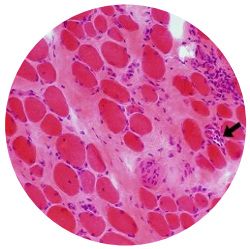
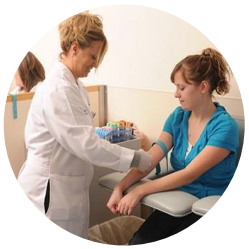
Clinical Trials Programs at NIAMS


Tom Cheever, Ph.D.

Program Director

Muscle Disorders and Therapies Program

Division of Musculoskeletal Diseases, NIAMS

National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH Institute Homes for Neuromuscular Diseases

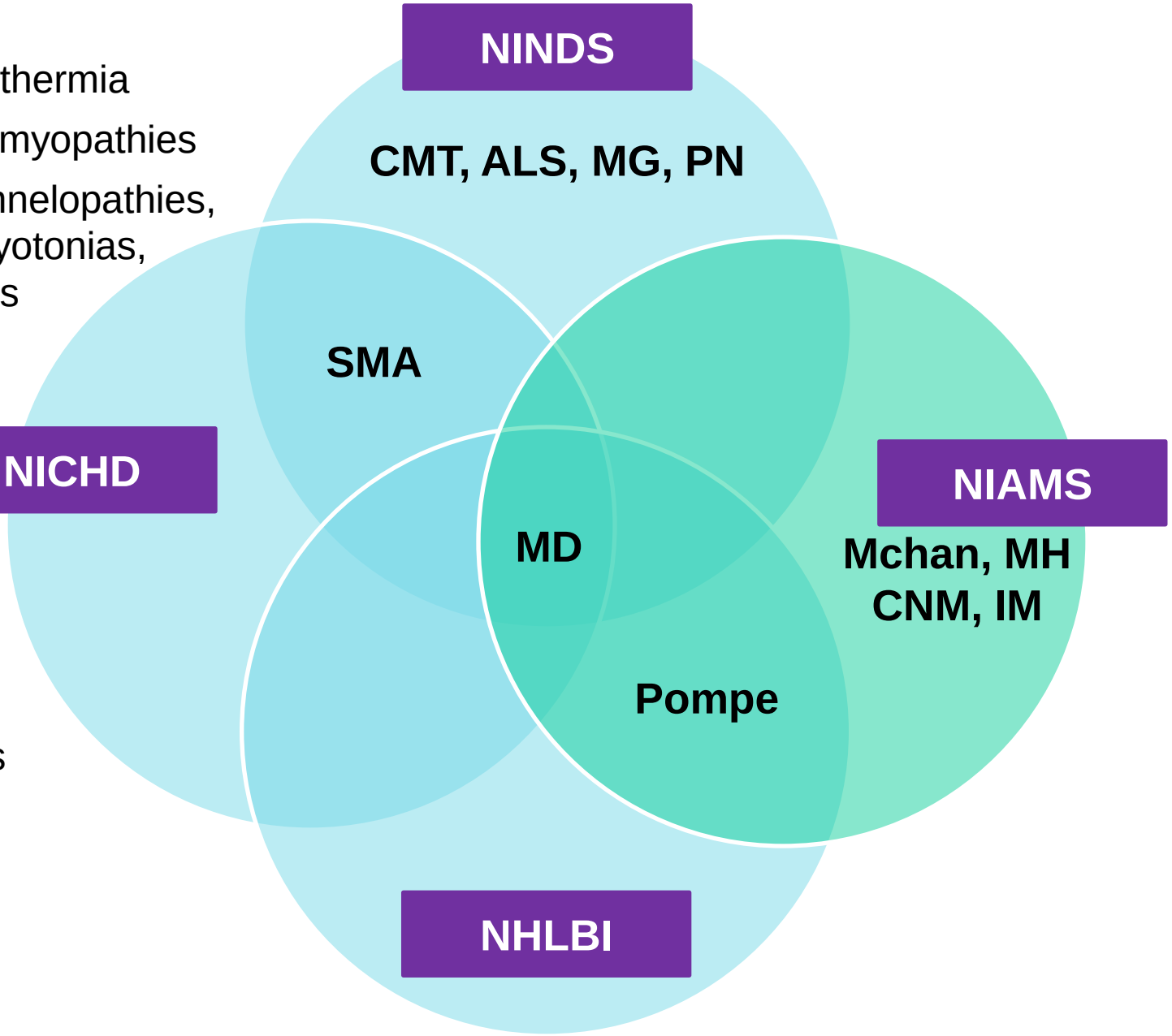
MH - malignant hyperthermia

CNM - centronuclear myopathies

MChan - muscle channelopathies, nondystrophic myotonias, periodic paralyses

IM - inflammatory myopathies, DM, PM, IBM

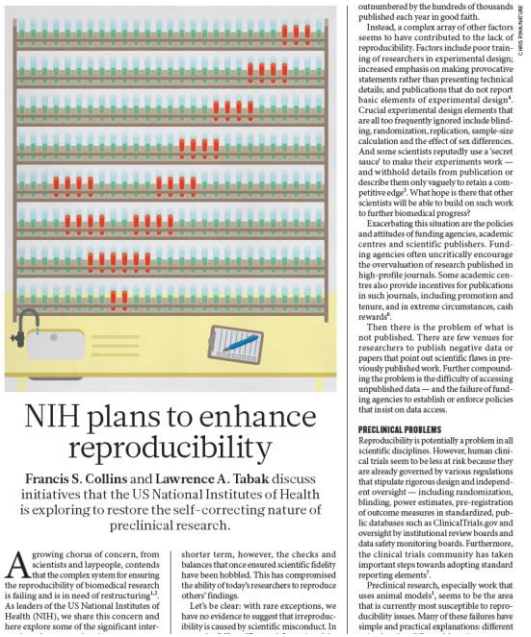
MD - DBMD, DM, FSHD, CMD, LGMD, OPMD, EDMD and others



Clinical Research and Clinical Trials at NIH

- NIH as a whole has been reviewing the process of scientific management and oversight of clinical trials

Premise and Reproducibility



NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring[1,2]. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant intershorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised the ability of today's researchers to reproduce others' findings.

Let's be clear: with rare exceptions, we have no evidence to suggest that irreproducibility is caused by scientific misconduct. In outnumbered by the hundreds of thousands published each year in good faith.

