

The NIAID Scientific Resource Development Team (SRDT) and
NIAID Division of Clinical Research (DCR)
Invite You to an NIAID Clinical Research Seminar

Sharing Best Practices: Data and Safety Monitoring



Thursday, May 1, 2008
12 to 3 p.m.

Lipsett Amphitheater, NIH Clinical Center, Building 10
(Simultaneous videocast to NIH at <http://videocast.nih.gov/>)

Agenda

Overview of Policies, Guidance and Regulation

Dennis O. Dixon, Ph.D.
Biostatistics Research Branch, Division of Clinical Research, NIAID

NIAID Division-Specific Practices and Case Studies

-Division of Allergy Immunology & Transplantation (DAIT)

James McNamara, MD, Chief, Clinical Immunology Branch, DAIT, NIAID

-Division of Clinical Research (DCR)

Kelly Cahill, RN, CCRC, RAC, Regulatory Compliance & Human Subjects Protection Branch, DCR, NIAID
William C. Blackwelder, PhD, Chair, NIAID Intramural DSMB

-Division of Microbiology & Infectious Diseases (DMID)

Joni Love, RN, BSN, Nurse Consultant, Office of Clinical Research Affairs, DMID, NIAID

-Division of Acquired Immunodeficiency Syndrome (DAIDS)

Lawrence Fox, MD, PhD, Captain, US Public Health Service (USPHS), HIV Research Branch, DAIDS, NIAID
Lydia Soto-Torres, MD, MPH, Captain USPHS, Microbicides Research Branch, Prevention Sciences Program, DAIDS, NIAID

There will be a 15-minute break between topics.

To pre-register, use SRDT's registration system at <http://osrdwms.niaid.nih.gov/>. For assistance with the system or to request reasonable accommodation, please email Amy DeLacy, <mailto:delacya@niaid.nih.gov>.

You can earn **one ESA credit** and **three project officer continuous learning points** (CLP) for attending this event.

Sharing Best Practices: Data and Safety Monitoring



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DATA AND SAFETY MONITORING -- OVERVIEW

Dennis O. Dixon, PhD
Biostatistics Research Branch
NIAID

May 1, 2008



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Data and Safety Monitoring: *Why?*

- To identify any safety problem rapidly
- To identify logistical problems
- To evaluate continued feasibility of trial
- To determine if trial objectives have been met and trial may be terminated early



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Data and Safety Monitoring: *What?*

- **Logistics**
 - Enrollment
 - Baseline Data, Comparability
 - Protocol Compliance
 - Specimen Collection
 - Data Quality

Develop specific benchmarks



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Data and Safety Monitoring: *What?*

■ Outcomes

- Adverse Events
- Interim Variables
- Response Variables
(Endpoints)



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Scope of Monitoring Responsibilities

- Evaluating accumulating data with regard to efficacy and toxicity
- Recommending termination or continuation of study
- Recommending other study modifications
- Reviewing study protocol
- Assessing study conduct
- Recommending additional analyses



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Data and Safety Monitoring: *Who?*

- Investigator(s)
- Sponsor
- Safety Monitor
- Ethics Committee(s)
- Regulatory Agencies
- Data and Safety Monitoring Board/SMC
(DSMB, DSMC, DMC, External DMB, etc)



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Data and Safety Monitoring Regs, Policies, Guidelines

- Regulations - **NONE**
- Policies - NIH
 - All trials need a plan – describe in application (2000 NIH Guide)
 - Phase III trials must use a DSMB (1998 NIH Guide)



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Data and Safety Monitoring Regs, Policies, Guidelines

- Policies – FDA -**NONE**
- Policies - NIAID
 - Clinical Terms of Award
 - NIAID Principles for Use of a DSMB for Oversight of Clinical Trials (2006, 2008)
- FDA Guidance on DMCs (2006)



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**ALL TRIALS NEED
MONITORING
BUT
NOT ALL TRIALS
NEED DSMBS**



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A Definition

A data and safety monitoring board (DSMB) is a group of independent experts that reviews the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial.



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Generally Accepted DSMB Principles

- Certain types of trials should have formal DSMBs
- DSMBs should be multidisciplinary
- A charter should describe operations and procedures
- DSMB members should be free of conflicts of interest
- Interim data should be considered highly confidential



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An *Independent* DSMB Is One in Which No Member Has

- Any basis for preferring the outcome to be in one or the other direction
- Any ability to influence the trial conduct in a role other than that of DSMB member



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Confidentiality of Interim Results

- Interim comparative data generally considered highly confidential, because
- Knowledge of interim data could affect
 - patient entry
 - patient care
 - patient assessment
 - sponsor action
- When knowledge of interim data potentially could influence trial conduct, interpretation of results could be muddled



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Statistical Concern

- Repeated testing over time inflates Type I (false positive) error rate if no adjustment made
- In “early days” of clinical trials, not uncommon to stop study as soon as p-value reached magic level of 0.05
- Currently, many methods available to permit early stop without increasing error rate



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Establishing a Committee

- Generally appointed by study sponsor
- Made up of
 - Clinicians (appropriate specialty)
 - Statisticians
 - Others as needed (e.g., bioethicist, subject advocate)
 - Executive Secretary (non-voting)
- Membership should be acceptable to trial leadership: DSMB given major responsibility



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Structure of DSMB Meetings

- **Open Session**
 - Process data
 - Attended by investigators, sponsor representatives, data site representatives
- **Closed Session**
 - Interim outcome data, adverse events by group
 - Attended by data presenter
- **Executive Session**
 - "Private" DSMB member discussion



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When Are External DSMBs Needed?

