NIMH Strategic Research Priorities: Brain Research/Geriatric Translational Science

Jovier D. Evans, PhD
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National Institute of Mental Health
NIMH
The Funding Context: Recent Developments, Strategic Priorities and NIMH Funding Programs

Jovier D. Evans, PhD
AGENDA

- Update on Context / Developments at NIMH
- General NIMH Priorities and Organizational Structure
- Geriatrics and Aging Processes Research Branch: Our Organization and Particular Interests
- Services Research and Clinical Epidemiology Branch
THE CURRENT CONTEXT

- NIMH Strategic Plan – Being Updated
- Research Domain Criteria (RDoC) Project Continuing -- New RDoC Unit
- Intervention Research -- New NIMH Policy on Clinical Trials
- Leading Role in BRAIN Initiative
- FY 2015 Budget Remains Uncertain
National Institute of Mental Health

Vision
NIMH envisions a world in which mental illnesses are prevented and cured.

Mission
The mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.
Two Types of Translation

Bench  ↔  Bedside  ↔  Practice

Pathophysiology
Diagnostic tests
Biomarkers
New treatments

Clinical Trials Networks
Practical trials
Services research
Handoff for dissemination
NIMH Funding Divisions

- Division of Neuroscience & Basic Behavioral Science (DNBBS)
- Division of Translational Research (DTR)
- Division of AIDS Research (DAR)
- Division of Services and Interventions Research (DSIR)
ORGANIZATIONAL CHANGES

- Newly Merged Division of Translational Research (DTR); director search ongoing

- Geriatrics and Aging Processes Research Branch: New Name
Division of Translational Research (DTR)

- Adult Psychopathology and Psychosocial Intervention Research Branch
- Clinical Neuroscience Research Branch
- Developmental Trajectories of Mental Disorders Branch
- Geriatrics and Aging Processes Research Branch
- Neurobehavioral Mechanisms of Mental Disorders Branch
- Traumatic Stress Research Program
- Research Training and Career Development Program

Acting Director: Phil Wang, MD
Deputy Directors: Jill Heemskerk, PhD & Kathleen Anderson, PhD
The NIH Division of Adult Translational Research and Treatment Development (DTR) and the Division of Developmental Translational Research (DDTR) have merged to create the Division of Translational Research (DTR). This change is effective as of October 1, 2014. Accordingly, all information previously available on the DATR and DDTR webpages has been merged into this DTR page.

Overview

The DTR directs, plans, and supports programs of research and research training that translate knowledge from basic science to discover the etiology, pathophysiology, and trajectory of mental disorders and develops effective interventions for children and adults. DTR supports integrative, multidisciplinary research on the following areas: the phenotypic characterization and risk factors for psychiatric disorders; neurobehavioral mechanisms of psychopathology; trajectories of risk and resilience based on the interactive influences of genetics, brain development, environment, and experience; and design and testing of innovative psychosocial, psychopharmacologic, and somatic treatment interventions.

Areas of High Priority

- Delineate specific neural circuits contributing to one or more major mental disorders or subtypes of mental disorders.
- Develop, test, and validate biological markers (e.g., genetic, proteomic, imaging) for diagnosing or detecting risk/vulnerability, onset, progression, and/or severity of mental disorders to
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Overview

The Geriatrics and Aging Processes Research Branch supports programs of research, research mid-career development, and resource development in the etiology, pathophysiology and course of mental disorders of late life, the relationships between aging and mental disorders, the treatment and recovery of persons with aging-related disorders, and the prevention of these disorders and their consequences. The program encourages collaborative multidisciplinary research programs using the tools of neuroscience, cognitive and affective sciences, and social and behavioral sciences to facilitate the translation of basic science and preclinical research to clinical research. Studies may involve use of brain imaging, genetics and genomics, molecular biology and other evolving neuroscientific methods to investigate factors related to neuropsychiatric disorders of aging, the interaction of these disorders with the processes of aging and neurodevelopment/neurodegeneration, and their assessment and treatment. Disorders of interest include: Mood, anxiety, and personality disorders; psychotic disorders and schizophrenia; psychiatric syndromes and behavioral disturbances in Alzheimer's disease and related dementias; suicide; and neuroregulatory and homeostatic disorders associated with irregularities of sleep, eating, and the menstrual cycle.

