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Presenter Disclosure **John A. Zaia, M.D.**

The following relationships exist related to this presentation:

No Relationships to Disclose

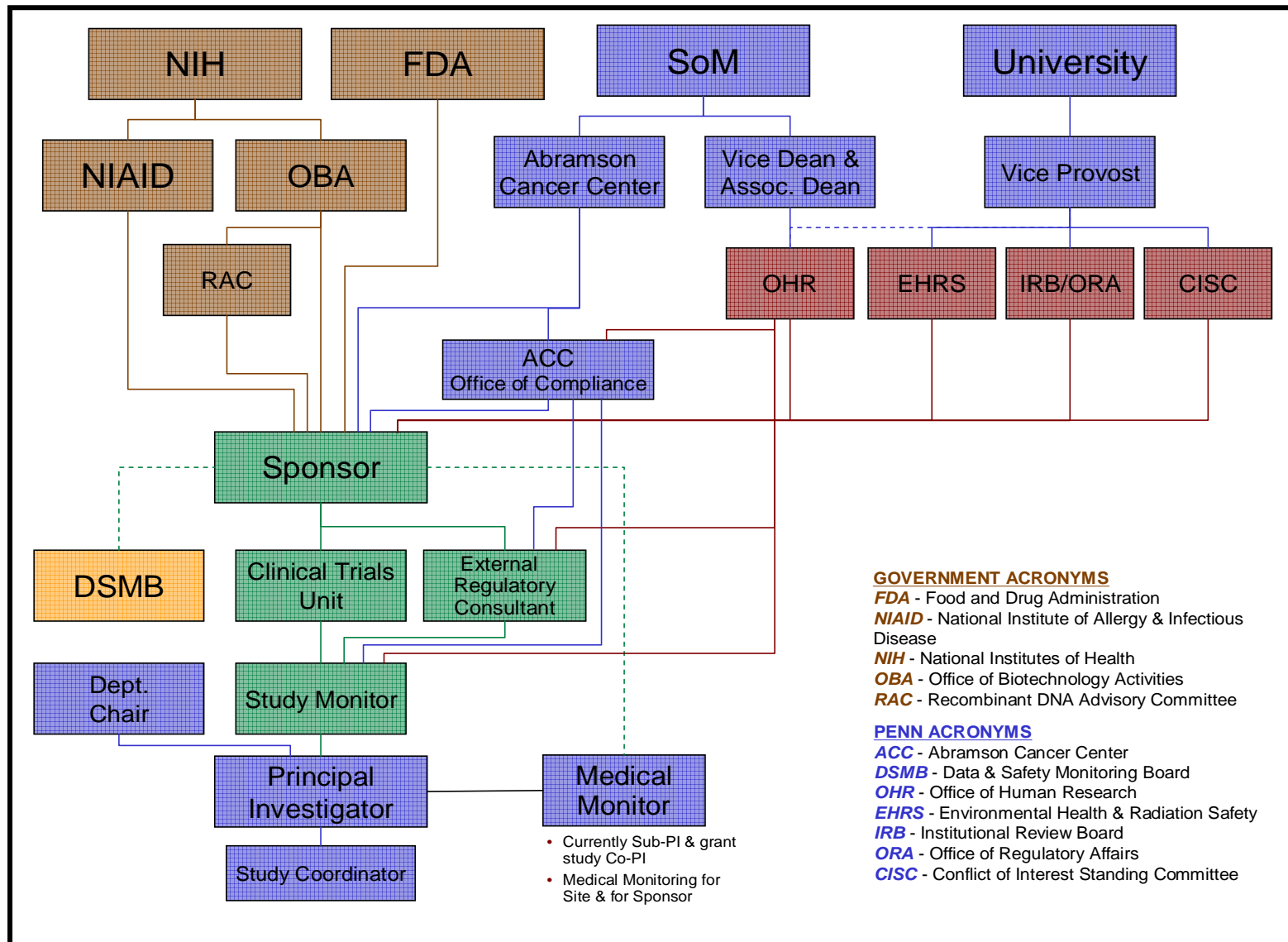
***Federal and Institutional
Approval Process
(IRB, IBC, NIH/RAC, FDA)***