Instead, a complex array of other factors seems to have contributed to the lack of reproducibility. Factors include poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting technical details; and publications that do not report basic elements of experimental design[3]. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences. And some scientists reputedly use a 'secret sauce' to make their experiments work — and withhold details from publication or describe them only vaguely to retain a competitive edge[2]. What hope is there that other scientists will be able to build on such work to further biomedical progress?

Exacerbating this situation are the policies and attitudes of funding agencies, academic centres and scientific publishers. Funding agencies often uncritically encourage the overvaluation of research published in high-profile journals. Some academic centres also provide incentives for publications in such journals, including promotion and tenure, and in extreme circumstances, cash rewards[4].

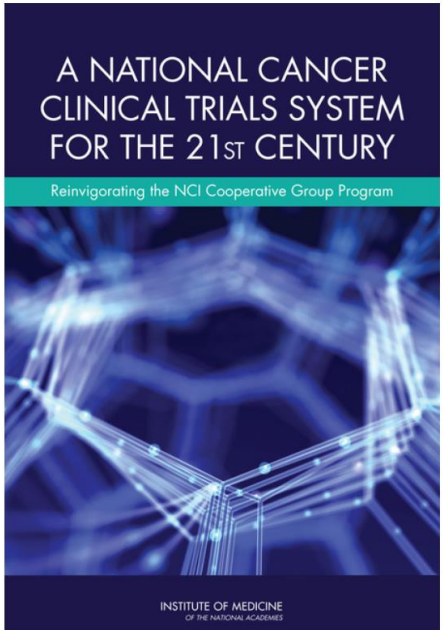
Then there is the problem of what is not published. There are few venues for researchers to publish negative data or papers that point out scientific flaws in previously published work. Further compounding the problem is the difficulty of accessing unpublished data — and the failure of funding agencies to establish or enforce policies that insist on data access.