Branch Chief

George T. Niederehe, Ph.D.
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301-443-1369, gniedere@nh.gov

Areas of Emphasis
Overview

This program supports studies of neurobiological factors and pathways that may influence the risk, presentation, course, and outcome of mental disorders in late life or in relation to the aging process. There is particular interest in supporting research consistent with NIMH’s emphasis on taking a dimensional and trans-diagnostic approach in studies of psychopathology, as articulated in the Institute’s Research Domain Criteria (RDoC) project. Relevant research typically uses the theories and tools of basic and translational neuroscience and related biological sciences to investigate the pathophysiology of mental disorders or dimensions of psychopathology, but also may involve other, more phenotypically oriented methods so as to examine the key variables across multiple levels of analysis. The integration of measures drawn from theories and research on the biological aging process so as to study the interplay of aging with mechanisms of psychopathology is highly encouraged. The studies supported may include middle-aged or older patients as well as older adults when there is a major focus on questions pertaining to the aging process, such as in research on the trajectories of mental disorders with aging.

Areas of Emphasis

Studies to understand how aging interacts with neurobiological mechanisms of psychopathology to mediate psychiatric symptom expression in older adults.

Studies to identify aging-related processes that may damage or protect brain structures involved in mental disorders or, conversely, that may be accelerated as a consequence of mental disorders.

Studies that identify key neurobiological aspects that shape and define the trajectories of mental disorders across the life course and extending into old age.

Research examining the interaction of genetic and environmental factors that may increase risk or be protective for the development of late-life mental disorders.

Contact

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Perspective: 2008 Strategic Plan

Strategic Objective 1:
• Promote Discovery in the Brain and Behavioral Sciences to Fuel Research on the Causes of Mental Disorders

Strategic Objective 2:
• Chart Mental Illness Trajectories to Determine When, Where, and How to Intervene

Strategic Objective 3:
• Develop New and Better Interventions that Incorporate the Diverse Needs and Circumstances of People with Mental Illnesses

Strategic Objective 4:
• Strengthen the Public Health Impact of NIMH-Supported Research
NIMH Strategic Plan: Goal 1.4

• Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures.”

• Identify fundamental behavioral components that may span multiple disorders (e.g., executive function, affect regulation)

• Develop reliable and valid measures of these fundamental components for use in basic and clinical studies

• Determine the full range of variation, from normal to abnormal

• Integrate genetic, neurobiological, behavioral, environmental, and experiential components
Research Domain Criteria (RDoC) Project

Framework to guide classification for research studies; based on 3 guiding principles:

- RDoC is conceived as a dimensional system spanning the range from normal to abnormal.
- RDoC is agnostic regarding current disorder categories.
- Will involve several different units of analysis for examining constructs for study (imaging, physiology, behavioral observations, self-reported symptoms).

Toward Precision Medicine in Psychiatry: Research Domain Criteria (RDoC)

IOM, “Toward Precision Medicine”, Nov. 2011

Insel et al., AJP, 2010
RDoC Summary Points

- Translational approach linking mechanisms and symptoms
- Dimensional approach involving multiple levels of analysis
- Framework to study mechanisms that cut across traditional diagnostic categories
- Goals: (1) Integration of biological and psychological constructs; (2) New treatment targets
- Increasing share of NIMH-funded clinical research
- Appropriate for psychopathology research, not most intervention or services research
Adaptation to Change

**Ecosystem**

- Increasing Public Health Burden
- BRAIN Initiative
- Changing Mental Health Care Landscape
- Technology
- Comparative Effectiveness
- New Sources of Research Support and Collaboration
- Citizen-centered Science
Cross-cutting Themes

Cross-cutting Research Themes

- Transforming Diagnostics
- Accelerating Therapeutics
- Digital Enterprise
- Preemptive Medicine
- Global Mental Health
- Mental Health Disparities
- Partnerships
- Investing in the Future

http://www.drn.nihr.ac.uk/em/experimental-medicine-studies.aspx
http://wdwprepschool.com/painted-medicine-bottles-cute-coin-containers/
Strategic Research Priorities

The NIMH Strategic Plan provides a framework to focus and accelerate mental health research so that breakthroughs in science become breakthroughs that can tangibly improve mental healthcare and the lives of people living with and affected by mental illness. The four objectives of the Plan describe the continuum of mental health research, ranging from understanding basic pathophysiology, to defining the trajectories of mental illness, to developing innovative treatment and prevention strategies, to ensuring public health impact.

For the Institute to most effectively pursue its mission of transforming the understanding and treatment of mental illnesses, we request that all new and competing applications be targeted to the research priority areas within the four objectives of the Strategic Plan. We invite the scientific community to apply for funding in these priority areas using the NIMH Parent Announcements for Investigator-Initiated Applications, NIMH-Sponsored Program Announcements and NIMH-Participating Program Announcements, and NIMH-Sponsored Requests for Applications and NIMH-Participating Requests for Applications. By using the Plan to guide funding decisions, we hope to accelerate the translation of research findings into public health impact.