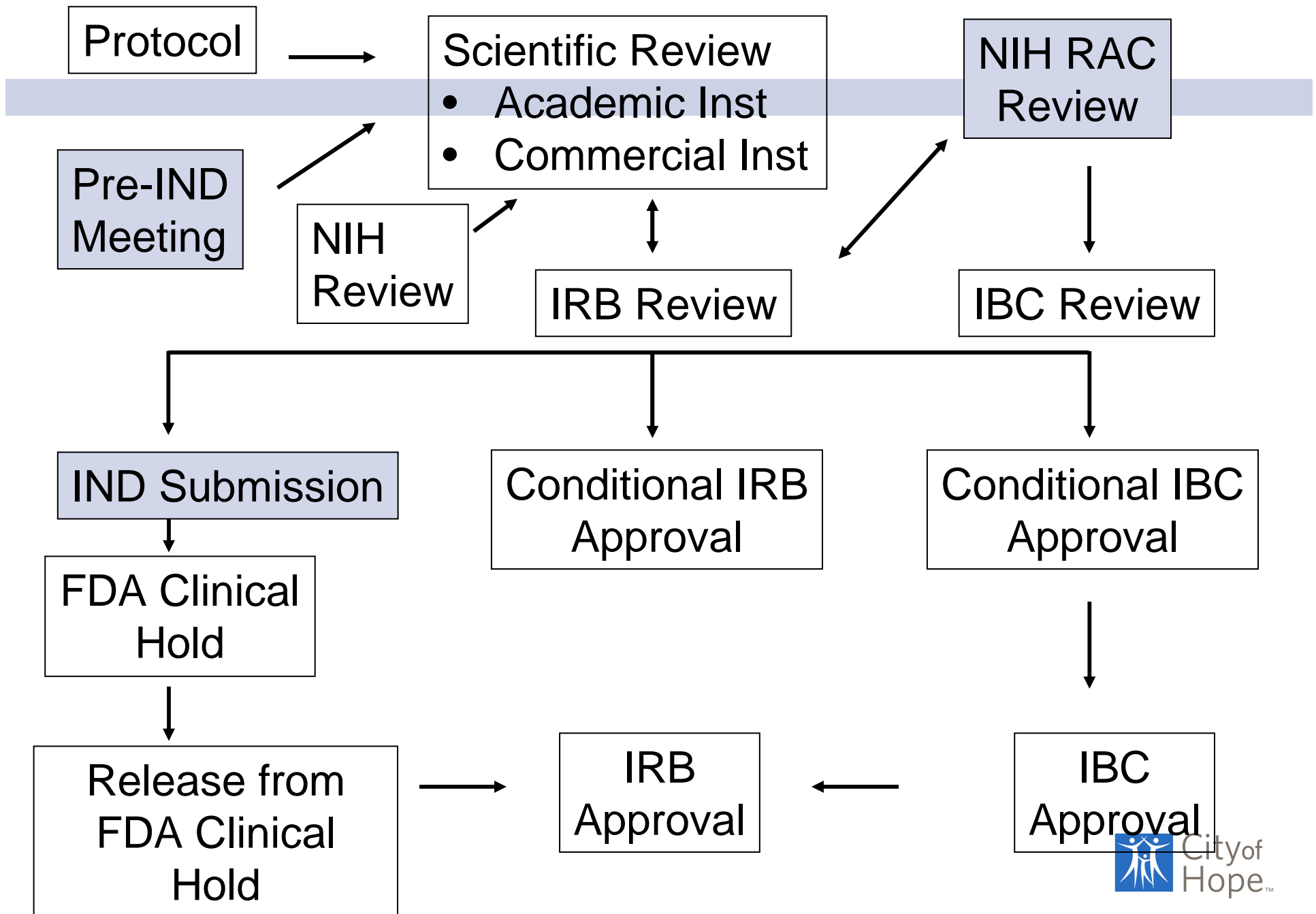
John A. Zaia, M.D.

