

Director's Report

NCATS Advisory Council and CAN Review Board

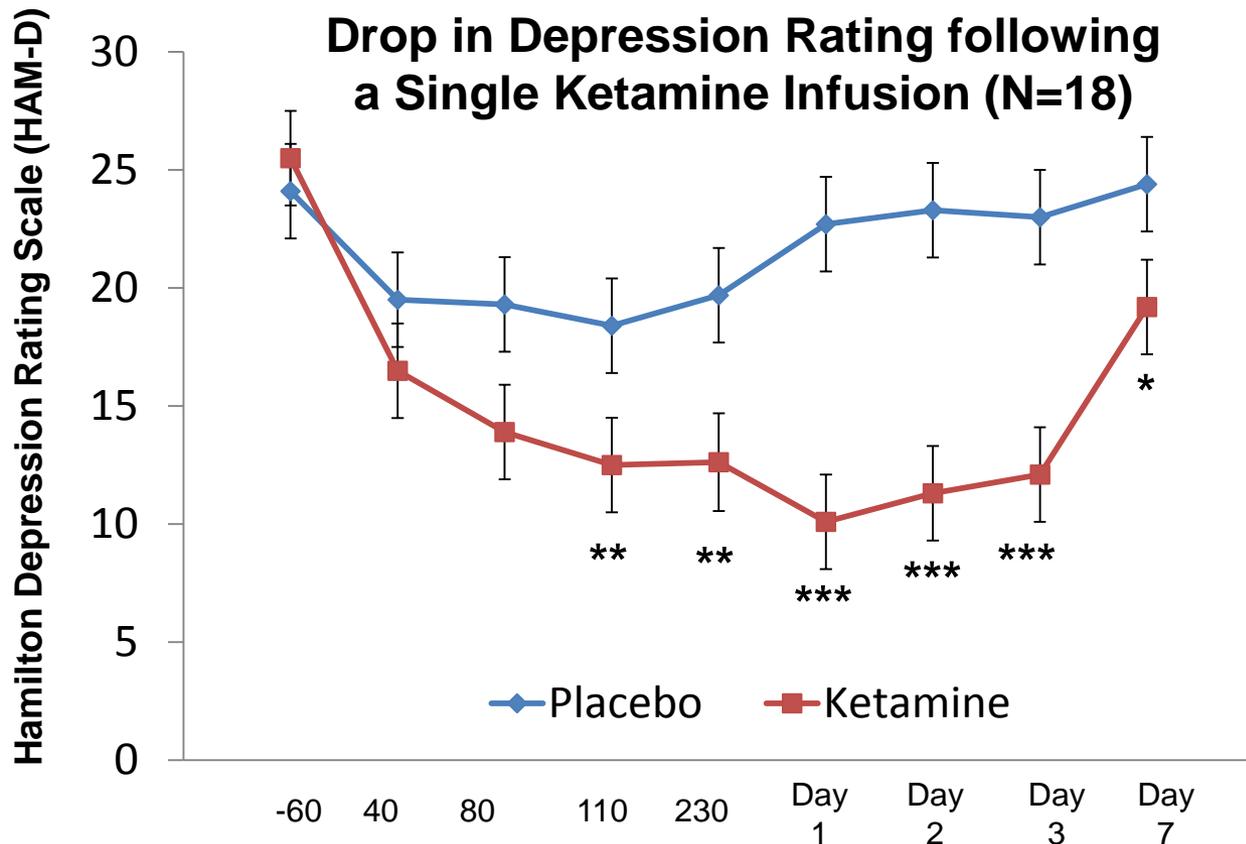
CHRISTOPHER P. AUSTIN, M.D.
DIRECTOR, NCATS
JUNE 13, 2016

NCATS

Selected Translational Innovation Highlights

- *Early-stage translation:* chemical probe/lead development for target validation and therapeutic hypothesis testing
- *Mid-stage translation:* preclinical development to first-in-human studies
- *Late-stage translation:* large-scale studies in humans

Rapid Antidepressant Effect of Ketamine in Unmedicated Treatment Resistant Depression



- Rapid Effect in Major Depressive Disorder
- Rapid Decreases in Suicidal Ideation
- Rapid Effect in Treatment Resistant Bipolar (BP) Depression