NIMH is also committed to supporting research that will address the public health challenge presented by HIV/AIDS. The Institute’s HIV/AIDS program will continue to be guided by the Trans-NIH Plan for HIV-Related Research coordinated by the NIH Office of AIDS Research.

**Strategic Objective 1**: Promote Discovery in the Brain and Behavioral Sciences to Fuel Research on the Causes of Mental Disorders

**Strategic Objective 2**: Chart Mental Illness Trajectories to Determine When, Where, and How to Intervene

**Strategic Objective 3**: Develop New and Better Interventions that incorporate the Diverse
Transforming the Culture of Discovery: Harnessing the Power of the Data

- Data Standardization
- Data Integration
- Data Sharing
- Crowdsourcing

NDAR National Database for Autism Research
Serving the autism research community

NITRC The source for neuroimaging tools and resources

Psychiatric Genomics Consortium
NIMH, Experimental Medicine, and Clinical Trials Research: New Directions and Opportunities

Jovier D. Evans, Ph.D.
Division of Translational Research

Denise Juliano-Bult, M.S.W.
Division of Services & Intervention Research
NIMH
I. Background: NIMH Strategy for Support of Clinical Trials

II. New Funding Opportunity Announcements (FOAs) for Intervention Development and Confirmatory Efficacy Trials
   I. U01
   II. R21/R33
   III. R33
   IV. R01
The need:

The goal is better outcomes, measured as improved real-world functioning as well as reduced symptoms. (Insel, Director’s blog, February 2014)

The challenge:

- Intervention development is slow, costly, and high-risk
- Evidence from animal research is often not predictive of response in patients
- Large effect sizes from small pilot studies often don’t hold up in fully-powered efficacy trials
- How to prioritize investments in new or improved therapies?
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

See more at:
August 2010 NAMHC Report, “From Discovery to Cure”

- Capitalize on findings of factors related to etiology or maintenance of mental disorders
- Identify potentially mutable factors as targets for novel interventions
- Move quickly into humans for proof-of-concept studies
  - Objective and reliable measures of target engagement
  - Demonstration of adequate dose or intensity
- Interventions as “probes” to inform about mechanisms of disease and treatment effects
- Prioritize interventions with potential for major—not incremental—impact on unmet therapeutic need
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Clinical Trial Pipeline and New NIMH Funding Initiatives

FOAs Apply to:
- Preventive, Therapeutic, & Services Interventions.
- Pharmacologic, behavioral/psychosocial, and device-based approaches.
New NIMH Policy on Clinical Trials Research

- Moving to an “Experimental Medicine”/ “Experimental Therapeutics” model for all trials research

- No longer accept clinical trials applications through the standard R01, R21 or R03 grant mechanisms (i.e., under their “parent” PAs); must apply under NIMH’s specific clinical trial FOAs

- There are some exceptions (e.g., biomarker or “probe” studies, certain joint PAs with other institutes)

- Same principles and priorities apply to other grant mechanisms if there is a clinical trial component (e.g., K award projects, SBIR, AREA)
NEW CLINICAL TRIALS WEB PAGE

Clinical Trials Funding Opportunity Announcements

Applicant Information

NIMH has released several funding opportunity announcements (FOAs) addressing a new direction for the clinical trials research that we support. Collectively, these opportunities define NIMH's focus on an experimental medicine approach when supporting clinical trial research. This shift in focus aims to accelerate treatment development and bring improved therapies to patients with mental disorders.

Currently available funding opportunity announcements include:

Exploratory Clinical Trials of Novel Interventions for Mental Disorders

These FOAs aim to support the efficient pilot testing of novel interventions for mental disorders in adults and children through an experimental therapeutics approach. Topic must be designed so that results, whether positive or negative, have potential to inform future grant applications.
NIMH Clinical Trials Funding Opportunity Announcements - Applicant FAQs

[Expand All]

1. What is different about the new NIMH-issued Funding Opportunity Announcements (FOAs) seeking Clinical Trials? What is an "experimental therapeutic approach" to designing a clinical study?

2. What is a target?

3. How is "target engagement" best measured?

4. What is the intent of the U01 announcement?

5. What is the intent of the R21/R33 FOA?

6. What is the intent of the R01 FOA for Effectiveness Research?

7. What is the intent of the R34 FOA for Effectiveness and Services Research?

8. How do I decide which FOA to apply for?

9. I want to apply for funding to test the efficacy of a novel intervention for which there is evidence of target engagement. Pilot studies provide evidence of feasibility, acceptability, and a signal for efficacy, but there is a need for a confirmatory, adequately powered clinical trial. I do not see a RFA that would support this type of trial. Should I use the parent R01 FOA?

