Requirements for DAIDS-supported Research Involving Recombinant DNA

Research supported by NIH funding that involves recombinant DNA is subject to special oversight requirements. These guidelines are contained in the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), which outline biosafety provisions and oversight by an Institutional Biosafety Committee (IBC). The NIH Guidelines can be obtained on line at:

http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

In addition, clinical trials testing products containing recombinant DNA – also known as human gene transfer trials – must be submitted to the NIH Office of Biotechnology Activities (OBA) for review by the NIH Recombinant DNA Advisory Committee (RAC), unless they are vaccine trials that have certain characteristics. This section describes all of these requirements in detail to help investigators and institutions understand and fulfill their associated responsibilities.

Applicability of Specific Requirements of the NIH Guidelines to DAIDS-supported Clinical Trials

As part of adherence to the NIH Guidelines, clinical trials testing recombinant DNA products must comply with Appendix M of the NIH Guidelines, *"Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants."* Recombinant DNA is defined in the NIH Guidelines as, *"molecules constructed outside of living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or molecules that result from [their replication]."*

In general, trials involving the administration of recombinant DNA to humans must be submitted to NIH OBA for review by the RAC, per Appendix M-I of the NIH Guidelines, and investigators must subsequently provide certain documentation, annual reports, and reports of serious adverse events to OBA as part of that compliance. However, vaccine trials are exempted from Appendix M-I if they are human studies in which:

(1) Induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal,

(2) Such an immune response has been demonstrated in model systems, and

(3) The persistence of the vector-encoded immunogen is not expected.

Whether or not a vaccine trial is exempted from Appendix M-I, sites conducting clinical trials on products containing recombinant DNA are subject to the NIH Guidelines and must establish an IBC (see below). The IBC must review and approve human gene transfer trials (including vaccine trials) before enrollment in these studies may begin. The IBC's review should include investigator responses to questions posed in Appendix M-II through M-V of the NIH Guidelines. Further, the IBC must conduct ongoing oversight of these trials to ensure compliance with the NIH Guidelines. For example, the IBC should ensure that investigators and other trial staff employ adequate biosafety practices, report serious adverse events to the IBC, and any accidents or violations of the NIH Guidelines to the IBC and to NIH OBA.

Institutional Biosafety Committee

An IBC is an institutional committee created under the NIH Guidelines to review research involving recombinant DNA. IBCs are also responsible for the review of other forms of research that entail biohazardous risks to study subjects and the environment.

Establishing an IBC

All institutions conducting DAIDS-supported research involving recombinant DNA must establish an IBC. Section IV-B-2 of the NIH Guidelines outlines the membership and competency requirements that all IBCs must meet. Specifically, IBCs must:

- Have at least five members;
- Include at least two non-institutional members who represent the interests of the surrounding community with respect to health and protection of the environment, and who can reflect community attitudes about research;
- Possess experience and expertise collectively in recombinant DNA research;
- Be competent to assess any environmental or public health risks posed by research involving recombinant DNA;

  and

- Be knowledgeable about institutional facilities, containment practices, personnel training, and standard operating procedures.

If the institution does not have the resources or infrastructure to administer its own IBC, the IBC may be remotely administered – such as by a university or a commercial IBC services provider – but must nonetheless retain all of the characteristics described above. Remotely administered IBCs generally must include a member from the trial site who has the experience and authority to take appropriate action and to report to the IBC in the event of a biosafety problem.

If an Institutional Review Board (IRB) already exists, the IBC can have membership that overlaps with or draws upon that of the IRB. However, the identity of the IBC and its review must be distinct and separate from those of the IRB. Further, the roster and minutes of IBC meetings must reflect the IBC's distinct identity and review activities.

The institution or site that establishes the IBC must register the IBC with NIH OBA. If the IBC is being remotely administered, the site must register the IBC, not the administering organization, and thus the letter covering the registration documents should be on the site's letterhead and signed by a responsible institutional official. More information on establishing and registering an IBC may be found on OBA's Web site at:

http://www4.od.nih.gov/oba/IBC/IBCindexpg.htm

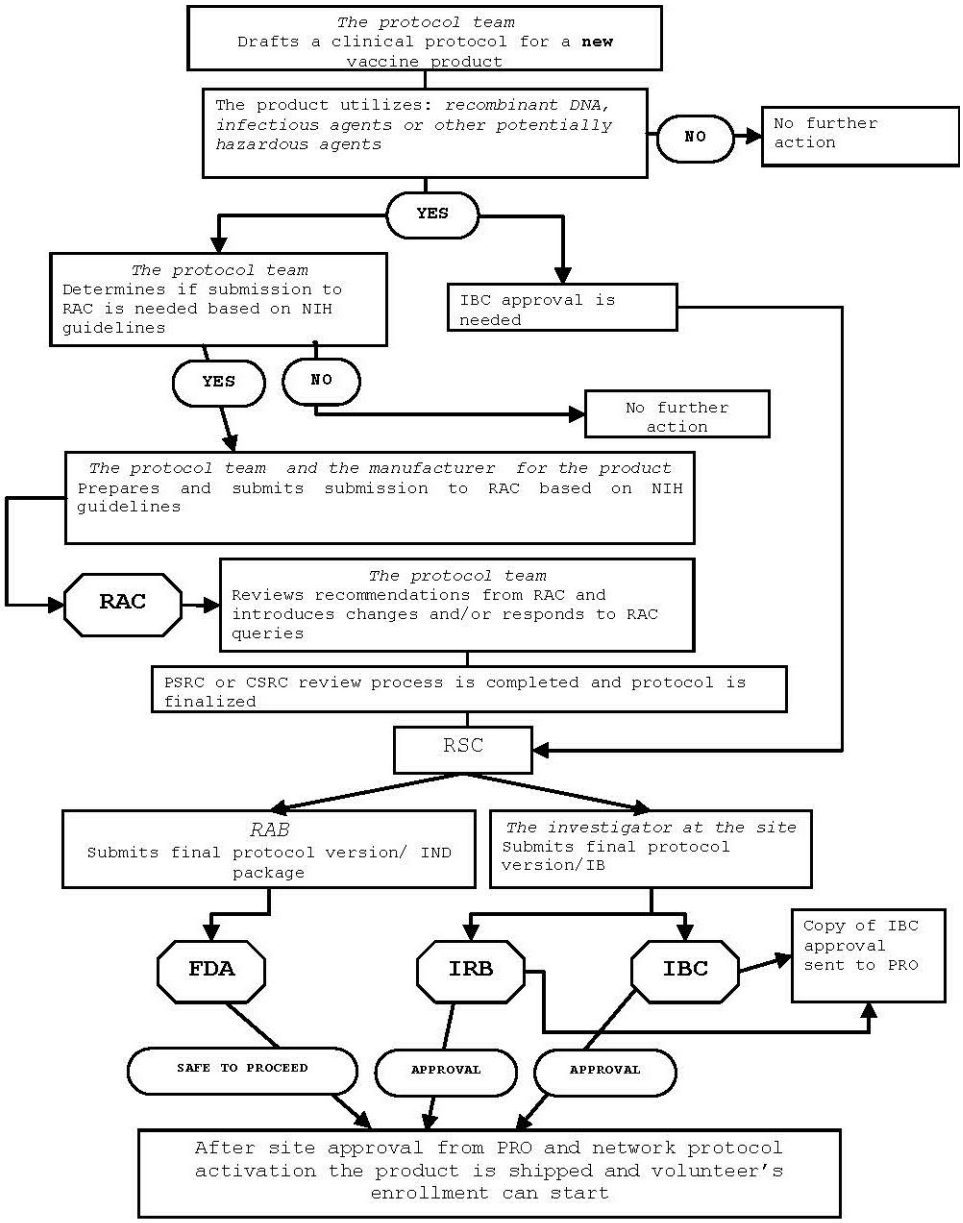

Fig 1: *Regulatory review requirements for IBC and RAC, from protocol concept to IND submission.*

Recombinant DNA Advisory Committee

With few exceptions human gene transfer trials conducted at or sponsored by institutions receiving NIH funds must be submitted to OBA for review by the RAC. Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. The majority of DAIDS investigational vaccines involves recombinant DNA and thus requires IBC review and approval (including a review of investigator responses to questions in Appendices M-II through M-V of the *NIH Guidelines*). Trials that fit the characteristics described in Appendix M-VI-A of

the *NIH Guidelines*, however, are exempt from the RAC review and OBA reporting requirements set forth in Appendix M-I. Exempt from Appendix M-I are:

- Experimental vaccines studied in humans in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal.

- Immune response to the experimental vaccine has been demonstrated in model systems, and

- The persistence of the vector-encoded immunogen is not expected.

In order to avoid delays in the protocol development process the *protocol team* should determine early on whether a protocol should undergo RAC review. RAC meets only 4 times a year and submissions need to be received by OBA eight weeks prior to the scheduled public RAC meetings. The *protocol team* will document this decision in the minutes of the protocol team meeting and will promptly notify the manufacturer of the product of this decision for timely preparation of the RAC submission material.

