A Vision for the Future of NICHD

Diana W. Bianchi, M.D.
Director, NICHD
A Time of Transition in the US and at NIH

Six months on the job!
Core Values

• Maintain a High Standard of Excellence
• Promote Transparency
• Time to Listen, Learn and Think
  • 90 Minute Meetings With Branches, Programs and Groups Within NICHD
• “Vision”=Observations, Suggested Path Forward, ?Strategic Plan
Show Us The Money:
FY2016 NICHD Direct Appropriations
$1.338 Billion Total

Extramural Total = $1.04 B
Intramural Total = $124 M
RMS Total = $45 M
Taps = $127 M
FY2016 NICHD Direct Appropriations
Extramural Only

- *Select contracts supporting networks included in Centers and Networks
- ** Other Research – G11, U13, R13, R24, R25, P2C, U24 and T15 (+others)

- Non-competing RPGs, 47.0%
- Competing RPGs, 18.0%
- **Other Research, 3.8%
- *Centers and Networks, 14.7%
- Training (F, T, Ks), 6.8%
- SBIR/STTR, 3.5%
- Contracts, 6.1%
The Importance of NIH-Congress Interactions

FY 2017 Congressional Resolution Expires May 5 2017
FY 2018 ???
President’s Proposed FY 2018 Budget

• HHS budget reduced by 23%
• NIH would absorb a $5.8 billion cut, bringing its overall funding to $25.9 billion
• “Major reorganization” of the 27 NIH institutes and centers
  • Eliminates the Fogarty International Center, a $69.1 million program
  • Agency for Healthcare Research and Quality moves to NIH
• A more detailed budget will be released in May
My Vision for NICHD-I

• Define “our brand” (what is our focus?)
  • Communicate the message
• Listen to the Voice of the Patient
• Advocate for personalized medicine in pediatrics, obstetrics and rehabilitative medicine
• Build bridges between other NIH Institutes and other organizations
• Catalyze innovation
My Vision for NICHD-II

• Analyze best way to identify trainees most likely to succeed

• Stress the importance of data science and sharing to leverage our investments

• Integrate obstetrics and pediatrics research at NICHD; take the long view (DoHaD)

• Emphasize the “A” in Advisory Council
Define Our Brand

- **Refine** or **Redefine** who we are
- **Communicate** the message
- **Advocacy**
Commitment to Medical Rehabilitation

Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Disabilities Were Present from the Start of NICHD

The 1961 task force members called for the founding of a "centralized unit," whose sole purpose was to launch concentrated research into disorders of human development, including intellectual and developmental disabilities (IDDs). The plan included three parts: the development of university-affiliated facilities to train personnel to help care for people with IDDs, the construction of 12 IDD research centers on university campuses to provide facilities and a focus for research, and the establishment of a new Institute within the NIH to conduct and support research on human development and developmental disabilities.
Communicate the Message
Institute Tag Lines

- **NINR**: “Building the scientific foundation of clinical practice”
- **NHGRI**: ”Advancing human health through human genomics research”
- **NIEHS**: “Your environment. Your health”
- **NIMH**: “Transforming the understanding and treatment of mental illness”
- **NEI**: “Research today. Vision tomorrow”
- **NICHD**: “Health research across the lifespan”
Updating the NICHD Website

• Of major strategic importance with regard to communicating our mission and achievements to a variety of stakeholders
  • “Our business card to the world”

• Pew data regarding mobile technology: no disparities

• Goal is to improve search functions, design/layout, navigation, management and maintenance, optimize for Google et al.

• Introduce new features that highlight NICHD’s scientific contributions, including clinical trial data
Draft Web Site Design
The Importance of Advocacy
Listen to the Voice of the Patient

Patient Advocacy Groups at NIPT Stakeholder Meeting July 2015
Building Bridges
Ensure Representation of NICHD Populations in Trans-NIH Initiatives

- Meetings held with Eric Dishman, Director and former VP at Intel & Stephanie Devaney, PhD, Deputy Director
- Adults with physical disabilities can be enrolled in Phase I, Alison is one of NICHD’s representatives
- Adults with intellectual disabilities can be enrolled once consent issues have been clarified
Integrate Obstetrics and Pediatrics Research at NICHD

12 Sites Enrolling Participants
15 Sites Enrolling Participants
8 Sites Have Both Networks
(UAB, Brown, Case, UT Houston, U Penn, U Utah, UNC and Ohio State)
Examples of NHGRI-NICHD Collaborations

