MEMORANDUM

Date: March 31, 2000

To: CRMB/TRP
William Duncan, Ph.D.

From: Mary Anne Luzar, Ph.D. Chief
Regulatory Affairs Branch
Division of AIDS

Subject: The Difference Between Clarification Memos and Protocol Amendments
In DAIDS-Sponsored Trials

A DAIDS- sponsored protocol can be modified by three methods:

1) Clarification Memo
2) Letter of Amendment
3) Full Protocol Amendment

These three modifications are used for both IND and Non-IND Protocols.
They are mutually exclusive with the caveat that an amendment (new protocol version) should be updated to include the information of all clarification memos written since the last version of the protocol.

Clarification Memo (CM):

Definition: A relatively short document written by members of the protocol team AFTER a full version number of the protocol has been submitted to the field. The CM provides further explanation or details to some area of the clinical research that is ALREADY present in the protocol.

Main points about a CM:

a. For IND protocols: There is no requirement to submit this document to the FDA as part of the IND because the memo is simply clarifying or stating in a different manner information already in the protocol. Submitting it to the IND would be redundant even if the CM is clearer than the material it covers that is in the protocol.

b. A CM is NOT related to patient safety and should not have any impact on the risk assessment of the version of the protocol to which it applies.

c. DAIDS does not require a CM to be submitted to the IRB(S) for review. Unless the site IRB requires review of such documents before implementation (and this is a local IRB decision), a CM may be implemented immediately upon receipt at the site.

d. A CM does NOT need to be filed in the regulatory documents of the site. It should be filed with the protocol or per instructions of the team.

e. A CM does NOT include information DIRECTLY related to the Informed Consent and is not part of the Informed Consent.

f Examples of topics appropriate for clarification memos are the following: Information related to laboratories already mentioned in the protocol (update an address or phone), drug distribution issues, clarification on blood amounts already included in the protocol and how they will be divided, batching procedures for samples, shipping instructions for samples, change in test tube size or brand, etc.

g. Sites participating in the protocol do NOT site register for a CM .

Letter of Amendment (LOA):

Definition: A short letter that replaces a full version protocol amendment. The letter is Prepared by the Protocol Team and is approved by the DAIDS Medical Officer and the Regulatory Affairs (RAB) Branch Chief for non-INDS and by the RAB official FDA liaison for IND protocols. Additional approval may be requested by RAB before final sign-off (e.g. pharmacist) if specialized areas are a focus of the letter of amendment, A letter of amendment is ideally used at the END of a trial and should not require follow-up by the protocol team with a Full Version Amendment of the protocol.

Main Points about a Letter of Amendment:

a. Minimal impact on patient safety. The letter should address how subjects are to be informed of the information presented.

b. The Informed Consent is usually affected by the letter of amendment, but this should be relatively minor and there should be no MAJOR safety concern. For example, a study consent will indicate the duration of the study and an extension by letter of amendment renders this part of the IC inaccurate. Subjects need to be informed of the letter of amendment content, but this does not automatically require reconsenting the subject or updating the current consent. In some cases the protocol team will recommend a patient letter or ask that the information be provided to the patient and noted in the chart. Local IRBS have the right to ask for any type of consent process consistent with local IRB policy - and it may well vary from the suggested consent information in the letter of amendment provided by the team. In that case, the local IRB request must be followed.

g. An LOA needs to be IRB - reviewed and approved before it is implemented and this MUST be stated in the actual LOA. The IRB may request a change to the consent or an addendum to the consent even if it is not required in the letter of amendment. This IRB request should be maintained in the regulatory file.

d. A letter of amendment should be filed in the regulatory file and other pertinent files.

e. If the letter of amendment is for an IND study, it is formally submitted to the FDA by RAB and is made part of the IND record.

f Some examples of use are for simple protocol extensions or bridging protocols or special follow-up with minimal risk of an arm or an-ns of a study after the study is closed.

g. Unless indicated otherwise by ROC in consultation with RAB, sites do not site register for a letter of amendment because the VERSION NUMBER OF THE PROTOCOL is UNCHANGED.

Full Protocol Amendments

This amendment is required for significant changes to the protocol and any change which has more than minimal impact on patient safety. It results in a NEW, Whole number VERSION of the Protocol. After the Protocol Team finalizes the amendment, it undergoes a regulatory review and medical officer sign-off before it is submitted to the sites and possibly the FDA (for IND studies only).

Full Protocol Amendments are managed like version 1.0 of the protocol. Sites MUST site register for a full amendment after IRB approval for BOTH IND and NON-IND protocols.

A full amendment may be preceded by an urgent communication to the sites performing the trial for SIGNIFICANT Patient Safety or Patient Management ISSUES. An example of this is a DAIDS Safety Alert. In such cases:

- The Team will write a letter to investigators outlining the reason for the upcoming amendment. The team may prepare a patient letter.
- The IRB must be notified of the important new information by use of the team letter(s).
- The local IRB decides what type of review is required (it may be expedited or full review) and issues instructions to the site.
- Patients will be consented verbally and a note will be made in the patient's chart that documents that they were informed and agree UNLESS the IRB has other specific instructions.
- Urgent communications are ALWAYS followed by a full protocol amendment that is IRB reviewed and approved.
- The letter or communication is submitted to the FDA IND for IND studies by RAB after DAIDS MO sign-off and the IND cover letter indicates that a full amendment will follow shortly.
- For IND studies, the Full Version Amendment is submitted to the FDA IND by RAB.

- Examples: new toxicity of a study drug is identified, dropping an arm because of toxicity, or drug availability.

Non-Urgent Full Protocol Amendments are prepared by the Protocol Team according to SOPS of the clinical trials group.

- For IND protocols, the amendment must follow federal regulations as outlined in CFR 312.30
- Requires IRB review and approval
- Full Protocol Amendment , Cont

CSRC review may be required:

Consent changes or additions may be needed and/or required

- Examples of full amendments: Informed Consent changes, new drug added to treatment regimen, or new safety information on existing drugs in the protocol, significant increase in patient number in an IND study (greater than I 0% is the guideline, but this may not apply to Phase I studies).

Protocol amendments are outlined in the Code of Federal Regulations (CFR Title 21) under part 312.30.