***ASGCT's Clinical Trials Training Course
Washington, D. C.
May 18, 2010***

Regulatory Oversight for Physician Sponsored IND

From Carl June

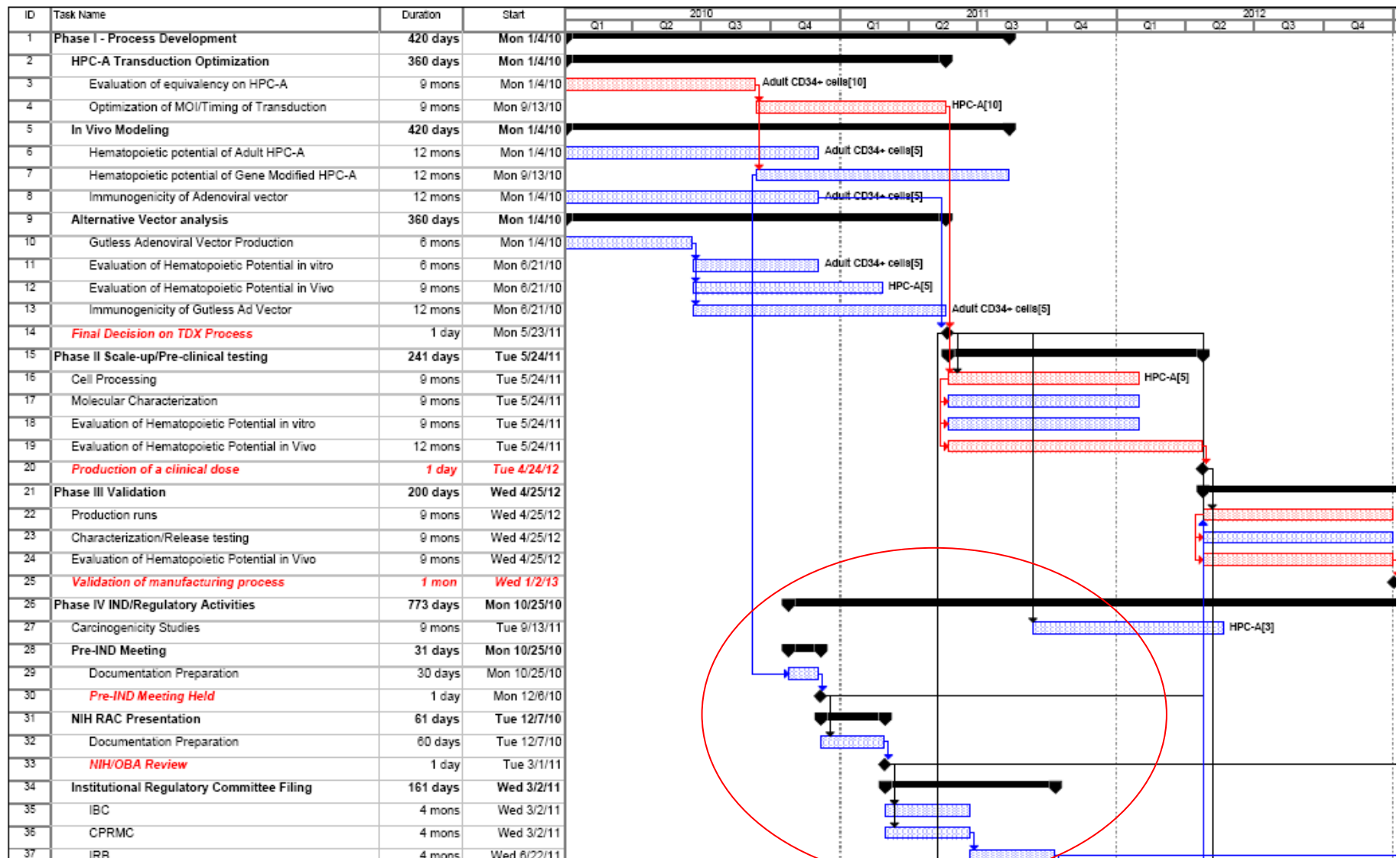




General Approach

- Schedule: Be disciplined. Use project planning tools.
- Preparation: Develop a working team that meets regularly with strict adherence to a time-line
- Build objective measurements into a Go-no-Go decision scheme
- Review the requirements of IND and RAC Appendix M

Time-line Example: Early FDA & RAC Contacts



<http://www4.od.nih.gov/oba/>

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The NIH Office of Biotechnology Activities (OBA) promotes science, safety, and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies. OBA accomplishes its mission through analysis, deliberation, and communication of scientific, medical, ethical, legal, and social issues.

OBA fulfills its mission through four important programs:

- [Recombinant DNA \(RAC\)](#)
 - **Upcoming training and professional development opportunities for IBCs, investigators, and others**
- [Genetics, Health, Society \(SACGHS\)](#)
- [Dual Use Research \(NSABB\)](#)
- [Clinical Research Policy Analysis and Coordination \(CRpac\)](#)

There is a separate home page for each of these programs. They can be reached from the links above, and they are also available from any page in the OBA website by using the items on the top menu bar.