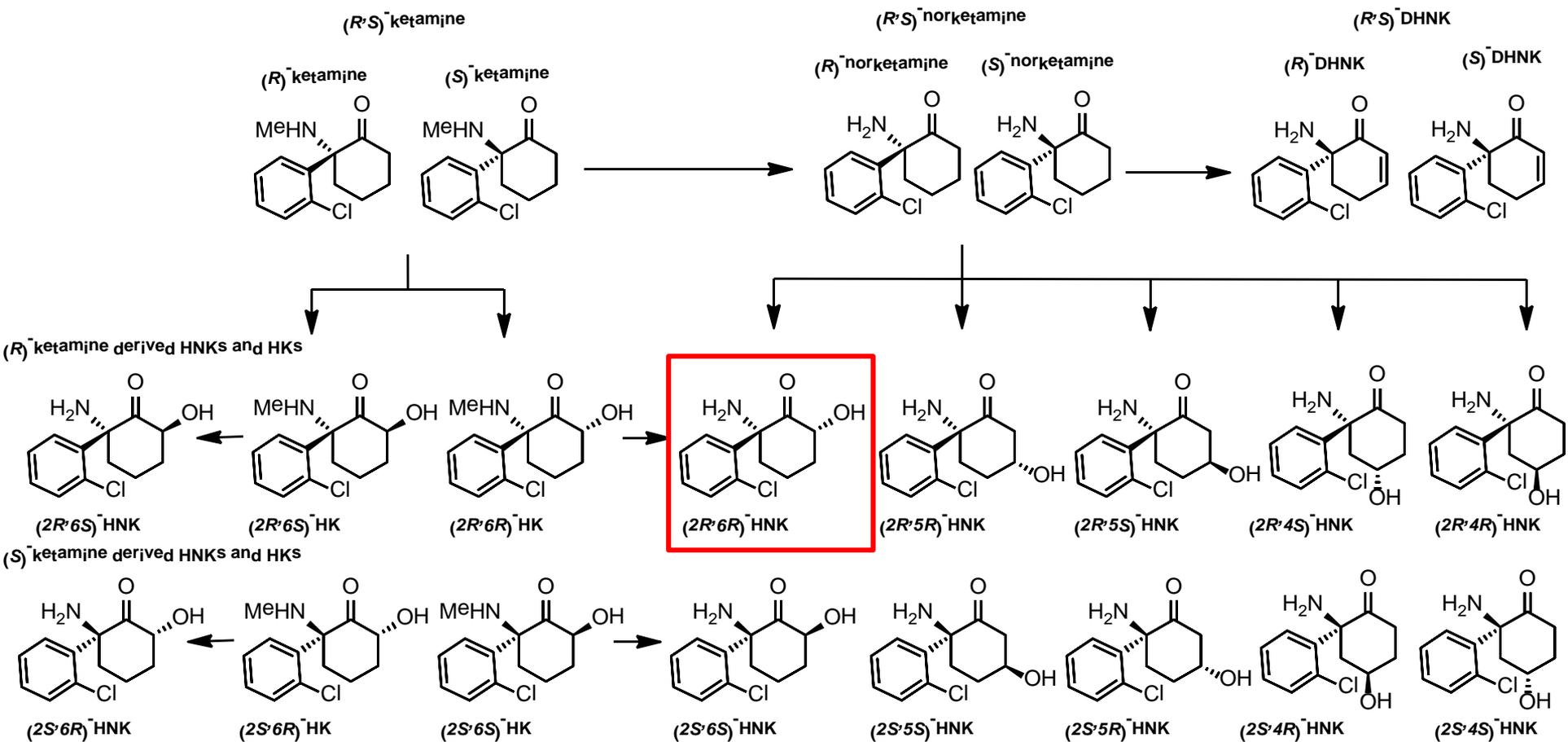
Zarate et al. Arch Gen Psychiatry 2006

DPI

Ketamine Metabolites for Depression

- Collaborators
 - University of Maryland School of Medicine
 - National Institute of Mental Health and National Institute on Aging
- Background
 - Severe depression affects ~16% of the world population
 - Current therapies require prolonged administration for clinical improvement and some patients are non-responsive
- Project
 - Non-competitive, glutamatergic NMDAR antagonist (R,S)-ketamine exerts quick and prolonged antidepressant effects after a single dose, but also has side effects.
 - Showed that ketamine metabolite ((2R,6R)-HNK) reversed depression-like behaviors in mice without triggering anesthetic, dissociative, or addictive side effects
 - **Data illustrate novel mechanism and have potential for the development of next-generation antidepressants**

Extensive metabolism of ketamine



NMDAR inhibition-independent antidepressant actions of ketamine metabolites

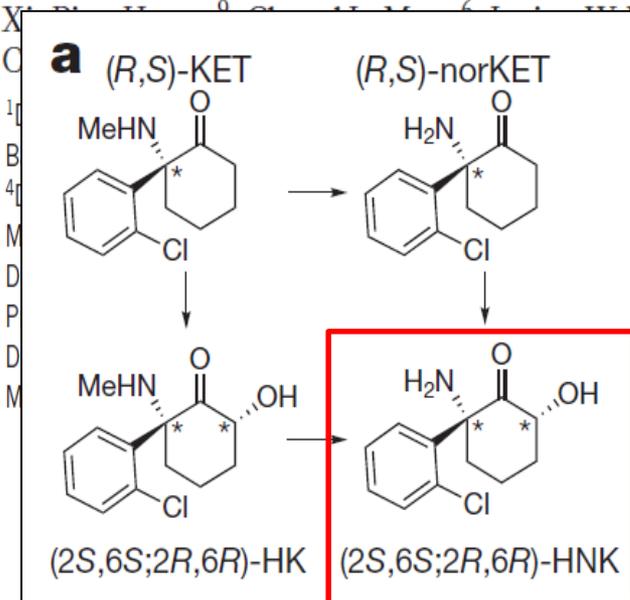
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¹Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ²Biomedical Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA. ³Division of Preclinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, Maryland 20850, USA.

⁴Department of Physiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ⁵Department of Pharmacology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ⁶Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, Maryland 21228, USA. ⁷Department of Epidemiology and Public Health, Division of Translational Toxicology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ⁸Experimental Therapeutics and Pathophysiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland 20892, USA. ⁹NIMH Psychoactive Drug Screening Program, Department of Pharmacology and Division of Chemical Biology and Medicinal Chemistry, University of North Carolina Chapel Hill Medical School, Chapel Hill, North Carolina 27516, USA. ¹⁰Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA. ¹¹Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.

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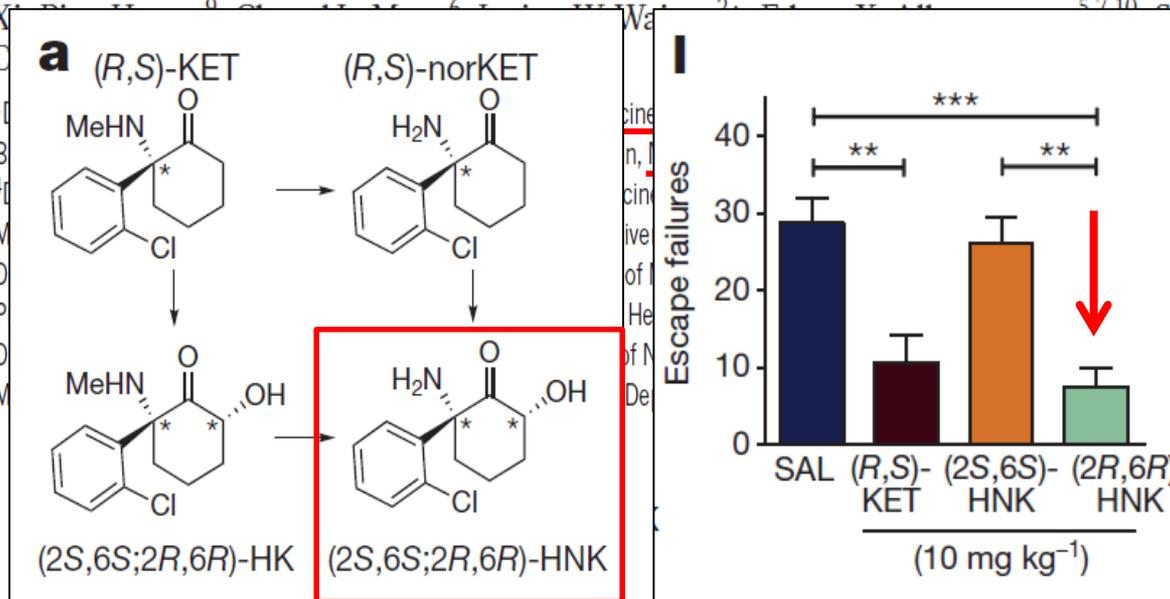
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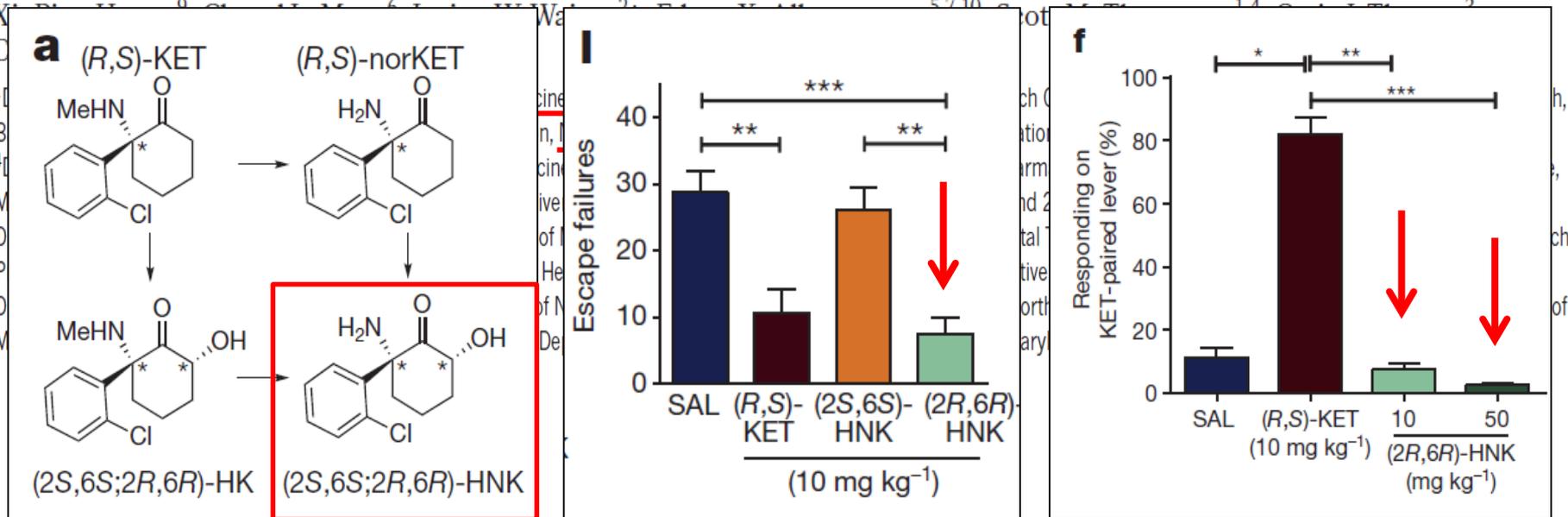
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NIH
ORDRINCATS, NCI, NHLBI,
NIAID, NIAMS, NICHD, NIDCR,
NIDDK, NIMH, NINDS, ODS