Newborn Sequencing In Genomic medicine and public Health (NSIGHT) program
NIH-Bill and Melinda Gates Foundation Partnership

Working groups with NICHD participation

- Maternal and newborn health
- Child health and development
- Pediatric pneumonia and indoor air pollution
- Contraceptive research
- HIV/AIDS

Photo: Bill Branson
Catalyze Innovation

![Chart showing change in number of tests per year and % procedures compared to 2011.](chart.png)
Investing Our Training Dollars in the People Most Likely to Succeed
Training and Career Development as a Percentage of Total Expenditures @ NICHD 1983-2015

Essentially stable over 30 years: no changes planned
Relative % of Funds Committed to Individual vs. Institutional Training by NIH Institute (FY2014)

- **NINDS**
  - Indiv K: 48.0%
  - K12: 4.4%
  - F: 23.7%
  - T32: 24.0%
- **NCI**
  - Indiv K: 38.5%
  - K12: 10.9%
  - F: 14.3%
  - T32: 36.3%
- **NIMH**
  - Indiv K: 60.5%
  - K12: 6.8%
  - F: 10.6%
  - T32: 28.9%
- **NIDA**
  - Indiv K: 52.3%
  - K12: 6.8%
  - F: 9.8%
  - T32: 31.2%
- **NIDDK**
  - Indiv K: 52.9%
  - K12: 4.4%
  - F: 9.3%
  - T32: 33.5%
- **NIAMS**
  - Indiv K: 55.9%
  - K12: 8.9%
  - F: 35.2%
- **NIAID**
  - Indiv K: 40.7%
  - K12: 9.4%
  - F: 50.0%
- **NICHD**
  - Indiv K: 20.4%
  - K12: 38.3%
  - F: 5.9%
  - T32: 35.4%
- **NHLBI**
  - Indiv K: 34.7%
  - K12: 11.2%
  - F: 6.3%
  - T32: 47.8%
- **NIGMS**
  - Indiv K: 17.5%
  - K12: 3.5%
  - F: 79.0%

Legend:
- Indiv K
- K12
- F
- T32
If we are going to emphasize individual training, how do we identify those individuals who are most likely to succeed?

We need a scientific version of Moneyball.

Data from ABIM (Marsh and Todd, Am J Med 2015)

- Predictors of long-term scientific engagement for clinician-scientists include prior graduate-level research training, any first author publications arising from pathway training, and receipt of an individual career development award.

- Learners who become interested in research at the conclusions of a clinical fellowship are at a disadvantage.
NICHD’s Commitment to Shared Resources
DASH is a centralized resource for researchers to store and access de-identified data from studies supported by NICHD.

DASH can help investigators meet NIH’s data sharing requirements for their own studies and find others’ study data for secondary analyses.

By supporting data sharing through DASH, NICHD aims to accelerate scientific findings and improve human health.

DASH was launched in August 2015 and is governed by the NICHD DASH Committee.

16 Study Topics Represented in DASH
(Number of studies in parenthesis; some studies with overlapping topics)

- Autism Spectrum Disorder (1)
- Children’s Bone Health and Calcium (1)
- High Risk Pregnancy (2)
- HIV/AIDS (18)
- Infant Care and Infant Health (3)
- Infant Mortality (1)
- Labor and Delivery (2)
- Necrotizing Enterocolitis (1)
- Pharmacology (2)
- Preconception Care and Prenatal Care (1)
- Preeclampsia and Eclampsia (2)
- Pregnancy (9)
- Preterm Labor and Birth (6)
- Rehabilitation Medicine (1)
- Stroke (1)
- Sudden Infant Death Syndrome (1)

37 Studies Available in DASH
7,767 Users
591 Registered DASH Users
45 DASH Data Requests

Contact supportdash@mail.nih.gov with any questions. For NICHD studies not archived in DASH, visit: https://dash.nichd.nih.gov/Resource/LinksToOtherArchives
ORIGINAL ARTICLE
Racial and social predictors of longitudinal cervical measures: the Cervical Ultrasound Study
EW Harville¹, KS Miller² and LR Knoepp³

OBJECTIVE: To evaluate whether the racial and socioeconomic disparities are present in adverse cervical parameters, and, if so, when such disparities develop.

STUDY DESIGN: A prospective cohort study was conducted. 175 women with a prior preterm birth had up to four endovaginal ultrasounds between gestational weeks 16 and 24 (Cervical Ultrasound Trial of the MFMU). Each sociodemographic factor (race/ethnicity, marital status, insurance funding and education) was examined as a predictor of short cervix or U/funnel shape, using multiple logistic and linear regression. Changes in the cervical length and shape across pregnancy and after pressure were also examined.