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About OBA

About OBA

OBA, which supports the [Office of Science Policy](#), within the [Office of the Director](#) of NIH:

- 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](#) and [Genetic Technologies](#);
- Manages the operation of, and provides analytical support to, the NIH Recombinant DNA Advisory Committee, the DHHS Secretary's Advisory Committee on Genetics, Health, and Society;
- Coordinates and provides liaison with Federal and non-Federal national and international organizations concerned with Recombinant DNA, Human Gene Transfer, and Genetic Technologies;
- Provides advice to the [NIH Director](#), other Federal agencies, and State regulatory organizations concerning Recombinant DNA research, Human Gene Transfer, and Genetic Technologies;
- Responds to requests for information on highly technical matters and matters of public policy related to Recombinant DNA, Human Gene Transfer, and Genetic Technologies;
- Develops and implements NIH policies and procedures for the safe conduct of Recombinant DNA Activities, and Human Gene Transfer;
- Reviews and evaluates the composition of [Institutional Biosafety Committees](#); and
- Develops registries of activities related to Recombinant DNA Research and Human Gene Transfer.

Check Guidance Documents

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Source of guidelines



NIH Guidelines for Research Involving Recombinant DNA Molecules

The current version of the Guidelines is available to review in HTML or PDF formats:

- For the [full text of NIH Guidelines \(HTML\)](#)
- For the [full text of NIH Guidelines](#) 
- [Printer-Friendly version of NIH Guidelines](#) 

Additional background information about the Guidelines is available including:

- [NIH Public Consultation on Proposed Changes to the NIH Guidelines for Synthetic Nucleic Acids](#)
- [Summary of Amendments and Corrections to the 2002 Guidelines](#) 
- [Links to Federal Register Notices Regarding the Guidelines since 1994](#)

Review NIH RAC Information

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About Recombinant DNA Advisory Committee (RAC)

The NIH established the Recombinant DNA Advisory Committee (RAC) on October 7, 1974 in response to public concerns regarding the safety of manipulating genetic material through the use of recombinant DNA techniques. Although the RAC's membership and responsibilities have evolved over time with scientific understanding and developments in this technology, it continues to serve the NIH, as well as the scientific and lay publics, as a critically important forum for open, public deliberation on the panoply of scientific, ethical, and legal issues raised by recombinant DNA technology and its basic and clinical research applications. Over the course of the Committee's existence, transparency and access have been its defining characteristics, enabling public acceptance of a critically important technology and creating an environment in which science can advance in an informed, safe, and ethical manner.

In keeping with its role as a federal advisory committee, the RAC issues recommendations to the NIH Director that are conveyed through the NIH Office of Biotechnology Activities (OBA), which is responsible for the NIH system of oversight of recombinant DNA research. The NIH initially charged the RAC with developing a set of NIH guidelines that would govern the safe conduct of recombinant DNA research by outlining appropriate biosafety practices and containment measures. These guidelines, now known as the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), were first published in 1976 and have evolved over time, with ample scientific and public input, to reflect new technical developments and current scientific understanding. While compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA, they have become a universal standard for safe scientific practice in this area of research and are followed voluntarily by many companies and other institutions not otherwise subject to their requirements.

In addition to seeking the RAC's advice on needed changes to the NIH Guidelines, the NIH asks the RAC to consider other matters pertinent to basic and clinical research involving recombinant DNA. A major responsibility of the RAC at present is to review human gene transfer research on behalf of the NIH. Human gene transfer trials conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research are registered with OBA and reviewed by the RAC. Protocols that raise novel or particularly important scientific, safety or ethical considerations are discussed by the RAC at one of its quarterly public meetings. RAC proceedings and reports are posted to the OBA Web site to enhance their accessibility to the scientific and lay publics.



Recombinant DNA Advisory Committee Meetings

- [Scheduled meetings for 2010](#)
- [Live Webcast of Current Meeting](#)  (Available when a meeting is in progress)
- [Workshops, Safety Symposia, and Safety and Policy Conferences](#)
- [Past meetings - Browse webcasts for publicly reviewed protocols](#)
- [Past meetings - Browse by date \(2010 to Present\)](#)
- [Past meetings - Browse by date \(2000 to 2009\)](#)
- [Past meetings - Browse by date \(1990 to 1999\)](#)
- [Federal Register Notices \(since 1994\)](#)

2010 RAC Meetings

The planned meetings and protocol submission deadlines for Public Recombinant DNA Advisory Committee (RAC) Review* for 2009 are shown below.

