



NIAID Clinical Research Seminar Series: Sharing Best Practices

Scientific and Regulatory Review of Clinical Trials
Friday, October 19, 2007

Registration and sign-in: 8 to 8:30 a.m.

Seminar: 8:30 a.m. to 12 p.m.

Lipsett Amphitheater, NIH Clinical Center, Building 10

**Co-sponsored by
NIAID Clinical Research Subcommittee and the
the NIAID Office of Scientific Resource Development**

Scientific and regulatory review of NIAID-funded clinical trials protects the rights and welfare of human subjects and ensures the quality and integrity of research data. In this seminar, leading NIAID experts share best practices in this area.

Jorge Tavel, M.D., Deputy Director, NIAID Division of Clinical Research, moderates a panel discussion with division representatives after each of the following presentations:

Regulatory protocol review

- **Julia Goldstein, M.D.**, Senior Regulatory Affairs Officer, DAIT
- **Robert Johnson, Ph.D.**, Chief, Office of Regulatory Affairs, DMID
- **Cynthia Kleppinger, M.D.**, Consultant, DIR/DCR
- **Mary Anne Luzar, Ph.D.**, Chief, Regulatory Affairs Branch, DAIDS

Scientific protocol review

- **Richard T. Davey, Jr., M.D., FACP**, Deputy Clinical Director, NIAID
- **Jorge Flores, M.D.**, Deputy Director, Vaccine Research Program, DAIDS
- **Cristian Rodriguez, M.D.**, Medical Officer, DAIT
- **Shy Shorer, M.D., MBA, RAC**, Acting Director, Office of Clinical Research Affairs, DMID

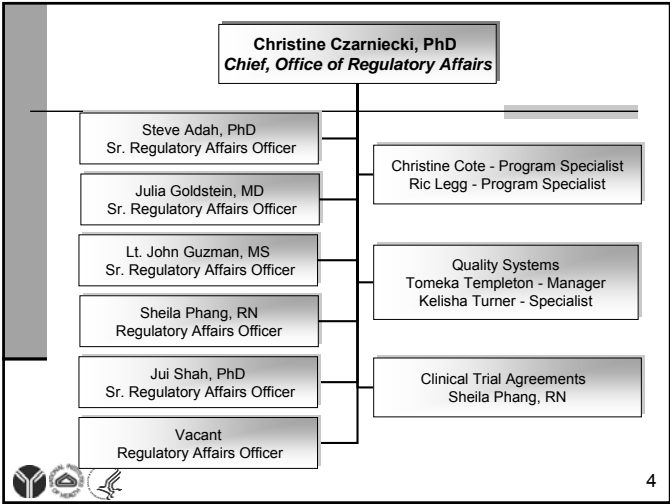
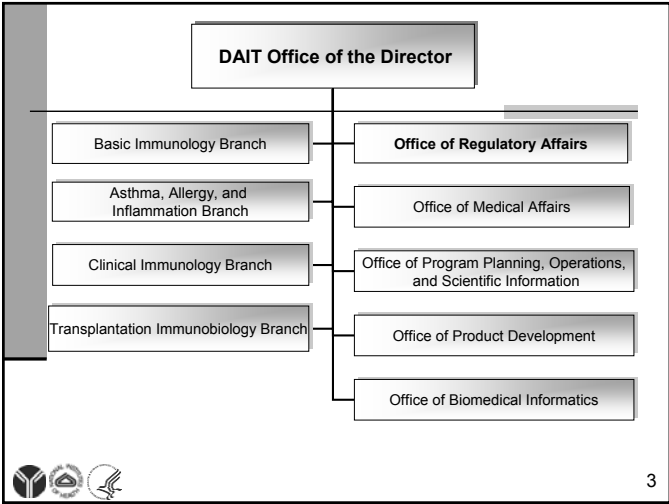
Attendees will earn **one ESA credit** and **three project officer continuous learning points** (CLP) for attending this event, in person.

NIAID Seminar Series

Regulatory Protocol Review

**Regulatory Review:
Division of Allergy, Immunology
& Transplantation (DAIT)**

Julia Goldstein, MD
Senior Regulatory Officer
Office of Regulatory Affairs
DAIT, NIAID



DAIT ORA: Who are we?

- **Background/experience:**
 - Industry - Genentech, MedImmune, ICOS, AXYS, InterMune, NABI Biopharmaceuticals, Hemagen
 - Government, FDA – CDER, CBER, NHLBI/NIH
 - CRO – Quintiles, SAIC
- **Expertise:**
 - Microbiology ■ Virology ■ Immunology ■ Biochemistry
 - Pharmacology ■ Toxicology ■ Biotechnology ■ Biologics (cellular/gene therapy products, recombinant proteins) ■ Drugs
 - Devices ■ Product Manufacture ■ Quality Systems (GMP, GLP,GCP) ■ International regulations ■ Regulatory Contracts



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DAIT ORA Mission Statement

Our mission is to:

- work with the project teams to develop the most efficient regulatory strategy which anticipates the needs and requirements of the health authorities to facilitate the transition of clinical projects from the planning to the operational stage; and
- ensure that DAIT-sponsored clinical trials are conducted in compliance with all applicable regulations and requirements to ensure the safety of the subjects and the scientific integrity of the data.



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DAIT Portfolio by Scientific Focus

TRANSPLANTATION

- Cooperative Clinical Trials in Pediatric Transplantation (CCTPT)
- Clinical Trials in Organ Transplant (CTOT)
- Clinical Islet Transplantation Consortium (CIT)

AUTOIMMUNITY

- Hematopoietic Stem Cell Transplantation (HSCT)
- Autoimmunity Centers of Excellence (ACE)



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DAIT Portfolio by Scientific Focus

ALLERGY AND ASTHMA

- Inner-City Asthma Consortium (ICAC)
- Atopic Dermatitis and Vaccinia Network (ADVNI)
- Food Allergy Network – Consortium for Food Allergy Research (CoFAR)
- Allergy & Asthma Disease Clinical Research Centers (AADCRC)

RADIATION - NUCLEAR MEDICAL COUNTERMEASURES

- Medical Countermeasures Program Against Radiation Threats (MCART)
- Centers for Medical Countermeasures Against Radiation (CMCR)


IMMUNE TOLERANCE NETWORK (ITN)



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DAIT Portfolio

| | |
|------------------------------------|---|
| • Active Protocols: | 95 |
| • Active US INDs: | 29 |
| • Active Drug Master Files: | 2 |
| • Countries: | US, Canada, Australia, Netherlands, UK Switzerland, Italy |


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FDA Divisions Regulating DAIT Studies

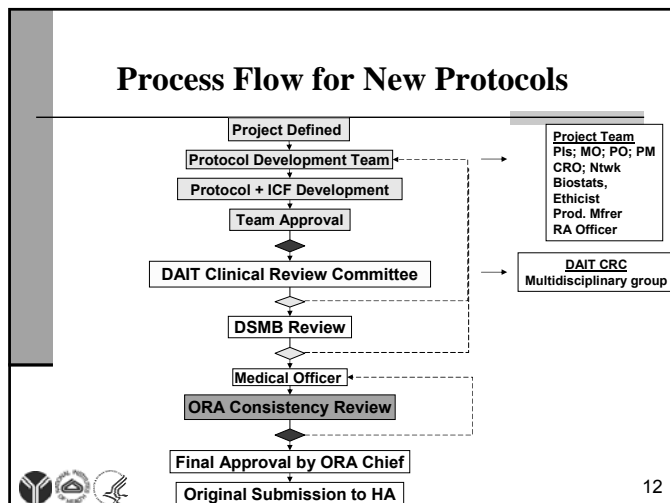
| CBER/FDA | CDRH/FDA | CDER/FDA |
|---|---|--|
| <ul style="list-style-type: none"> • Cellular and Gene Therapies • Bacterial, Parasitic and Allergenic Products • Hematology | <ul style="list-style-type: none"> • Immunology and Hematology Devices | <ul style="list-style-type: none"> • Metabolism and Endocrinology Products • Analgesics, Anesthetics, and Rheumatology Products • Cardiovascular and Renal Drug Products • Oncology Products • Dermatology and Dental Products • Neuropharmacological Products • Biological Oncology Products |


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Protocol-Supporting Activities by ORA

| Regulatory Activities | Operations Activities |
|---|---|
| <ul style="list-style-type: none"> • Original submission: <ul style="list-style-type: none"> • Facilitate communications between HA and team • Negotiate agreements with HA • Create/implement regulatory strategies • Provide scientific & regulatory guidance • Review and edit IND sections • Subsequent interactions: <ul style="list-style-type: none"> • Implement devised strategy • Continue communications with HA • Ensure reaching regulatory milestones • HA Submissions (SAE, AR, protocol amendments, updated investigator documentation, information requests etc.) | <ul style="list-style-type: none"> • Oversight of Regulatory Support Contract • Regulatory compliance throughout study • SAE Reporting and tracking • QA oversight of drug manufacturers, if needed • GCP, GMP and GLP audits • Trial Agreements Negotiations • Participate in site initiations/training • Review of investigator documentation and recruitment advertisements • Site "registration" and maintenance of study documentation through CRO • Authorization of first drug shipment to sites |


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New Protocol Development and Review

- **Early Stage:**
 - Feasibility Assessments
 - Sections of the protocol and ICF
 - Supporting documents
 - Time: team-specific, ~ 5-7 business days for each
- **DAIT Clinical Review Committee (CRC)/DSMB**
 - DRAFT Protocol
 - Time: ~ 5-7 business days
- **ORA Consistency Review**
 - Final Draft Protocol (signed-off by Medical Officer)
 - A) No deficiencies: Final Protocol (Version 1.0) →CRO
 - B) Deficiencies → Team
 - Time: ~ 5-7 business days



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ORA Consistency Review

- **What?**
 - Specific sections of protocol
 - Rationale for selected dose
 - Stopping rules
 - Study risks description
 - SAE/AE reporting
 - Statement allowing sponsor to access records
 - Product description
- **How?**
 - Compliance with applicable:
 - Federal, local and state regulations
 - Guidelines (NIAID, FDA, ICH)
 - Previous agreements with HA
 - Consistency with other documents (IB, ICF, package insert, IND sections etc.)