Submission of protocol for RAC review

If a new vaccine candidate is not exempt according to the above criteria (appendix **M-VI-A** of the NIH guidelines for research involving recombinant DNA molecules), the *protocol team and the manufacturer of the product* must prepare and submit a package of information for RAC review.

- The documents required for this submission are:

- A cover letter signed by the principal investigator and co-investigators that :

    - Acknowledge that the documentation complies with the requirements outlined in appendix M-I-A.

    - Identify the IBC and IRB that are responsible for approval of the protocol.

    - Acknowledge that no enrollment will take place until RAC review is completed, IBC and IRB approval is obtained and the protocol is considered safe to proceed by the FDA.

- A scientific abstract.

- A non-technical abstract.

- The proposed clinical protocol, including tables, figures and relevant manuscript.

- The proposed informed consent document.

- CVs for the principal investigator(s).

More information on submission of human gene transfer protocols can be found in a series of Frequently Asked Questions (FAQs) on the NIH OBA Web site at:

http://www4.od.nih.gov/oba/RAC/RAC_FAQs.htm

Once the protocol is reviewed by RAC *the protocol team* will consider RAC recommendations and revise the protocol if applicable. The DAIDS protocol development will then continue through PSRC/CSRC review and the protocol will be finalized for FDA, IRB and IBC submissions.

Reporting to OBA

Investigators conducting protocols that are not exempt from Appendix M-I must submit certain reports after the completion of RAC review.

Beginning of the study

Within 20 working days of enrolling[1] the first participant in the trial, the investigator at the site must provide OBA with the documents and information listed below (per Appendix M-I-C-1 of the *NIH Guidelines*). .

- A copy of the protocol approved by the IBC and IRB.
- A copy of the informed consent approved by the IRB.
- A copy of the IBC approval of the clinical site.
- A copy of the final IRB approval.
- A document outlining the responses to RAC's recommendations and any modification to the protocol required by the FDA.
- The IND number.
- The NIH grant number.
- The date of initiation of the trial.

It should be noted that this report is provided only once and not by every site involved in the trial. The guidelines allow for formal delegation of all or part of the investigator reporting requirements. Some NIH-funded networks may choose to handle the 20-day reporting centrally through the network leadership.

[1] Enrollment is defined as the process of obtaining informed consent from a potential research participant to undergo a test or procedure associated with the gene transfer experiment.

Additional Clinical Trial Sites

When adding new sites to the clinical trial, no research participant should be enrolled at the site until the following documentation has been submitted to NIH OBA:

- Institutional biosafety committee approval from the clinical site;
- IRB approval;
- IRB-approved informed consent document;
- Curriculum vitae of the Principal Investigator(s) – no more than two pages in biographical sketch format; and
- NIH grant number(s) if applicable

During the study

During the conduct of the study, *the principal investigator*[2] is responsible for providing OBA with safety reports and annual reports. In such cases OBA requires that these documents[3] follow the timelines for submission and format of the homologous FDA mandatory reports (Fig 2).

All information communicated to OBA is publicly available unless it is clearly labeled as confidential. Since annual reports to the FDA may contain proprietary information, RSC will provide the annual report to the protocol team which, in concert with the product manufacturer will edit the annual reports to remove any proprietary information prior to submission to OBA. The DAIDS medical officer will sign off on the redacted annual report before submission to OBA.

The safety reports can be sent simultaneously to FDA and OBA by the RSC SAE Office.

[2] The principal investigator may delegate the task of reporting to another party (such as the sponsor or clinical trial coordinator). A letter signed by the PI on the PI's institutional letterhead must document this delegation.

[3] These submissions will be prepared by the RSC using data provided by site investigators (through SCHARP for HVTN studies).