- June 15-17, 2010, RAC -- Hilton Washington DC/Rockville Hotel & Executive Meeting Center
 - Deadline for protocol submission: April 20, 2010.
- September 16-17, 2010, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 6, Bethesda, MD
 - Deadline for protocol submission: July 22, 2010.
- December 6-8, 2010, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 6, Bethesda, MD
 - Deadline for protocol submission: October 11, 2010.

Consent Guidance



NIH Guidance on Informed Consent

Prior to the first clinical gene transfer trial enrolling subjects, the National Institutes of Health (NIH) and its Recombinant DNA Advisory Committee (RAC) have sought to assist investigators in developing good consent forms and processes for clinical gene transfer research. Specifically, Appendices M-III and M-IV of the NIH Guidelines address points and issues related to informed consent that would benefit from particular attention. These appendices address issues unique to gene transfer, as well as issues that gene transfer has in common with other forms of clinical research.

The requirements of Appendix M were always intended to be complementary to and are consistent with other requirements, regulations, and guidance documents, including 45 CFR 46, 21 CFR 50, and 21 CFR 56, and other guidance from the Office for Human Research Protections and the Food and Drug Administration. However, even after the promulgation of Appendix M-III and M-IV, NIH has continued to seek ways to assist investigators and others involved in the consent process for gene transfer trials.

In 2002, the NIH Office of Biotechnology Activities (NIH OBA) formed a RAC Informed Consent Working Group - composed of members of the RAC, outside experts, and representatives of the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) - to assist the in the development of a comprehensive, web-based guidance document to supplement Appendix M. After an extensive development process, the guidance document was endorsed by the RAC in December 2003.

[Go directly to the web-based guidance document.](#)

Submission to NIH RAC

Locate the outline and instructions for NIH RAC application at http://oba.od.nih.gov/oba/rac/guidelines_02/Appendix_M.htm

1. A cover letter on institutional letterhead, signed by the Principal Investigator(s), that:
1) acknowledges compliance with Appendix M-I-A, *Requirements for Protocol Submission*; (2) identifies the Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) at the proposed clinical trial site(s) and (3) acknowledges that no research participant will be enrolled (see definition of enrollment in [Section I-E-7](#)) until the RAC review process and all applicable regulatory authorizations have been obtained.
2. The scientific abstract.
3. The non-technical abstract.
4. The proposed clinical protocol, including tables, figures, and relevant manuscripts.
5. Responses to Appendices M-II through M-V, *Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues*. Responses to Appendices M-II through M-V may be provided either as an appendix to the clinical protocol or incorporated in the clinical protocol. If responses to [Appendices M-II](#) through M-V are incorporated in the clinical protocol, each response must refer to the appropriate Appendix M-II through M-V.
6. The proposed informed consent document (see [Appendix M-III](#), *Informed Consent*).
7. Biosketches of the principal investigator(s)

Project-related Concerns

- Understand the importance of the project
 - Is this a first-in-human trial?
 - Has this vector been used before?
 - Is the therapy likely to be toxic?
- Plan your approach based on whether the main issues are expected to be vector related, transgene related, or protocol/patient related
- Assign each question from the Appendix M to a team member and discuss/finalize the response at a scheduled team meeting

AAV-based Rx of Hemophilia

Lentivirus Stem Cell Therapy

T Cell Immunotherapy

Protocol/Patient Related Concerns

- Why is this disease selected for experimental treatment?
- Natl history of this disease and objective measures of rx?
- Do alternative therapies exist? Pros and Cons of proposed rx?
- How will the gene transfer be delivered relative to the site of disease?
- How will the effects of the rx be monitored and correlated to transgene expression?
- Potential harmful effects? Minimalization of pathogenicity?
- Could the transgene be inadvertently delivered to germ cells? Sensitivity of the assay for transgene?

