April 26, 2012

Research 2012:

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From Bench to Bedside

Sponsored by the Office for Clinical and Translational Research

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'Professor Marvel never guesses…he knows!'

What Clinical Research Professionals Need to Know About NIH-Sponsored Research

JP Clancy, MD

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Objectives

- To understand the basic structure of the NIH and the process of grant submission, review, and feedback for clinical research studies.
- To appreciate the various names and types of NIH awards, such as R, U, and K awards.
- To identify and recognize the skills and expertise necessary for RCs and investigators to successfully conduct NIH-supported clinical research.

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Overview

- What the heck is the NIH?
  - History and organizational structure
- What are all of these Rs, Ks, and Us about?
  - Types of grants
  - Grant applications
  - Grant expectations
- What's the same, and what's different regarding NIH vs industry-sponsored research?
  - Required skills
  - Very helpful skills

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Why me?

- Clinical trial research experience for >10 years
  - NIH funded
  - Non-NIH, non-profit
  - Industry-sponsored
  - Interventional, observational, biomarker development
- Daily interactions with clinical research professionals
- Research review roles
  - NIH and CFF, DSMBs, PRCs, SACs

(…good question…)

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What is the NIH and what are it's origins?

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What is (are) the National Institutes of Health?

- Part of the US Department of Health and Human Services
  - Nation's medical research agency
  - Largest source of funding for medical research in the world
  - Responsive to congressional legislation
  - 80% of budget directed to >300,000 researchers at institutions (internationally)
  - 6,000 scientists within the intramural program on NIH campus
  - NIH Clinical Center (on campus) – largest clinical research hospital in the world
  - Support of several types of training programs
  - >130 Nobel prize winners have received NIH support

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The NIH (National Institutes of Health)

- 27 components
  - Institutes and centers
  - 300 acres in Bethesda, MD

- Office of the Director = central office
  - Frances Collins, MD
    - Human Genome Project
    - CF-causing gene
- ***Mission: science in pursuit of knowledge to improve human health***

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Accomplishing the mission

- *Fostering fundamental discoveries, innovative research, and their applications in order to advance the nation's capacity to protect and improve health*
- *Developing, maintaining, and renewing the human and physical resources that are vital to ensure the Nation's capability to prevent disease, improve health, and enhance quality of life*
- *Expanding the knowledge base in biomedical, behavioral, and associated sciences in order to enhance America's economic well being and ensure continued high return on the public investment*
- *Exemplifying and promoting the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.*

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Origins and evolution…

- **1798** – The Marine Hospital Service (for sick and disabled seamen)
- **1879** – the National board of Health created (1st organized, comprehensive national medical research effort)
  - Hot topics: cholera, leprosy, Rocky Mountain spotted fever
- **1887** – Laboratory of Hygiene established (Bacteriological laboratory, first research lab of the NIH)
- **1912** – Public Health Service established
- **1915** – Chamberlain-Kahn Act: PHS grants to 25 institutions to study venereal disease (first federal efforts to seek assistance from researchers through grants)
- **1930** – Ransdell Act – Redesignated the Hygienic Laboratory as the National Institute of Health
- **1937** – NIH = 8 divisions (including NCI)
- **1946** – Research Grants division created; expansion of grounds
- **1950** – Surgeon General can establish new institutes
- **1953** – NIH becomes part of the Dept. Health, Education and Welfare
- **1961** – Surgeon General established Center for Research in Child Health

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A little more evolution…

- **1966** – Summit of NIH leadership with LBW regarding how benefits of research findings could be brought more rapidly to citizens
- **1970s** – renaming and reconfiguring institutes
- **1980** – DHEW becomes DHHS (Department of Health and Human Services)
- **1985** – NIH and Howard Hughes Medical Institute chose the first HHMI-NIH scholars
- **1987** – 13 member Commission on the HIV Epidemic named by Ronald Reagan
- **1990** – Recombinant DNA Advisory Committee established (RAC); National Center for Human Genome Research established
- **1999** – PubMed repository established
- **2000** – ClinicalTrials.gov rolled out
- **2001** – Microarray (gene chip) technology applied to hereditary breast cancer
- **2003** – Human Genome project completed; NIH roadmap announced
- **2005** – Electronic grant submissions; institutional Clinical and Translational Science Awards announced
- **2007**- GWAS results about DM risk factors; reprograming skin cells into stem cells
- **2009** - ARRA