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Resources and Tools for Protocol Review

- | | |
|--|--|
| <ul style="list-style-type: none"> ■ Resources <ul style="list-style-type: none"> ▪ ICH guidelines ▪ US CFR ▪ FDA, country-specific guidelines ▪ State and Local Regulations ▪ Other US regulations (e.g., HIPAA, OHRP) ▪ NIAID Policies ▪ DAIT SOPs and Project Work Instructions ▪ IB and package insert ▪ Other IND sections ▪ Previous communications with HA ▪ Personnel training, experience | <ul style="list-style-type: none"> ■ Review Tools <ul style="list-style-type: none"> ▪ Templates <ul style="list-style-type: none"> ▪ Protocol ▪ ICF ▪ Checklists <ul style="list-style-type: none"> ▪ ICF |
|--|--|



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DAIT Organization Approach: Challenge


- **Staffing: Maintaining the number of qualified Regulatory Affairs Officers to provide optimal levels of support for the programs**



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DAIT Organization Approach: Advantages

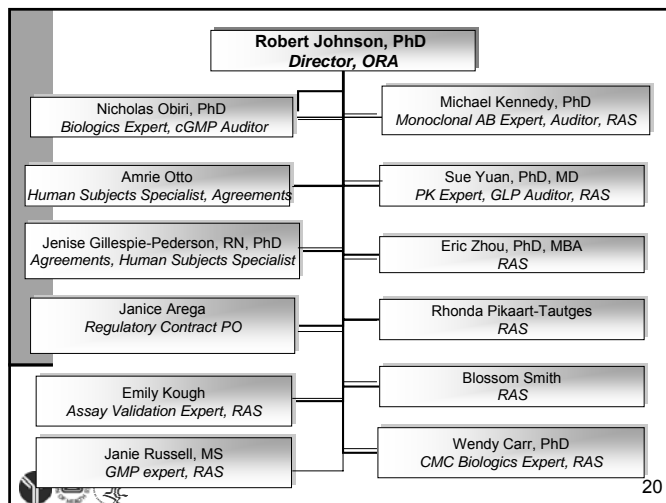
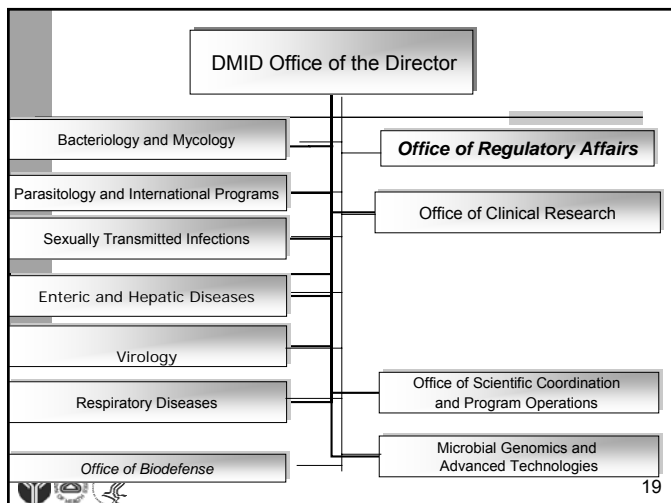
- **Assignment and identification of the RO with a clinical program**
 - Rapport with FDA review team and PDT
 - Continuity across protocols within a program
 - Consistency of approach
 - Capitalization of experiences across protocols within a program
- **Early involvement in the project**
 - Identification of key/controversial issues
 - Early formulation of regulatory strategy - facilitate project planning, budgets, etc.
- **Sharing expertise/experiences within ORA**
 - Back-ups



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DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID)

ROBERT JOHNSON, PhD
DIRECTOR
OFFICE OF REGULATORY AFFAIRS



DMID: What ORA Reviews

- Review of all protocols with an interventional product
 - Filed under DMID sponsored IND
 - Filed under a manufacturer's or investigator's IND
 - Not filed under IND but filed under European CTA or other IND equivalent
- Review of protocols with human subjects without an interventional product
 - For protocols that include vulnerable subjects
 - For protocols with special human subjects protections concerns



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DMID: Portfolio

- Active INDs and Master Files
 - 50 INDs with CBER
 - 23 INDs with CDER
 - 11 Master Files with CBER
 - 2 Master Files with CDER
 - 2 International CTAs
- Approximately 133 active protocols under DMID IND
- 18 international protocols or protocols with both international and domestic sites.



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DMID: PROTOCOL REVIEW

Integrated Process

- | | |
|---|--|
| Internal <ul style="list-style-type: none">■ Regulatory■ Program■ Medical/Safety■ Clinical Operations | External <ul style="list-style-type: none">■ PI--Author■ Possibly the Manufacturer |
|---|--|



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DMID: Who Performs Regulatory Protocol Review

- Regulatory Affairs Specialist assigned to project
- Mini-team within ORA for specialized expertise



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DMID: What Is Reviewed

Concept
+
Development
Consultation


→

Documents Reviewed

- Clinical Trial Concept
- IB
- Other product information as necessary/available
- Audit reports


Objective

- Determine adequacy of non-clinical and existing clinical data to support proposed trial
- Determine need for IND and pre-IND meeting
- Determine resource requirements



Protocol Supporting Efforts

- Assess the quality of the product
- Assess trial feasibility from a regulatory perspective
- Consult on assays, formulation and manufacture
- Assess capabilities through GMP and GLP audits
- Provide guidance on product development pathways /strategies consistent with current FDA requirements/guidances
- Author regulatory documents/IND sections



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DMID: What Is Reviewed

Protocol
Review


→

Documents Reviewed

- Protocol
- Consent and Subject Info
- IB
- All IND sections and supporting documents, as applicable
- Responses to Pre-IND issues
- SOP and CRF for product handling

Objective

- Product testing supports the proposed study
- Human subjects requirements met
- All other applicable regulations + policies met or addressed
- Consistency between documents




DMID: Requirements/Resources

- Code of Federal Regulations
- FDA Guidance Documents
- HHS/NIH/NIAID/DMID Policies
- International Conference on Harmonisation
- Non U.S. Country Regulations
- State/Local Regulations/Requirements
- Other Licensing/Certifying Authorities

Tools

- Protocol Template
- Consent Check List

- IB Checklist



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DMID: How Long Does It Take

- 10 Working days
- Timeline is the same for all stages
 - Concept
 - Supporting IND documents
 - Consultations on early protocol drafts
 - Final draft
 - Review of amendments
- Requires all supporting drafts to start the clock



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DMID: Process Challenges

- Variety of organisms, test products, and clinical trial designs makes harmonization/standardization of review difficult
- Requires A wide range of expertise and with current/projected resources limited back-up
- Consolidation and resolution of comments from multiple reviewers can be time consuming
- Working with new regulatory strategies with evolving interpretation



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DMID: Process Strengths

- Division team approach ensures appropriate subject expert review of all protocols and supporting regulatory documents
- Early involvement in all protocol aspects
 - Issues resolved and document finalization prior to IND/amendment preparation/submission
 - Regulatory strategy/development plan
 - Quick turn around on final documents
 - Reduces risk of product development delays



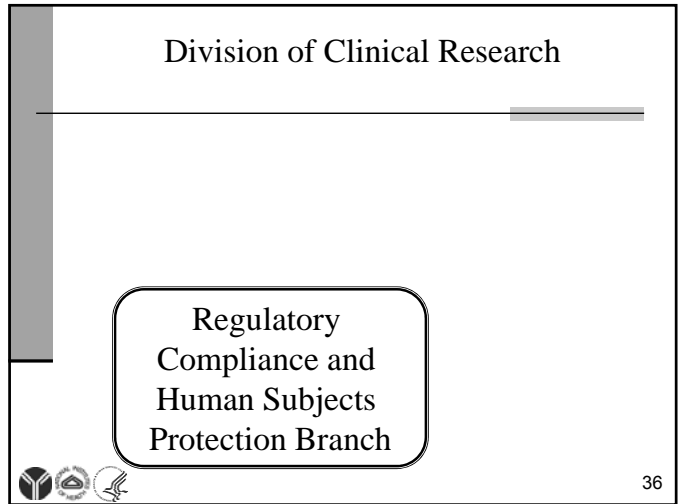
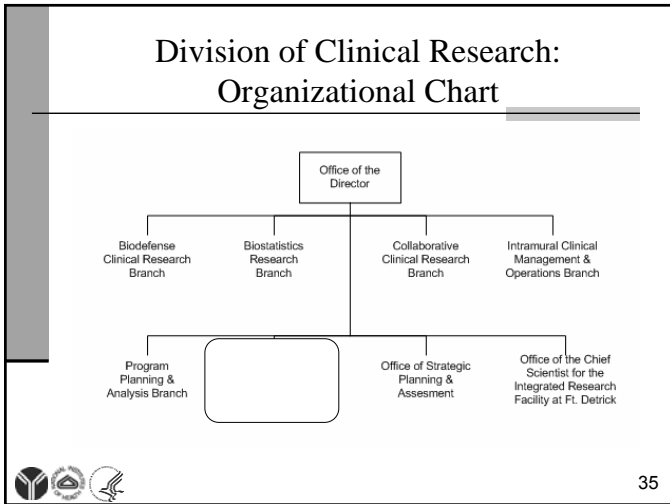
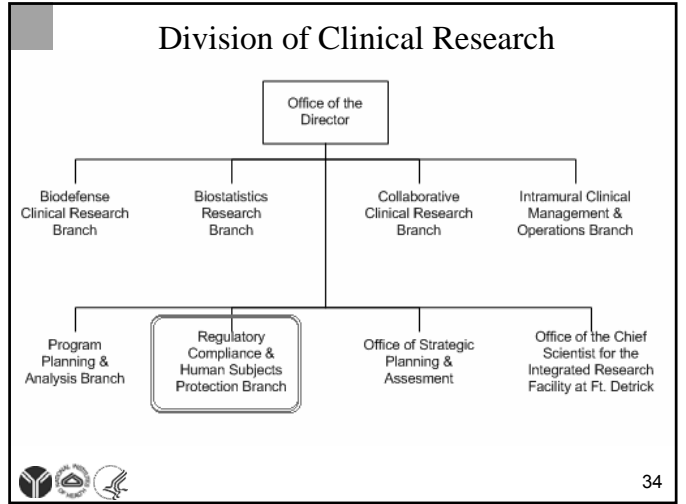
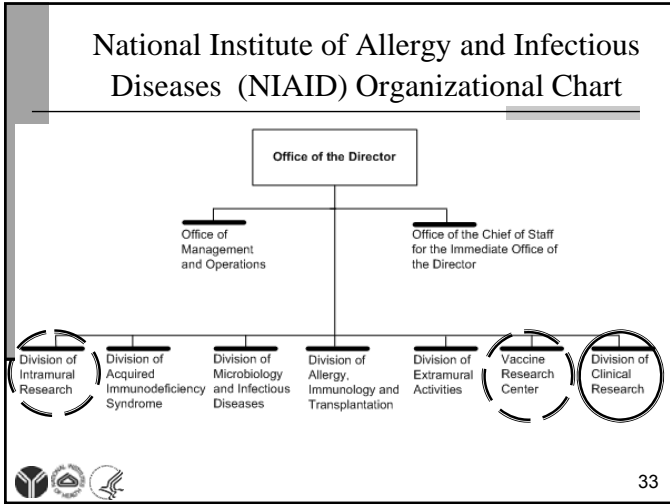
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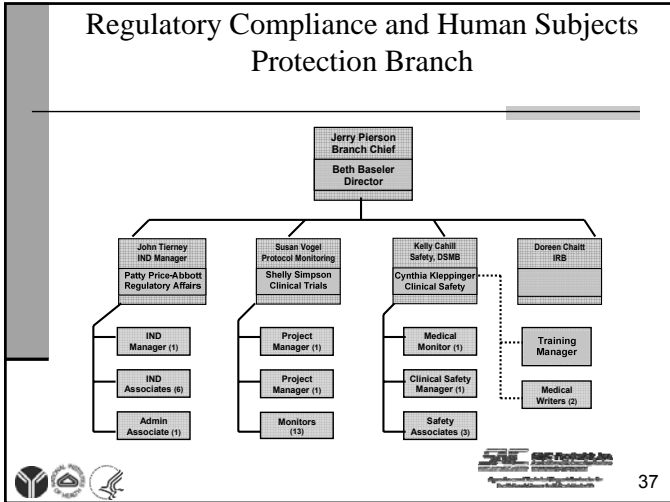
Regulatory Protocol Review