**Coalition of Patient
 Advocacy Groups
 (CPAG for RDCRN)**

**Porphyria Rare Disease Clinical
 Research Consortium**

**Dystonia
 Coalition**

**North America Mitochondrial
 Diseases Consortium**

**Developmental Synaptopathies
 Associated with TSC, PTEN
 And SHANK3 Mutations**

**Primary Immune Deficiency
 Treatment Consortium**

**The Frontotemporal Lobar
 Degeneration Clinical
 Research Consortium**

**Brittle Bone Disorders
 Consortium**

**Inherited Neuropathies
 Consortium**

**Chronic Graft Versus
 Host Disease**

**Nephrotic Syndrome
 Study Network**

**The Data Management and
 Coordinating Center**

**Rare Lung Diseases
 Consortium**



- Collaborative Clinical Research
- Centralized Data Coordination and Technology Development
- Public Resources and Education
- Training

**Urea Cycle Disorders
 Consortium**

**Lysosomal
 Disease Network**

**Brain Vascular
 Malformation Consortium**

**Rare Kidney
 Stone Consortium**

**Genetic Disorders of
 Mucociliary Clearance**

**Vasculitis Clinical
 Research Consortium**

**Consortium of Eosinophilic
 Gastrointestinal Disease Researchers**

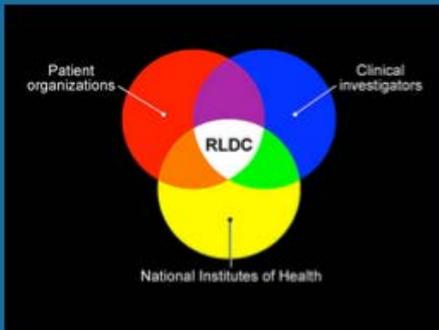
**Clinical Research in ALS & Related
 Disorders for Therapeutic Development**

**Autonomic Disorders
 Consortium**

**Sterol and Isoprenoid
 Diseases Consortium**

**Rett, MECP2 Duplications
 and Rett-Related
 Disorders Consortium**

ABOUT US



The RLDC is a unique collaboration among patient organizations, clinical investigators and the National Institutes of Health.

Our **Mission** is to conduct molecular pathway-driven clinical research to develop novel diagnostics and therapeutics for rare lung diseases, provide clinical research training, and to provide information about rare lung diseases to patients, physicians, researchers, and the public.

Goals

Geographic Distribution of RLDC Partners

Clinical Centers

Rare Lung Disease Clinical Network

Patient Leadership

Academic Leadership

NIH Leadership

Data Management

Diseases Under Current Investigation

Diseases of Interest

Lymphangioleiomyomatosis

Pulmonary Alveolar Proteinosis

Hermansky-Pudlak Syndrome



Lymphangioleiomyomatosis (LAM) is a rare, progressive lung disease that primarily affects women of childbearing age that is often fatal

RDCRN-Rare Lung Diseases Consortium (RLDC)

Development of sirolimus for LAM

- Sirolimus (aka rapamycin, Rapamune) is an mTOR inhibitor originally approved for prevention of transplant rejection
- LAM is associated with inappropriate activation of mTOR signaling, which regulates cellular growth and lymphangiogenesis
- RLDC conducted Multicenter International LAM Efficacy and Safety of Sirolimus (MILES) trial
 - PI: Frank McCormack, University of Cincinnati
 - Collaborative effort among RDCRN-RLDC, Pfizer, LAM Foundation
- FDA approved sirolimus for LAM in March 2015
 - *First drug approved by FDA for the treatment of this rare disease*

New Therapeutic Uses Program

- First round of projects

Disease	Academic Partner	Pharma Partner
Alzheimer's Disease	Yale	AstraZeneca
Alcoholism	U Rhode Island/NIAAA	Pfizer
Calcific Aortic Stenosis	Mayo Clinic	Sanofi
Duchenne Muscular Dystrophy	Kennedy Krieger/UWash	Sanofi
Lymphangi leiomyomatosis	Baylor	AstraZeneca
Peripheral Artery Disease	U Virginia	AstraZeneca
Smoking Cessation	VCU/Pittsburgh	Janssen
Schizophrenia (2)	Indiana U	Lilly
	Yale	Pfizer

- Translational Innovation Success Measures

- Does use of template agreements speed negotiation time?
- Does crowdsourcing of indications generate new ideas?
- Do studies result in new indications/approvals?