Vector-Related Concerns

- Emphasis will be on what is known about the vector.
- Full history of how it was constructed with sequence of the plasmids from which the vector is derived
- If the vector is not novel, and has been used in other studies, it will not be a significant concern unless those other studies were 'problematic'
- What is known about the vector in the cell system proposed? And how does this vector help you reach the objectives of the proposed research?
- Explain the major safety concerns and how these will be approached; evidence for replication non-competency

Transgene-Related Concerns

- Emphasis will be on what is known about the transgene and why this choice of gene transfer is most appropriate
- Full history of how it was derived; full DNA sequence
- What are its regulatory elements? Copies per cell?
- Describe the “preparation, structure, composition” of the materials used to treat the cells or patient
- Results to demonstrate safety, efficacy, and feasibility
- Efficiency and duration of expression; integration of gene? rearrangement of transgene? Minimal expression needed for effect? Cell/Animal models of rx effect? Cell biology of transgene expression?

Informed Consent

- Submit the consent that you intend to send to the IRB
- Use the readability indices in WORD to tone-down the verbiage
- Consider guidance document from OBA
http://oba.od.nih.gov/rdna/informed_consent_intro.html
- Minimize therapeutic misconception
- Develop a consenting procedure that involves a third party
- Anticipate significant suggestions from the RAC
- Your IRB will review these suggestions and decide on how the final consenting procedure and forms

Readability Index

- In WORD, use the  icon to determine the reading level

- Example:

If you agree to participate in this study, you will undergo the following screening tests and procedures to make sure that you are eligible to receive the study drug: physical examination, x-rays, CT scans (an x-ray transmitted onto a computer that provides pictures of the inside of your body), urine test, blood tests requiring about 4 teaspoons of blood, electrocardiogram (EKG, test of your heart rhythm) and echocardiogram (use of high frequency sound waves to monitor the heart). If you are a woman of childbearing potential, you will also have a serum pregnancy test. If the screening evaluation shows that you are not eligible to receive study treatment, you will be taken off study and alternatives will be discussed.

Flesch Reading Ease 40.2; Flesch-Kincaid Grade Level 12.0

[Reader's Digest = 75; Harvard Law Rev = 30]

Readability Index

If you agree to this study, tests will be done to make sure that you can have this treatment. These are a physical exam, x-rays, CT scans (x-rays and computer pictures of the inside of your body), urine test, blood tests using about 4 teaspoons of blood, EKG and ECHO (tests of your heart rhythm and size). For those able to have children, a pregnancy test is done. If these tests show that you are not eligible for the study, other treatment is then discussed.

Flesch Reading Ease 73.7; Flesch-Kincaid Grade Level 8.2

The Flesch index shows whether the writing is difficult to read. It is based on the number of syllables per word and words per sentence.

It was invented by Rudolph Flesch.

$$206.835 - 1.015 \left(\frac{\text{total words}}{\text{total sentences}} \right) - 84.6 \left(\frac{\text{total syllables}}{\text{total words}} \right)$$

Response to NIH RAC Concerns

- Anticipate a list of concerns from 2-4 reviewers assigned the protocol application
- Prepare a response to each concern
- This will become a document that is available to the RAC and to the public at this meeting
- Focus the oral presentation on the issue that were identified by the reviewers as a concern

Preparation for the RAC Meeting

- It is likely that more than one person will need to be prepared to address questions: the vectorologist, the cell biologist, and the clinician. But one person should be the main presenter.
- Make sure these persons are available by notifying them weeks in advance
- Anticipate a preparatory speaker if this is a novel use of gene transfer, e.g. siRNA
- Use the concerns of the reviewers to guide your presentation, I.e., do not waste your time on non-issues

What to expect at the NIH RAC meeting

- The committee will contain experts but no one will know the specific field of investigation better than you.
- The committee will want to understand the project and most questions will focus on explanations that were not obvious in the text provided.
- Accept all questions as honest attempts to understand and do not read more into them (nor answer more) than what is asked/
- The committee will assemble its recommendation and read it into the minutes; use this opportunity to rebut any issues with which you disagree.
- Do not hesitate to point out problems that could arise from the committee's recommendations

Summary

- Determine your rationale and approach
- Decide which issues are going to be important and focus on these: VECTOR, TRANSGENE, PROTOCOL
- Be efficient in preparing the documents by developing a systematic approach to covering the questions posed in the NIH RAC Appendix M
- Follow the on-line requirements and guidance
- Submit your proposal to the RAC when you are ready for your pre-IND meeting and ideally before your IRB/IBC submissions