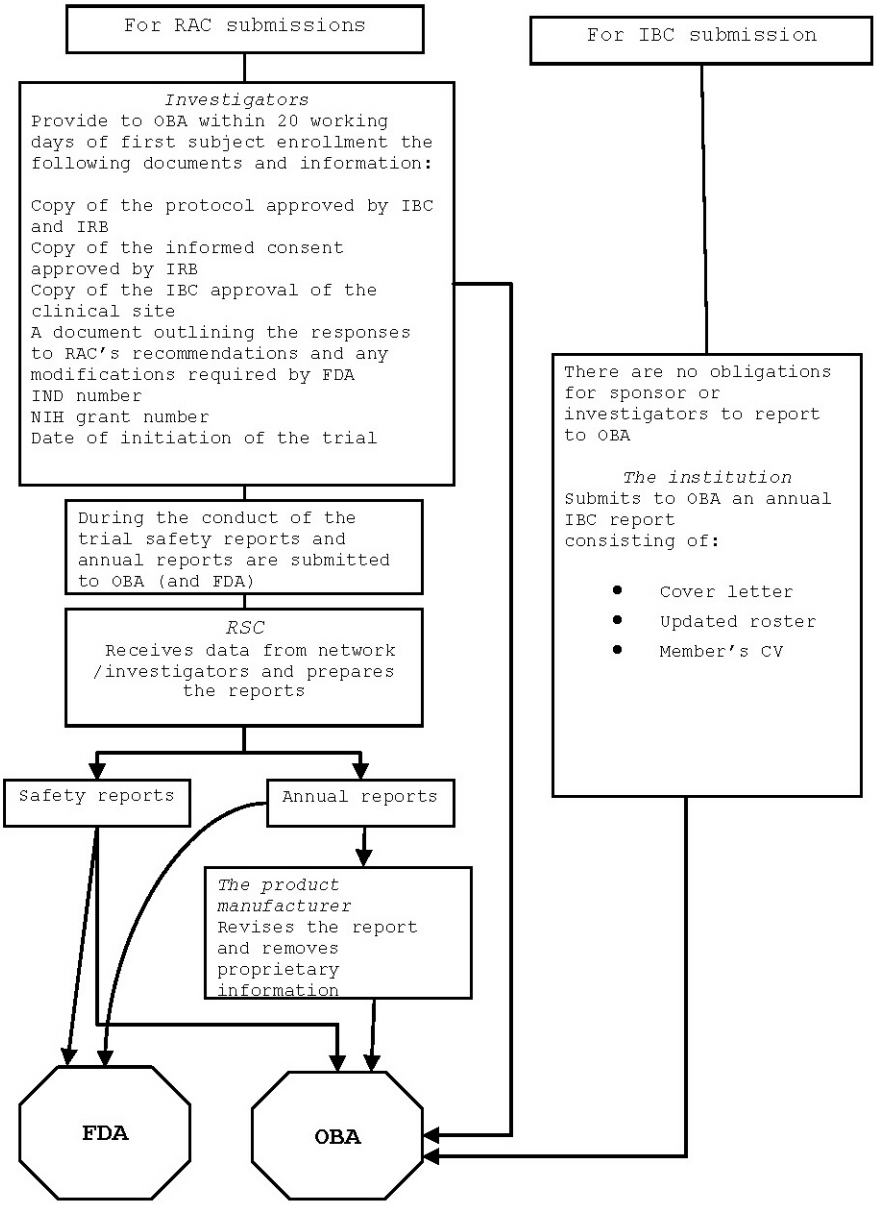

Fig 2: *Regulatory requirements for IBC and RAC/OBA after trial enrollment*

Conclusion

For more information on requirements pertinent to the conduct and oversight of research involving recombinant DNA, contact the NIH Office of Biotechnology Activities at:

NIH OBA
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20892-7985
USA

Phone: 301-496-9838
Fax: 301-496-9839

Email: oba@od.nih.gov

Website: http://www4.od.nih.gov/oba

Appendix A

[ADDRESSED TO THE LOCAL IBC CHAIRPERSON]

Dear Dr [NAME],

Enclosed is a phase [I, II] protocol entitled [NAME OF THE PROTOCOL] for the study of [NAME OF THE PRODUCT] as an experimental vaccine for the prevention of HIV infection in humans. This study was designed by me and investigators associated with the HIV Vaccine Trial Network (HVTN) and it is sponsored by the Division of Acquired Immunodeficiency (DAIDS), NIAID, NIH. The study will be conducted at this institution and at [OTHER SITES AS APPLICABLE].

We are submitting the protocol for your review and approval in compliance with the NIH guidelines for research involving recombinant DNA molecules. This protocol has been [will be] submitted to the [INSTITUTION NAME] Institutional Review Board and to the Food and Drug Administration for their review and approval. [DAIDS] will hold the IND for this trial.

[THE FOLLOWING PARAGRAPH WHEN APPLICABLE] In accord with appendix M-VI-A of the current guidelines issued by the Office of Biotechnology Activities (OBA), NIH, we believe the clinical investigation in this protocol is exempt from Recombinant DNA Advisory Committee (RAC) review because the following apply:

- This is a study in humans with the major goal of induction of immune response to the HIV virus.

- Immune response to this experimental vaccine has been demonstrated in a model system, [REFERENCE TO PERTINENT SECTION OF THE PROTOCOL OR INVESTIGATOR BROCHURE].

- The persistence of the vector-encoded immunogen is not expected.

Please feel free to contact me at [ADDRESS, TELEPHONE NUMBER, ETC.] if you have any questions.

Sincerely yours

[PRINCIPAL INVESTIGATOR NAME AND ADRESS]