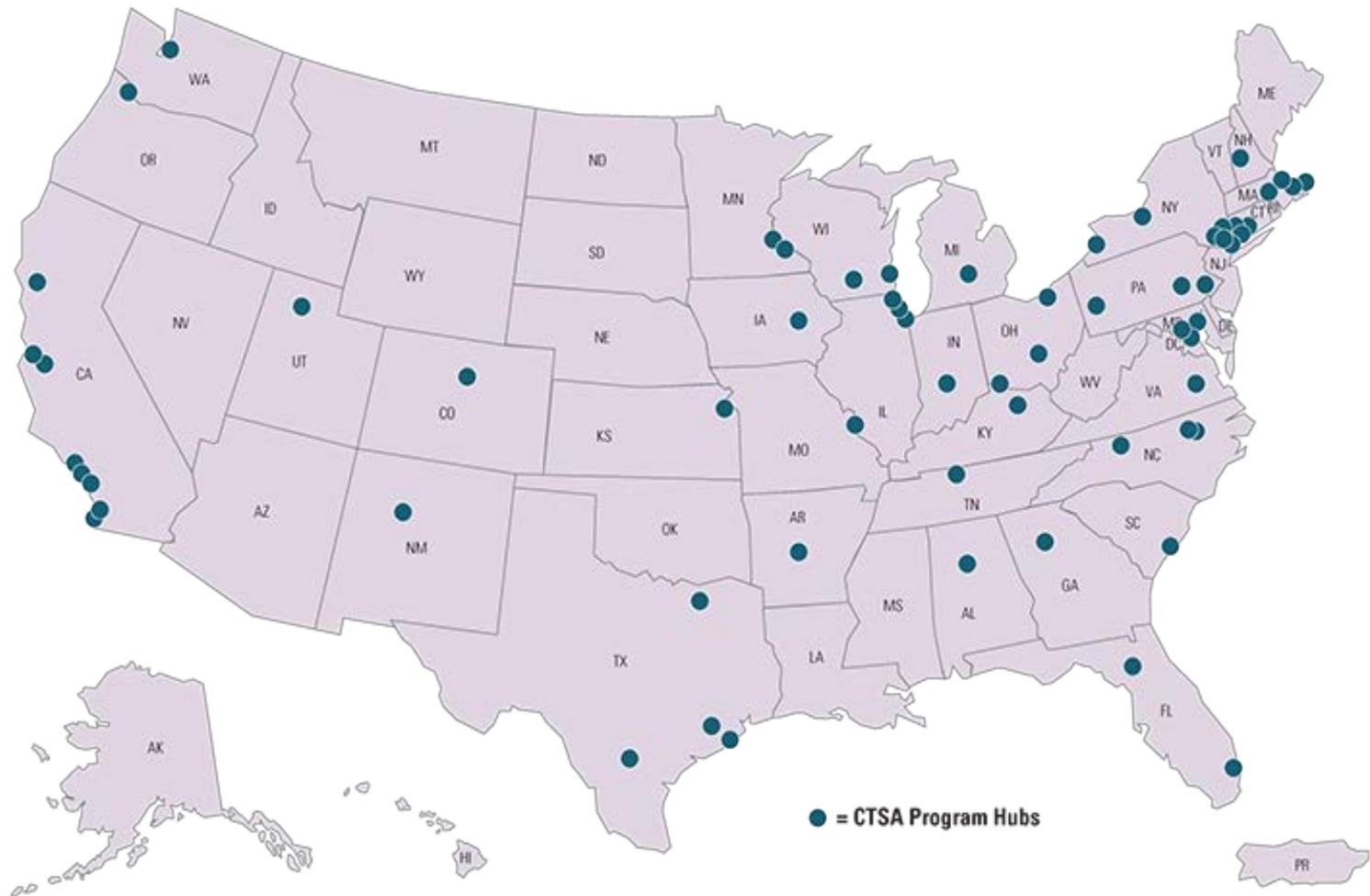
NTU project: AZD0530 (saracatinib) for LAM

- Src family kinase inhibitor originally developed for cancer
 - Also being tested in NTU for Alzheimer's Disease
- Src is activated in LAM cells
 - Contributes to oncogenic properties of LAM cells
- NTU LAM Phase 2a trial ongoing
 - PI: Tony Eissa (Baylor)
 - **Frank McCormack (University of Cincinnati)**
 - Stephen Rouss (Stanford University)
 - Daniel Dilling (Loyola University, Chicago)
 - Elizabeth Henske & Souheil El-Chemaly (Brigham and Women's Hospital)

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The NCATS Clinical and Translational Science Awards Program *CTSA Hubs*





Clinical Trials

Opportunity for Operational Innovation

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD

Deborah A. Zarin, MD

Judith M. Kramer, MD, MS

Rachel E. Sherman, MD, MPH

Laura H. Aberle, BSPH

Asba Tasneem, PhD

Context Recent reports highlight gaps between guideline recommendations and evidence from clinical trials that support strengthened reporting requirements for studies registered on ClinicalTrials.gov. This study provides a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of clinical trials registered in the ClinicalTrials.gov database.

ORIGINAL INVESTIGATION

HEALTH CARE REFORM

Characteristics of Oncology Clinical Trials

Insights From a Systematic Analysis of ClinicalTrials.gov

Asba Tasneem, PhD; John Horton, MS; Amy P. Abernethy, MD

The State of Infectious Diseases Clinical Trials: A Systematic Review of ClinicalTrials.gov

Neela D. Goswami^{1,9}, Christopher D. Pfeiffer^{2,3,9}, John R. Horton⁴, Karen Chiswell⁴, Asba Tasneem⁴, Ephraim L. Tsai

Portfolio of Clinical Research in Adult Cardiovascular Disease as Reflected in ClinicalTrials.gov

Karen P. Alexander, MD; David F. Kong, MD; Aijing Z. Starr, MS; Judith Kramer, MD; Karen Chiswell, PhD; Asba Tasneem, PhD; Robert M. Califf, MD

Using ClinicalTrials.gov to Understand the State of Clinical Research in Pulmonary, Critical Care, and Sleep Medicine

Jamie L. Todd^{1,2}, Kyle R. White², Karen Chiswell², Asba Tasneem², and So

¹Duke University Medical Center, Durham, North Carolina; and ²Duke Clinical Research

The Landscape of Clinical Trials in Nephrology: A Systematic Review of ClinicalTrials.gov

Jula K. Inrig, MD,^{1,2} Robert M. Califf, MD,¹ Asba Tasneem, PhD,¹ Radha K. Vegunta, MD,³ Christopher Molina, BS,⁴ John W. Stanifer, MD,¹ Karen Chiswell, PhD,¹ and Uptal D. Patel, MD¹

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Current Work Models

Small, frequently single-center studies

Inconsistent power, rigor

Poor enrollment

Suboptimal scientific impact

Operational Challenges

Research: Clinical parallel universes

Fragmented, duplicative infrastructure

Lack of collaborative efforts

Misaligned incentives

Using ClinicalTrials.gov to Understand the State of Infectious Diseases Research: A Systematic Review of ClinicalTrials.gov

Jamie L. Todd^{1,2}, Neela D. Goswami^{1,3}, Christopher D. Pfeiffer^{1,3}, John R. Horton⁴, Karen Chiswell⁴, Asba Tasneem⁴, Ephraim L. Tsai

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Asba Tasneem, PhD

The
System
Need
Eph

Using Clinical Trials in Pulmonary Medicine

Jamie L. Todd^{1,2},
¹Duke University Medical Center

Opportunity for Operational Innovation



Invent and deploy new approaches to clinical studies

John Horton, MS;

ease as

asneem, PhD;