PRECLINICAL PROBLEMS

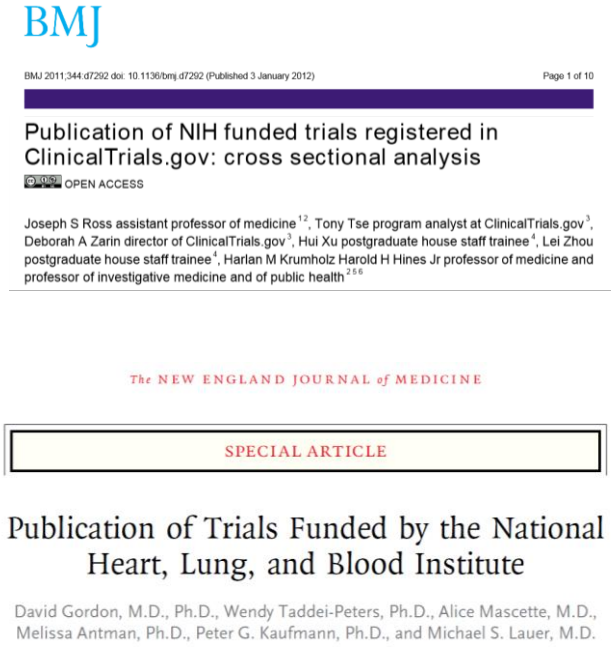
Reproducibility is potentially a problem in all scientific disciplines. However, human clinical trials seem to be less at risk because they are already governed by various regulations that stipulate rigorous design and independent oversight — including randomization, blinding, power estimates, pre-registration of outcome measures in standardized, public databases such as ClinicalTrials.gov and oversight by institutional review boards and data safety monitoring boards. Furthermore, the clinical trials community has taken important steps towards adopting standard reporting elements[5].

Preclinical research, especially work that uses animal models[6], seems to be the area that is currently most susceptible to reproducibility issues. Many of these failures have simple and practical explanations: different

Trial design and Implementation



Time to Publication



BMJ

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012) Page 1 of 10

Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

OPEN ACCESS

Joseph S Ross assistant professor of medicine [1 2], Tony Tse program analyst at ClinicalTrials.gov [3], Deborah A Zarin director of ClinicalTrials.gov [3], Hui Xu postgraduate house staff trainee [4], Lei Zhou postgraduate house staff trainee [4], Harlan M Krumholz Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health [2 5 6]

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Publication of Trials Funded by the National Heart, Lung, and Blood Institute

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D., Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.

Revision NIH Definition for Clinical Trials

- In January of 2015, revised NIH definition of clinical trials took effect
  - A research study in which one or more human subjects are **prospectively assigned** to one or more **interventions** to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes**
- Why the new definition?
  - So that clinical trials can be identified and adequately monitored for:
    - Safety
    - Recruitment / inclusion
    - Reporting / publication
- What does this mean for researchers?
  - Many NIH ICs have revised policies on how clinical trials are accepted and reviewed