10. Where are applications submitted in response to these FOAs reviewed?

11. My trial does not fit any of these FOAs. Can I just submit an application to the parent NIH FOAs [PA-13-302 (R01) and PA-13-303 (R21)]?

12. Which types of clinical studies involving a clinical trial component may be submitted to the parent R01 or R21 announcements, as outlined in NOT-MH-14-007?

13. Are multi-site trials allowed?

14. Are multi-site trials expected to have a single Institutional Review Board (IRB)? Who will organize a single IRB?

15. Is it necessary to register all clinical trials with clinicaltrials.gov?

16. Is data sharing encouraged? When are investigators expected to share the data?
Primary Features of the New Approach

- Experimental medicine approach
- Emphasis on mechanisms
- Target engagement (biological, functional, clinical, service system)
- Emphasis on dosage (vis-à-vis the target, not the outcome)
- Make “Go – No Go” decisions about the target/intervention
- Fast-fail; learn something from failed trials
- RDoC or similar dimensions as treatment indications
What Is a “Target?”

- “Hypothesized mechanism of action”

- Variable thought to be an underlying factor/mechanism in a disorder/service delivery challenge that the intervention is hypothesized to act on and change

- Thus, need evidence showing the variable’s implication in the disorder/challenge of interest

- If the experimental therapeutics shows that change ensues when the target is manipulated, then can attribute the intervention’s benefits to this “mechanism of action”
Attention Bias as a Target in CBT

- Directly manipulating attention bias reduces anxiety.

Amir et al. (2009)
Proof of Concept in Treatment Development

Ligand

PET Imaging

Receptor

Evoked Potential – Efficiency/Sensitivity

Eye Tracking - Attention

Mechanism of Action

Improvement in Social Function
Proof of Concept in Treatment Development

Eye Tracking - Attention

Social Attention Training

Evoked Potential – Efficiency/Sensitivity

Mechanism of Action

Improvement in Social Function
Special Features of the Clinical Trials Policy

- 3 submission dates for the RFAs
- Discontinued the previous R34 & collaborative R34 pilot mechanisms (used to develop interventions prior to efficacy trials)
- Now have the R21/R33 and R33 mechanisms for pre-efficacy pilot work, and R34 exclusively for effectiveness/services pilot work
- Data Sharing Expectation for NIMH-funded Clinical Trials (NOT-MH-14-015); NIMH will establish a National Database for Clinical Trials Related to Mental Illness (NDCT); data deposit expected
Transforming the Culture of Discovery: Harnessing the Power of the Data

- Data Standardization
- Data Integration
- Data Sharing
- Crowdsourcing

Psychiatric Genomics Consortium
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Clinical Trial Pipeline and New NIMH Funding Initiatives

- **First in Human (Drugs)**
  - Exploratory Experimental Therapeutics
    - Target engagement
  - Companion R33
    - Exploratory Clinical Trials of Novel Interventions for Mental Disorders
  - U01
    - First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders

- **Confirmatory Efficacy**
  - R21/R33
    - Exploratory Clinical Trials of Novel Interventions for Mental Disorders
  - R01
    - Confirmatory Efficacy Trials of Non-Pharmacological Interventions

- **Effectiveness (Prevention, Treatment, Services)**
  - R34
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  - Collaborative R01
    - Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions
  - R01
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First in Human and Early Stage Clinical Trials of Novel Investigational Drugs or Devices for Psychiatric Disorders (U01)

• **Goals:**
  - Build efficient, *mechanism-based* therapeutic development programs
  - Rapid collection of data to "de-risk" novel investigational drugs, novel drugs for use in pediatric populations, devices or combination treatments
  - Attract private funding for further clinical development as FDA-approved treatments.

• **U01 Cooperative Agreements:**
  - NIMH will facilitate collaborative partnerships between biomedical researchers and biotechnology or industry researchers
  - I.P., patent life, necessitate moving quickly
  - NIMH staff provide support/resources
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**National Institute of Mental Health**
All types of interventions supported: drug, psychotherapeutic, cognitive, devices

- **R21/R33 Supports Phased POC and pilot studies**
  - R21 up to 2 years to test target engagement
  - R33 up to 3 years to confirm target engagement and relate change in target to change in clinical symptoms
  - R21/R33: program review of milestones determines go/no-go for R33

- **R21/R33 or stand-alone R33?**
  - Is there preliminary data of target engagement/dose/feasibility?
  - Can you stage the study to manage risk?
  - How much time do you need?
**Goal**: To build more efficient, mechanism-based therapeutic development programs (similar to U01)