RESULTS: The strongest associations were seen between race and government-funded insurance and short cervix and U shape per funneling (race and length < 25 mm per funnel: adjusted odds ratio (OR) 5.52, 2.24 to 13.63; government-funded insurance and length < 30 mm per funnel: adjusted OR 3.10, 1.34 to 7.15). Changes in cervical length were not associated with sociodemographics.

CONCLUSION: African-American race and, to a lesser extent, insurance funder, are associated with cervical length and shapes that have been associated with preterm birth, and those properties are present largely early in pregnancy.

Journal of Perinatology advance online publication, 12 January 2017; doi:10.1038/jp.2016.240
Emphasize the “A” for Advice from the Advisory Council

• Need to leverage the collective expertise and wisdom of this group

• Should NICHD undergo a strategic planning process?
  • Analyze potential impact, probability of success, gaps in portfolio?

• What should be our funding priorities?
  • Difficult choices…the pie may not get bigger
  • How should we train physician-scientists?

• Are there strategic partnerships?
Thank You and Questions?

Endocrinology and Metabolism Rotation at Clinical Center, circa 1979
NIH Rehabilitation Research Plan: The Way Ahead

Alison Cernich, Ph.D.
Jennifer Jackson, Ph.D.
Trans NIH Medical Rehabilitation Coordinating Committee
• All data presented for consideration are draft and are presented for the purpose of illustrating capabilities.
  - These data are not final nor have they been fully subjected to quality controls
  - Feedback is needed to determine if these are the types of data needed to track progress on the research plan
  - Challenges and caveats are presented for consideration
Agenda

• Overarching Strategy
• Coding and Guidance
• Example Data from the Research Project Portfolio
• Infrastructure
• Impact
• Persons Funded
• Challenges
Baseline data taken from 2015 portfolio

- Prior to plan publication
- Allows for the year prior to serve as an “as is” for the rehabilitation portfolio

Using only the Rehabilitation Research, Condition and Disease Category (RCDC)

- Official categories that are verified by the Institutes and Centers
- Lists of projects available to the public
- Official dollars verified by Financial Management at NIH
- Contains the Physical Rehabilitation Category

Removed Intramural projects
## The Portfolio: 2015

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<th>Funding Institute/Center</th>
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Each project categorized in two “Tiers”

- **Tier 1** – Based on a keyword approach for the 6 categories within the Rehabilitation Research Plan; primary and secondary codes are based on the primary and additional aims of each project
  - Rehabilitation Across the Lifespan (A)
  - Community and Family (B)
  - Technology Use and Development (C)
  - Research Design & Methodology (D)
  - Translational Science (E)
  - Research Capacity and Infrastructure (F)

- **Tier 2** – This is the phase of research for each project: basic, disease-related basic, or applied (translational or clinical)
NCMRR codes each IC’s portfolio using the coding rules agreed upon by the group

- Each project is coded separately by two coders and the codes are reconciled for agreement
  - Will run statistics for level of agreement for primary, secondary, and Tier II

Each IC receives the reconciled portfolio and confirms or revises NCMRR’s proposed coding

All ICs will be integrated for the final analysis

Each year will be coded for new grants only
Example Abstract: 1R01HD084423-01 (Morrow)