NIAMS Clinical Trial Policies

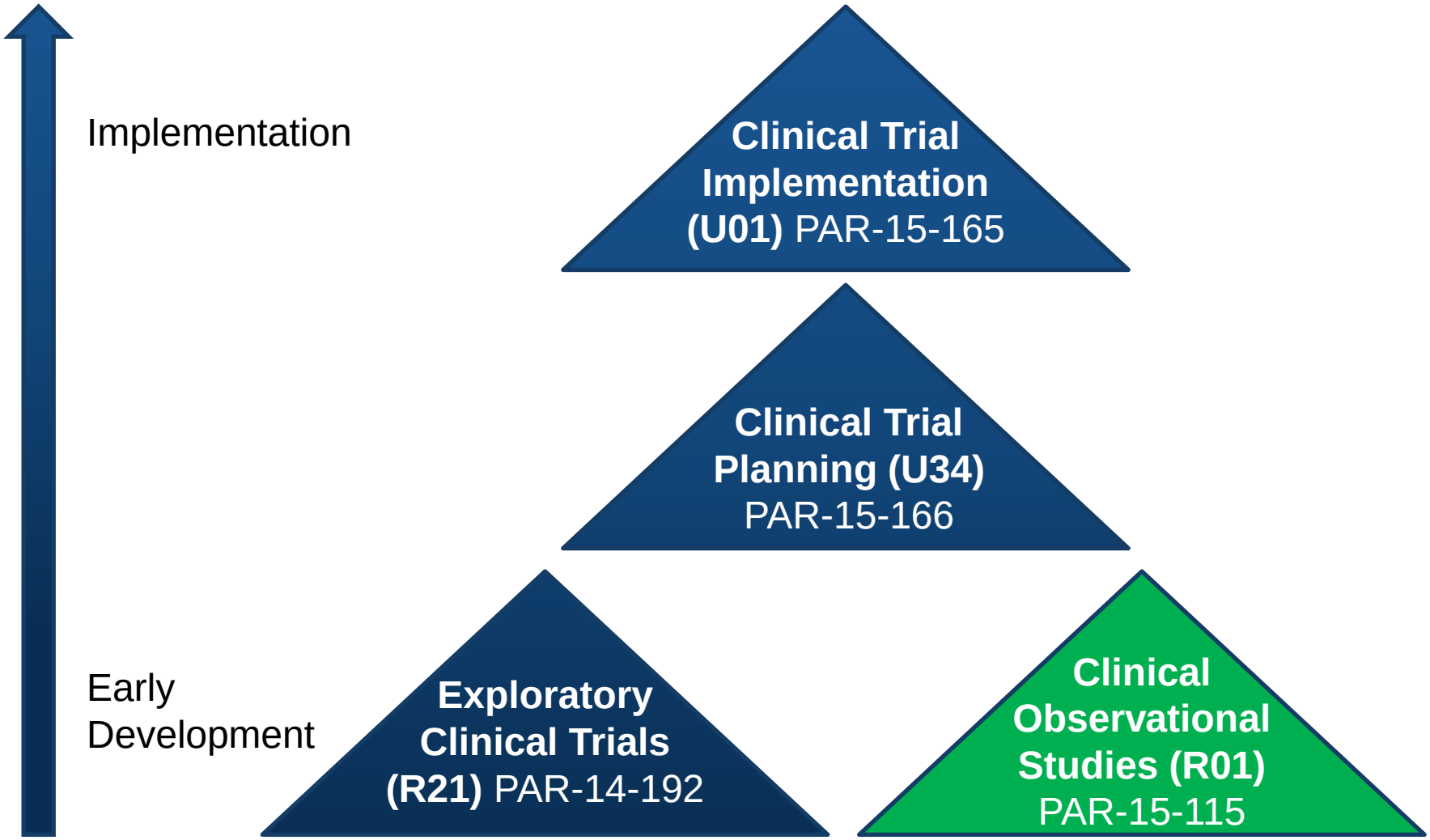
- **NIAMS does not accept clinical trials received through parent announcements (NOT-AR-14-021)**
  - Investigator-initiated applications submitted to NIAMS must be submitted to one of the NIAMS program announcements with special review (PAR) specifically designed for clinical trials

- Why?
  - Increase the rigor, timeliness, and impact of trials supported

  - Review by NIAMS standing study section (AMSC)
    - Members include clinical trialists, statisticians, physician-scientists
    - Consistency of advice
    - Note: Panel includes reviewers with expertise across entire NIAMS mission

- Are similar policies in place across the entire NIH? Varies by institute.
  - NINDS also requires all clinical trials be submitted to specific PAR reviewed within NINDS

NIAMS Clinical Trial Opportunities



http://www.niams.nih.gov/Funding/Clinical_Research/clinical_main.asp

Clinical Observational Studies in Musculoskeletal, Rheumatic, and Skin Diseases

- **R01** (PAR-15-115)

- **Goal: To obtain data necessary for designing clinical trials**
  - Address significant obstacles or questions in the design of clinical trials
    - Determine appropriate outcome measures
    - Disease progression
    - Study recruitment strategies
    - Standard of care data to be used as control in future trial
    - Support biomarker development and validation (but not discovery)
      - Relate biochemical or imaging biomarker with established surrogate markers

- ***No interventions***

- Most responsive applications will have clear connection enhancing future clinical trials
  - Other natural history /observational studies may be best served by parent R01 (CSR review)

Exploratory (Pilot) Clinical Trial Grants

- **R21** (PAR-14-192)

- **Goal:** Facilitate short-term interventional studies to obtain data needed to launch future clinical trials

    - First-in-human studies
    - Safety / tolerability / dosing
    - Testing new formulation or delivery of intervention
    - Trials aimed at prevention, delayed or halted progression
    - Feasibility studies focused on novel, cost-effective, or alternative designs

