

Requirements for IBC and RAC submissions

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HVTN Full Group Meeting October 2004



Introduction

Research supported by NIH funding that involves recombinant DNA is subject to special oversight requirements

NIH guidelines issued by the Office of Biotechnology Activities (OBA)

Clinical trial protocols for the study of *investigational recombinant DNA molecules, infectious agents or carcinogens* in humans

OBA has determined that these guidelines apply, with some exceptions, to experimental vaccines.

Outline

Why oversight of research with recombinant DNA is needed

Brief overview of:

- Office of Biotechnology Activities (OBA)
- Institutional Biosafety Committee (IBC)
- Recombinant DNA Advisory Committee (RAC)

When submissions to IBC and RAC for review are needed

Reporting to IBC and OBA

Oversight of Research with Recombinant DNA

- New types of organisms can be introduced into the environment
- Potential for carcinogenicity of the gene transfer
- Potential for transmission to progeny

NIH Office of Biotechnology Activities (OBA)

In compliance with appendix M of NIH guidelines for recombinant DNA:

“Points to consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into one or More Human Research Subjects”

Recombinant DNA molecules as defined by OBA:

“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”

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

NIH Office of Biotechnology Activities (OBA)

Develops and implements NIH policies and procedures for the safe conduct of Recombinant DNA Activities and Human Gene Transfer.

Monitors scientific progress in human genetics research in order to anticipate future developments, including ethical, legal, and social concerns, in basic and clinical research involving Recombinant DNA, Genetic Technologies

Manages the operation of, and provides analytical support to, the NIH Recombinant DNA Advisory Committee.

Coordinates and provides liaison with Federal and non-Federal national and international organizations concerned with Recombinant DNA, Human Gene Transfer, Genetic Technologies.

Provides advice to the NIH Director, other Federal agencies, and State regulatory organizations concerning Recombinant DNA research, Human Gene Transfer, Genetic Technologies.

Reviews and evaluates the composition of Institutional Biosafety Committees

Develops registries of activities related to Recombinant DNA Research and Human Gene Transfer.

Institutional Biosafety Committee (IBC)

An Institutional Biosafety Committee is a review body appointed by an institution to review and approve bio-hazardous research

IBCs were established to provide local, institutional oversight of research with recombinant DNA

OBA reviews and evaluate the composition of IBCs

Institutional Biosafety Committee (IBC)

IBCs sets containment levels in accordance with the NIH and CDC Guidelines

The IBC is a distinct entity from the Institutional Review Board (IRB)

Recombinant DNA Advisory Committee (RAC)

The Recombinant DNA Advisory committee was established in October 1974

Guidelines first published in 1976

Public concerns regarding the safety of manipulation of genetic material through the use of recombinant DNA techniques

Recombinant DNA Advisory Committee (RAC)

The RAC is an advisory committee to the Director of NIH

Current state of knowledge and technology regarding recombinant DNA

RAC examines clinical trials that involve the transfer of recombinant DNA to humans

Regulatory Actions During Protocol Development

Sponsor and investigators need to submit documentation to:

Recombinant DNA Advisory Committee RAC

Institutional Biosafety Committee IBC

Institutional Review Board IRB

Food and Drug Administration FDA

Outside the US: national regulatory authorities

Submissions

- IBC all studies with recombinant DNA
- RAC only the vaccines not exempted

	How many protocols are affected?	When is action required during protocol development?
IBC	Most	Late
RAC	Few	Early

IBC review

The ***protocol team*** determines if IBC review is needed.

The ***investigator at the site*** is responsible for submissions to IBC

Instruction for investigators available in the HVTN Manual of operations (MOP)

How to Obtain IBC Review

The *investigator* is responsible for submitting the clinical protocol to the local IBC for review

If an institution does not have a standing IBC or, for international sites, an equivalent of an IBC, then the institution must establish a duly constituted IBC registered with NIH, OBA

How to Obtain IBC Review (Other Options)

Review and approval can be obtained from an **IBC committee at a separate clinical institution** in the same geographical area

The members of the **local IRB can fulfill the duties of an IBC** with the inclusion of **A) two additional members*** and **B)** as long as the meetings are held separately from the regular scheduled IRB meetings

The investigator can rely on a **remote IBC** with the inclusion of two additional members *

A US-based core of experts can be appointed to serve as the IBC with the inclusion of two additional members *

* **Must have knowledge of biosafety and the surrounding community**

Submission to RAC

The *protocol team* determines if RAC review is needed.

The *protocol team* and the *company sponsor for the product* prepares and submits to RAC based on NIH guidelines

A template with instructions for RAC submission will be available from HVTN

Exemption from RAC Submission

(The good news)

- Experimental vaccines studied in humans with the major goal of induction of an immune response to a vector-encoded microbial immunogen.
- Immune response to the experimental vaccine has been demonstrated in a model system.
- The persistence of the vector-encoded immunogen is not expected.

Appendix **M-VI-A** of the guidelines

What is Needed for RAC Submission

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).

IND number

NIH grant number

RAC Review

Initial RAC review is completed within 15 working days of receipt of a complete submission.