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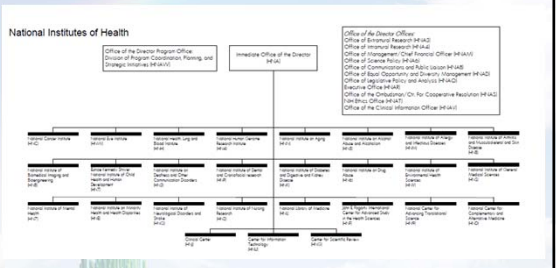
Organizational chart



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The Institutes (and centers)

- Office of Director
- National Cancer Institute
- National Eye institute
- National Heart, Lung and blood Institute
- National Human Genome Research Institute
- National Institute on Aging
- National Institute on Alcohol and Alcoholism
- National Institute of Allergy and Infectious Diseases
- National Institute of Arthritis and Musculoskeletal and Skin diseases
- National Institute of Biomedical Imaging and Engineering
- National Institute of Child Health and Human Development
- National Institute on Deafness and Other Communication Disorders
- National Institute of Dental and Craniofacial Research
- National Institute of Diabetes and Digestive and Kidney Diseases
- National Institute of Drug Abuse
- National Institute of Environmental Health Sciences
- National Institute of General Medicine Sciences
- National Institute of Mental Health
- National Institute of Minority Health and Health Disparities
- National Institute of Neurologic Disorders and Stroke
- National Institute of Nursing Research
- National Library of Medicine
- Center for technology
- Center for scientific review
- Fogarty International Center for Advanced Study in the Health Sciences
- National Center for Complimentary and Alternative Medicine
- National Center for Advancing Translational Sciences
- NIH Clinical Center

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Types of NIH Awards

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Extramural grants/award types

- NRSA – Ruth L. Kirschstein National Research Service Awards
- T awards: Institutional Training Grants
  - T32 (post-doctoral training program)
  - T34 (undergraduate student training in academic research)
  - T35 (short term institutional training awards - undergraduates)
  - T90 (interdisciplinary training)
- F (fellowship) awards
  - F30 NRSA predoctoral MD/PhD support (6 years)
  - F31 NRSA predoctoral MD/PhD support (promote diversity)
  - F32 NRSA Post-doctoral fellowship (3 years)
  - F33 NRSA Individual Senior fellowships (2 years)

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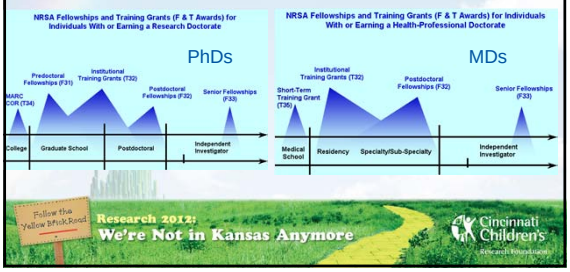
Extramural grants/award types

- NRSA – Ruth L. Kirschstein National Research Service Awards



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Extramural grants/award types

- **K (career development) awards (junior faculty)**
  - K01 mentored
  - K02 independent
  - K07 Academic career
  - ***K08 Mentored clinical scientist**
    - Clinical doctorate degree
    - Biomedical, behavioral, translational research
  - ***K23 Mentored patient-oriented research career**
    - POR – human subjects or material from human subjects for which investigator directly interacts with human subjects
  - K24 Midcareer investigator in patient-oriented research
  - K25 Mentored Quantitative Research Center

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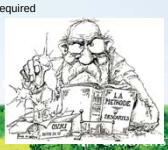
Extramural grants/award types

- **R (Research Project Grant) awards**
  - ***R01:** support investigator-initiated research on a discreet, specified, circumscribed project
    - 3-5 years, of support, no specific dollar amount (>$500,000 requires permission), renewable
  - ***R03:** Small Research Grants
    - two years of funding, $50,000/year, non-renewable
  - R15 Academic Research Enhancement Awards
  - ***R21:** Exploratory/Development Grants
    - Up to two years, $275,000 total, no preliminary data required
  - R41, R42, R43, R44 (Small Business grants)
    - Small business Innovation Research Awards
    - Small Business Technology Transfer Awards



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Extramural grants/award types

- **P and U awards**
  - **P01**(program project grants, or PPGs)
    - Integrated, multi-project research projects involving a number of independent investigators who share common knowledge and
    - Common theme and resources
  - **U01**
    - Collaborative project between the Institute and investigator
    - Institute wishes to have input into multi-institution study