- DESCRIPTION (provided by applicant): Of the 1.7 million wheelchair users in the United States (US), 90 percent, or 1.5 million persons use manual wheelchairs (MWCs). People with traumatic and non-traumatic spinal cord injuries (SCI) make up approximately 20% of the MWC users, and 12,000 new traumatic SCIs occur every year. While MWCs are immediately available and enable independence, 63% of MWC users will have one or multiple rotator cuff tears after decades of WC use as compared to 15% of age-matched able-bodied adults. A crucial gap in knowledge exists in understanding how the shoulder of MWC users functions from an almost permanent seated position as an agent for mobility, weight bearing, and hand grasping; and how this altered function translates to longitudinal shoulder health decline. The objective of this application is to define the longitudinal components of the early phase (before chronic symptom onset) of shoulder health decline specific to new MWC users by characterizing the exposure to altered shoulder function and the associated MRI signs of early onset of shoulder pathology. We propose to: (Aim 1) quantify shoulder joint motion and loading in the real world over 3 years in 60 new MWC users and a matched able-bodied cohort; (Aim 2) define early, preclinical changes on shoulder MRI specific to the MWC users, over 3 years, in comparison to the matched cohort; and (Aim 3) identify specific exposure measures as risk factors for early changes on MRI in the MWC users. Three central and novel aspects of this proposal will pave the way for targeting primary prevention: (1) characterizing the altered shoulder function in new MWC users in the real world with hardware and instrumentation suitable for multiple, day long collections, (2) defining the early, preclinical pattern of disease in users compared to a matched able-bodied cohort, and (3) investigating the combined effect of shoulder motion and loading and its relationship to the incidence of shoulder pathology. Successful completion of this project will define how the shoulder responds to MWC use (Aim 1), identify the MWC-specific pattern of shoulder disease on MRI (Aim 2), and determine how altered shoulder function has contributed to shoulder health decline (Aim 3). This work provides the foundation for understanding the relative impact of shoulder elevation and loading in shoulder health decline. Additionally, this work provides the first building block in defining the complete natural history of shoulder disease in MWC users. We expect the overall impact to be a powerful influence on environmental and assistive technology redesign, post-SCI rehabilitation practices, insurance reimbursement for shoulder health-preserving equipment, and understanding shoulder pathology in the general population.

- Coded Tier 1: A, C
- Coded Tier 2: Disease-related basic
Example Project 1

**Determine human or animal**
- Human

**Analyze primary and secondary aims**
- Identify processes associated with manual wheelchair use
- No intervention
- Mechanism focused
- Developing sensor systems
- Coded A, C

**Determine Tier II**
- Looking at shoulder pathology in people with SCI
- No intervention or application
- Disease-related basic
Example Project 2

• Example: Abstract, 1R43HD083083-01 (Bertsch)
  - DESCRIPTION (provided by applicant): Silicone roll-on prosthetic liners are widely used by lower limb amputees. Most patients, however, complain of skin-related issues due to the warm, moist environment. **The long term goal of this SBIR project is to develop and commercialize a vastly improved silicone prosthetic liner with antimicrobial properties so as to improve hygiene and greatly reduce risk of infection from dangerous pathogens. Phase I specific aims will establish proof of concept by demonstrating produceability of polysiloxane material that exhibits potent biocidal function, with negligible impact on mechanical performance.** Polysiloxane formulation and halogenation will be mathematically optimized for antimicrobial effectiveness vs. material properties. Mechanical performance will be assessed using ATSM F22042-00(2011) guidelines recommended for silicone elastomers used in medical applications. In addition, we will confirm stability and rechargeability of the material by verifying that no halogen leaching occurs in simulated sweat environments, and antimicrobial potency can be regained by wiping dilute hypochlorite solution if halogenation is discharged. **Skin compatibility will be confirmed using the Draize Skin Test performed by the University of South Dakota Animal Resources Center.**

• Coded Tier 1: C, E

• Coded Tier 2: Applied-translational
Example Project 2

Determine human or animal

Partial biomechanical
Partial animal

Analyze primary and secondary aims

Primary aim is polymer development
Some testing in animals for safety
Coded C then E

Determine Tier II

Development of a polymer with potential for human application
Applied-translational
Cerebral palsy (CP) is the most common pediatric neurological disorder. CP is caused by damage to brain motor areas during development. CP results in weakness, altered tone and abnormal coordination. Therapies for CP have largely been scaled from adult stroke therapies. However, the motor circuits involved in adult stroke are quite different from those in children with CP. Effective therapies for children with CP should be built on a specific understanding of motor circuit control in children with CP. We propose to identify the neurophysiological underpinnings of hand control in children with CP and will determine predictors of the efficacy of hand therapy. Building an understanding of hand motor control in children with CP fills an important gap and will set the foundation for further development of hand therapies for children with CP. Two types of intensive hand training have shown efficacy in children with unilateral spastic CP (USCP), whose motor deficits are largely restricted to one side of the body. In constraint-induced movement therapy (CIMT), the dominant arm is restrained while the impaired hand is trained in unimanual tasks. In hand-arm intensive bimanual training (HABIT), alternatively, children use both hands together. It has been reported that the efficacy of CIMT is affected by the pattern of corticospinal tract connectivity in children with USCP. The central hypothesis of the proposed research, supported by our pilot data, is that efficacy of hand training is differentially affected by connectivity of motor circuit and type of training. We also hypothesize that neurophysiological biomarkers of motor circuit dysfunction can predict which type of hand training is ideal for an individual. Two important questions remain unanswered: 1) How do motor circuits interact and change in response to intensive hand therapy? 2) Does the efficacy of intensive hand therapy depend on laterality of the corticospinal tract that controls the affected hand? The proposed experiments will answer these questions. Children are not little adults. Therapies for USCP must be built on a strong understanding of motor control in USCP. By identifying the neural circuit effects of CIMT vs. HABIT, we can tailor therapies to children most likely to benefit. This work will also provide a framework for developing new activity-based therapies for USCP.
Example Project 3