- Trials with mortality or major morbidity endpoints
- Trials for which assessment of serious toxicity requires comparison of rates
- Trials of novel, potentially high-risk treatments



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External DSMBs Generally Not Needed For

- Single-arm trials
- Early phase trials
- Short-term trials of treatments to relieve common symptoms
- Any trial for which there is no ethically compelling need to monitor the interim comparisons of safety or efficacy



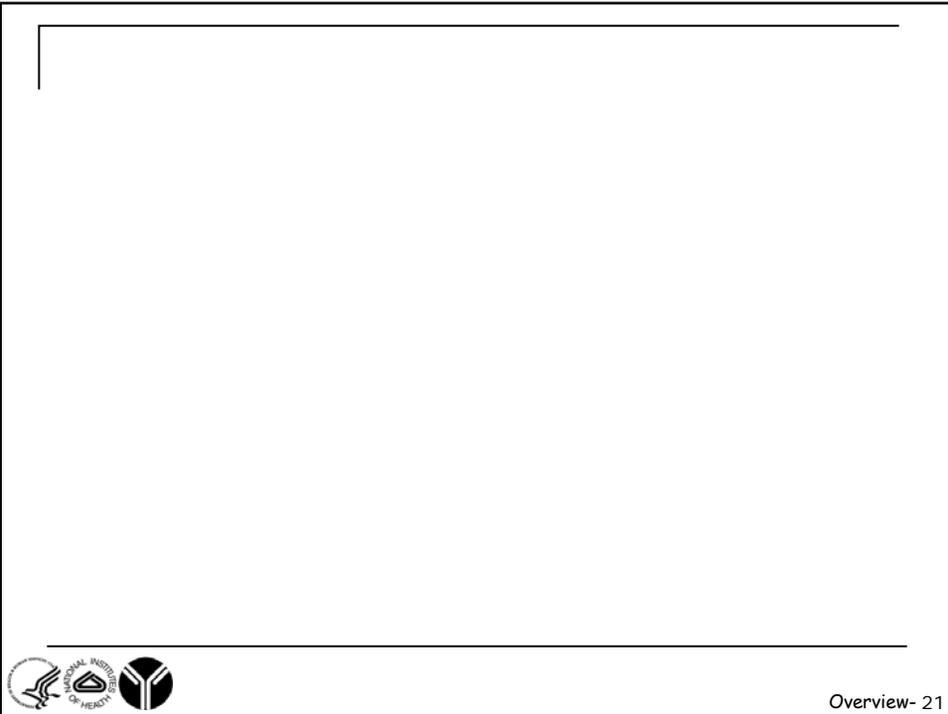
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Are There Disadvantages to Having a DSMB?

- YES!
 - Increases complexity of trial management
 - Increases costs



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U. Wisconsin CCC Protocol Review and Monitoring System

- Disease/modality groups are primary
- Quarterly or semi-annual reports to a central Clinical Trials Monitoring Committee that meets regularly and as needed
- CTMC monitors compliance with plans
- CTMC reviews whenever a prespecified AE threshold is reached



Preventing Mother-Infant HIV Transmission

- Zidovudine able to slow progression of HIV in adults with advanced disease
- AIDS Clinical Trials Group Protocol 076 designed to assess both safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies



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Preventing Mother-Infant HIV Transmission

- Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of life) relative to projected rate of 30%
- Target N was 748; began April 1991
- Projected accrual to take at least 5 years and 15% dropouts



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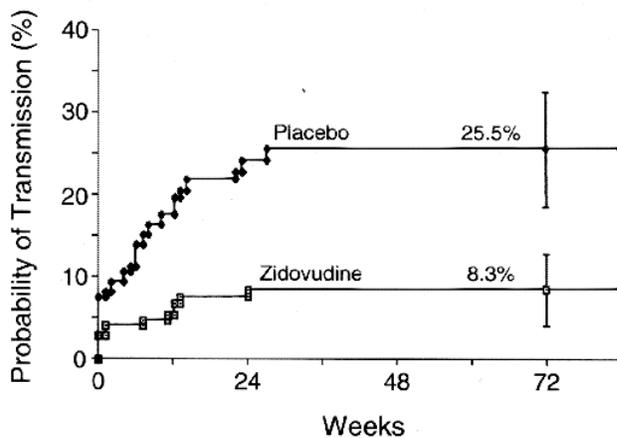
Preventing Mother-Infant HIV Transmission

- DSMB met twice a year to monitor safety
- Efficacy reviews planned after each 1/3 of projected infant infections
- 1st efficacy review took place in February 1994, based on mothers enrolled up to December 1993 and their babies



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At First Interim Analysis



Placebo	183	84	42	37
Zidovudine	180	105	51	43



P = 0.00006

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Preventing Mother-Infant HIV Transmission

- DSMB recommended stopping (after careful review of data quality and completeness, toxicity, transmission rates)
- Trial leaders and NIAID agreed
- Zidovudine provided to those in control group
- PHS Guidelines modified



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Monitoring STEP and Phambili

- 2 test-of-concept trials of Merck rAd5 HIV vaccine candidate
- STEP began in Dec. 2004 in North and South America and Australia
- Phambili began in Feb. 2007 in South Africa
- Separate DSMBs



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Monitoring STEP and Phambili

- At 1st planned review in Sept. 2007 STEP DSMB recommended stopping for futility
- Merck, NIH and HIV Vaccine Trials Network stopped STEP and suspended Phambili, pending DSMB review
- At emergency review of STEP results Phambili DSMB recommended stopping Phambili and unblinding volunteers



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Male Circumcision to Prevent HIV Acquisition

- Phase III controlled trials began at about the same time in South Africa, Kenya, and Uganda
- Designs similar
- South African trial reported clear evidence of efficacy in July 2005
- NIH DSMB recommended continuing other trials in August 2005, June 2006, stopping in December 2006