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From a proposal to a grant

- **Submitting grants to the NIH**
  - Unsolicited or solicited
  - Choose institute with goals in line with applicant
  - Peer review (Center for Scientific Review) → *unscored*
  - Scientific assessment – priority score
  - Percentile → *Below threshold or payline*
  - Funding (5-10%)

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NIH grant – Human subjects section

- **Human Subjects.**
- **1. Statement of whether the proposal involves human subjects, with justification.**
- **2. Statement of whether the proposal includes a phase III clinical trial, with justification.**
- **3. Protection of human subjects from research risk.**
  - *3.1. If exemptions apply, state which ones and justify.*
  - *3.2. Subjects involved and characteristics.*
  - *3.3. Sources of research material.*
  - *3.4. Recruitment and Informed Consent.*
  - *3.5. Potential risks.*
  - *3.6. Protection against such risks.*
  - *3.7. Benefits.*

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NIH grant – Human subjects section

- **INCLUSION OF WOMEN**
- *Inclusion/exclusion plan and justification.*
- *Analysis plan.*
- *Outreach.*

- **INCLUSION OF MINORITIES**
- *Inclusion/exclusion plan and justification.*
- *Analysis plan.*
- *Outreach.*

- **INCLUSION OF CHILDREN**
  - *Inclusion/exclusion plan and justification.*
- *1.2. Analysis plan.*
- *1.3. Outreach.*
  - Data safety and monitoring plans.

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Enrollment tables

Study Title: MR predictors of infection, inflammation, and structural lung damage in CF

Total Planned Enrollment: 60

*The "Ethnic Category Total of All Subjects" must be equal to the "Racial Categories Total of All Subjects."

TARGETED/PLANNED ENROLLMENT: Number of Subjects

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	2	2
Not Hispanic or Latino	28	28	28
Ethnic Category Total of All Subjects*	30	30	30
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	28	28	56
Racial Categories: Total of All Subjects *	30	30	60

What are the expectations of NIH and/or non-NIH supported clinical research?

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My background related to NIH clinical research

- DSMB Chair: Disorders of Mucociliary Clearance (NIH)
  - Multicenter observational trial
- DSMB member: Rare Diseases Clinical Research Network (NIH)
  - Multiple therapeutic and observational projects
- DSMB member: MILES trial (NIH)
  - Multicenter and multi-national therapeutic trial (CCHMC and UC coordinating site)
- DSMB executive secretary: Nebulized xylitol for the treatment of cystic fibrosis (NIH)
- Adenosine regulation of CFTR (R01- PI)
  - Single center trial

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My background related to Non-NIH clinical research

- Personal non-NIH experience based upon:
  - National PI: VX-809 treatment of CF caused by the F508del CFTR mutation (Vertex Pharmaceuticals)
    - Multicenter interventional trial
  - International Co-PI: Phase II and Phase III program – Arikace® (Insmed)
    - Multi-national therapeutic trials
  - Joint Development Committee: CFF and Vertex Pharmaceuticals
    - Multi-center and multi-national therapeutic trials of CFTR modulators
  - CFF-TDN research network committees
    - Steering Committee, Protocol Review Committee
  - CFF-TDN site principal investigator
  - Scientific Advisory Board member
    - Gilead Pharmaceuticals, Vertex Pharmaceuticals, Insmed
  - Spinal Muscular Atrophy Association
  - Neurofibromatosis Advisory Committee

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What are the typical expectations NIH and non-NIH

- Good Clinical Practice (GCP) regulations
- 21 CFR 312 (IND)
- 21 CFR 50 (Human Subjects Protection)
- 21 CFR 54 (Financial Disclosure)
- 21 CFR 56 (IRBs)
- EU Commission Directive (2001/20/EC (Clinical Trials)
- EU Commission Directive (2005/28/EC (GCP)
- Rules Governing Medical Products in the European Community, Volume IV, Annex 13

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Following GCP: Relevant to NIH and non-NIH research

- Informed consent
  - Process, re-consent for new information, remote, documentation
- Subject protection
  - Welfare (IB, protocol design, medical supervision, safety reporting, IRB/IEC oversight)
- Data integrity
  - Follow protocol, qualified personnel, appropriate equipment, record and report all data, drug accountability, maintain files and source documents