Systematic

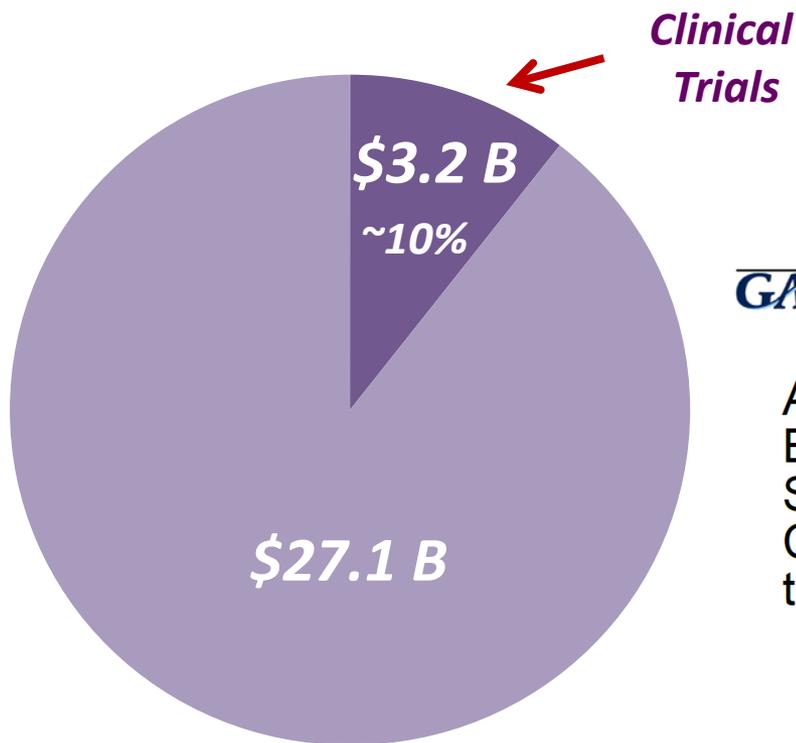
PhD,¹

Naana K. Veeramani, MD, Christopher Molina, BS, John W. Stanifer, MD,¹
Karen Chiswell, PhD,¹ and Uptal D. Patel, MD¹

NIH Clinical Trials

Opportunity for Operational Excellence

NIH Budget – FY 2015

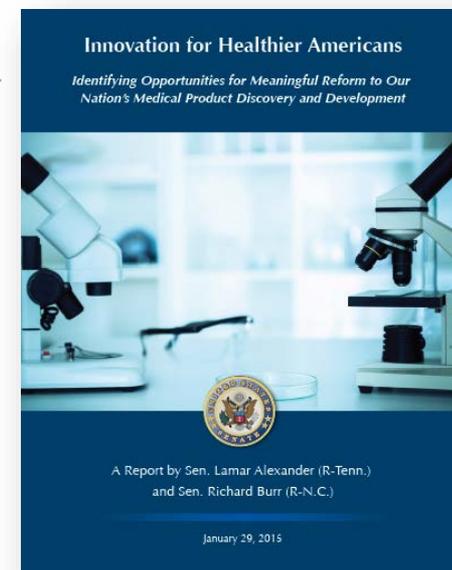


NIH tackles clinical trial shortcomings

The NIH is developing new tools, and overhauling its clinical trial funding system, to improve the stewardship of NIH-funded clinical trials

GAO United States Government Accountability Office
Report to Congressional Committees

Additional Data Would Enhance the Stewardship of Clinical Trials across the Agency



NIH Budget Office; Mullard A. Nature Reviews Drug Disc 2016; [GAO Report](#), 2016; [Innovation for Healthier Americans](#), 2015

NIH Clinical Trials

Opportunity for Operational Excellence

NIH Budget – FY 2015

Results of Current Work Models

Trials not finishing on time or within budget

Frequently large unobligated balances

Suboptimal return on research investments

Decreased public trust

Operational Challenge

*Enhance stewardship and
accountability of NIH clinical trials*



NIH Budget Office; Mullard A. Nature Reviews Drug Disc 2016; [GAO Report](#), 2016; [Innovation for Healthier Americans](#), 2015

NIH Clinical Trials

Opportunity for Operational Excellence

NIH Budget

Opportunity for Operational Excellence



**Execute trials
better, faster,
& more
cost-effectively**

al trial

cal trial funding system,

on for Healthier Americans
opportunities for Meaningful Reform to Our
ical Product Discovery and Development



Report by Sen. Lamar Alexander (R-Tenn.)
and Sen. Richard Burr (R-N.C.)

January 29, 2015

NIH Budget Office; Mullard A. Nature Reviews Drug Disc 2016; [GAO Report](#), 2016; [Innovation for Healthier Americans](#), 2015

Imagine ... A Clinical Trials Superhighway

A Network that Accelerates the Translation of Novel Interventions to Evidence Based Treatments

- Single IRB Reliance Model
- Master Contracts
- Harmonized Data Collection
- Streamlined Protocols
- Poised Research Teams
- Patient Engagement

su·per·high·way

[.sōōpər'hīwā, 'sōōpər.hīwā]

NOUN

1. **NORTH AMERICAN**
an expressway.
2. an extensive electronic network such as the Internet, used for the rapid transfer of information such as sound, video, and graphics.