- **Not for First-in-Human; not for testing novel drugs in pediatric populations**
- **Alternative to the U01 when:**
  - The agent is *specific/selective* in order to test target engagement; and
  - Hypothesizing and testing a specific mechanism of treatment effect; but
  - Not on a regulatory path, e.g., using as a tool compound or probe to test target engagement and explore biology; do not need the close partnership with industry
Exploratory Clinical Trials (R21/R33 and R33) for Cognitive and Psychotherapeutic Interventions

• **Basic Principles:**
  - Milestone-driven testing and validation of a novel intervention’s mechanism of action, assess feasibility and acceptability, optimal exposure/dose (POC)
  - Refine intervention and methods, relate changes in the targeted mechanism to clinical effects (*pilot study*)

• Target = known to be associated with symptoms; mediator or hypothesized mechanism of action

• Target Engagement = Test of the intervention’s effect on the mechanism

• Dose = intensity, number of sessions needed to see change in objective measures of target engagement
Clinical Trial Pipeline & New NIMH Funding Initiatives

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Confirmatory Efficacy Clinical Trials of Non-Pharmacological Interventions (R01)

- Therapeutic and preventive interventions; adults and children
- Behavioral, cognitive, psychotherapeutic, device-based

- Pre-requisites (from preliminary studies)
  - Unmet therapeutic need
  - Target engagement and validation demonstrated
  - Evidence of adequate dose
  - Preliminary efficacy signal
  - Potential for high impact
Requirements:

- Powered for clinical efficacy
- An appropriately-justified comparison condition
- Use of valid, reliable measures of symptoms and real-world functioning
- Replicate target engagement/validation
- Measurement of treatment fidelity
- Plan to develop/evaluate mediators, moderators, early indicators of effect
- Inform the next stage of intervention development (e.g., effectiveness trial, implementation research, or dissemination)
Clinical Trial Pipeline and New NIMH Funding Initiatives

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National Institute of Mental Health
FOAs: Effectiveness of Treatment, Preventive, & Services Interventions

- RFA-MH-15-320: Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (R01)

- RFA-MH-15-325: Clinical Trials to Test the Effectiveness of Treatment, Preventive, and Services Interventions (Collaborative R01)

• The FOAs support trials research in *community and practice settings* that tests the effectiveness of treatment, preventive, and services strategies *for which there is already evidence of efficacy*

• The intervention research covered under these announcements is explicitly focused on *practice-relevant questions*
Preventive and Therapeutic Interventions
- Pharmacologic, Psychosocial (psychotherapeutic & behavioral), somatic, & combined interventions
- Symptomatic and functional outcomes

Services Interventions:
- Patient-, Provider-, Organizational-, or Systems-level Interventions
- Service Access, Engagement, Quality, Coordination, Delivery, Dissemination, Implementation, Sustainability of Effective Interventions
R34: Pilot Effectiveness or Services Studies

- Refine or optimize interventions with demonstrated efficacy to move into testing with broader target populations or in community practice settings.

- Evaluate feasibility, tolerability, acceptability, safety; obtain preliminary data to justify a larger-scale effectiveness trial.

- Studies should test whether the intervention engages the mechanism that is presumed to underlie the intervention effects.
  - Mechanism = what accounts for changes in clinical/functional outcomes, changes in provider behavior, etc.
R01/Collaborative R01:

- Studies designed to determine an intervention’s effectiveness in comparison to usual care or alternative interventions/services
- Studies also test predictors and moderators of effectiveness and the mechanisms that underlie clinical benefit.

Collaborative R01:

- Used when two or more sites are needed to complete the study, to
  - expedite enrollment (e.g., low base rate conditions)
  - enhance geographic/racial/ethnic diversity and generalizability
  - capitalize on complementary cross-site expertise
**KEY Emphases**

**IMPACT**

*Demonstrate the magnitude of likely improvements in efficacy, safety/tolerability, value and efficiency, or dissemination potential, as compared to existing approaches.*

- **TARGET ENGAGEMENT/MECHANISMS**
  
  *The study must explicitly address whether the intervention engages the mechanism that is presumed to underlie the intervention effects.*

- **EMPIRICAL JUSTIFICATION for ADAPTATIONS**
  
  *Adaptations or augmentations of efficacious interventions should only be undertaken if there is an empirical rationale for the adaptation target and for the corresponding mechanism by which the adapted intervention is expected to substantially enhance outcomes.*
IMPACT

- **TARGET ENGAGEMENT** – *Address whether the intervention engages the mechanism presumed influence the intervention effects.*
  - Why?
    - Understand disease/change mechanisms,
    - Confirm that change mechanisms in efficacy studies are operative in the effectiveness context, and
    - Facilitate the interpretation of trial results
  - How?
    - Use the most direct and objective measures feasible in the effectiveness context

- **EMPIRICAL JUSTIFICATION** for ADAPTATIONS
KEY Emphases

- **IMPACT**
  
  The application must justify the potential impact of the proposed intervention/services models on practice and public health in terms of the magnitude of likely improvements in efficacy, safety/tolerability, value and efficiency, or dissemination potential, as compared to existing approaches.