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Regulatory reviews - Top deficiencies at study sites

- Protocol not followed (deviations)
- Lack of PI oversight
- Inadequate records
- Informed consent
- Ineligible subjects (Inclusion/exclusion criteria not met)
- IRB/IEC reporting
- Drug accountability
- Inadequate regulatory binder

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Investigator obligations

- Conduct the study according to the protocol
- Document deviations
- Ensure consent, IRB review (ongoing)
- Learn and know the IB
- Pharmacy oversight
- Report (Serious) AEs
- PI oversight:
  - Delegate responsibilities to qualified and trained individuals
  - Medical decisions made by Qualified practitioners (MD, DO, NP, PA, etc.)

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PI oversight – what does this mean?

- Stay involved
  - Appropriate time commitment
  - Regular meetings with study staff (document)
  - Meet monitors
  - Document time spent with study subjects/visits
    - Subject adherence/non-adherence, sponsor visits
  - Timely review of reports (with dates and initials)
- Staff training:
  - SIV, investigator meeting attendance, training documents

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Documentation

- Permanent
- Legible
- Immediate
- Accurate
- Consistent
- Complete
- Attributable
- Truthful

Confidentiality (country specific)

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So how is this my problem?

- **PI often focused on science, while research professional focused on process**
  - PI medical/legal responsibility for all aspects of study conduct at site, but…
  - Everyone suffers for noncompliance
  - PI:RC trusting relationship critical
- **Many of these are about process**
  - Conduct the study according to the protocol
  - Document deviations
  - Consent and IRB
  - IB
  - Pharmacy
  - Reporting
  - PI oversight

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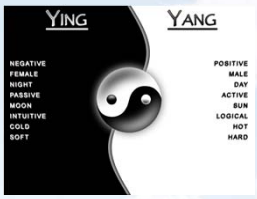
Yin/Yang of clinical research conduct (Research professional and PI)

- "…how polar opposites or seemingly contrary forces are interconnected and interdependent in the natural world, and how they give rise to each other in turn. Opposites thus only exist in relation to each other."
- "Yin (and) Yang are not opposing forces (dualities), but rather complimentary opposites that interact within a greater whole, as part of a dynamic system"



Wikipedia (Apr.2012)

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What is unique when conducting NIH-sponsored clinical research

- 'Grassroots' feel to the research
  - Fewer research professionals in the mix
  - Study team functions with much more autonomy vs industry sponsored trial
  - Typically no CRO
  - No industry sponsor
  - Responsibilities are assigned and conducted at the local level
  - Data management can be local or centralized

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What is unique when conducting NIH-sponsored clinical research

- Lead PI and study team (if part of a research network)
  - Role of the Research Health Professional for lead site:
    - Development of IB, protocol, CRFs, ICFs
    - Organization of data and updates
    - Scheduling of communications
    - Interaction with stakeholders
      - Sites, NIH personnel, data management, statistician, DSMB chair and members, IRBs
    - Documentation
    - PI involvement
    - Non-competitive renewals
      - Enrollment tables

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What is unique when conducting NIH-sponsored clinical research

- Develop DSMB/OSMB specific to the trial
  - Chair, Executive Secretary, members, biostatistician, NIH representatives, data management personnel
  - Regular DSMB reviews (face-to-face and teleconferences)
    - Enrollment (target, actual)
    - Site activation (IRB approval, contract approval, site initiation)
    - Data quality (entry, completion - sites, total)
    - AEs and SAEs
    - Deviations and violations
    - Stopping rules; blinded analysis for safety, efficacy, futility
    - Open and closed sessions
  - Summary documents
    - To PI, NIH

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Examples of NIH-sponsored progress report (OSMB)

Multiple sites, observational trial

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Study synopsis and progress to date

- 2-3 page summary of protocol (table form)
- Summary of:
  - Recruitment
  - Protocol adherence
  - Site performance
  - Study results
  - Adverse events
  - Current amendments

III. Study Progress to Date
Accrual Summary by Institution

Site	Registered	Eligible	Enrolled to Date	Off Study (Due to Death, LTF, or Withdrawn)	Currently On Study
	62	62	62	9	53
	13	11	11	0	11
	15	15	15	0	15
	5	4	4	1	3
	29	28	28	0	28
	124	*120*	*120*	*10*	*110*