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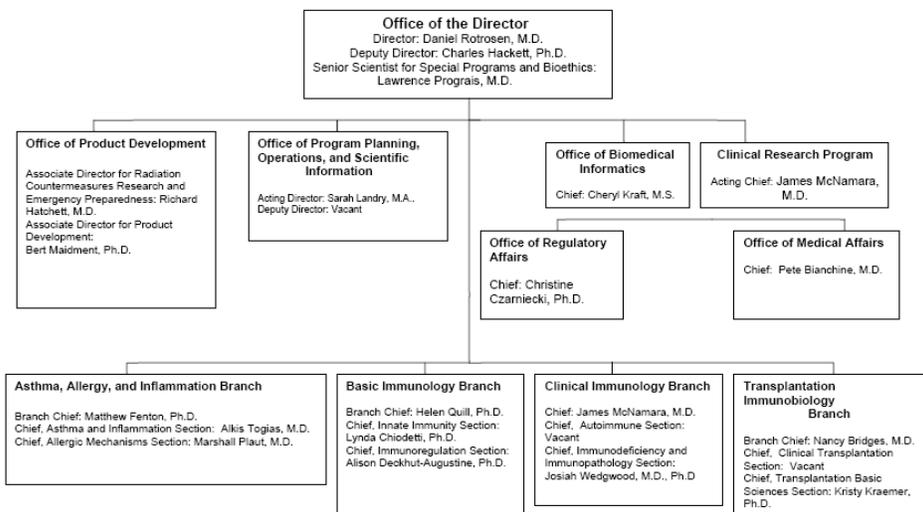
DAIT Data and Safety Monitoring Board Activities

James McNamara, MD
Chief, Clinical Immunology Branch
Division of Allergy, Immunology and Transplantation



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DAIT – Organizational Structure



Revised: April 2008

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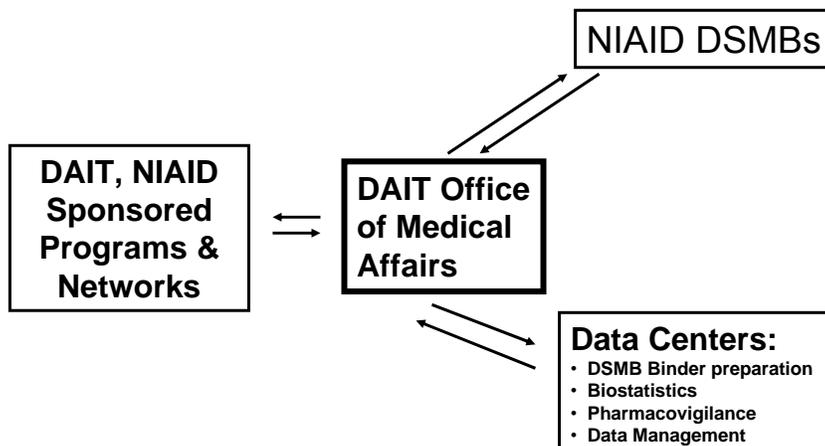
DAIT Office of Medical Affairs and DSMBs

- **Office of Medical Affairs at DAIT, NIAID.**
 - Peter Bianchine, MD, Chief
 - Marilyn Johnson, Program Specialist
 - Vanessa Schaaf, Program Specialist
- **Administrative support for scheduling reviews, travel, honoraria, COI review, staffing, and planning of DSMB Meetings and Teleconferences.**
- **Coordinating data/protocol delivery to DSMB from DAIT data management CROs.**
- **Communication between DSMBs, Network PIs and staff**
- **Support from BRB, DCR, NIAID – Erica Brittain, PhD**



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DAIT – DSMB Interactions



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DAIT Sponsored Networks

- Immune Tolerance Network (ITN)
- Autoimmunity Centers of Excellence (ACE)
- Stem Cell Transplantation Consortium (SCTC)
- Clinical Trials In Organ Transplantation (CTOT)
- Clinical Islet Transplantation (CIT)
- Renal and Lung Living Donors Evaluation (RELIVE)
- Cooperative Clinical Trials in Pediatric Transplantation (CCTPT)
- Solid Organ Transplant in HIV (HIVTR)
- Consortium of Food Allergy Research
- Inner City Asthma Consortium (ICAC)
- Asthma and Allergic Diseases Cooperative Research Centers (AADCRC)
- Atopic Dermatitis and Vaccinia Network (ADVN)

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Approximately 73 Clinical Trials are Under DSMB Review in DAIT, NIAID.

- ITN trials: 20
- ICAC trials: 4
- ADVN trials: 6
- CoFAR trials: 4
- AADCRC trials: 6
- Stem Cell trials: 2
- ACE trials: 11
- CTOT & CIT trials: 10
- CCTPT trials: 3
- Relive & HIVTR: 6
- Non-Network: 1 (SBIR)

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DAIT DSMBs

■ DAIT Created and Managed:

- Autoimmunity DSMB
 - ITN, ACE, and a SBIR study
- Allergy/Asthma DSMB
 - ITN, CoFAR, ICAC, AACRC
- Transplant DSMB
 - ITN, CIT, CTOT, RELIVE, CCTPT
- Hematopoietic Stem Cell Transplant DSMB
 - ITN, HSCT Consortium

■ DAIT Supported and Affiliated:

- TrialNet-ACEs-ITN DSMB
 - ITN and ACE studies for T1DM.



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DSMB Composition:

- Chair – typically experienced with DSMBs, clinical trials, and worked with NIAID previously.
- Other members provide scientific, medical, statistical, or ethical expertise.
- Typically nominated by NIH staff and asked to submit their C.V. for review.
- If qualified, and no obvious conflict, each candidate is asked to complete a Conflict of Interest (COI) form.
- Overall package is reviewed by NIAID and offer(s) is/are made to potential new members.