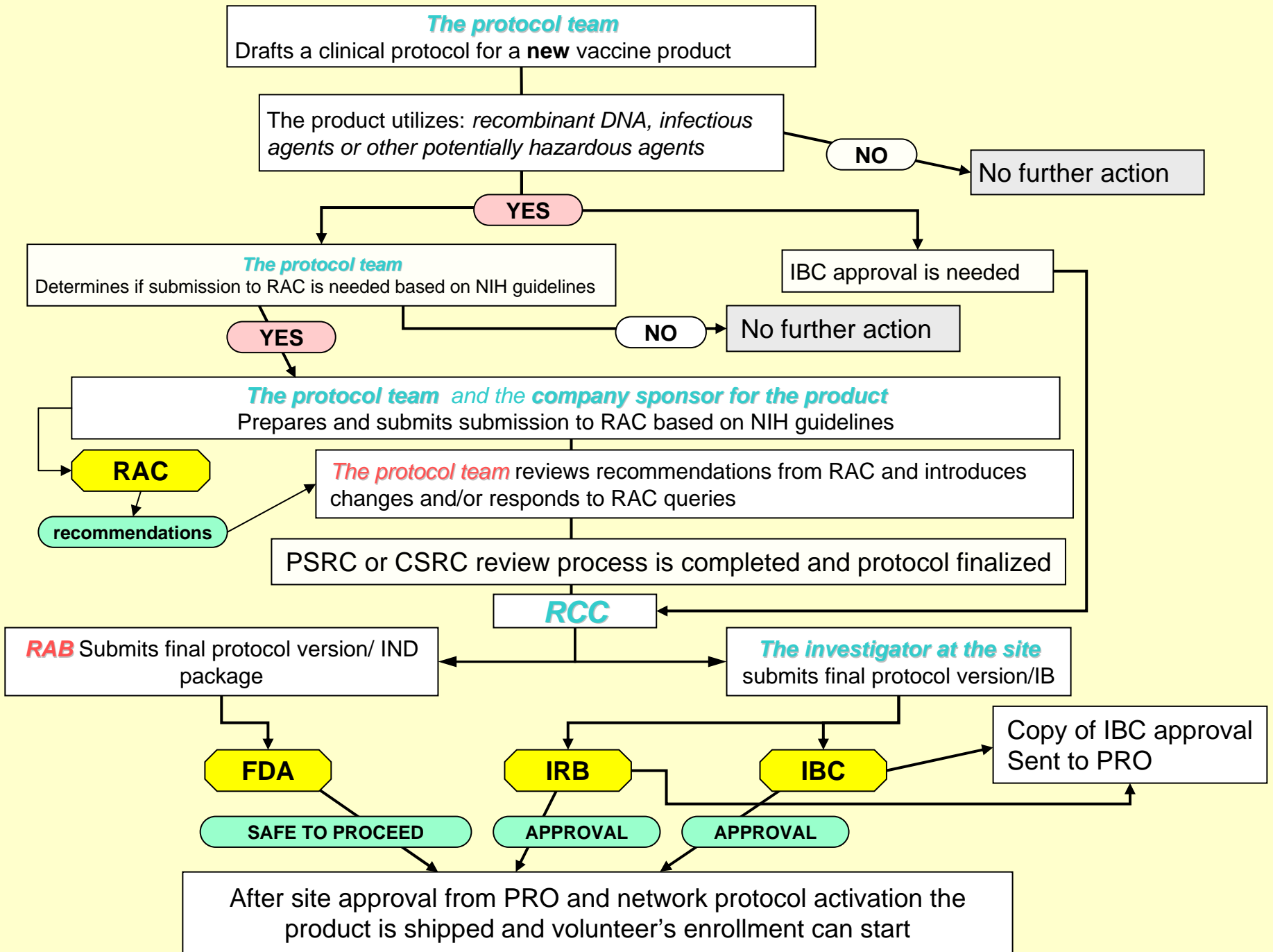
Two outcomes are possible:

- The clinical trial does not present characteristics that warrant further review and discussion and is therefore exempt from public RAC review and discussion
- The clinical trial presents characteristics that warrant public RAC review and discussion

Public Discussion by RAC

Factors that may contribute to public discussion of a protocol by the RAC include:

- New vectors/new gene delivery systems.
- New diseases.
- Unique applications of gene transfer.
- Other issues considered to require further public discussion.



Reporting to OBA

Beginning of study

Investigators will provide OBA within 20 days of first subject enrollment the following documentation:

- Copy of protocol approved by IBC and IRB
- Copy of informed consent approved by IBC and IRB
- Copy of IBC approval of clinical site
- Copy of final IRB approval
- Response to RAC's recommendations
- Response to FDA's recommendations
- IND number
- NIH grant number
- The date of initiation of the trial

Reporting to OBA

During the study

Safety reports:

The principal Investigator* will submit using the same format used for FDA safety reports

*can be delegated to other party (RCC)

Reporting to OBA

During the study

Annual reports:

Same format used for FDA annual reports

Redaction will be necessary: ***The product manufacturer*** will edit the reports to remove proprietary information

Reporting to IBC

During the study

Institutional IBCs have the authority to request safety reports, *the investigator* will submit them upon request.

For RAC submission

Investigators

- Provide OBA within 20 days of first subject enrollment the following
 - Copy of protocol approved by IBC and IRB
 - Copy of informed consent approved by IBC and IRB
 - Copy of IBC approval of clinical site
 - Response to RAC's recommendations
 - Response to FDA's recommendations
 - IND number
 - NIH grant number

During the conduct of the trial **safety reports** and **annual reports** are submitted to OBA (and FDA)

RCC

Receives data from network/investigators
And prepares the reports

Safety reports

Annual reports

The product manufacturer

Revises the report and removes
Proprietary information

FDA

OBA

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For IBC submission

There are no obligations for *sponsor or investigators* to Report to OBA

The institution submits annually to OBA the following documents about the IBC:

- Cover letter
- Updated roster
- Member's CVs

Were to Find this Information

HVTN Manual of Operations (MOP)

DAIDS Registration Policy and Procedure Manual

DAIDS RCC website

<http://rcc.tech-res-intl.com/forms.html>

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