be used. NTFs usually focus on just one element requiring action. In contrast, CAPA plans can include more than one activity, and the activities can be different. Whereas NTFs usually address a problem or issue that has occurred, CAPA plans can include preventative actions for potential problems and issues.

To prepare a CAPA plan, follow and document the following seven steps[5]:

1. Identification. Identify the problem or potential problem.
2. Evaluation. Assess the magnitude and impact of the problem.
3. Investigation. Research the problem.
4. Analysis. Determine the root cause of the problem.

5. Action Plan. Create a list of required actions and due dates to eliminate the problem and prevent its reoccurrence.
6. Implementation. Execute the action plan.
7. Follow-up. Verify and assess the effectiveness of the plan.

References

1. ICH-GCP 5.18
2. FDA Guidance for Industry: "Guideline for the Monitoring of Clinical Investigator." November 1998
3. FDA Guidance for Industry: "Investigator Responsibilities – Protecting the Rights, Safety and Welfare of Study Subjects." October 2009
4. van der Schalie, B. PowerPoint Presentation: "What the FDA Warning Letters Tell Us About Clinical Monitoring: Diverse Perspectives on a Critical Process. Mastering Clinical Trial Monitoring." Royal Sonesta Hotel, Cambridge, Massachusetts. June 2010
5. "Corrective/Preventative Action CAPA Guidelines" from R. M. Baldwin, Inc. Written guidelines for developing and documenting a comprehensive corrective/preventative actions program.
6. Sather, S. "Good Clinical Practice Q&A: Focus on Documentation: In what ways are notes to file overused, and what are considered to be inappropriate uses of notes to file?" Journal of Clinical Research Best Practices. December 2008

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Support

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does the mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

This project was supported in part by the National Institute of Allergy and Infectious Diseases.