Determine human or animal

Human

Analyze primary and secondary aims

Compare effectiveness of two types of training
Examine mechanisms underlying change
Coded D, A

Determine Tier II

Applied intervention with humans
Applied-clinical
Example Abstract: 2P2CHD065702-06 (Ottenbacher)

- **ABSTRACT: ADMINISTRATIVE OVERSIGHT CORE** The Administrative Oversight Core of the Center for Large Data Research and Data Sharing in Rehabilitation will provide the administrative infrastructure and leadership to support the activities of the Center. The goal of the Administrative Oversight Core is to oversee Center activities and ensure that the overall mission of the program is accomplished, which is to build knowledge and research capacity related to rehabilitation data. Our focus is two-fold. The first involves research using large datasets to examine questions relevant to rehabilitation science, an extension of our current program. The second involves archiving existing rehabilitation and disability datasets to make them available for sharing and secondary analyses, a new focus of the program. The **Specific Aims of the Administrative Oversight Core are to:**
  - **Aim 1:** Provide overall management and direction for all Center activities, and administer the program.
  - **Aim 2:** Communicate with the NIH and the rehabilitation community. The Administrative Oversight Core will include an Executive Committee (core directors and co-directors at UTMB, Cornell University and the University of Michigan), an Evaluation and Monitoring Committee, and an External Advisory Board to ensure the goals of the Center and each core are accomplished. Multiple approaches designed to facilitate communication, promote scientific coherence and idea-generation, and bring new investigators to rehabilitation research will be followed. One approach will be structural and include administrative functions; the other approach will be more proactive and personalized. A Logic Model will be used to evaluate outcomes and monitor accountability across all P2C Center programs. The leadership team, or Executive Committee, is committed to fostering multidisciplinary training and research related to rehabilitation. Its members have extensive experience in administering research and training programs and excellent records of mentoring. Our experience in administering the current R24 program and the joint expertise of our leadership team - members both old and new - provide an excellent environment to achieve the proposed aims and continue building research capacity in rehabilitation.

- **Coded Tier 1:** F
- **Coded Tier 2:** Unable to categorize
Example Project 4

Determine human or animal

Human

Analyze primary and secondary aims

Research infrastructure

Determine Tier II

Infrastructure is considered unable to categorize
Example Analysis:
NICHD Portfolio – Primary Tier 1

- **Rehabilitation Across the Lifespan**: 40
- **Community And Family**: 2
- **Technology Use and Development**: 34
- **Research Design and Methodology**: 76
- **Translational Science**: 22
- **Research Capacity**: 50

Heather Robinson,整理
Example Analysis:
NICHD Portfolio – Primary and Secondary Tier 1

Primary and Secondary Tier 1 Category Combination

Number of Projects

A 8
A-C 9
A-D 17
A-E 5
B-A 1
B-D 1
C 13
C-A 9
C-D 6
C-E 3
D 3
D-B 7
D-C 13
D-E 10
D-A 43
E 10
E-A 11
E-C 1
F 50

0 5 10 15 20 25 30

0 5 10 15 20 25 30

National Institutes of Health
Example Analysis:
NICHD Portfolio – Primary and Secondary Tier 1
Example Analysis: NICHD Tier 2

Number of Projects

Tier 2 Category

- Basic: 7
- Disease-basic: 36
- Applied - Clinical: 118
- Applied - Translational: 14
- Unable to Categorize: 49
Analysis of this section requires a different approach though training and infrastructure related grants are included in the portfolio analysis:

- Medical Rehabilitation Research Infrastructure Network (data this afternoon)
- Use of and contribution to training programs (included in portfolio review; subcommittee to be formed in December)
- Current model for training in rehabilitation and strategy to develop availability and partnership (subcommittee to be formed in December)
- Availability of funding announcements (list provided)
- Methods to encourage knowledge translation (clinical impact)
- Interdisciplinary collaboration (network analysis)
- Recruiting individuals with disability into the field (subcommittee to be formed in December)
• NICHD conducting a broad review of training programs and approaches to training that is continuing through Council