Regulatory Compliance and Human Subjects Protection Branch

Cynthia Kleppinger, MD
Director, Clinical Safety Office
October 19, 2007

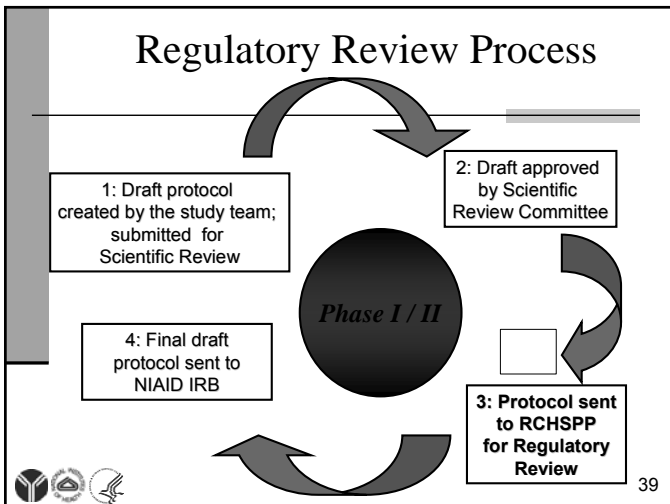




Regulatory Compliance and Human Subjects Protection Program

- Established in late 2001
- Mission:
 - To provide guidance, policies, procedures and services that facilitate the work of the investigators in the intramural community and those sponsored by the NIAID intramural programs to conduct clinical research of the highest quality in accordance with applicable regulations, standards and appropriate guidelines.

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Regulatory Protocol Review Staff

SAIC-Frederick, Inc. staff:

- 2 Medical Monitors (Licensed, board certified physicians)
- 3 Clinical Safety Associates (1 physician and 2 nurses)
- 2 Medical Writers (2 PhDs)
- 9 Regulatory Associates (Director and Assoc Director)
- 16 Clinical Research Associates (Director and 2 Mgrs)
 - CRA I (7 total) do not review protocols independently

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RCHSPB: How Long Does Review Take?



- New protocols
 - Turn around 7 working days
- All amendments
 - Turn around 3-5 working days

“Policy for NIAID Regulatory Review Process for Intramural Protocol and Informed Consent/Assent Documents”



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RCHSPB: Required Reviews

Reviews protocols from all Laboratories and Branches within the NIAID intramural research program and other Institutes that submit protocols and related documents to the NIAD IRB.



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RCHSPB: Portfolio

| | |
|-----------------------------|-----------|
| • Active INDs | 43 |
| • With 2 protocols included | 2 |
| • With 4 protocols included | 1 |
| • Pending INDs | 6 |
| • Master Files | 6 |
| | |
| • Non-IND studies monitored | 43 |
| | |
| • Total protocols reviewed* | 30 |
| • Amendment reviews | 16 |

(*Jan 1, 2007 - June 30, 2007)



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RCHSPB: Trial Sites

Domestic sites

- NIH
- JHU
- Vanderbilt
- Dept. of Defense: CA, TX, HI, VA, MD, DC

International sites

- Canada
- South America: Peru, Argentina, Brazil
- Europe: 7 countries
- Africa: Mali, Uganda, South Africa
- Asia: Vietnam, Cambodia, Korea, Thailand, Indonesia, Hong Kong, India

*One current study has 128 sites in 11 countries



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RCHSPB: How Review is Performed

- Document Control sends e-mail to all managers to assign staff.
- Medical Writer
 - Reviews document for grammatical / typographical errors, formatting, inconsistencies within the document and between documents
 - Develops Table of Contents, if needed
 - Formulates List of Abbreviations, if needed



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RCHSPB: How Review is Performed

- Regulatory Associate focuses more attention on elements of the protocol concerning:
 - IND status
 - IND requirements and any inconsistencies between IND documents
 - 'Human Subject Protections' section
 - 'Remuneration Plan for Subjects' section
- Reviews informed consent(s) for required elements



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RCHSPB: How Review is Performed

- Clinical Safety Associate focuses more attention on these elements of the protocol:
 - 'Adverse Event Reporting Plan'
 - 'Plan for Monitoring Subjects and Criteria for Withdrawal of Subjects from the Study'
 - 'Data and Safety Monitoring Plan'
- Reviews informed consent(s) for:
 - Inclusion of all risks and safety hazards
 - Descriptions of all procedures and safety monitoring reflected in the protocol
 - Ability to be understood by the general public



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RCHSPB: How Review is Performed

- Clinical Research Associate focuses more attention on these elements of the protocol:
 - 'Data Management Plan'
 - 'Protocol Monitoring Plan'
 - 'Plan for Use and Storage of Biological Samples'
- Implementation issues
 - Study procedures
 - Table of Events / study schedule
 - Study agent / dosing requirements
 - Feasibility of procedure implementation



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RCHSPB: How Review is Performed

- Medical Monitor reviews entire protocol and all informed consent(s):
 - Reviews, edits and reconsolidates all comments
 - Finalizes documents
 - Sends documents to investigator
- Final review of amendments done by Reg Affairs and Clin Trials Mgmt managers



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Medical Monitor Review / Consolidation of Comments

7 Working Days

Copies of Review sent to RCHSPB Chief, CROMs and RCHSSP staff

PI Receives Protocol / Informed Consent
And, if applicable, approval comment for NIAID IRB



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2 Working Days - Final Review of Changes

Discuss Unresolved Issues with Clinical Director or designee

Final Revised Draft Protocol and Informed Consent to NIAID IRB



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Sources of Requirements

- Code of Federal Regulations (CFR)
- Department of Health and Human Services (DHHS)
- NIH Clinical Center (CC) Policies
- NIH Office of Human Subjects Research (OHSR)
- Office for Human Research Protections (OHRP)
- NIAID Policies
- NIAID Institutional Review Board (IRB)



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Other Regulations and Guidelines

- International Conference on Harmonization (ICH)- E6 Good Clinical Practice standards
- ICH- E3 Structure and Content of Clinical Study Reports
- ICH E-8 General Consideration for Clinical Trials
- Council for International Organizations of Medical Science (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects
- Consolidated Standards of Reporting Trials (CONSORT)



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RCHSPB: Tools / Resources

- SAIC Guidance for Writing a Protocol
- SAIC Guidance for Writing Protocols in Manuscript Form for Publication
- NIAID Protocol Template
<http://www3.niaid.nih.gov/research/resources/toolkit/protocol/>
- NIAID Institutional Review Board (IRB) web site
<http://intramural.niaid.nih.gov/ocd/IRBWeb/default.html>
- SAIC SOPs/Checklists



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RCHSPB: Review Process Challenges

- Rapid protocol review cycle
- No minimum standard for version of draft protocol submitted for review
- Minimal to no previous involvement of review staff with protocol development
- Expertise rests on contractor staffing - need to hire and retain most qualified personnel
- Final approval of review rests on one person- the Medical Monitor



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RCHSPB: Review Process Advantages

- Rapid protocol review cycle
- All documents submitted to/stored at one place
- No need to invite reviewers for a committee
- Each group understands their role in the review
- Returned documents to investigators have edits and language inserted
- Monitoring experience in previous trials inserted into comments



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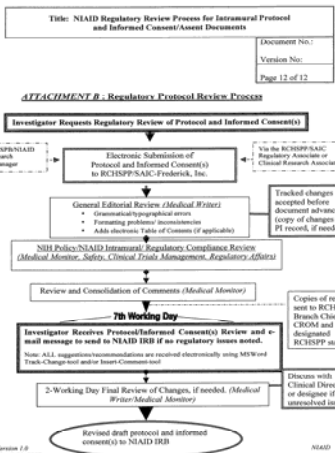
Questions?

- Feel free to contact me – Cynthia Kleppinger
ckleppin@mail.nih.gov
 (301) 846-7257

New York Yankees rookie players pitcher Joba Chamberlain, pitcher Ian Kennedy, infielder Shelley Duncan and pitcher Phil Hughes during their annual rookie hazing .
 (Source: Reuters.com)

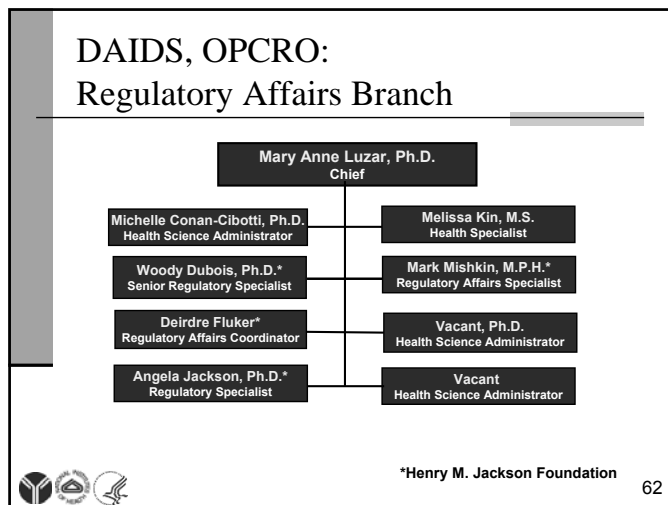
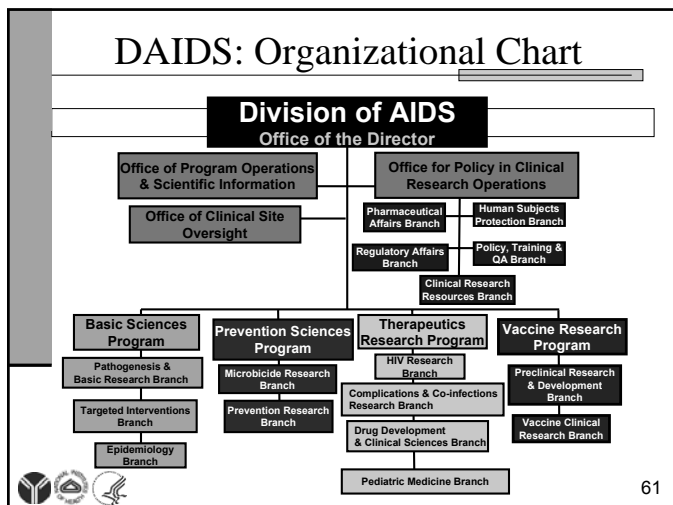


Special thanks to Dr. Terry Mainprize and Dr. Barry Eagel for their help on the slides.