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DAIT DSMB Activity

- All clinical trials are monitored by NIAID Data and Safety Monitoring Boards.
- Why?
 - Limited number of investigators with special expertise.
 - Synergy associated with an experienced DSMB across medical/scientific disciplines.
 - Consistency of review and recommendations.
 - High visibility and high risk studies.



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DAIT DSMB Activity

- Impact?
 - While most DAIT trials are not of the public health impact associated with a traditional DSMB some are.
 - Needs careful management of DSMB/staff activities to distinguish relative roles.
 - DSMB reports associated with different levels of data for review.
 - Overall level of detail in review is modulated
 - Different activity of NIAID staff associated with a phase I vs. phase III study.



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DSMB Process

- **DAIT Clinical Review Committee**
 - DSMB monitoring plan reviewed and approved before study initiation, usually near protocol finalization.

- **Initial DSMB protocol review**
 - Study presented by Protocol Chair / team members.
 - Extensive discussions on role of DSMB in monitoring study.
 - DSMB provides comments/recommendations to team.
 - Team responds to comments and resulting changes communicated to DSMB.



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DSMB Process

- **Ongoing DSMB monitoring reviews**
 - Meetings quarterly; 1-2 times/yr face-to-face.
 - All studies reviewed at least annually.
 - Study chairs participate in, or available for, reviews.
 - Recommendations to NIAID and investigators.
 - Summary letter prepared for DSMB chair approval.
 - Ad hoc meetings by conference call as needed.
 - Protocol teams expected to provide responses at time of next DSMB review unless emergent issues need rapid attention.



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Lessons Learned: Each DSMB is Different

- Same process for selection and same charters.
- Voice of the collective DSMB is unique for each committee and greatly influenced by the Chair.
- Practical implications:
 - Important to review expectations for committee performance with new committees and Chairs. For example:
 - DSMB makes recommendations not specific required changes.
 - Study team rebuttals allowed.
 - Work to establish rapport between NIAID and committees



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Lessons Learned: Quality of Advice is Related to Quality of Data

- Overly complex CRFs lead to data management issues which impact DSMB monitoring efforts.
- Scenario: Autoimmunity study - Team notified 6mo in advance of upcoming DSMB Interim Analysis Data Review, however:
 - DAIT forced to delay DSMB review due to inability of the sites to collect data in a timely way.
 - When DSMB report developed clear discrepancy between study team understanding of number of endpoints and that seen in the report → CRF errors.
 - Result: Delay in the DSMB's ability to assess "futility" as per protocol.



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Lessons Learned: DSMBs Really Are Independent

- DSMB recommendations can not always be anticipated. Staff need flexibility to respond expeditiously to them.
- Scenario: Stem Cell Transplantation study
 - Problem - no subjects enrolled in the first 18 months with three sites open and screening.
 - Prior to DSMB, NIAID staff met with the study team and set milestones for continuation of the study over a six month period.
 - The DSMB questioned whether proposed changes to the protocol were sufficient to permit timely enrollment. Concerned that study no longer feasible and enrolling only a small number of patients would not be ethical.
 - After discussion, DSMB unanimously recommended to DAIT that the study be closed to accrual and further development.
 - Result: NIAID accepted recommendation for early termination.

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Division of Clinical Research: Regulatory Compliance and Human Subjects Protection Program

Kelly Cahill, RN, CCRC, RAC (US)
DCR/RCHSPB
Clinical Research Oversight Manager



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Part 1: How DCR Functions

- DCR/RCHSPP overview and portfolio
- DCR Policies
- Safety Office services
- Function of DCR DSMB and SMCs
- Recruitment/Training/COI
- Preparing reports
- Recommendations
- Contact information
- References



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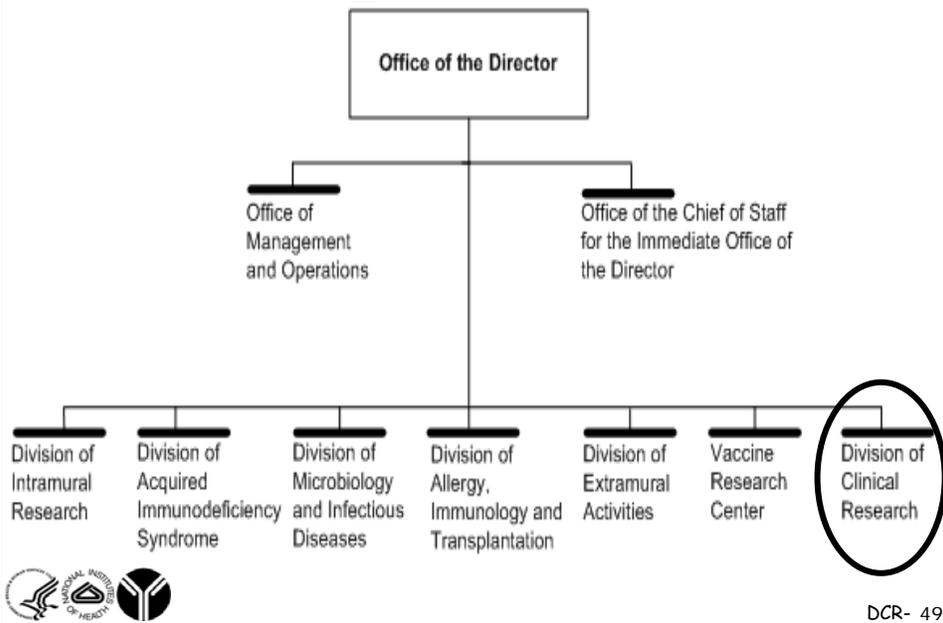
Part 2: DCR Lessons Learned

