

## TREAT Trip Report Follow-up Form

Investigator Name: Anne Kirkman-Campbell

Investigator Site Number: 1129

PPD SM CRA Name: Joyce Vito

PPD Field Monitor Name: Ann Marie Cisneros

Re:  Interim Visit  Closeout Visit

Date of Visit: February, 18, 19 and 21, 2002

Was there any follow-up required for this Monitoring Trip?  N/A  No  Yes, (if yes please indicate below the follow-up that was needed)

The following attempts were made to complete the follow-up for action items identified during the Interim Monitoring Visit on February 18, 19 and 21, 2002:

5/7/02, 5/15/02 (fax), 5/16/02 (fax), 5/20/02, 5/23/02 (phone call and letter sent to site via FedEx), 5/28/02 (phone and fax), 5/30/02, 6/4/02, 6/5/02, 6/11/02 (phone and fax), 6/14/02, 6/17/02, 6/18/02 (phone call and letter sent to the site via FedEx), 6/20/02, 6/24/02, 6/25/02, 7/3/02, 7/5/02, 7/8/02 (phone and fax), 7/9/02 (phone and fax) and 7/10/02 (phone, fax and FedEx letter), 7/11/02 (phone and fax). Several deadlines were provided and extended to the PI/Site to complete the review of the action items listed. The final deadline was set per Roxann Evans, Project Manager, for all action items to be reviewed and completed by no later than Wednesday, 7/10/02, 5:00 PM/EST. The site did not meet this deadline, therefore, the Follow Up letter is being submitted incomplete. The Memos-to-File that are attached (with the exception of the ones dated 4/18/02 and 4/19/02) were retrieved from Stephanie Love, CRA and Beth Hedging, CRA II (PPD Field Monitors) during their onsite Interim Monitoring/Close-out visit in April, 2002. The PI/Site was informed of their responsibility to forward all Memos-to-File to the IRB regarding any protocol violations/GCP deviations listed pertaining to this letter. (See the attached PCRs that correlate with the above dates).

Because the site did not meet their final deadline, the PI/Site was contacted on 7/11/02 at 5:14 PM and was given the following instructions (Per Jean Noone, Sr. Project Manager):

- The site was informed that because they have had ample time to complete their Interim Monitoring follow up, PPD will no longer be available to assist with regard to the completion of the action items listed.
- The PI/Site will be responsible to provide written documentation referencing each issue on the follow up letter.
- The PI/Site will need to provide documentation as to what was done to correct the issues noted.
- The PI/Site will need to include detailed explanations ie; dates/times that subjects returned to the site to correct ICF issues.
- The PI/Site was instructed to forward this written documentation to PPD within a timely manner.

(See the attached PCR, dated 7/11/02).

- The protocol violations noted need to be followed up as detailed below. The site was instructed to report all protocol violations to the IRB as soon as possible, and to forward to PPD Development a copy of the notification. A sample memo to file was left at the site for reporting protocol violations.

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- ◇ Subjects 327, 328, 331-333, 337-340, 343, 350-352, 357, 358, 363, 366, 370, 371, 374, 376, 377, 382-385, 389-400, 402, 404, and 405: It appears the study staff dated the subject's signatures on the ICFs. 21 CFR 50.27 and ICH 4.8.8 require that prior to a subject's participation in the trial, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative and by the person who conducted the informed consent discussion. Please document in a memo to file that the ICFs were dated by the PI/Study Coordinator and send a copy of this memo to the IRB and PPD Development. *See the attached Memo-to-File and additional comments, dated 4/4/02.*
  - ◇ Subjects 348, 367, 376, and 355-359: Informed consents contained pages with missing words:
    - 348: pages 1-5, bottom cut off
    - 367: page 3, bottom cut off
    - 376: page 3, bottom cut off
    - 355-359: pages 4 and 5, right side cut offThe site was instructed to explain the process of copying the ICFs and confirm that the subjects received a copy with no information deleted/omitted.
  - ◇ Subject 349: Informed Consent is missing page 6. The site was instructed to re-consent the subject with all pages present.
  - ◇ Subjects 333, 336, 341, 345, 346, 348, 352, 355, 356, 361, 364, 365, 367, 369, 370, 373, 381, 386, 387, and 403: Overwrites or changes were made to the subject signature dates on the ICFs. These changes or overwrites were not initialed and dated. The site was instructed to obtain the signature and date from the subject and indicate when the consent was originally signed. *See the attached Memo-to-File, dated 4/4/02.*
  - ◇ Subjects 069, 161, 188, 318, 333, 355, 361, and 407: Potential violation: The method of birth control and pregnancy test results were not indicated in the source documents. The site was instructed to specify if a pregnancy test was completed, the results, and means of birth control in the source documents. If not done, the site was instructed to notify the IRB.
- The GCP (Good Clinical Practice) deviations noted need to be followed up as detailed below. The site was instructed to report all GCP deviations to the IRB at the end of the study with their final report.
- ◇ Subjects 327-346, 350-377, 381, 387, 393-405, and 407: It appears the study staff dated the PI's signature on the ICFs. The PI was instructed to re-sign and date the ICFs, along with a notation regarding the original date the ICFs were signed.
  - ◇ The site was informed that numerous overwrites and date changes were noted throughout the subject charts and case report forms. The site was instructed and re-educated that all corrections should be made by one line deleting, rewriting, initialing, and dating.