- **TARGET ENGAGEMENT/MECHANISMS**
  
  The study must explicitly address whether the intervention engages the mechanism that is presumed to underlie the intervention effects.

**EMPIRICAL JUSTIFICATION for ADAPTATIONS**

Adaptations of efficacious interventions are supported only when there is an empirical rationale for a different target or mechanism by which the adapted intervention is expected to substantially enhance outcomes.
Which FOA to apply for?

- **U01** for drugs and devices
  - Must be used for First in Human and First in Children testing
  - Dose finding must be completed in 1 year

- **R21/R33** and **R33** have the same goal: Target Engagement proof of concept

- Choose FOA based on:
  - Time required to generate PoC (3, 4 or 5 years, depends on preliminary data)
  - Is there a clear interim go/no go break to manage risk? If so, use R21/R33

- **R34** is for pilot effectiveness research and pilot services studies

- **Confirmatory efficacy RO1** is for nonpharmacological interventions.

- **R01** is to establish effectiveness of an intervention with established efficacy

- **Collaborative R01** to be used to improve efficiency/expand samples
Studies considered nonresponsive

- Studies without mechanism-driven dose finding/target engagement, e.g., focused on feasibility, efficacy, effect size.

- “Nutraceuticals” and other multi-target drugs (possible exception if target engagement measures are not ambiguous).

- Well-studied mechanisms of action (e.g., serotonin reuptake for depression).

- Adaptations of known interventions for a sub-population without empirical evidence of need for adaptation.
Studies considered nonresponsive

- Applications that fail to justify the potential impact of the proposed intervention/services models on practice and public health

- Trials that randomize large numbers of participants in pursuit of incremental gains in effect size, (espec. without attention to response modifiers that can be used to personalize care)

- Studies of preventive-, therapeutic-, or services-interventions with limited potential for broad implementation in community practice settings.

- Trials using patented medications that lack superior efficacy or safety relative to currently available off-patent medications.
Take Home Messages

• Be clear about where along the treatment development spectrum you will focus
  - the priorities/methodologies vary significantly along that spectrum.

• The NIMH emphasis is on early-stage development of innovative treatments

• For early-phase intervention research (Type 1 translation), important to collaborate with basic scientists
Take Home Messages-2

• Consider the eventual dissemination/implementation/sustainment of your intervention in the community:
  ■ What providers are available in what settings
  ■ Feasibility of scale up for widespread usage
  ■ Prospects for reimbursement, etc.
  ■ Who’s input should you be getting now?

• Talk with Program staff early
Contact Information

Geriatrics & Aging Processes Research Branch (301-443-1369)

• Psychosocial Intervention and Aging
  ➢ George Niederehe, PhD (301-443-9123; gniedere@mail.nih.gov)

• Pharmacologic and Somatic Intervention and Aging
  ➢ Jovier D. Evans, PhD (301-443-6328; jevans1@mail.nih.gov)

Services Research & Clinical Epi Research Branch

➢ Denise Juliano-Bult, M.S.W. (301-443-1638; djuliano@mail.nih.gov)
Services Research & Clinical Epidemiology Branch (SRCEB)

• Develop a knowledge base to increase the uptake of evidence based treatments and services in diverse community settings

• Identify and test factors in community services that can optimize functioning and sustain community integration

• Understand how traits of individuals, families, providers, organizations, and socio-cultural environments affect help-seeking, provision of care, quality of care, and outcomes

• Enhance research capacity through strategic partnerships, community engagement, and information technologies
• Child and Adolescent Services
• Disparities in Mental Health Services
• Dissemination and Implementation
• Financing and Managed Care
• Methodology Development
• Primary Care
• Systems of Care
• Research on the role of organizational structures, cultures, and patterns of communication in maximizing access, appropriateness of care and improve outcomes for persons with mental illness.(within and across systems)

• Research on the delivery, access, and effectiveness of services for adults with autism.

• Research on innovative services for people with co-occurring substance use and mental disorders and elimination of structural barriers that preclude appropriate high quality care.