Regulatory Protocol Review

Division of Acquired Immunodeficiency Syndrome (DAIDS),
 Mary Anne Luzar, Ph.D.
 Chief, Regulatory Affairs Branch, Office for Policy in Clinical Research Operations (OPCRO), DAIDS



DAIDS: Regulatory Affairs Branch Mission

- To ensure that DAIDS-sponsored human clinical trials comply with all applicable U.S. laws, Code of Federal Regulations (CFR) and federal guidelines
- To provide guidance, regulatory expertise and manage all DAIDS regulatory submissions in compliance with the CFR for IND applications and serve as official liaison to the FDA.

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DAIDS: Regulatory Review Portfolio and Statistics

- 110 INDs
- 400 Protocols
 - 200 IND protocols
 - 200 non-IND protocols
- 40 Countries
- Regulatory reviews conducted in RAB since 1997

| <u>Continents</u> | <u>Scope</u> |
|-------------------|---------------------|
| Africa | Drugs |
| Asia | Vaccines |
| Australia | Microbicides |
| Europe | Immune Modulators |
| North America | Biological Products |
| South America | Gene Therapy |

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DAIDS: Who Performs Regulatory Review

Currently, 5 RAB Members Perform Regulatory Reviews of Protocols:

- 3 NIH FTEs (2 Ph.D.; 1 M.S.)
- 2 Henry M. Jackson Foundation Members (2 Ph.D.)

Expertise

- Biochemistry and Molecular Biology • HIV-1 Basic Research
- FDA • Government Regulatory Contracts • Microbiology
- Pharmaceutical Industry • Public Health • Virology



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DAIDS: Who Performs Regulatory Review (continued)

17 Technology Resources International Inc.-Regulatory Compliance Center (RCC) Staff Members

- 2 Regulatory Compliance Specialists per Regulatory Review
- 1 Quality Control Specialist per Regulatory Review
- 6 Ph.D.; 2 J.D., 1 Pharm.D.; 5 M.S.; 1 M.H.S.; 1 M.H.S.A.; 1 M.P.H.

Expertise

- Biomedical Sciences • Biotechnology Law • Cellular and Molecular Biology • Government Regulatory Contracts • FDA • Immunology • Manufacturing • Microbiology • Pharmaceutical Industry • Pharmacology • Public Health • Quality Assurance • Quality Control • Regulatory Affairs • Virology



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DAIDS: How Review is Performed

Delegation of Responsibilities

DAIDS RAB Staff

- Branch Chief assigns each protocol to 2 DAIDS Regulatory Affairs Branch Members
 - 1 Primary IND Manager: Responsible for Content of Regulatory Review (signs 1571s for INDs and signs-off on non-IND studies)
 - 1 Back-up
- Some factors to consider in delegation of protocols/INDs
 - **Reviewer:** Previous IND experience, professional goals, workload, skills sets and expertise
 - **Protocol:** Level of visibility, priority, scientific scope
 - **IND:** Intensity balance

RCC Regulatory Team

- Regulatory manager assigns each protocol to 3 RCC Regulatory Compliance Specialists
 - 2 Primary Reviewers
 - 1 Quality Control Specialist



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DAIDS: How Long Does Review Take?



New Protocol Regulatory Review

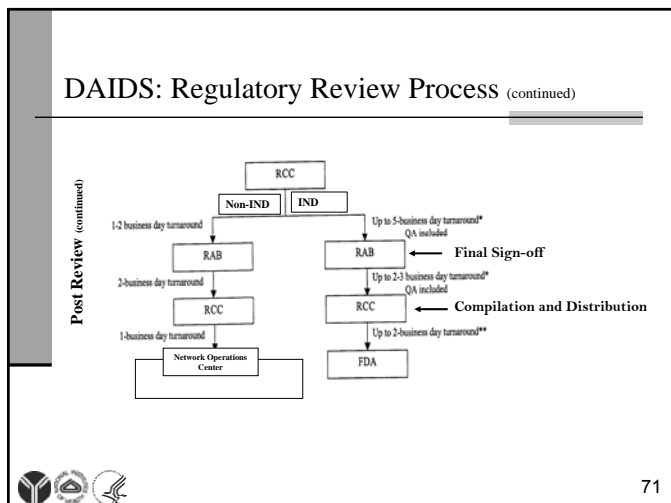
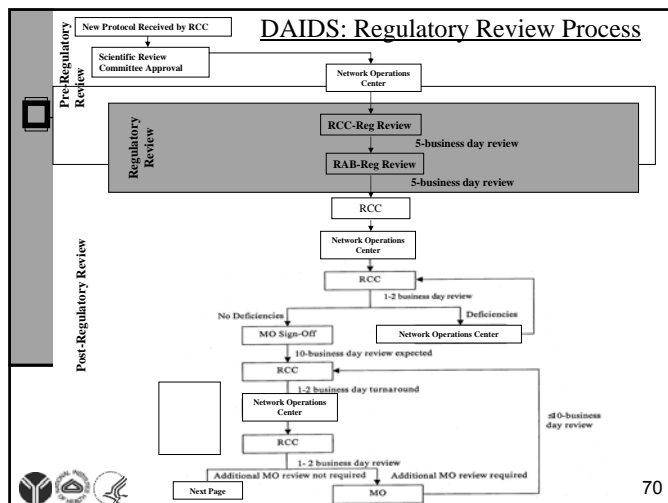
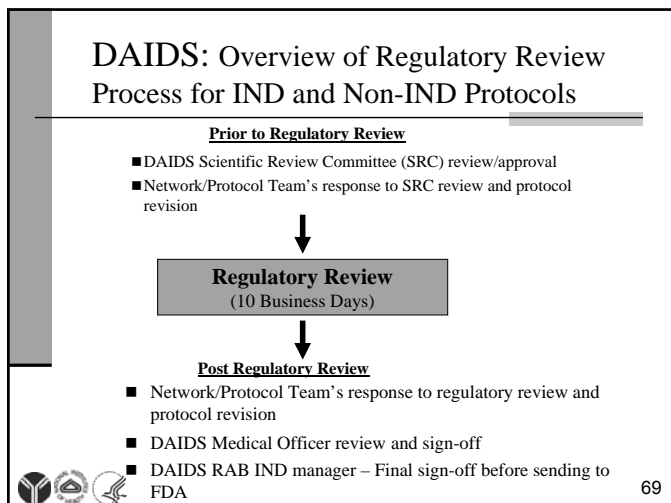
- Up to 10 business days
- Clock starts and ends with email notification from RCC to RAB and protocol team

Protocol Amendment Review

- Up to 5 business days
- Same general review procedure as new protocol
 - Not as extensive because many regulatory concerns have already been addressed



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- ### DAIDS: How Review is Performed
- Tools/Resources:
- Code of Federal Regulations
 - International Conference on Harmonisation
 - Written Standard Operating Procedures
 - Regularly Updated
 - Checklists
 - Investigator's Brochure and package inserts
 - Previous FDA comments on given study product
 - Established FDA guidance
 - Network protocol templates
 - DAIDS policies and manuals
 - Foreign government regulations and guidance documents
-
- 72

DAIDS: How Review is Performed

Review Criteria

- Accuracy and completeness of scientific references
- Accuracy of sponsorship
- Appropriate intent and content
- Formatting according to network/group protocol template
- General consistency throughout document
- Pre-IND and/or FDA comments have been addressed
- Principal Investigator and Investigator Brochure are consistent with protocol and investigator's contact information is correct
- Schema matches text
- Scientific Review Committee comments have been addressed
- Spelling and grammar (those that impact meaning)
- Title is consistent throughout and reflects objectives
- Verify requirement for IND cross-reference letters



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DAIDS: Review Process

Advantages

- Accountability- Fixed time for completion
- Consistent process for all networks and both IND and Non-IND protocols
- Enables review of multiple protocols simultaneously (in 10 days)
- Two phase approach allows contract to focus on routine issues while RAB is free to concentrate on specialized areas

Challenges

- Diverse subjects/interaction with varied departments within FDA
- Diverse international regulatory environments and requirements
- Length of time for review may be too long for certain stakeholders
- Limiting scope of comments to regulatory issues
- Need to avoid redundancy in 2-tiered process
- Special requests for expedited review
- Volume of protocols and amendments vs. limited turnaround time



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DAIDS: Regulatory Review Process Summary

- Standardized two (2) tiered review process with time limit (10 business days) and effective quality control
- Focused on pertinent regulatory issues central to successful conduct of both IND and Non-IND protocols



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NIAID Intramural Protocol Scientific Review Process

Rick Davey

Deputy Clinical Director,
Division of Intramural Research
NIAID

1

Intramural Scientific Review Committees: Basic Tenets

- Each Laboratory within DIR is responsible for ensuring rigorous scientific review of its protocols before review by the IRB.
- The purpose of such scientific review is to ensure that clinical trials are well designed: that the research question is valid and that the proposed study has a reasonable likelihood of answering the research question.
- The committee must also consider the protocol's quality, originality, and importance to science or clinical practice, and its relevance to the Institute's mission.

2

Intramural Scientific Review Committees: Recent Status

- ✦ Mechanisms of scientific review have varied widely among the Laboratories, often as a function of the number of clinical researchers available to participate in such reviews or other resource issues.
- ✦ Overall, a compelling need was identified for greater harmonization in the scientific review process according to a uniform set of written standards.

3

Intramural Scientific Review Committees: Volume

- ✦ In recent years the various DIR/VRC Scientific Review committees have forwarded a total of approximately 32-35 new protocols per annum to the NIAID IRB for review

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**Intramural Scientific Review Committees:
Recommendations**

- ✦ An *NIAID Policy on Intramural Scientific Review Committees* was prepared and implemented

- ✦ Each Laboratory should draft and implement a scientific review committee policy that addresses the scientific review criteria and procedures within its Branch based upon the *NIAID Policy on Intramural Scientific Review Committees*.