- Unblinding issues
- Common DSMB questions and recommendations



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NIAID Organizational Chart



DCR/RCHSPP Overview

- RCHSPB vs. RCHSPP
- RCHSPP Services:
 - Regulatory (IND) management
 - Site monitoring
 - Safety management (SAE/DSMB/SMC/MM)
 - Training
- Primarily Support:
 - Division of Intramural Research (DIR)
 - Vaccine Research Center (VRC)



DCR/RCHSPB Portfolio

- RCHSPP provides support for:
 - 54 IND studies
 - 49 non-IND studies
- 1 NIAID Intramural DSMB
 - 40 protocols require DSMB oversight
 - 43 DSMB reviews completed in 2007
- 5 Safety Monitoring Committees
 - 4 SMC reviews completed in 2007
- Safety Office Medical Monitor on 5 trials



Safety Office

*SAIC/Contract Employee

Kelly Cahill, RN, CCRC, RAC
DSMB/SMC Oversight Manager

***Cynthia Kleppinger, M.D.**
Director, Safety Office

Medical Monitors

*Cynthia Kleppinger, M.D.
*Barry Eagel, M.D.

Clinical Safety Assoc.

*Priya Kapoor M.B.B.S., MPhil.
*Stephanie Mizell, RN, MPH
*Venus Shahamatdar, M.D.

DSMB Exec. Sec.

*Awie Turay, RN, BSN



DCR Policies

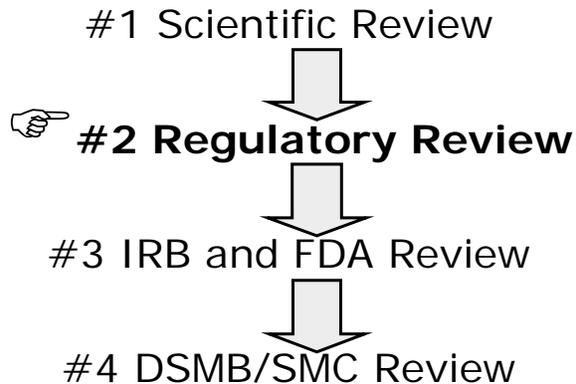
- DCR DSMB Policy (Revised 9/12/06)
- DCR SMC Policy (Effective 2/11/08)
- DCR ISM Policy is in draft form
- NIAID DSMB Policy (Feb. 11, 2008)
 - Must be compliant with DCR DSMB policy if conducting intramural trials



	DSMB	SMC	ISM	MM
RCHSPB Policy	Yes	Yes	Draft	No
Total members	5 (No NIH employees)	3 (within NIH acceptable)	1 (within NIH acceptable)	1 Not an "independent" review
Trial Design (DCR)	Phase I-III <ul style="list-style-type: none"> • All gene therapy • Randomized, <u>blinded</u> • Other studies at the discretion of the Clinical Director or NIAID IRB 	Phase I-II Short duration, minimal known about study agent, more than minimal risk, single site, unblinded, review pre dose escalation	Phase I-II Short duration, more than minimal risk, low accrual, single site, for real-time assessment, non-randomized	No current policy
Request by	NIAID Clinical Director, PI, RCHSPB, or IRB	NIAID Clinical Director, PI, RCHSPB, or IRB	IRB	IRB



Protocol Review Process



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Safety Office DSMB/SMC Services

- Assist PI in forming an SMC
- Arrange review meetings
- Obtain conflict of interest statement and CV
- Provide the DSMB or SMC policy to PI
- Take notes or tape the review meetings
- Write and distribute DSMB or SMC summary reports
- Maintain randomization codes
- Ensure the DCR DSMB and SMC policies are followed
- Communicate significant safety issues to the NIAID Clinical Director



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What Protocols will be Reviewed by the DCR DSMB or an SMC?

- The majority of subjects are the direct responsibility of NIAID
- The PI is a NIAID employee
- Funding of the study is provided by NIAID and/or
- RCHSPB holds the IND



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DCR DSMB

- Established in June 2002
- Core members:
 - **William C. Blackwelder, Ph.D. (Chair)**
Specialty: Biostatistics
 - **Virginia Kan, M.D.**
Specialty: Infectious Diseases
 - **Carol O. Tacket, M.D.**
Specialty: Vaccines
 - **Lawrence Moulton, Ph.D.**
Specialty: Biostatistics
 - **James Baraniuk, M.D.**
Specialty: Allergy/Immunology



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Function of DCR DSMB

- Conducts pre-enrollment initial reviews of protocols and informed consent(s) with focus on:
 - Study monitoring plan (expectations of DSMB)
 - Stopping/halting rules
 - Statistical /data analysis plan
 - Safety information in informed consent
- Monitors the trial data, primarily for safety and efficacy (when appropriate), so that participants in clinical protocols are not exposed to unreasonable or unnecessary research risks
- Reviews proposed changes to protocols that may affect safety and/or efficacy outcomes
- Makes recommendations to the NIAID Clinical Director concerning continuation, modification or suspension of studies



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Recruitment/Training/COI /Qualifications

- DSMB Recruitment ➡ Difficult
- SMC Recruitment usually done by PI
- No standard training is available for DSMB or SMC members
- COI obtained yearly by RCHSPB
- Qualifications



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Preparing Reports for Review

- Expectations must be clearly outlined during the initial DSMB or SMC review meeting
- DSMB data templates are available on the NIAID DCR Regulatory Compliance portal
- Refer to the “Data and Safety Monitoring Board Guide for Investigators” document on the NIAID DCR Regulatory Compliance portal



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Recommendations

- Initial via e-mail
- Immediate Action Notification
- Final Summary report
- 10 business days to respond to DSMB recommendations
- If disagreement with recommendations, then involvement of:
 - NIAID Clinical Director
 - Possibly, Scientific Review Committee and/or NIAID IRB