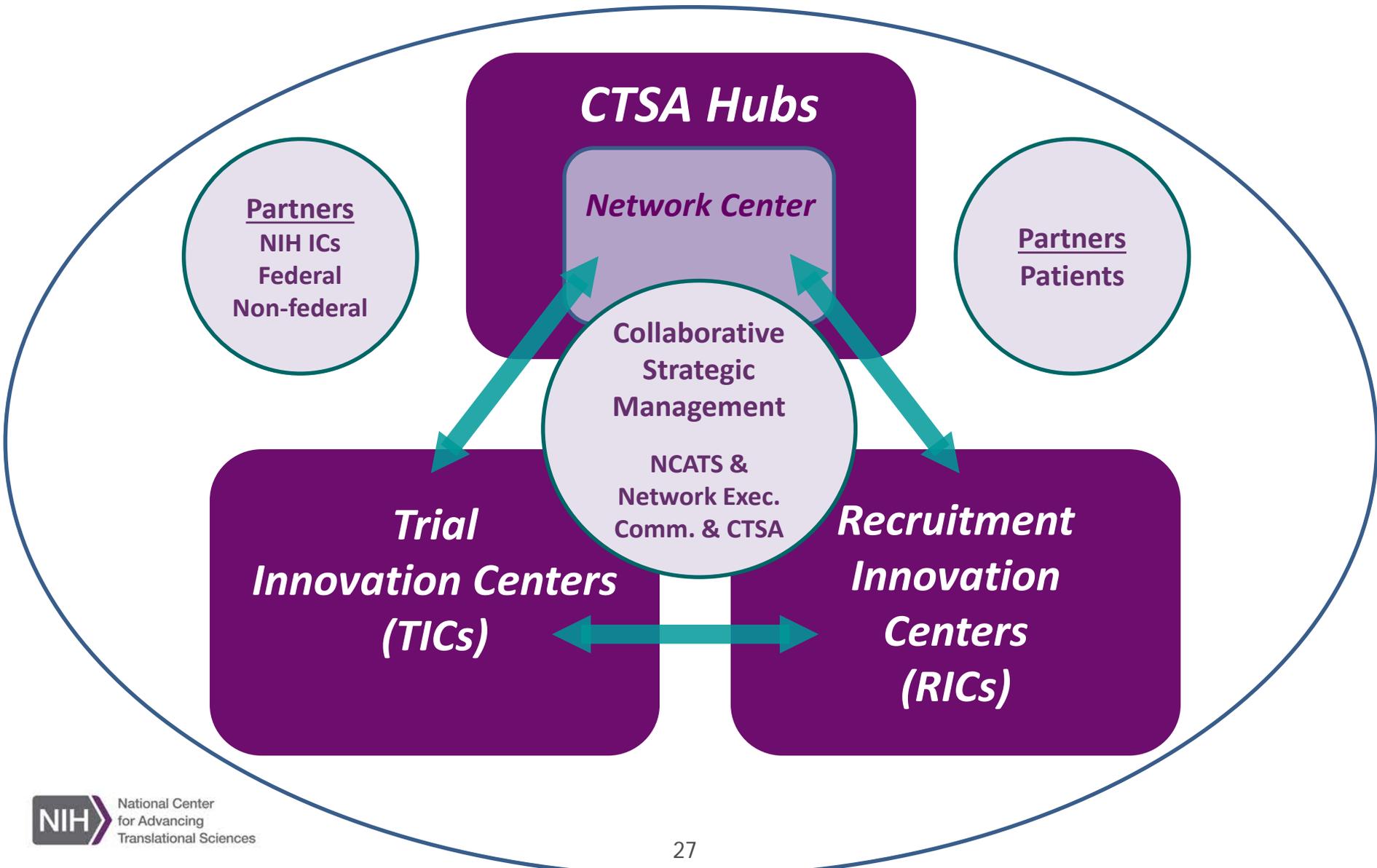
NCATS Trial Innovation Network

Mission

- Leverage the unmatched talent, expertise, and resources of the CTSA Program to transform clinical trials
 - Collaborative national network
 - Accelerate planning & implementation of high quality multi-center trials & studies
 - Provide more treatments to more patients
 - Improve public health
- Create a national laboratory to study, understand, and improve multi-center clinical trials

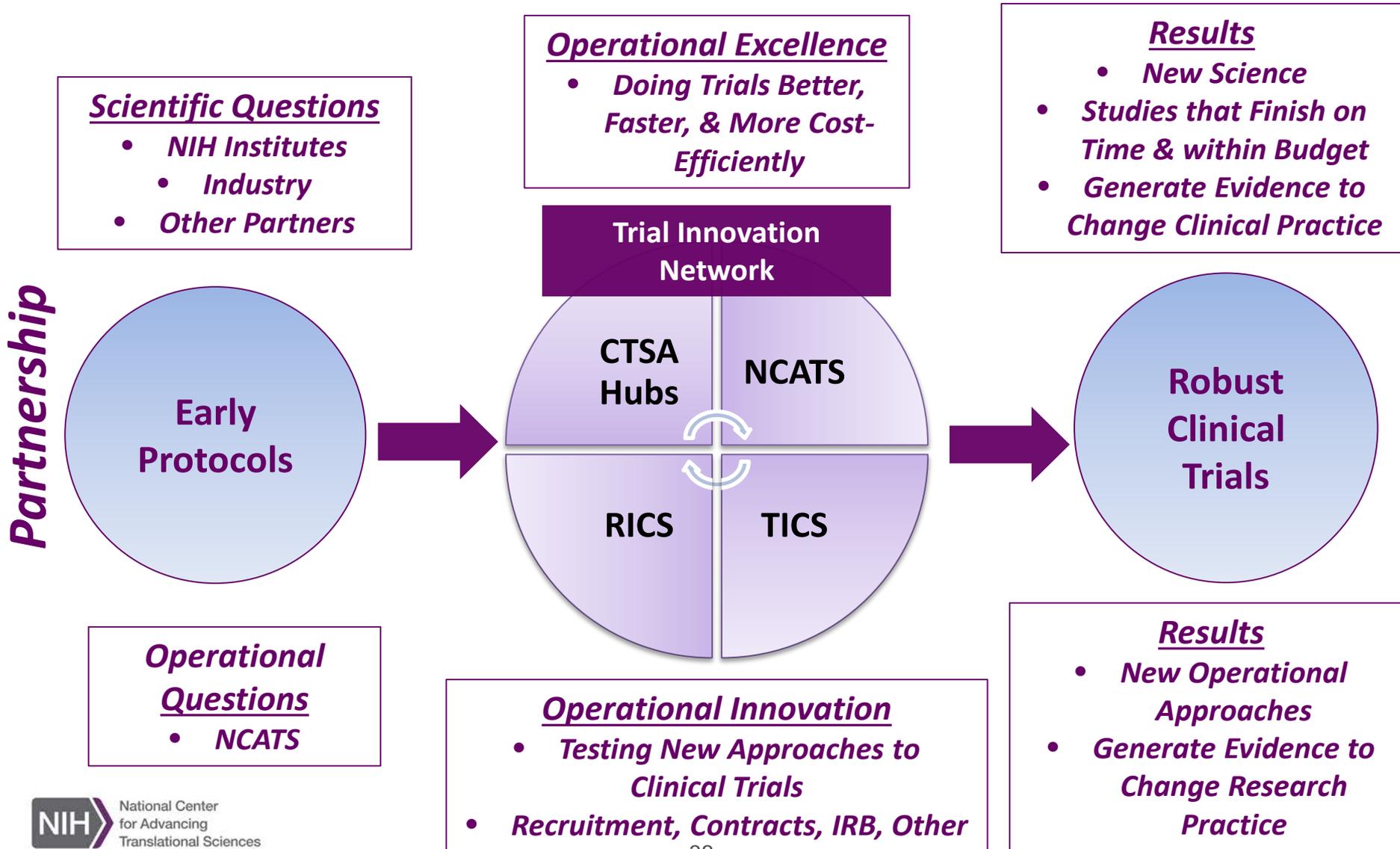
NCATS Trial Innovation Network

What Is It?



NCATS Trial Innovation Network

How Will It Work?



NCATS Trial Innovation Network

Value Proposition

- For Investigators
 - One-stop shopping to implement clinical trials
 - TICS & RICS - expertise in operational innovation & operational excellence
 - CTSA Hubs - broad expertise; large, diverse patient populations
 - More competitive clinical trials applications to NIH ICs, industry
- For NIH Institutes and Industry Partners
 - Trials completed on time and within budget
 - Shared NIH mission to innovate & transform clinical trials & optimize stewardship

NCATS Trial Innovation Network: *Implementation Timeline*

Collaborative Strategic Planning & Management



*Operationalize SMART IRB Model, Master
Contracts, Workflows, Other Strategic Priorities
in Demonstration Studies*

CAN Update



FY2016 Budget

- November 2, 2015: President signed Bipartisan Budget Act of 2015 (P.L. 114-74)
 - Raises Sequester caps for FY16 and FY17
- Continuing Resolutions: thru Dec. 11, Dec. 16, and Dec. 22
- December 18, 2015: President signed Consolidated Appropriations Act, 2016 (P.L. 114-113)
 - NIH: \$32 B (\$2 B increase over FY 15)
 - NCATS: \$685.4 M (\$52.7 M increase over FY 15)
 - CTSA: \$500 M
 - Includes \$22.7M increase to implement IOM recommendations, such as building network capacity (i.e. TICs, RICs, CCIAs)
 - CAN: \$25.8 M (\$16M increase over FY 15)

New CAN Program:

Biomedical Data Translator Program

- New signature initiative, utilizing OTA
- Informatics platform enabling interrogation of relationships across full spectrum of data types:
 - Disease names
 - Clinical signs & symptoms
 - Organ and cell pathology
 - Genomics
 - Drug effects
 - ...
- First stage: Team-based proposals to address architecture needs to build Translator and assess technical feasibility
- Timeline
 - Call for projects posted: April 29
 - Proposals received: June 1
 - In person presentations: June 29-30
 - Negotiations begin: July
 - Awards announced: September

Policy and Legislative Updates



FY 2017 Budget

- February 9, 2016: President releases FY 2017 budget
 - NCATS' request is \$685.417 million (same as FY16)
- Congressional Hearings
 - House: March 16, 2016
 - Witnesses: Drs. Collins, Fauci (NIAID), Hodes (NIA), Lowy (NCI), Volkow (NIDA)
 - Senate: April 7, 2016
 - Witnesses: Drs. Collins, **Austin**, Hodes (NIA), Koroshetz (NINDS), Lowy (NCI), and Volkow (NIDA)



Congressional Visit to NIH

- April 12, 2016 – Five Representatives visited NIH to learn more about NIH’s mission and programs
 - David Valadao (R-CA)
 - Susan Brooks (R-IN)
 - Robert Dold (R-IL)
 - Katherine Clark (D-MA)
 - Joseph Kennedy (D-MA)
- Met with Drs. Collins, Austin, Gibbons (NHLBI), and Volkow (NIDA)





RARE DISEASE DAY at NIH

Feb. 29, 2016 | National Institutes of Health, Bethesda, MD

#RDDNIH

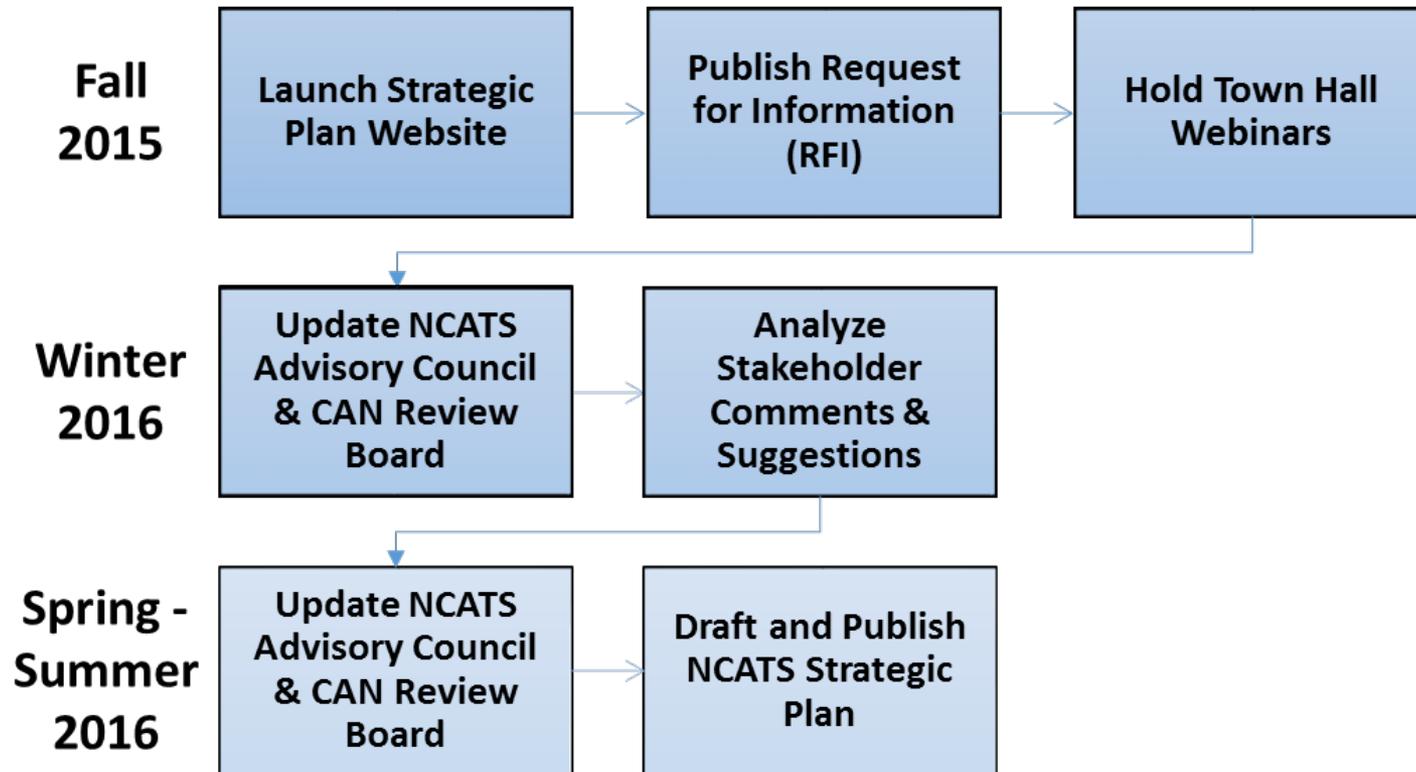
- Organized by NCATS and CC
- Featured speakers included
 - Rare Disease Congressional Caucus - 4 co-chairs
 - Senator Orrin Hatch (R-UT) - via video
 - Senator Amy Klobuchar (D-MN)
 - Rep. Leonard Lance (R-NJ)
 - Rep. Joseph Crowley (D-NY)
 - Sharon Terry, President & CEO, Genetic Alliance
 - Mike Porath, Founder & CEO, The Mighty
 - Martha Rinker, Vice President of Public Policy, National Organization of Rare Disorders (NORD)
- Reached >900 people
- View the videocast at <http://1.usa.gov/1Q8Exi9>