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**Intramural Scientific Review Committees:
Recommendations, cont.**

- ✦ The written policy should address:
 - conflicts of interest of Committee members
 - what constitutes a quorum for meetings
 - meeting frequency schedule
 - document distribution timeframe
 - what to do when a reviewer cannot attend a scheduled meeting
 - actions the Committee may take regarding reviewed protocols
 - Policy for recording written comments about the protocol
 - documentation of scientific review for IRB submission
 - retention of Committee meeting records and
 - whether annual review will be required for ongoing protocols.

6

**Intramural Scientific Review Committees:
Major Changes**

- ✦ a Scientific Review Committee should be composed of a minimum of four qualified individuals, one of whom must be a statistician, and at least one of whom must be a clinical research expert who is not a member of the sponsoring Laboratory/Branch (this should not include the statistician).

- ✦ The Scientific Review Committee must have a Chairperson designated by the Laboratory/Branch, authorized to conduct the protocol review and certify the Committee's deliberations on the protocol before IRB review.

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**Intramural Scientific Review Committees:
Major Changes, cont.**

- ✦ The BRB, DCR, has committed to provide a biostatistician to each Laboratory to perform statistical assessment of each new protocol as part of the scientific review process.

- ✦ The RCHSPB will maintain an active list of qualified subject matter experts who have volunteered to serve as external ad hoc reviewers for intramural scientific review committees

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Intramural Scientific Review Process

**Major Reference for NIAID
Intramural Investigators:**

<http://intramural.niaid.nih.gov/OCD/IRBWeb/Forms/IRBScientificReview.html>

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**Division of Acquired Immunodeficiency
Syndrome (DAIDS)**

Jorge Flores, M.D.,
Deputy Director,
Vaccine Research Program,
DAIDS, NIAID

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Breadth of Clinical Research - DAIDS

| Phase | ACTG | IMPAACT | INSIGHT | MTN | PTN | VTN | ALL |
|-----------------|---------------|--------------|---------------|--------------|---------------|--------------|---------------|
| I | 12 | 15 | | 1 | | 15 | 43 |
| II | 31 | 4 | | 1 | 2 | 2 | 40 |
| IIB, III | 13 | 12 | 3 | 1 | 9 | 2 | 40 |
| IV | 4 | | | | | | 4 |
| Other | 35 | 8 | | 2 | 1 | 1 | 47 |
| N trials | 95 | 39 | 3 | 5 | 12 | 20 | 174 |
| N vol | 15,522 | 8,141 | 10,630 | 3,450 | 16,410 | 5,134 | 59,287 |

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Scientific Review Process - DAIDS

DAIDS Review Committees

Clinical Science Review Committee (CSRC)

- Therapeutics Research Program

Prevention Science Review Committee (PSRC)

- Prevention Sciences Program and
- Vaccine Research Program

Policies: CSRC and PSRC SOPs, Review guidelines and considerations

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Scientific Review Process - DAIDS

Objectives of CSRC/PSRC review are to assess:

- Relevance of proposal to NIAID/DAIDS scientific priorities
- Scientific merit – primary objectives and study design
- Volunteer safety – eligibility requirements, study evaluations, toxicity management, and data and safety monitoring plans
- Feasibility
- Compliance with OHRP and FDA regulations – regulatory and ethical considerations
- Statistical plan and proposed analysis plan
- Drug administration and drug handling
- Whether protocol merits implementation and/or requires revision and re-review

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Scientific Review Process - DAIDS

What is reviewed?

Clinical protocols developed through funding where peer review evaluated general scientific plan

- Networks (est. 80-90%)
 - ACTG, HPTN, HVTN, IMPAACT, INSIGHT, MTN
- Non-Network (est. 10-20%)
 - POI programs
 - Cooperative Agreements – UO1, U19, R34
 - Contracts

Responses to previous reviews from committee and other scientific review committees

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Scientific Review Process - DAIDS

- Committees meetings are weekly and more frequently as needed
 - Expedited reviews are used for focused and follow-up issues
- Protocols are reviewed 2 weeks after receipt by CSRC/PSRC
- Written comments are provided to PI within 2 weeks of CSRC/PSRC review

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Scientific Review Process - DAIDS

What is covered in review process?

- Evaluation of protocol, IC, IB and package inserts
- Reviews:
 - ✦ Clinical – Study objectives, design and safety
 - ✦ Biostatistics – Statistical plan, analysis, sample size and monitoring
 - ✦ Pharmacy – drug administration and handling special issues
 - ✦ Regulatory issues and Human Subjects Protection
 - ✦ Bioethics
- Input from across and outside DAIDS through selection of reviewers and staff comments at meeting

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Scientific Review Process - DAIDS



What is not covered in scientific review?

- Details of Implementation
- Site readiness and study operations – different mechanisms for evaluations
- Budget review

Scientific Review Process - DAIDS



Benefits

- Standardized process
- Timely
- Leverage expertise within and outside the Division to enhance depth of review
- Opportunity for DAIDS staff to have an overview of studies in development within DAIDS
 - Potential to reduce redundancy
 - No formal review of what else is being done to address the question

Scientific Review Process - DAIDS



Limitations

CSRC/PSRC cannot:

- Predict how long it will take to get a study up and running
- Have an impact on getting studies implemented in a timely way
- Predict what budget needs will be
- Predict what issues will impact recruitment at sites

**NIAID Intramural
Protocol Scientific Review Process**



Rick Davey

Deputy Clinical Director,
Division of Intramural Research
NIAID

Intramural Scientific Review Committees: Basic Tenets

- Each Laboratory within DIR is responsible for ensuring rigorous scientific review of its protocols before review by the IRB.
- The purpose of such scientific review is to ensure that clinical trials are well designed: that the research question is valid and that the proposed study has a reasonable likelihood of answering the research question.
- The committee must also consider the protocol's quality, originality, and importance to science or clinical practice, and its relevance to the Institute's mission.

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Intramural Scientific Review Committees: Recent Status

- ✦ Mechanisms of scientific review currently varied widely among the Laboratories, often as a function of the number of clinical researchers available to participate in such reviews or other resource issues.
- ✦ Overall, a compelling need was identified for greater harmonization in the scientific review process according to a uniform set of written standards.

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Intramural Scientific Review Committees: Recommendations

- ✦ An *NIAID Policy on Intramural Scientific Review Committees* was prepared and implemented
- ✦ Each Laboratory should draft and implement a scientific review committee policy that addresses the scientific review criteria and procedures within its Branch based upon the *NIAID Policy on Intramural Scientific Review Committees*.

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Intramural Scientific Review Committees: Recommendations, cont.

- ✦ The written policy should address:
 - conflicts of interest of Committee members
 - what constitutes a quorum for meetings
 - meeting frequency schedule
 - document distribution timeframe
 - what to do when a reviewer cannot attend a scheduled meeting
 - actions the Committee may take regarding reviewed protocols
 - Policy for recording written comments about the protocol
 - documentation of scientific review for IRB submission
 - retention of Committee meeting records and
 - whether annual review will be required for ongoing protocols.

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**Intramural Scientific Review Committees:
Major Changes**

- ✦ a Scientific Review Committee should be composed of a minimum of four qualified individuals, one of whom must be a statistician, and at least one of whom must be a clinical research expert who is not a member of the sponsoring Laboratory/Branch (this should not include the statistician).
- ✦ The Scientific Review Committee must have a Chairperson designated by the Laboratory/Branch, authorized to conduct the protocol review and certify the Committee's deliberations on the protocol before IRB review.

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**Intramural Scientific Review Committees:
Major Changes, cont.**

- ✦ The BRB, DCR, has committed to provide a biostatistician to each Laboratory to perform statistical assessment of each new protocol as part of the scientific review process.
- ✦ The RCHSPB will maintain an active list of qualified subject matter experts who have volunteered to serve as external ad hoc reviewers for intramural scientific review committees

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Intramural Scientific Review Process

**Major Reference for NIAID
Intramural Investigators:**

*[http://intramural.niaid.nih.gov/OCD/IRB
Web/Forms/IRBScientificReview.html](http://intramural.niaid.nih.gov/OCD/IRBWeb/Forms/IRBScientificReview.html)*

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**Division of Allergy, Immunology and Transplantation (DAIT)
Clinical Research Committee (DCRC)**

Cristian Rodriguez MD
Medical Officer
Medical Affairs Branch
Office of Clinical Applications
DAIT, NIAID

Linna Ding, MD, PhD
Medical Officer
Medical Affairs Branch
Office of Clinical Applications
DAIT, NIAID

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DAIT Clinical Research Committee (DCRC)

- **Purpose**
 - It is necessary to establish a process that contributes to the success in the creation, implementation and completion of all protocols and related documents .
- **Scope**
 - All clinical protocols within the Division will be reviewed at a DAIT Clinical Research Committee (DCRC) clinical review meeting and will occur prior to the initiation of enrollment.

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Background

- The role of the DCRC is to provide an evaluation of all DAIT-sponsored clinical trials. The primary objective of this review is to provide recommendations regarding the safety and study design to help ensure the successful completion of DAIT trials. DAIT staff will review the protocol documents and provide constructive feedback in the form of oral and/or written comments.
- Each DAIT sponsored clinical trial protocol must comply with the requirements for format and content agreed upon by the DCRC. Reviewers are recommended to use as a template for assessment the document "ICH Guidelines for Industry - E6 Good Clinical Practice; section 6, ICH September 1996." and the DAIT clinical protocol template (<http://www3.niaid.nih.gov/research/resources/toolkit/protocol/>).
- DCRC is composed by:
 - ✦ DAIT Medical Officers and Scientists
 - ✦ NIAID Protocol (Project) Team members
 - ✦ DAIT Project Managers/Nurses
 - ✦ Statisticians (DIR)
 - ✦ DAIT Regulatory and Bioethics staff

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DAIT-Sponsored Clinical Studies

- **Allergy and Asthma**
Atopic Dermatitis and Vaccinia Network (ADVN), Consortium of Food Allergy Research (CoFar), Asthma and Allergy Diseases Cooperative Research Centers (AACRC), Inner City Asthma Consortium (ICAC), etc.
- **Transplantation**
Clinical trials in Organ Transplantation (CTOT), Cooperative Clinical trials in Pediatric Transplantation (CCTPT), Islet cell Transplantation, Genomics of Transplantation Cooperative Research program (GTCRP), etc.
- **Autoimmune Diseases**
Stem Cell Transplant for Autoimmune Disease Consortium (SCTADC), Autoimmune Centers of Excellence (ACE), Juvenile Diabetes Research Foundation International (JDRE), etc.
- **Immune Tolerance Network (ITN)**

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DCRC Protocol Review Meeting

- DCRC meets weekly
- New clinical protocols (1-2/Month)
 - Mechanistic studies
 - Prevention studies
 - Studies under IND (phase I-III)

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Focus of DCRC Review

- Protocol structure- IHC guidelines for GCP.
 - Clarity of objectives and endpoints and correlation with study design and background information.
 - Participant selection criteria
 - Safety assessment
 - Toxicity management
 - Stopping rules
 - Interim analysis
 - Adverse event reporting
 - DSMB review
- Study drug and pharmacy information
 - Properties
 - Procedures
 - Dispensation
 - Statistical analysis
 - Informed consent
 - Bioethics
 - Regulatory aspects

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Procedure

- After a protocol has been created based on previously agreed goals of clinical approach, numbers of subjects/patients, time frames, previous study data, etc., a draft will be submitted with a completed *DCRC Review Request Form* to the OCA Chief of Medical Affairs (or Medical Affairs Program Specialist) at least 2 weeks before desired date of DCRC review.
- The Medical Affairs Program Specialist will forward copies of the protocol and related documents to the members of the DCRC, and will schedule the DCRC Clinical Review meeting at least one week after distribution of draft protocol.
- The DCRC review of the protocol will be scheduled to coincide with the review performed by the appropriate Data Safety Monitoring Board (DSMB).