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Contact Information

- DSMB communication: niaiddsmbia@mail.nih.gov
 - (DSMB Executive Secretary- Awie Turay)
- SMC communication: with individual assigned as the SMC Executive Secretary or via Safety Office mailbox niaidrchspsafety@mail.nih.gov
- Safety Office (SAIC/Frederick, MD): 301-846-5301
- Kelly Cahill (NIAID DSMB/SMC Oversight Manager): cahillke@niaid.nih.gov, 301-451-2438



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Reference Information

- DCR/RCHSPP portal: <http://my.nih.gov>
- Enter your User Name and Password which is the same as the network login you use every day
- Under “My Communities” select: “NIAID DCR Regulatory Compliance”
- To add “NIAID DCR Regulatory Compliance” to the “My Communities” list complete the following steps:
 - Click the “My Communities” tab
 - Click “Join Communities”
 - Type “NIAID DCR Regulatory Compliance” in the “Search for Communities box and then click the arrow to search
 - Check the box in front of “NIAID DCR Regulatory Compliance”
 - Click the “finish” button in the upper right corner of the screen



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(Lessons Learned)

Issues Associated with Double-blind Studies

- ❑ Conditions and process for unblinding should be specified in the protocol to avoid inappropriate unblinding
- ❑ Site staff training is necessary
- ❑ The DSMB does not review unblinded data unless it considers it necessary
- ❑ The DSMB should be informed of any unblinding (planned or unintentional)
- ❑ Discussions should take place with the DSMB regarding any non-emergent FDA request for randomization codes



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5 Common DSMB Recommendations

- Clarify stopping/halting rules
- Clarify how often and what the DSMB is to review
- Clarify how/if replacement of subjects will occur
- Specify if SAEs are to be reviewed in real-time or at planned review times
- Submit a narrative explanation of SAEs, as well as summary listing.



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DSMB Questions

- The DSMB will ask questions pertaining to:
 - Safety data
 - Enrollment status
 - Protocol violations
 - Follow-up plan if subjects are withdrawn
 - Unanticipated problems (pregnancy/security breach)
 - Outstanding IRB and/or FDA concerns
 - Adequacy of protocol and IC amendments after a study has been stopped for safety concerns
 - Statistical analysis plan



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Thank You

- Dr. Bill Blackwelder (DSMB Chair)
- Dr. Jerry Pierson, Chief, RCHSPB
- Safety Office staff
 - Cynthia Kleppinger, M.D.
 - Barry Eigel, M.D.
 - Priya Kapoor, M.B.B.S., MPhil
 - Stephanie Mizell, RN, BSN, MPH
 - Awie Turay, RN, BSN
 - Venus Shahamatdar, M.D.



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DMID

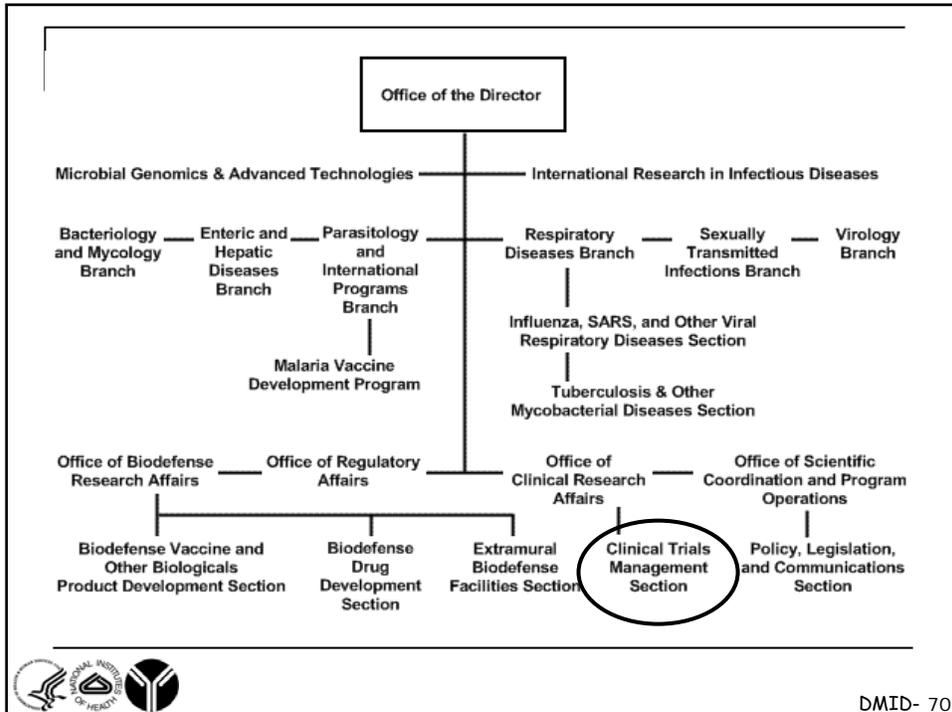
Data and Safety Monitoring

Joni Love RN, BSN

Nurse Consultant, Office of Clinical Research Affairs
Division of Microbiology and Infectious Diseases



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Clinical Trials Management Section

- Performs management, operational and logistical functions in support of studies.
- **Safety oversight of human subjects with centralized pharmacovigilance and safety monitoring.**
- Provides resources to facilitate conduct of clinical research in compliance with Good Clinical Practices.



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Data and Safety Monitoring – Why?

- Ensures the safety of participants.
- Ensures the validity & integrity of the data.
- Policy/Guidelines: NIH, NIAID, DMID
- DMID requires a plan for studies that:
 - Evaluate investigational test articles
 - Potential harm to participants.
 - Need independent assessments to assure objectivity.



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Data and Safety Monitoring Policy/Guidelines Links

- NIH
 - <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>
 - <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
- NIAID
 - <http://www3.niaid.nih.gov/research/resources/toolkit/guidance/>
- DMID
 - <http://www3.niaid.nih.gov/research/resources/DMID/ClinRsrch/safetyoversight.htm>



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Data and Safety Monitoring-What?