NCATS Strategic Plan

Updated Timeline

<https://ncats.nih.gov/strategicplan>

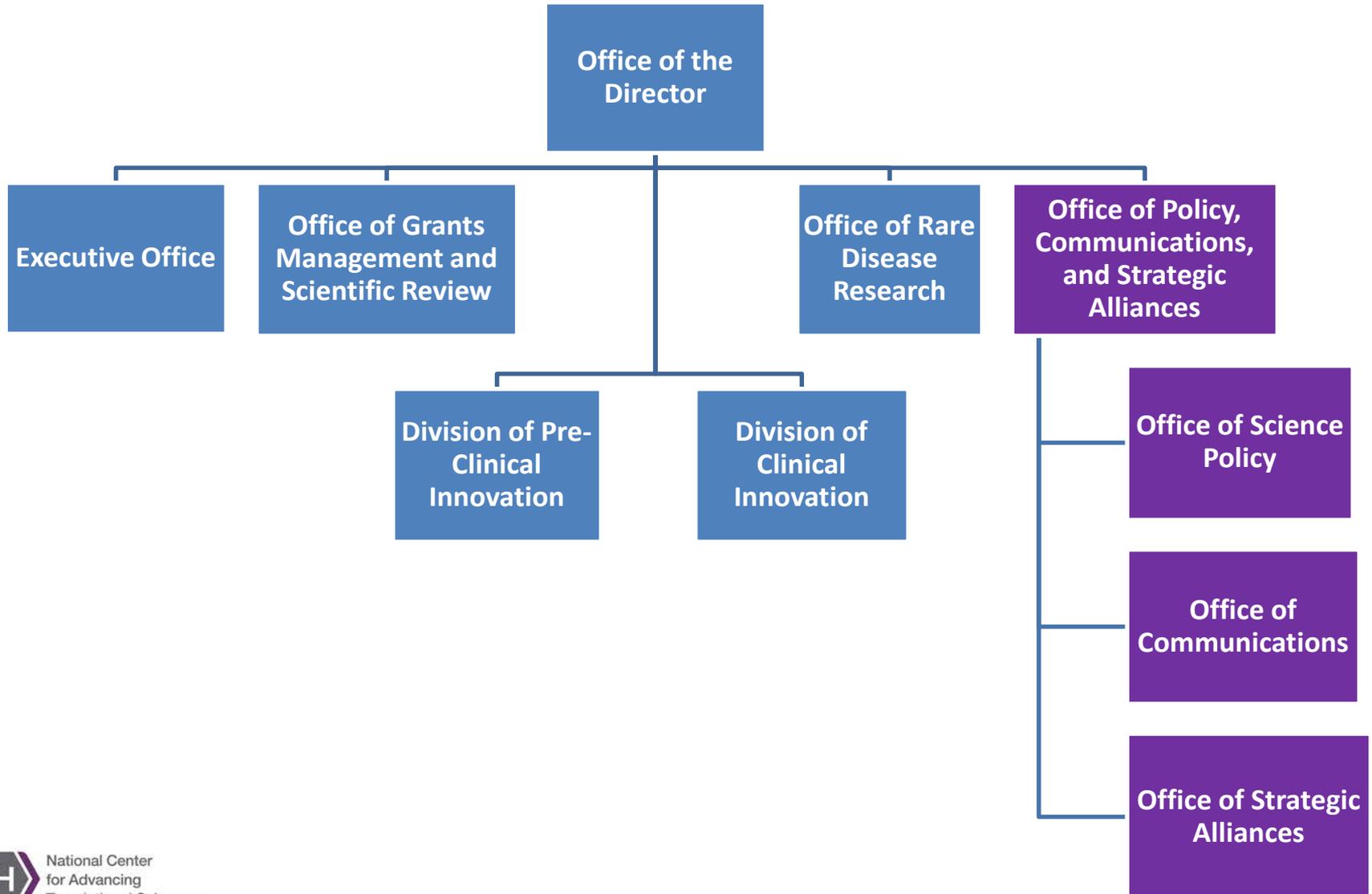


NCATS Office of Policy, Communications and Strategic Alliances

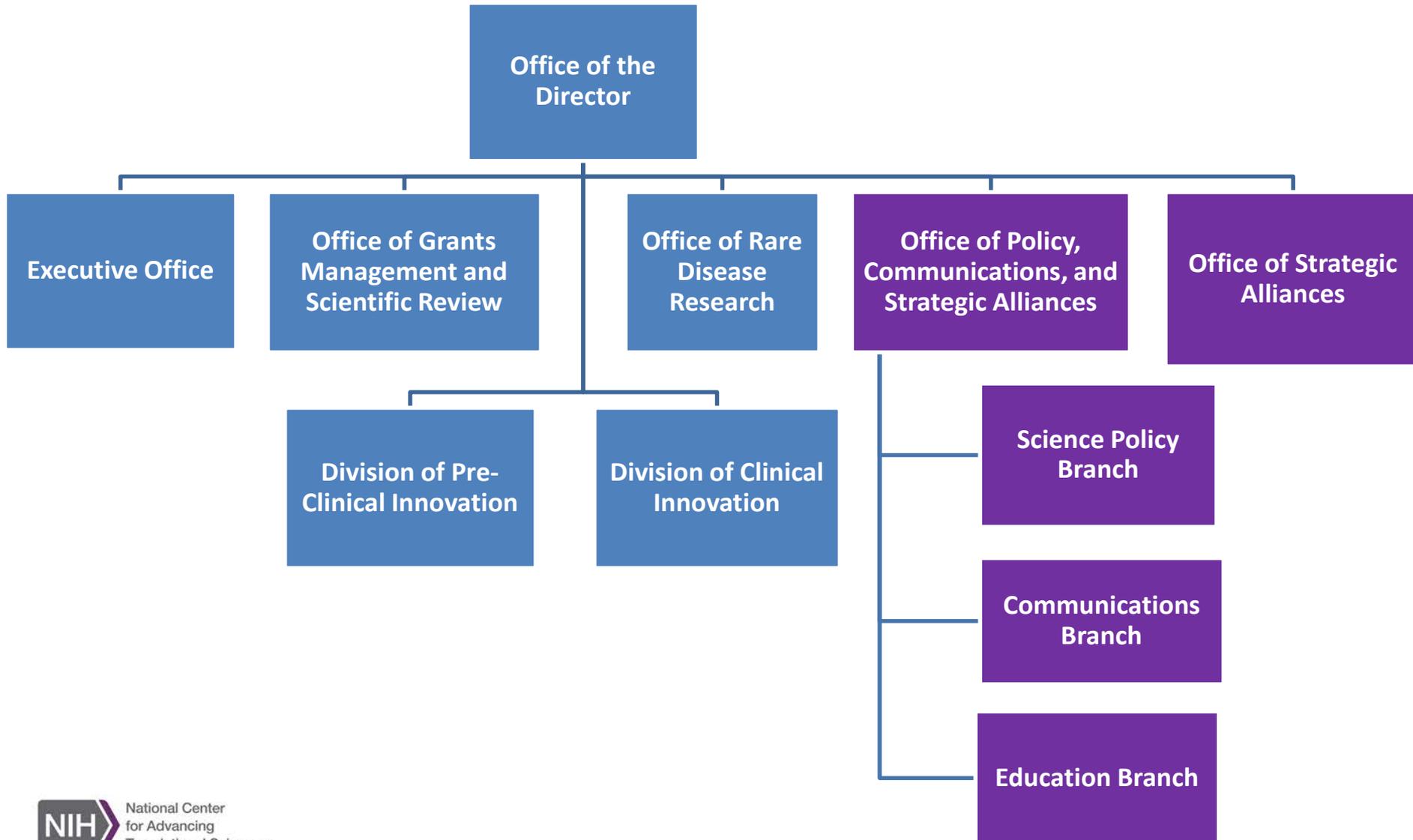
Proposed Changes

- Remove the Office of Strategic Alliances from the Policy and Communications Office
 - Better reflection of NCATS alignment and priorities
- Establish an Education Office
 - Ensure NCATS remains a leader in public education and community involvement related to translational science
- Both changes are budget neutral and will utilize existing resources within the Center

Existing OPCSA Structure



Proposed New Structure



Questions or Comments

- Please email NCATSReOrgComments@mail.nih.gov by *Thursday, June 30*
 - Include your name, and when applicable, your professional affiliation
- NCATS will respond to your email by *Friday, July 15*

Discussion