Contact
• Denise M. Juliano-Bult, M.S.W.
  301-443-3364, djuliano@mail.nih.gov
Flexible multi-disease mgt strategies that PC can use with depression comorbid with chronic medical conditions

Use of paraprofessionals to deliver EBPs in low-resource settings

Training PC staff to optimize detection, tx, and care management

Improving the medical health status of persons with SMI

Brief interventions to increase adherence to EB mental health treatments

Implementing decision support systems to improve quality of MH care

Use of technology to improve mh outcomes

Contact

Susan T. Azrin, PhD
301-443-3267, Susan.Azrin@nih.gov
• Development and testing effectiveness of innovative dissemination strategies (such as new technologies, use of multimedia approaches)

• Development of novel methods development to address the multidimensional components of dissemination and implementation (consumer, practitioner, clinic, organization, state)

• Implementation studies addressing organizational outcomes around sustainability

Contact

• Denise Pintello, PhD, MSW
  303-451-1481, Denise.Pintello@nih.gov
Strengthen Public Health Impact of NIMH Research

**Strategy 4.1**: Improve the efficiency and effectiveness of existing mental health services through research

**Strategy 4.2**: Establish comprehensive research-practice partnerships to improve dissemination, implementation, and continuous improvement of evidence-based mental health services

**Strategy 4.3**: Develop innovative service delivery models to dramatically improve outcomes of mental health services received in diverse communities and populations

**Strategy 4.4**: Develop new capacity for research that evaluates the public health impact of mental health services innovations
IMPACT

TARGET ENGAGEMENT – Address whether the intervention engages the mechanism presumed influence the intervention effects.

Why?
- Understand disease/change mechanisms,
- Confirm that change mechanisms in efficacy studies are operative in the effectiveness context, and
- Facilitate the interpretation of trial results

How?
- Use the most direct and objective measures feasible in the effectiveness context

EMPIRICAL JUSTIFICATION for ADAPTATIONS
Contact Information

Services Research & Clinical Epi Research Branch

- Denise Juliano-Bult, M.S.W. (301-443-1638; djuliano@mail.nih.gov)
QUESTIONS
Priorities for Aging Research at NIMH: Overview of the Geriatrics & Aging Processes Branch

Jovier D. Evans, PhD
Division of Translational Research
Geriatrics and Aging Processes Research Branch
Geriatrics and Aging Processes
Research Branch

**Emphases:**
- etiology and pathophysiology
- risk and protective factors
- comorbidities
- assessment
- treatment and recovery; prevention

**Research Tools:**
- molecular biology and neuroscience
- cognitive sciences
- social and behavioral sciences
- brain imaging
- pharmacogenetics
- genomics, proteomics, metabolomics
Geriatrics and Aging Processes Branch: Intervention Research Programs

- Behavioral Science of Mental Disorders and Aging
- Neuroscience of Mental Disorders and Aging
- Psychosocial Intervention and Aging
- Pharmacologic and Somatic Intervention and Aging
Geriatric Intervention Research

- Observational and experimental outcome studies:
  - pharmacologic and somatic interventions
  - behavioral and psychosocial interventions
  - algorithms for combining or sequencing multiple interventions

- Treatment, prevention, or rehabilitation

- Acute, continuation, or maintenance phases

- Primary outcomes can include:
  - relapse prevention
  - enhancement of function or reduction of disability
  - enhancement of treatment access, acceptance, adherence
Support effectiveness as well as efficacy studies

Produce practical information (findings applicable in current health care context)

Emphasize research with potential to “change practice”

Emphasize interventions with high likelihood of broad usage

Expand range of outcomes assessed (e.g., not only symptoms, but also functioning, quality of life, use of other services, etc.)
• Capitalize on basic science discoveries in formulating new intervention targets
• Foster collaborations between neuroscience and behavioral science in treatment development
• Identify and enhance mechanisms of change
• Develop new preventive as well as treatment interventions
• Increase access to treatments via using nontraditional delivery methods
Areas of Special Opportunity

- Studies of the neurobiological effects of psychosocial and behavioral interventions

- Studies of pharmacogenetics, age-related changes (e.g., cognitive, affective, neurobiological), and patient preferences as factors that may predict the individual’s capacity to benefit from particular lines of treatment

- Non-pharmacological treatment of agitation and other psychiatric or behavioral disturbances in older adults with dementia

- Increasing rapidity of treatment response

- Development of new preventive interventions, including suicide prevention
Other Examples

- Mental health treatment of and services for racial/ethnic minority elders
- Increasing access to treatments via nontraditional methods
- Broadening the dissemination and implementation of effective psychosocial interventions into new geriatric care settings

Note: Many important intervention questions shade into the domain of mental health services research

Systems-level intervention research goes to the NIMH Services Research and Clinical Epidemiology Branch
Geriatrics and Aging Processes
Research Branch: Programs