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- ◇ The site was informed that there were apparent late entries in the medical charts that were not correctly documented as late entries. The site was instructed and re-educated that late entries should be initialed and dated and noted as late entries.

In addition to the points noted above and the recommendations thereof, some elements would need clarification. The site was instructed to provide a written explanation of the following issues observed during the monitoring visit:

- ◇ A description of the informed consent process at the site and an explanation of the following ICF issues observed: *See the written description of the informed consent process on the attached Memo-to-File, dated 4/18/02.*
  - Subjects 361/SMD, 388/DLB and 335/FSC: Initials on each Informed Consent page differ from page to page. *See the attached Memo-to-File, dated 4/18/02.*
  - Subject 333/BLW: Initials on each ICF page differ from the subject's signature. The date of signature was changed from 1/17/02 to 1/18/02 and 'verified' by the subject, however, the initials do not appear to match the subject's signature. *See the attached Memos-to-File, dated 4/4/02 and 4/18/02.*
- ◇ The site was instructed to explain the source documentation practices followed and to clarify the following issues observed at the monitoring visit: *See the written explanation of the source documentation practices on the attached Memo-to-File, dated 4/19/02.*
  - Subject 361/SMD: The medical chart was only 3 pages (one page was blank) in length. The chart had no identifying information other than the subject's name and no documentation of the subject's medical history was present. The only study data present in the chart was the diagnosis and drug dispensed. *See the attached Memo-to-File, dated 4/19/02.*
  - Subject 333/BLW: The day of Visit 1 was changed from 1/17/02 to 01/18/02 on only one page of the 2 page medical chart. The subject was being seen for follow up on hypertension. In different ink "sinus congestion x2 days" was added. (See informed consent issue for this subject above). *See the attached Memos-to-File, dated 4/4/02 and 4/19/02.*
  - Subject 272/JW: Subject was randomized in the IVRS and the day of Visit 1 on the CRF occurred on 1/16/02, however the consent was signed and blood sent in on 01/09/02. The subject's medical chart does not indicate a visit on 1/9/02, however the subject had labs drawn (not study related) on 01/08/02. In the medical chart there is documentation of a visit occurring on 01/08/02, however that date was changed via an overwrite to 1/16/02. It is apparent the subject did not date their signature on page 6 of the ICF. The lab results from 01/08/02 are similar to those sent in to Covance on 01/09/02. Labs were not sent in on 1/16/02. *See the attached Memo-to-File, dated 4/19/02.*
  - Subject 405/NCG: The day of Visit 1 was the first day the subject was seen in the office. The subject's chief complaint was back pain, in different ink in the middle of the medical history page, "chest congestion 2-3 days" was written in. The subject did not have a history of chronic bronchitis, or any respiratory problems. *See the attached Memo-to-File, dated 4/19/02.*

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- Subjects 312, 361, 344, 355, 300, 263, 223, 196, 359, 407, 405, 393, 188, 161, 135, 077, 063 were diagnosed with AECB, however, had no documentation of a past history of bronchitis. See *the attached Memo-to-File, dated 4/19/02.*
- ◊ The time of randomization in the IVRS was noted to be very short between several subjects randomized. The randomization of subjects in blocks/clusters within a short period of time appeared unusual. The PI was instructed to explain the randomization process followed by their site.
- ◊ Few Adverse Events, including the five AESIs consisting of abnormal Liver Function tests, were reported for the 407 subjects enrolled. The site was instructed to explain the process at the site for obtaining and documenting Adverse Events from subjects? See *the attached Memo-to-File, dated 4/19/02.*
- ◊ As a follow up of the letter dated January 21, 2002, the site was instructed to provide an answer to the question asked (total number of patients seen by your site in the months of October, November and December 2001).

The site was informed that other outstanding issues from the visit are listed below, and will be followed-up by their Site Management CRA:

- The site was instructed to resolve and initial all Monitoring/Editing Notes left for subjects 001, 004, 007, 008, 013, 014, 037, 063, 069, 075, 077, 107, 124, 135, 161, 176, 188, 196, 215, 223, 249, 263, 269, 300, 312, 318, 333, 334, 344, 355, 359, 361, 382, 393, 405, and 407. Upon completion, the site was instructed to forward the originals to their Site Management CRA. *The PI/Site was requested to send the resolved, initialed, original Monitoring/Editing Notes to PPD via FedEx on the following dates: 5/16/02 (letter sent to site via FedEx), 5/20/02, 5/23/02 (phone call and letter sent to site via FedEx), 5/28/02 (fax), 5/30/02, 6/4/02, 6/5/02, 6/17/02, 6/20/02, 6/24/02, 6/25/02 and 7/11/02. As of 7/11/02, no initialed, original Monitoring/Editing Notes have been received from the site. (See the attached PCRs which correlate with the above noted dates).*
- The site was instructed to request that their Site Management CRA complete an IVRS change form to correct the date of birth for subjects 007 and 077. *(Per Jean Noone, Sr. PM: the completion of an IVRS change form is not necessary to correct the date of births for subject's 007 and 077 at this point in time).*
- The site was instructed to continue to follow-up with PVG for the hepatic adverse events of interest for subjects 047, 191, 298 and 315.

PPD CRA Signature: \_\_\_\_\_

*J. Vite*

Date: \_\_\_\_\_

*7/11/2002*

PPD Manager Signature: \_\_\_\_\_

*Jane A. Miller*

Date: \_\_\_\_\_

*23 July 2002*



Phone Contact Report			
<b>Study</b>			
<b>Sponsor</b>	Aventis Pharma	<b>Name</b>	Aventis Ketek
<b>Site</b>			
<b>Investigator</b>	Anne Kirkman-Campbell	<b>System ID</b>	31530
<b>Phone Number</b>	(256) 549-0018	<b>Site Number</b>	1129
<b>Site Fax</b>	(256) 547-7383	<b>Recruitment Number</b>	
<b>Journal Entry</b>			
<b>Date of Contact</b>	07/11/2002	<b>Journal ID</b>	404048
<b>Contact Name</b>	Michelle Snedeker (Study Coordinator)	<b>Direction</b>	Outbound
<b>PPD Personnel</b>	Joyce Vito	<input type="checkbox"/> <b>Legal/Financial</b>	

**Notes**

At 4:54 PM/EST: I received a message in person from John Reynolds, CRA, who informed me that he just got off the phone with Nadine Grethe, Aventis Study Manager, who had spoken to Dr. Kirkman-Campbell's site this afternoon. John informed me that Nadine stated the site is now willing to cooperate with regard to the continuation of the IMV/COV follow up review, and requested that I contact Michelle within the next 10 minutes to continue our discussion.

Addendum: 4:59 PM/EST: I discussed this issue in detail with Jean Noone, Sr. PM. I informed Jean of the multiple attempts that have been made in order to complete the phone follow up review, pertaining to the IMV Follow Up letter, dated 3/18/02 and the IMV/COV Follow Up letter, dated 4/25/02. I discussed the fax that was sent to the site on 7/10/02 at 6:25 PM/EST, pertaining to the sites final notice informing them that their deadline was over. Jean agreed with the information noted on the fax and provided the following directives:

- Contact the site and inform them that we are no longer available to assist them in the completion of their IMV/COV follow up issues. Reiterate that the site has had ample time to comply and has not done so.
- If the site is willing, they can provide written documentation referencing each issue on the IMV Follow Up letter, dated 3/18/02. The site will be responsible to provide documentation as to what was done to correct the issues noted. The site will need to provide detailed explanations and dates/times that subjects returned to the office to correct certain issues, if applicable. Especially if the issue involves a correction to the ICF.
- The site is welcome to forward this written documentation to PPD in a timely manner.

Addendum: 5:20 PM/EST: I contacted the site as requested and spoke to Michelle Snedeker, SC. I reminded Michelle that the final deadline to comply with the phone follow up (IMV/COV) review ended on Wednesday, 7/10/02 at 5 PM/EST. I informed her that I discussed this issue with Jean Noone, Sr. PM (in the absence of Roxann Evans, PM), and informed Michelle of Jean's directives, listed above. In addition to Jean's directives, I also informed Michelle that because I did not receive the information/documents needed with regard to the IMV/COV Follow Up letter, dated 4/25/02, the follow up form was submitted on 7/10/02 at 5 PM/EST with the information obtained within the given time frame.

NOTE: Linda Karolak, CRA, was available to witness my entire conversation with Michelle Snedeker, SC.

NOTE: The information/documents that remain outstanding with regard to the IMV/COV Follow Up letter, dated 4/25/02, are as follows:

- Outstanding AE CRF pages pertaining to all applicable subjects listed on the IMV/COV letter, dated 4/25/02.
- ALL outstanding resolved, Initialed, original Monitoring/Editing Notes (From the February, 2002 and April, 2002 visit).
- A written/typed explanation from the site, explaining their source documentation practices.
- A written/typed clarification of the following issue: Visit 2 and 3 data was entered directly on the CRF and no source documentation was present to support the data for these visits. Per CFR 312.62 and ICH GCP 4.9 and 4.9.2, an investigator is required to prepare and maintain adequate and accurate source documentation on study subjects.
- 5 amended MTFs.

**Subjects**

Interim Monitoring

*Linda Karolak, CRA II  
7/11/02*