Accrural

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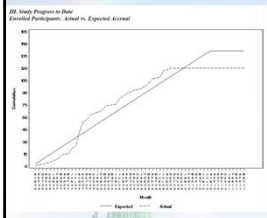
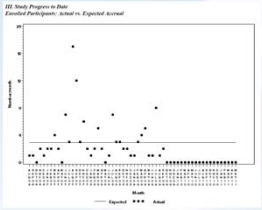
Enrollment numbers and graphs





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Enrollment reports

III. Study Progress to Date
Gender, Race, and Ethnicity of Enrolled Participants

PART A: TOTAL ENROLLMENT REPORT: Number of Participants (Cumulative) by Ethnicity and Race

	Sex/Gender			
Category	Females	Males	Unknown or Not Reported	Total
Ethnic Categories				
Hispanic or Latino Origin	7	6	0	13
Not Hispanic or Latino Origin	52	53	0	105
Unknown (individuals not reporting ethnicity)	0	2	0	2
	59	*62*	*0*	*120*
Racial Categories				
American Indian/Alaska Native	1	0	0	1
Asian	9	5	0	14
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	2	0	0	2
White	46	53	0	99
More Than One Race	1	3	0	4
Unknown or Not Reported	0	0	0	0
	59	*62*	*0*	*120*

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Protocol adherence

III. Study Progress to Date
Protocol Adherence - By Institution

			Data Point Collection Status									
			Not Done		Done		Unknown		Submitted		Complete	
Institution	Number of Participants with an Expected Data Point	Expected Data Points N	Per Tracking System N	% of Expected	N	% of Expected	N	% of Expected	N	% of Expected	N	% of Expected
	62	1296	9	0.69	1	0.08	65	5.02	1223	94.21	1203	92.67
	13	246	0	0.00	0	0.00	15	6.10	231	93.90	231	93.90
	15	308	7	2.27	0	0.00	0	0.00	301	97.73	300	97.40
	5	72	15	20.83	0	0.00	0	0.00	57	79.17	57	79.17
	29	633	0	0.00	0	0.00	45	7.11	588	92.89	581	91.79
	124	*2555*	*31*	*1.21*	*1*	*0.04*	*125*	*4.89*	*2388*	*93.86*	*2370*	*92.76*

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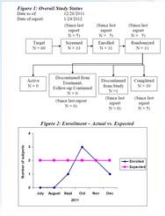
Examples of NIH-sponsored progress report (OSMB)

Single site, interventional trial

- Protocol changes and requests
- Project summary
- Screen fails
- Deviations/violations
- AEs/SAEs (severity, relatedness)
- Closed session review



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Examples – AE and severity summaries

Table 5: Incidences of Adverse Events

Date as of: 12/28/2011
Date of report: 1/24/2012

Event	Group A N (%)	Relatedness	Group B N%	Relatedness
URI symptoms	1 (6%)	unrelated	0	
Abnormal Labs	4 (23%)	Unrelated	1 (7%)	Possibly related
Hematological DVT			1 (7%)	Unrelated
Bronchospasm			1 (7%)	Related

Pts: subject developed nausea and fever after randomization and decided to withdraw from the study before the first study drug was administered.
DVT: subject was admitted with an occluded port and then randomized to the study. 2 days after randomization, evaluation of admission access problem showed clot in the port and the vein.
Bronchospasm: Screen Failure

Table 6: Severity of Adverse Events

Event	Group A			Group B		
	Total N = Mild	Total N = Moderate	Total N = Severe	Total N = Mild	Total N = Moderate	Total N = Severe
URI symptoms	1	0	0	0	0	0
Lab values	4	0	0	1		0
Hematological		0	0		1	0
Bronchospasm		0	0		1	0

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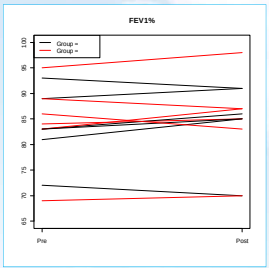
Closed session

- Safety review
- Futility review
- Blinded or unblinded
- DSMB members, NIH representatives, biostatistician
- Candid discussions
- Investigative team joins after closed session
  - Summary, next steps



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Summary

- NIH
  - Large government entity, broad goals related to advancing science, improving health and welfare of citizens
- NIH grants
  - Complex and slow process
  - Several potential avenues to support research
- NIH – clinical research expectations
  - GCP + ground level responsibility for communication and conduct

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Questions?

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