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Procedure (Cont.)

- During the DCRC Clinical Review meeting, the protocol will be presented by the DAIT Medical Officer for that study. This meeting is moderated by the OCA Chief of Medical Affairs, or a designee from OCA.
- All reviewing members of the DCRC will submit comments, suggestions and corrections (oral and/or written response) to the OCA Chief of Medical Affairs or the OCA designee.
- A summary of the major recommendations and comments will be produced by the OCA Chief of Medical Affairs, or the OCA designee, within seven business days following the DCRC Clinical Review meeting and forwarded to the OCA Director for review prior to submission to the team.

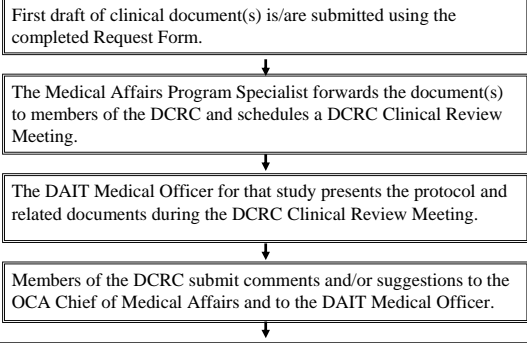
35

Procedure (Cont.)

- The Protocol Team (PT) and DAIT Medical Officer will subsequently provide a response to the DCRC review and address the major recommendations and comments in the next version of the protocol.
- A change document (a list of specific changes made to the protocol by section number) and the next version of the protocol should be provided back to the OCA Chief of Medical Affairs for review and sign-off by the OCA Director prior to the start of enrollment on study.

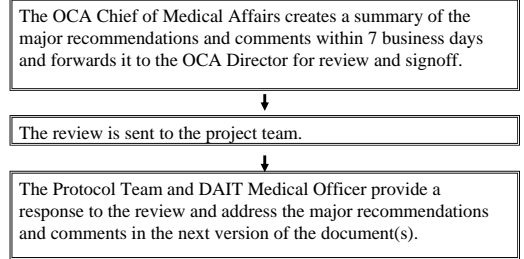
36

Clinical Review Meeting Process



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Clinical Review Meeting Process (cont.)



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DMID Protocol Review

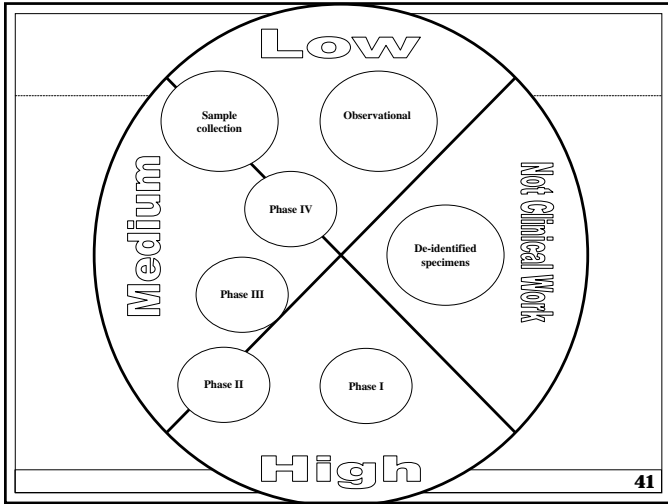
Shy Shorer, MD, MBA, RAC
Acting Director
Office of Clinical Research Affairs
DMID

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Protocol Classification

- Series of **objective** questions
- Evaluate the extrinsic factor to the trial
- Classified into 3 (resource) categories
- Performed when grant is awarded, or when a clinical research initiated.

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Central Resources

- **Low**
 - No central resources
 - Program level review and oversight
- **Medium**
 - Variable central resources
 - Program level review and oversight
- **High**
 - Central resources
 - Variable program level review and oversight

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Low Protocols

- No central resource allocations
- Oversight done by local IRBs
- Program staff provide additional oversight as needed

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Central Resources Allocation

| | |
|--|--|
| <p>Medium</p> <ul style="list-style-type: none"> • Non-Interventional <ul style="list-style-type: none"> ○ Variable operational resources • Interventional <ul style="list-style-type: none"> ○ Safety Review ○ Variable operational resources | <p>High</p> <ul style="list-style-type: none"> • Safety Review • Operational Review |
|--|--|

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Safety Review

Medical Monitor

- Safety protocol review
 - I/E
 - Study procedures
 - Halting rules
 - Safety oversight

- SAE Reviews

Pharmacy

- Product Review
 - Shipping
 - Handling
 - Mixing
 - Administration

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Operational Review

- Study procedure and operational review
- Clinical Monitoring
- Data Management
- Safety Oversight
- Safety Committees
- Regulatory Support (Essential Documents)
- Other Support

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Number of Protocol

- 2007 – 54* (as of October 1)
- 2006 – 97
- 2005 – 147
- Total in the tracking system - 507 protocols

- 40% low, 30% medium, 30% high

* Changes were made to the requirement of protocols to be tracked

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INFORMED CONSENT CHECKLIST

§46.116 -Basic and Additional Elements

- ___ A statement that the study involves research
- ___ An explanation of the purposes of the research
- ___ The expected duration of the subject's participation
- ___ A description of the procedures to be followed
- ___ Identification of any procedures which are experimental
- ___ A description of any reasonably foreseeable risks or discomforts to the subject
- ___ A description of any benefits to the subject or to others which may reasonably be expected from the research
- ___ A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
- ___ A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
- ___ **For research involving more than minimal risk,**
- ___ an explanation as to whether any compensation for injury, and
- ___ an explanation as to whether any medical treatments are available, if injury occurs and, if so,
- ___ what they consist of, or
- ___ where further information may be obtained
- ___ An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
- ___ **Research Questions**
- ___ **Rights Questions**
- ___ **Injury Questions**
- ___ A statement that
- ___ participation is voluntary,

INFORMED CONSENT CHECKLIST

___ refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and

___ the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

Additional elements, as appropriate

___ A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable

___ Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent

___ Any additional costs to the subject that may result from participation in the research

___ The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject

___ A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject

___ The approximate number of subjects involved in the study

___ A statement that there is an additional informed consent document for future use of specimens collected under the trial.

Consent for future use of specimens collected under the research trial (if a separate consent is not used, the following must be included in the study consent.)

If biological specimens are to be kept for **non**-protocol-defined research, the investigator should create a consent document covering each of the sections in the model consent template. At the very least, subjects should be told:

___ What kind of specimens will be collected and the means of collection.

___ What type of research will be done with the specimens,

___ Whether the biological specimens will be shared with other investigators,

___ Whether biological specimens will be **coded** or **anonymized** (no way of tracing back to subject/uncoded or code destroyed),

___ Whether the subject may be contacted for additional consent.

INFORMED CONSENT CHECKLIST

- ___ If possible, how long the biological specimens will be stored. (Short-term: current protocol only or other current research; Long-term: future studies on disease or condition, repository, etc.)
- ___ Foreseeable risks or benefits to subjects in the collection, storage, and subsequent research use of specimens.
- ___ What will be done with the biological specimens if the subject refuses permission ("anonymized"—stripped of identifiers--or destroyed).
- ___ What will be done with the research results. (Research results should not be placed in the individual subject's medical record.)

IRB Waiver or Alteration in some or all of the ELEMENTS OF CONSENT

Conditions required for IRB approval of Waiver or Alteration in consent elements.

- ___ The research or demonstration project is to be conducted by, or subject to the approval of, state or local government officials, and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; **and**
- ___ The research could not practicably be carried out without the waiver or alteration.

OR

- ___ The research involves no more than minimal risk to the subjects;
- ___ The waiver or alteration will not adversely affect the rights and welfare of the subjects;
- ___ The research could not practicably be carried out without the waiver or alteration; and
- ___ Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

§46.117 Documentation of Informed Consent

Except as provided in **IRB waiver of requirement for signed informed consent form** (below), informed consent shall be documented by the use of a written consent form approved by the IRB, and signed by the subject or the subject's legally authorized representative. A copy shall be given to the person signing the form.

The informed consent method may be either of the following:

WRITTEN

INFORMED CONSENT CHECKLIST

___ An IRB approved written consent document that embodies the elements of informed consent required by §46.116. This form may be read to the subject or the subject's legally authorized representative, but in any event, the investigator should give either the subject or the representative adequate opportunity to read it before it is signed.

ORAL

___ An IRB approved short form written consent document, stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative.

___ An IRB approved written summary of what is to be said to the subject or the representative.

___ There must be a witness to the oral presentation.

___ The **subject or the subject's representative** shall sign the **short form**.

___ The **witness** shall sign both the **short form** and a copy of the **summary**, and

___ The **person actually obtaining consent** shall sign a copy of the **summary**.

___ A copy of the summary shall be given to the subject or the representative.

___ A copy of the short form shall be given to the subject or the representative.

IRB WAIVER OF REQUIREMENT FOR SIGNED INFORMED CONSENT FORM

___ An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects, if it finds either:

___ The only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

___ The research presents no more than minimal risk of harm to subjects, and involves no procedures, for which written consent is normally required outside of the research context.