- DMID-sponsored clinical trials, regardless of funding mechanism: grant/contract.
- Provides independent/objective review of interim safety and if appropriate, efficacy data.
- Monitoring bodies are advisory to DMID and their recommendations, while given careful consideration, are not binding.



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Data and Safety Monitoring- How?

- Monitor according to degree of risk to subjects, size and scope of the research.
- Three standard formats used by DMID:
 - DSMB (data and safety monitoring board).
 - SMC (safety monitoring committee).
 - ISM (independent safety monitor).
- Types of meetings: organizational, ad hoc and scheduled data reviews.
- Monitoring plan: protocol and charter.



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DMID Data and Safety Monitoring Activity

- There are 89 studies with active DSMB/SMC and/or ISM monitoring
 - 33 DSMBs (Phase 3, earlier phase also)
 - 39 SMCs (Phase 1, smaller phase 2)
 - 17 ISM only (Early phase, small, low risk)
- There are currently approximately 300 individuals participating as DSMB/SMC members or as ISMs.



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DMID Data and Safety Monitoring Process

- Scientific branch and Medical Monitor.
 - Review of protocol, DSMB/SMC charters, reports.
- Central meeting support: contractor (PPD)
- Volunteer members:
 - Expertise relevant to the study.
 - Absence of significant conflict of interest (assessment by DMID)
 - No direct involvement in the conduct of the study.
 - Not under the supervision of the trial investigator.



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DMID Data and Safety Monitoring Process (cont.)

- Open session with participation from stakeholders.
- Closed session with voting members only.
- Recommendations: verbal and written.
 - DMID review and implementation.
 - Communication: study investigators to IRBs.
- Regulatory communication for DMID held INDs.



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Lessons Learned:

Flexibility needed due to diversity

- Structure appropriate to design of study.
- Monitor according to the population.
- Modify process appropriate to the type of collaboration.
- Plan monitoring appropriate to type of product.
- Implement structure that addresses novel scientific approaches.



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Lessons Learned:

Data Presentation is Key

- Provide adequate data to address issue.
- Conduct an appropriate investigation.
- Provide displays that answer the question.
- Plan time for report preparation/ review.
- Utilize appropriate media.
 - Data provided electronically, website and hard copy.
 - Teleconference and electronic reviews.



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Lessons Learned: Need for Special Expertise

- Recruit members with appropriate expertise for anticipated monitoring issues.
- Obtain additional expertise for the DSMB/SMC as issues are identified.
- Utilize internal and external resources.
- Plan for needs according to clinical plan.
- Identify expertise to access in the future.



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DMID Data and Safety Monitoring: Going forward

- Continue to develop monitoring strategies.
- Continue to share best practices.
- Further develop data presentations.
- Develop training for DMID staff.
- Explore utilizing standing DSMBs/SMCs.
- Explore training of DSMB/SMC members.

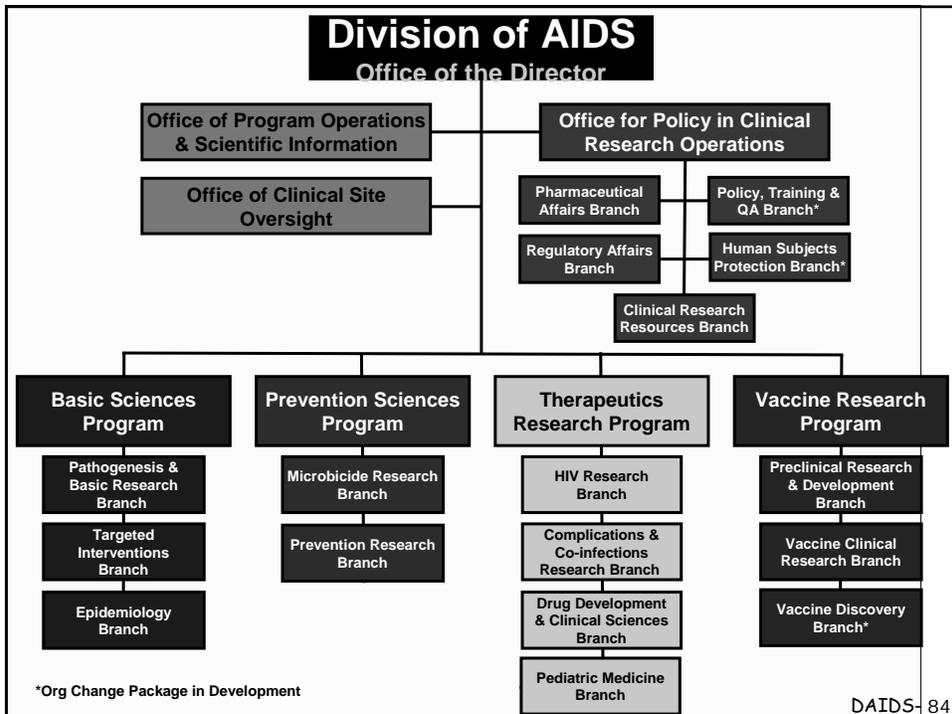


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DAIDS Safety Monitoring

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Total Protocols Currently Being Monitored

	Network	Non-Network
BSP	0	4
PSP	12	9
TRP	57	24
VRP	17	7



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The Networks

- ACTG AIDS Clinical Trials Group
- IMPAACT International Maternal, Pediatric and Adolescent Clinical Trials
- INSIGHT International Network for Strategic Initiatives in Global HIV Trials
- HPTN HIV Prevention Trials Network
- HVTN HIV Vaccine Trials Network
- MTN Microbicides Trials Network