• Behavioral Science of Mental Disorders and Aging

• Psychosocial Intervention and Aging

• Neuroscience of Mental Disorders and Aging

• Pharmacologic and Somatic Intervention and Aging

See:
Geriatrics and Aging Processes
Branch: T1 Translational Programs

- Behavioral Science of Mental Disorders and Aging
- Psychosocial Intervention and Aging
- Neuroscience of Mental Disorders and Aging
- Pharmacologic and Somatic Intervention and Aging
Geriatric Translational Emphases

- Factors in vulnerability/resilience to mental disorder in late life
  - Pathophysiology – aging-related brain structures and processes
  - Risk factors -- Interactions of multiple influences (genetic, epigenetic, environmental, psychosocial, lifestyle, earlier life trauma)
  - Role of aging process and medical comorbidity (e.g., neuroinflammation, neurodegeneration)
- Understanding mechanisms mediating psychiatric symptom expression among elders
- More reliable / valid phenotypes, assessments, and biological / behavioral markers
Some Key Directions in Geriatric Translational Science

• Move from descriptive studies toward molecular mechanisms of pathophysiology

• Incorporate measures from biological models of aging (e.g., free radicals, oxidative stress, telomere shortening, fat deposition, mitochondrial changes) as well as from social and psychological aging theories

• Study trajectories of neurobiological factors from middle into older age

• Study protective as well as risk factors

• Study greater diversity of mental disorders
Understudied Areas of Disorder

- Bipolar disorder (esp. depressive phases)
- Schizophrenia; psychosis
- Suicide
- Chronic SMI
- Psychiatric syndromes (depression, anxiety, psychosis), behavior problems, and emotional processing in dementia
- Trauma; PTSD and aging
- Complicated bereavement
Areas of Special Opportunity

- Trajectories of chronic mental illnesses across the lifespan
- Mapping the neurocircuitry involved in late-life mood and anxiety disorders
- Mechanisms underlying psychiatric and behavioral disturbances in late-life neurodegenerative disorders
- Pathways of influence of earlier life trauma
- Long-term consequences of mental disorder (e.g., increased risk of dementia or premature mortality, accelerated biological aging)
Total FY14 Funding by Program Area

- Neuroscience: 38%
- Psychosocial Intervention (incl. Centers): 30%
- Psychopharmacologic & Somatic Intervention: 26%
- Behavioral Science: 6%
A scientific conference in which 50 renowned scientists discussed the extent to which the physiological effects of aging represent a common major risk factor for chronic diseases affecting the aging population.

Visit www.geron.org/gerosciencesummit.
## Format of the Summit Conference: Overview

**Opening**
- Francis Collins

**Keynote Presentations**
- Christopher Murray
- Brian Kennedy
- Linda Fried

### Scientific Sessions

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Advancing Health Through Geroscience

Chronic Disease

Cancer
Dementia
Sarcopenia
Arthritis
Osteoporosis
Neurodegeneration

CVD
CKD
COPD
Diabetes
Hearing
Frailty
Vision

Stress Adaptation
Epigenetics & RNA
Damage
Metabolism

Stem Cells
Proteostasis
Inflammation
Other Biology

Advancing Health Through Geroscience
Special Issue: GSIG Summit Perspective (overview and 7 “opinion pieces” on key issues in each of the research areas) – *Journals of Gerontology: Biological Sciences and Medical Sciences*, 2014 June; 69(S1): S1-S42.

Depression in Late Life

- Subsyndromal or minor depression more common than major depression
- Depression without sadness frequent
- Somatic symptoms common
- Late-onset depression may be an early manifestation of dementia
• Different phenotype?

• Co-morbidity / medical burden issues are HUGE

• Late-onset versus early-onset/chronic patterns -- to what degree overlapping with vascular and/or early dementing processes?
Interplay of Geriatric Depression with Cognitive Impairment and Dementia

- Cognitive dysfunction in depression and illness course in late life – depression as risk factor for (or prodromal phase in?) dementing illnesses
- Depression-dementia interface (imaging)
- Brain morphological correlates of depression in Alzheimer’s Disease
What Kind of Approach to Geriatric Depression Issues?

• Encourage taking broad (perhaps trans-diagnostic) perspective on geriatric mood and anxiety disorders

• Rather than focusing on phenotypic symptom clusters, deconstruct disorder into key components based on what is known about fundamental brain functions and neurocircuitry (e.g., executive dysfunction, emotion regulation, cognitive and perceptual biases, motivation/appetitive and reward-seeking behavior)

• Think dimensionally (e.g., anhedonia, rumination)

• Develop / use new methodologies and clinical research platforms, and mechanistically informative patient populations
NIMH Geriatrics and Aging Processes Research Branch  (301-443-1369)

• Behavioral Science of Mental Disorders and Aging
  ➢ George Niederehe, PhD (301-443-9123; gniedere@mail.nih.gov)

• Neuroscience of Mental Disorders and Aging
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