___ If waiver granted, written statement regarding the research

INFORMED CONSENT CHECKLIST

Special Requirements - 45 CFR 46 Subpart D - Additional DHHS Protections for Children Involved as Subjects in Research

Assent

The IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children, and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances, in which consent may be waived in accord with §46.116 of Subpart A.

- IRB require minor assent
- IRB approved method of documenting assent.
- IRB Waiver of assent requirement .

Parent Permission

The IRB may find that the permission of **one parent** is sufficient for research to be conducted under

- §46.404 [Research not involving greater than minimal risk.] or
- §46.405 [Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects].
- One parent permission
- Permission of both parents (unless one parent is deceased, unknown, incompetent, or not reasonably available) for research to be conducted under
- §46.406 [Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition] OR
- §46.407 [Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children],
- Both parents permission.

INFORMED CONSENT CHECKLIST

If the IRB determines that a research protocol is designed for conditions or for a subject population, for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children),

- IRB waiver of the consent requirements in Subpart A of this 45CFR46 and parent permission provided that
- IRB approved appropriate mechanism for protecting children participating in the research **AND**
- Waiver is not inconsistent with Federal, state or local law.

INFORMED CONSENT CHECKLIST

Special Requirements - 45 CFR 46 Subpart B: Additional Protections for Pregnant Women, Human Fetuses Involved in Research , and Pertaining to Human In Vitro Fertilization.

§46.207 Research involving pregnant women or fetuses prior to delivery as subjects.

Except for research exempt under 46.101(b)(1) through (6), this subpart applies to all research involving pregnant women or human fetuses, and to all research involving the in vitro fertilization of human ova, conducted or supported by the DHHS.

Pregnant woman or fetuses prior to delivery may be involved as a subject in an activity covered by this subpart if:

_____ Scientifically appropriate preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, conduct and provide data for assessing risk in pregnant women and fetuses.

_____ **Risk to fetus:**

___ **Not** greater than minimal,

OR

___ Any risk **greater than minimal** is caused solely by interventions or procedures that hold out the prospect of **direct benefit for the woman or the fetus;**

_____ Any risk is the **least possible** for achieving the objectives of the research;

_____ **Consent** of woman's or her legally authorized representative

_____ The woman or her legally authorized representative, as appropriate, is fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child;

_____ **Pregnant children:** assent and permission are obtained in accord with the provisions of subpart D.

_____ No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

_____ Individuals engaged in the research

_____ will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

_____ will have no part in determining the viability of a fetus.

§ 46.205 Research involving fetuses after delivery.

After delivery, fetuses may be involved in research if all of the following conditions are met:

INFORMED CONSENT CHECKLIST

- ___ Scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to fetuses.
- ___ The individual(s) is(are) fully informed regarding the reasonably foreseeable impact of the research on the fetus or resultant child.
- ___ No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- ___ Individuals engaged in the research
- ___ will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
- ___ will have no part in determining the viability of a fetus.
- ___ The requirements for informed consent have been met as applicable.

Fetuses of uncertain viability. After delivery, and until it has been ascertained whether or not a fetus is viable, a fetus may not be involved in research covered by this subpart unless the following additional conditions are met

- ___ The research holds out the prospect of enhancing the probability of survival of the particular fetus to the point of viability, and any risk is the least possible for achieving the objectives of the research,

OR

- ___ The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no risk to the fetus resulting from the research;

AND

- ___ The legally effective informed consent of either parent of the fetus

OR

- ___ if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of **either parent's legally authorized representative** is obtained in accord with subpart A of this part, unless altered or waived in accord with Sec. 46.101(i) or Sec. 46.116(c) or (d).

Nonviable fetuses. After delivery, a nonviable fetus may not be involved in research covered by this subpart unless all of the following additional conditions are met:

- ___ Vital functions of the fetus will not be artificially maintained;
- ___ The research will not terminate the heartbeat or respiration of the fetus;
- ___ There will be no risk to the fetus resulting from the research;
- ___ The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

INFORMED CONSENT CHECKLIST

_____ The legally effective informed consent of both parents of the fetus is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of Sec. 46.116(c) and (d) do not apply.

OR

_____ If either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable fetus will suffice to meet the requirements of this paragraph.

The consent of a legally authorized representative of either or both of the parents of a nonviable fetus will not suffice to meet the requirements of this paragraph.

Viable fetuses. A fetus, after delivery, that has been determined to be viable is a child as defined by Sec. 46.402(a) and may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§46.206 Research involving, after delivery, the placenta, the dead fetus, or fetal material.

_____ Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable Federal, State, or local laws and regulations regarding such activities.

_____ **Linked data:** If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subject and all pertinent subparts of this part are applicable.

Sec. 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women or fetuses.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of Sec. 46.204 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women or fetuses; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the Federal Register, has determined either:

(1) That the research in fact satisfies the conditions of Sec. 46.204, as applicable, or

(2) The following:

INFORMED CONSENT CHECKLIST

- (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women or fetuses;
- (ii) The research will be conducted in accord with sound ethical principles; and
- (iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part, unless altered or waived in accord with Sec. 46.101(i) or Sec. 46.116(c) or (d).

INVESTIGATOR'S BROCHURE CHECKLIST

PRODUCT _____ REVIEWER _____

Title Page

- Identifies the sponsor -----Y N
- Identifies the product (by research number, chemical or generic name, trade name) -----Y N
- Identifies the version number and release date -----Y N
- Notes that this replaces previous version #, dated__ -----Y N N/A

General

- Includes confidentiality statement, if desired-----Y N N/A
- Includes Table of Contents-----Y N N/A

Summary

Is the following information relevant to this stage of development summarized:

- Significant physical / chemical / pharmaceutical information Y N N/A
- Significant pharmacological and toxicological information ---Y N N/A
- Significant pharmacokinetic and metabolic information -----Y N N/A
- Significant clinical information-----Y N N/A

Introduction

Does the introductory statement contain:

- Chemical / generic / trade name of product -----Y N N/A
- All active ingredients -----Y N N/A
- Product's pharmacological class and position (i.e. advantages) within the class-----Y N N/A
- Rationale for the investigational product-----Y N N/A
- Anticipated indication for the product -----Y N N/A
- General approach to be followed in evaluating the investigational product -----Y N N/A

Physical, Chemical and Pharmaceutical Properties and Formulation

- Describes the investigational product substance(s), including chemical and /or structural formula -----Y N N/A
- Briefly summarizes relevant physical, chemical, and pharmaceutical properties -----Y N N/A
- Describes the formulation, including excipients, and if needed, justifies-----Y N N/A
- Provides instructions on proper storage and handling -----Y N N/A
- Mentions any structural similarities to other known compounds -----Y N N/A

Nonclinical Studies

Nonclinical Pharmacology

Summarizes studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) of the investigational product

- Describes the study design including species, number and sex of animals per group, dose, dose interval, route of administration, duration of dosing, duration of post-exposure follow-up -----Y N N/A
- Describes most important study findings including nature, frequency, intensity, time to onset, reversibility, and duration of pharmacologic effect(s) as well as dose response relationship -----Y N N/A
- Graphical / tabular format used to enhance clarity of presentation -----Y N N/A
- Describes the relevance of this information to humans (i.e. proposed dosing) -----Y N N/A

Summarizes studies that assess safety pharmacology (e.g. special studies to assess pharmacological actions other than the intended therapeutic effects) of the investigational product

- Describes the study design including species, number and sex of animals per group, dose, dose interval, route of administration, duration of dosing, duration of post-exposure follow-up -----Y N N/A
- Describes most important study findings including nature, frequency, intensity, time to onset, reversibility, and duration of effect(s) as well as dose response relationship -----Y N N/A
- Graphical / tabular format used to enhance clarity of presentation -----Y N N/A
- Describes the relevance of this information to humans (i.e. proposed dosing) -----Y N N/A

Pharmacokinetics and Product Metabolism in Animals

Summarizes studies that assess the pharmacokinetics, biological transformation, and disposition of the investigational product

- Describes the study design including species, number and sex of animals per group, dose, dose interval, route of administration, duration of dosing, duration of post-exposure follow-up -----Y N N/A
- Describes study results including information on absorption, distribution, metabolism and excretion of the investigational product as well as dose response relationships -----Y N N/A
- Graphical / tabular format used to enhance clarity of presentation -----Y N N/A
- Describes the relevance of this information to humans (i.e. proposed dosing) -----Y N N/A

Toxicology

Summarizes toxicological effects of the investigational product found in relevant studies conducted in different animal species.

- When appropriate, studies are described under separate headings for single dose, repeated dose, carcinogenicity, special studies (e.g. irritancy and sensitization), reproductive toxicity, genotoxicity (mutagenicity) -----Y N N/A
- Describes the study design including species, number and sex of animals per group, dose, dose interval, route of administration, duration of dosing, duration of post-exposure follow-up -----Y N N/A
- Describes most important study findings including nature, frequency, intensity, time to onset, reversibility, and duration of toxicological effect(s) as well as dose response relationship -----Y N N/A
- Graphical / tabular format used to enhance clarity of presentation -----Y N N/A
- Describes the relevance of this information to humans (i.e. proposed dosing) -----Y N N/A

Effects in Humans

Pharmacokinetics and Product Metabolism in Humans

- Summarizes information on the pharmacokinetics of the investigational product, including metabolism, absorption, plasma protein binding, and elimination, if available-----Y N N/A
- Summarizes information on the bioavailability of the investigational product (absolute, where possible, and / or relative) using a reference dosage form, if available-----Y N N/A
- Summarizes DMPK in relevant population subgroups (e.g. gender, age, and impaired organ function), if available -----Y N N/A
- Summarizes any interactions (e.g. product-product interactions, effects of food), if known-----Y N N/A
- Summarizes any other pharmacokinetic data (e.g. results of population studies performed within clinical trials)-----Y N N/A
- Graphical / tabular format used to enhance clarity of presentation -----Y N N/A

Safety and Efficacy

- Summarizes results from previous human trials with the investigational product regarding the safety, pharmacodynamics, efficacy, and dose response
- When multiple clinical trials have been completed
 - Summarizes safety and efficacy across studies by indications in subgroups-----Y N N/A
 - Includes tabular summaries of adverse reactions for all clinical trials -----Y N N/A
 - Discusses important differences in adverse reaction patterns / incidences across indications or subgroups-----Y N N/A
- Discusses the implications of this information
 - Describes the possible risks and adverse reactions to be anticipated on the basis of prior experiences with the investigational product and with related product -----Y N N/A
 - Describes the precautions and special monitoring to be done as part of the investigational use of the product-----Y N N/A

Marketing Experience

- Identifies any countries where the investigational product has been marketed or approved -----Y N N/A