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The DSMBs

- Therapeutic
- ESPRIT/SILCAAT/STALWART
- Multinational
- Asia
- Africa
- Vaccine and Prevention
 - Note: This DSMB may review early phase data as well as the typical phase 3 large scale review
- CAMELIA
- PENPAC



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Medical Officer Safety Functions

- Reviews protocol for sound science, subject safety and safety monitoring plans; may be full team member involved in protocol development
- Involved in Clinical Sciences Review Committee or Prevention Sciences Review Committee review of protocol
- Receives real time adverse event reports and assesses for relatedness, expectedness, and severity, recommending whether reportable to FDA and other regulatory bodies
- Receives periodic summaries of adverse events, typically monthly and/or quarterly
- May recommend unscheduled safety review, typically by SMC
- Attends open sessions of DSMB to provide supplementary information. At the invitation of the DSMB may be invited to closed session
- In special circumstances receives access to some closed safety data



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Protocol Safety Review Team (PSRT) Monitoring

- Monitoring of healthy volunteers may include additional layers of monitoring performed at more frequent intervals (e.g., PSRT, SMB, etc.)
- The PSRT provides a blinded safety review of summary data as indicated by a specific protocol. Detailed individual safety reports and aggregate blinded data are reviewed weekly and on emergent bases.
- For DAIDS funded vaccine trials, a PSRT monitors the assessment, follow-up, and reporting of AEs, serious adverse experiences (SAEs), clinical laboratory results, and reactogenicity to study agents.
- The PSRT is composed of Clinical Trials Physicians, Safety Specialists, Protocol Chairs, and DAIDS Medical Officers. For unresolved issues or outstanding concerns, the PSRT consults with either the HIV Vaccine Trials Network Safety Monitoring Board (HVTN SMB) or the NIAID Vaccine and Prevention DSMB.



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Safety Monitoring Board (SMB) Reviews

- The HVTN SMB reviews all HIV Vaccine Trials Network (HVTN) clinical trials safety data from phase I and II trials every four months and addresses safety issues on an ad hoc basis.
- For scheduled reviews, cross protocol and protocol-specific analyses and summaries are prepared. The reports include analyses of adverse events and overall safety data, analyses of lab values, including basic summaries and longitudinal analyses, summaries of adherence to pause rules, etc.
- The SMB is an independent multidisciplinary group consisting of biostatisticians, clinicians and experts in HIV vaccine research with experience in the conduct and monitoring of vaccine trials and the management of patients with HIV infection. The SMB, like the NIAID DSMBs, follows a charter to operate within the HVTN.



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SMC

- A small group of qualified reviewers, not associated with the protocol but typically from within the network, including a statistician.
- The medical officer and protocol statistician also participate in reviews which may include unblinded data, but do not vote (NB: consensus, rather than vote, is the usual outcome)
- Periodic reviews, at least once per year, are planned at the time of protocol development, often when certain benchmarks are achieved (e.g.: completion of a dosing arm, when a specified number of serious adverse events has occurred, when a portion of subjects has reached a specified end point, etc.)
- SMC makes recommendations to higher levels of network committees and to DAIDS
- Network executive committees make recommendations to the study team, with DAIDS approval
- Medical officers may request unscheduled SMC review based on their own review of safety reports



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DSMB

- Groups with expertise in medical science, clinical trials, statistics, ethics and a community representative providing big picture review
- Meet at specified time periods, not necessarily corresponding to protocol benchmarks; look for patterns not apparent on small scale
- Provide at least annual review
- Initially have an introduction to the protocol early in its conduct.
- Review blinded aggregate safety data and endpoint data by protocol arm and may elect to review unblinded data.
- May recommend modifications to enhance safety, including closing arms of the study or halting the study, either due to unacceptable risk or because of overwhelming evidence of efficacy
- May also recommend ending study or closing an arm due to clear evidence of futility to achieve sufficient endpoints
- Recommendations are made to DAIDS and are non-binding
- Protocol team, including medical officer, present during open sessions, rarely medical officer may be invited to review some closed safety data



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Lessons Learned #1

- Share the workload with the networks. SMCs can nimbly respond to review data at specified benchmarks in the protocol because of their small membership and its link to the network.

- During protocol design carefully consider what should trigger an SMC review, especially for safety concerns.



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Lessons Learned #2

- Carefully consider what data should be included in pre-specified reviews described in the protocol:
 - DAIDS requirement that CD4 count be included in interim review of ACTG 290 in addition to the usual toxicity review led to the early closure of the ZDV+d4T arm for lack of efficacy in ZDV experienced subjects and a public health alert changing the standard of care months before the completion of the trial.
 - Be careful what you ask for: the request that an annual SMC review of a small phase 1/2 ACTG dose-seeking trial of human keratinocyte growth hormone include a recommendation whether an arm showing lack of effect on CD4 count might be closed led to recommendation to consider closing the whole trial, despite the lack of any safety concerns and the arbitrary selection of primary endpoint.



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Lessons Learned #3

- Futility analysis is very important in DSMB review of large clinical trials: SMART, a randomized comparison of continuous ART versus CD4 driven discontinuous ART, was eventually closed early, even before completing enrollment of 6000 subjects, when the discontinuous arm was observed to be highly unlikely to be able to demonstrate the endpoint of decreased non-AIDS related events. A very important public health observation was made, at great saving of clinical resources.
- Principle Investigator convened DSMBs have sometimes been reluctant to consider closure of trials for futility, consequently all DAIDS-supported trials needing a DSMB review must now utilize a DAIDS DSMB.





ACTIVITY EVALUATION FORM
NIAID Clinical Research Seminar Series: Sharing Best Practices
Data and Safety Monitoring
May 1, 2008

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 data and safety monitoring.**
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. **Do you have additional comments to enhance the utility or impact of the Seminar?**