- Other opportunities to consider: NCATS BrIDGs and TRND; NINDS Blueprint Neurotherapeutics

Clinical Trial Planning Cooperative Agreement Grants

- **U34** (PAR-15-166)
- **Goal:** Facilitate design of studies and completion of administrative activities prior to implementation phase
- **NIAMS requires all clinical trial implementation awards (U01) *first* go through a U34 planning phase**
  - Exceptions can be made if preparatory work is sufficiently far along
    - Contact NIAMS PO

Planning Activity	Status				Comments (please include additional detail regarding the status of the activity including any anticipated dates of completion if the activity is not yet complete)	NIAMS Internal Use Only
	Completed	In process*	Not started*	Not applicable*		
Study protocol						
Budget proposal for U01 application						
Identification and qualifications of clinical trial sites, pharmacies and laboratories						
Investigator Brochure (IB) or equivalent						
MOOP						
Data and safety monitoring plan						
Finalize plans to obtain intervention related products (drugs, placebo, device)						
Develop Clinical Trial Agreement (CTA) and/or Cooperative Research and Development Agreement (CRADA)						
Develop template informed consent (and assent form, if applicable)						
Develop case report forms						
Program database						
Establish data collection system for primary and/or remote sites						
Submit/obtain approval for IND/IDE						
Develop and plan materials for training and site initiation						
Initiate IRB approval/request applicable waivers (e.g., HIPAA)						
Documentation of adequate co-funding, if applicable and necessary for completion of the trial						
Other:						

http://www.niams.nih.gov/Funding/Clinical_Research/clinical_milestone_checklist.asp

Clinical Trial Implementation Cooperative Agreement Grants

- **U01** (PAR-15-165)
- **Goal:** Support clinical trial implementation phase
- Activities that would fall under this FOA:
  - Enrollment of subjects
  - Data collection, analysis and oversight
  - Preparation of final study report and other post-enrollment activities
- ***Note:*** Preceding U34 planning grant required unless waiver granted
- Pre-submission consultation with NIAMS Program Officer is strongly encouraged prior to submitting an application

NIAMS Clinical Research/Trial Program

Study Type	Mechanism	Budget Caps (Direct Cost)	Review	Special Considerations
Clinical Observational	R01	$450K** over 3 years	NIAMS (AMSC)	How will this inform / enhance subsequent trials?
Pilot / Exploratory	R21	$400K** over 3 years	NIAMS (AMSC)	How will this inform / enhance subsequent trials?
Planning	U34	$250K per year for up to 2 years	NIAMS (AMSC)	Required for U01 unless waiver granted
Implementation	U01	No budget cap^^, up to 5 years	NIAMS (AMSC)	Requires prior U34 unless waiver granted

** excludes consortium F&A

^^ Applications requesting ≥ $500K in direct costs in any year (excluding consortium F&A) requires approval prior to submission (10 weeks prior)

Request for Information – Feedback on NIAMS Clinical Trial Programs

- Ways the current NIAMS suite of clinical trials Funding Opportunity Announcements can be improved
  - Goal: adequately provide opportunities for all types of clinical trials
- Types of funding support that are necessary for the different stages of clinical trial implementation
  - Conceptualization → full implementation
- Ways the NIAMS can optimize the early review of a future clinical trial concept
  - Benefits that might result from having the NIAMS review a clinical trial concept at an early stage
- Other areas relevant to optimizing NIAMS clinical trials support
- See NOT-AR-15-019
  - Responses due by October 15, 2015
  - Email to NIAMSclinicaltrials@mail.nih.gov

Look Forward to Working with You

- **Pre-application discussion or letter of intent always welcome**

- **For scientific/programmatic questions**

  Tom Cheever, Ph.D.
  Program Director
  thomas.cheever@nih.gov

- **Clinical trial policy questions**

  Shahnaz Khan, MPH
  Clinical Coordinator
  khanshah@mail.nih.gov

  Anna Nicholson, MSHS
  Clinical Coordinator
  nicholsona@mail.nih.gov

- **Helpful Links**
  - NIAMS Clinical Research Funding Info Page
    - Policies, FOAs, FAQs, more
    - http://www.niams.nih.gov/Funding/Clinical_Research/clinical_main.asp