- Summarizes any significant information arising from the marketed use (e.g. formulations, dosages, routes of administration, and adverse product reactions) -----Y N N/A
- Identifies any countries where the product was not approved for marketing or was withdrawn from marketing-----Y N N/A

Summary of Data and Guidance for the Investigator

Provides the investigator with an informative interpretation of the available data (i.e. physical, chemical, pharmaceutical, pharmacological, toxicological and clinical data) and with an assessment of the implications of the information for future clinical trials

- Provides an overall discussion of the nonclinical and clinical data regarding the investigational product-----Y N N/A
 - Summarizes information from various sources-----Y N N/A
 - Discusses published reports on related products, when appropriate-----Y N N/A
- Provides a clear understanding of the possible risks and adverse reactions-----Y N N/A
- Provides a clear understanding of the specific tests, observations, and precautions that may be need for the clinical trial -----Y N N/A
- Provides guidance on the recognition and treatment of possible overdose and adverse reactions based on previous human experience and on the pharmacology of the investigational product -----Y N N/A

Appendix X
PSRC Procedures – Guidance for PSRC Reviewers

Background Rationale and General Considerations for PSRC Reviewers

1. Has language been included in the background and rationale section of the protocol that describes the purpose of the study?
2. Is the rationale and content adequately presented?
3. Is the preclinical data on safety and immunogenicity sufficient to justify a clinical trial? (must be presented in the protocol)
4. Are the criteria/rationale for the dosage level, number of doses and schedule defined for all treatment groups in the clinical protocol?
5. Are the criteria/rationale for the dosage level, number of doses and schedule supported by preclinical data?
6. Are all the preclinical studies mentioned in the clinical protocol included and adequately described in the investigators brochure?
7. If there is previous human experience with the product under study or with the class of products, is the data adequately described to support the current study?
8. For studies with a part A and a part B: Is a rationale adequately described and are instructions provided for moving from part A to part B?
9. Are ethical considerations discussed in the clinical protocol?
10. Are provisions for care of injured subjects contained in the protocol?
11. As a summary of this section: Are the risks of the proposed study acceptable in view of its objectives?

Study Design

12. Is there a rationale for the study sample size?
13. Is a control group necessary for this study?
14. Is the control group appropriate for the study design?
15. Are the study-subjects registration procedures adequately described?
16. For randomized studies: Is the method of randomization adequately described in the protocol?
17. If the protocol includes stratification: Are the criteria for subjects stratification (*e.g.*, gender, HLA subtype, presence and level of antibodies to vector/component of vaccine, *etc.*) adequately described?
18. Is the study design unblinded or single-blind?
19. If blinded, is the blinding appropriate for the study design?
20. Are the proposed dose cohorts adequate to assess the most effective biological dose?
21. Is the duration of the study treatment phase specified in the clinical protocol?
22. Is the duration of the study follow-up phase specified in the clinical protocol?
23. Is the follow-up long enough to assess and capture data on pregnancies (and their outcomes) that might have occurred in relation to the last vaccination?
24. Is the follow-up adequate to the objectives/profile of the product?
25. Are risk factors for HIV infection being measured at baseline and during follow-up? (not strictly necessary)

- 26. For phase II studies: Is there a provision for capturing accrual rate data by study site? (not strictly necessary)
- 27. As a summary of this section: Is the study design adequately detailed?

Study Objectives

- 28. Are the primary objectives of the study clearly stated?
- 29. Are there secondary objectives?
- 30. Are there an objective and a formal hypothesis to reduce the risk of HIV infection and other STD included in the protocol?
- 31. Are the methods for assessing the primary objective/s clearly defined? Are novel assays validated and described in detail? (particularly important for phase II studies)
- 32. Is behavioral risk assessment included in the study evaluation?
- 33. As a summary of this section: Are the study objectives clear and based on a sound rationale?

Eligibility Criteria

- 34. Are the inclusion criteria clearly defined and appropriate?
- 35. Are the exclusion criteria consistent with the preclinical toxicology data?
- 36. Are subjects allergic to vaccine components excluded from the study?
- 37. Is a list of contraindicated concomitant treatments and medications included in the eligibility criteria?
- 38. Are subjects with high/low-risk sexual behavior included/excluded in the study?
- 39. Are women who are pregnant or nursing excluded from the protocol?
- 40. Is pregnancy appropriately prevented?
- 41. Are contraceptive measures appropriate for the risks associated with the investigational product?
- 42. As a summary of this section: Are the eligibility criteria adequate to study this vaccine?

Study Product

- 43. Is the product information in the clinical protocol consistent with the information provided in the investigators brochure?
- 44. Is the investigational vaccine/s adequately described?
- 45. Is the stability data of the vialled product/s compatible with study time frame?
- 46. Are the vaccine diluent/s and placebo (when applicable) adequately described?

Study Schema

- 47. Is the study schema adequately described?
- 48. Are there provisions for restriction of the number of subjects/day for products that are entirely new or products with an anticipated toxicity profile?
- 49. Is the interval between dose cohorts adequate for the class of product under study?

50. Are the procedures for preparation and administration of the vaccine, including special precautions, adequately described? Is blinding (if applicable) maintained?
51. Does the protocol include a table summarizing all planned dose levels?
52. Are the procedures listed in the table mentioned above consistent with the procedures defined in the text?
53. Is the total amount of blood needed for the safety and immunological studies less than or equal to 500 ml/8 weeks?

Safety Monitoring

54. Is safety monitoring adequately described?
55. Is the safety monitoring period (duration) adequately defined and appropriate?
56. Are additional monitoring procedures dictated by the preclinical toxicity profile included in the monitoring plan?
57. Are specific organ toxicities addressed?
58. Are provisions for grading of adverse events adequately described?
59. If a DSMB is monitoring the study, are the roles of the DSMB adequately described in the protocol?
60. As a summary of this section: Are the risks adequately appreciated?

Toxicity Management

61. Are there management guidelines for reactogenicity included in the protocol?
62. Are there management guidelines for potentially serious AEs suspected for the vaccine under study?
63. Does the toxicity evaluation plan contain rules for appropriate description, attribution and expectedness/unexpectedness of the adverse events?
64. Is the issue of providing antiretroviral therapy for subjects who become infected during the study addressed?
65. Are there criteria for treatment modifications in response to toxicities included in the protocol?
66. Are criteria for removal of individual subjects (subject escape rules) from the study listed and clearly defined in the protocol?
67. Are criteria for stopping the study adequately described in the protocol?
68. For the 3 points above: Is this information presented in a consolidated fashion?
69. Are adverse event reporting guidelines to IRB and FDA, including appropriate time frames, described in the protocol?
70. As a summary of this section: Are adequate precautions being taken?

Immunogenicity Assessment

71. Is the number of visits to assess immunogenicity appropriate to address the study objectives?
72. Are all assays needed to evaluate vaccine response listed and adequately described in the protocol?
73. For phase II studies: Are the assays being utilized in this study validated? If not, is a justification provided?
74. Does the protocol include a list of post vaccination evaluations?
75. Does the protocol include a table summarizing all the evaluations and procedures planned for the study?

76. Are the tests and procedures listed in the table consistent with the tests and procedures described in the text of the protocol?

Statistical Considerations

77. Are all primary and secondary endpoints clearly defined including safety, immunogenicity, and efficacy?
78. Are the analytical methods to evaluate the data adequately described and appropriate to address the objectives of the study?
79. Has the justification for sample size for safety been included?
80. For studies with multiple dose levels: Are procedures for advancing to the next dose level described?
81. Are the potential biases and the strategy to address them included within the data analysis section?
82. For blinded studies: Are the procedures for emergency unblinding addressed in the protocol?
83. Are there provisions for interim safety analysis contained in the protocol?
84. As a summary of this section: Is the statistical plan adequate to provide data that will achieve the study objectives?

Informed Consent

85. Is the purpose of the study clearly identified in the informed consent document?
86. Is the treatment plan, as described in the informed consent, consistent with the clinical protocol?
87. Are all the test and procedures to be performed during the study, including the risks associate with such procedures, clearly described in the informed consent document?
88. Are all potential risks associated with participation in the vaccine trial (physical, psychological, social, legal or other) adequately addressed in the informed consent document?
89. Are the risks of testing positive for HIV with conventional tests clearly described in the informed consent documents?
90. Are potential toxicities suggested by the preclinical toxicity profile or prior human experience adequately described in the informed consent document?
91. Are provisions for care of injured subjects adequately explained in the informed consent document?
92. Are contraceptive measures appropriate for the risks associated with the investigational product adequately described for the volunteers?
93. As a summary of this section: Are subjects adequately informed through informed consent document?

Housekeeping

94. Is there consistency (such as regarding implementation of the objectives, and safety endpoints) across all sections of the protocol including the synopsis, tables, footnotes etc.?
95. Is the spelling, grammar and formatting across the protocol correct?
96. Does the document contain “boilerplate” language that does not apply to this protocol?

General Scientific Merits of the Protocol¹ **[To be discussed in the closed session of PSRC]**

¹ Based on information not necessarily provided in the protocol under review

97. Does the protocol address an important scientific question/s ? Is it possible to address the question/s by other means?
98. Does this protocol address a priority research area of DAIDS?
99. Are there other trials underway investigating similar products or similar combinations of products?
100. Are the preclinical immunological data for the product under review similar or better than data available with similar products?
101. Will it be possible to pool the data obtained from the study under review with data obtained from other studies with similar products?
102. Will the study as written provide data to support the use of this product in combination with other products in a multivalent vaccination strategy?
103. Can enrollment be expanded for potential benefit/indications among other populations such as adolescents, pediatric, elderly?



ACTIVITY EVALUATION FORM
NIAID Clinical Research Seminar Series: Sharing Best Practices
Regulatory and Scientific Review
October 19, 2007

To indicate your answers, please use the rating scale that is shown by circling the number that represents your answer.

Scale: 1-None/Not at all, 2-Very little, 3-Moderately, 4-Considerably, 5-Completely, N/A - Not applicable

A. Rating of Objectives and Activity

1. **Please rate the attainment of objectives:**
 - a) **This session helped to increase my knowledge about the best practices in regulatory review.**
1 2 3 4 5 N/A
 - b) **This session helped to increase my knowledge about the best practices in scientific review.**
1 2 3 4 5 N/A
2. **The overall quality of the instructional process was an asset to the activity:**
1 2 3 4 5 N/A
3. **To what extent will participation in this activity enhance your professional effectiveness?**
1 2 3 4 5 N/A

B. Comments:

1. **What will you do differently as a result of attending this educational activity?**
2. **What topics would you like to see addressed in future NIAID Seminars?**
3. **How many times per year would you like to attend the NIAID Clinical Research Seminar Series?**
4. **Do you have additional comments to enhance the utility or impact of the Seminar?**