• NICHD Leadership and Trans NIH group agreed that training analysis would hold until December to ensure coordination between Council and NABMRR

• Subcommittee to be formed in December and NABMRR liaison will need to serve on both the NICHD and NABMRR committee

• Agenda in December will include other federal efforts to recruit individuals with disability
Availability of Funding Announcements

• NCMRR is the proponent of the Rehabilitation Listserv at NIH
  ■ Funding opportunities both from NIH and federal and other partners are disseminated
  ■ Meetings are promoted
  ■ NIH-related news conveyed
• Addended is a list of rehabilitation relevant FOAs from the ICs since 2015
• Analysis is underway to look at type and theme relative to the grant portfolio
• **1,454 (7%)** are not found by *iTrans*.
  ▪ Of these, 951 (65%) are pre 1995 and 27% are 2017 (i.e. 92% are years not included in *iTrans*).

• **4,068 (18%)** have no Human, Animal or Molecular/Cellular MeSH terms so sit outside the triangle.

• **16,761 (75%)** have H, A or M/C MeSH terms and are shown in the triangle of biomedicine.
  ▪ Of these 10,076 (60% of those with H, A or M/C MeSH terms) have only Human MeSH terms (probably as you would expect).

• **5,623 (27%)** of the 20,829 publications in *iTrans* have been cited by a clinical trial or guideline.
Draft Clinical Impact: The Animated Version

- Human
- Mol/Cell
- Animal
Biosketch Analysis of the 2015 portfolio in collaboration with the Office of Portfolio Analysis

- Used 1,370 ApplIDs provided by NICHD.
- Identified Type 1 and 2 applications since 2000 (as these contain full bio-sketches). Biosketches identified for 1,178 projects (86%).
- Ran code to identify Rehabilitation specialties.
- Identified most recent ApplID for each project number. Within project numbers, sorted by year (newest first), Application type (Type 1s first), ApplID (highest [newest] first). Selected first ApplID for each project number for analysis.
- Identify main specialties by looking at broad category with the most matches for each PI.

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Draft Percent of Physical Rehabilitation applications with specialty in biosketch

Percent of Physical Rehabilitation applications with specialty in biosketch

- 1. Physician specialties: 63%
- 2. Physical Therapist: 17%
- 3. Occupational Therapist: 7%
- 4. Speech language pathologist: 6%
- 5. Rehabilitation nurse or nurse (general): 8%
- 6. Rehabilitation psychologist, neuropsychologist or psychologist: 61%
- 7. Bioengineer or Rehabilitation engineer: 58%
- 8. Kinesiologist: 10%
- 9. Neuroscience: 48%
- 10. Neurosurgery / Neurobiology / Neurophysiology: 39%
- 11. Physiology: 36%

* Percentages calculated on 1,178 projects (with Type 1s and 2s applications identified from 1,370 Medical Rehabilitation project numbers)
Draft Specialties listed by lead PI in medical rehabilitation biosketches

Next Steps:
1. Refine specialties as needed
2. Deal with duplicate searches due to key word strategy in algorithm

Specialties listed by lead PI in Rehabilitation application biosketches

- 1. Physician specialties: 26%
- 2. Physical Therapist: 7%
- 3. Occupational Therapist: 2%
- 4. Speech language pathologist: 2%
- 5. Rehabilitation nurse or nurse (general): 1%
- 6. Rehabilitation psychologist, neuropsychologist or psychologist: 29%
- 7. Bioengineer or Rehabilitation engineer: 31%
- 8. Kinesiologist: 3%
- 9. Neuroscience: 22%
- 10. Neurosurgery / Neurobiology / Neurophysiology: 14%
- 11. Physiology: 14%
- PIs with no Rehabilitation specialties: 16%

* Percentages calculated on 1,178 Applications (Type 1s and 2s between 2007 and 2018 from 1,370 Medical Rehabilitation project numbers)
### Draft Collaborations

#### % of applications featuring other investigators referencing:

<table>
<thead>
<tr>
<th>Primary Investigator specialty</th>
<th>Number of Applications</th>
<th>Physician specialties</th>
<th>Physical Therapist</th>
<th>Occupational Therapist</th>
<th>Speech Language Pathologist</th>
<th>Rehabilitation nurse or nurse (general)</th>
<th>Rehabilitation psychologist or psychologist or neuropsychologist</th>
<th>Neurosurgery / Neurobiology / Neurophysiology</th>
<th>Physiology</th>
<th>Other Specialty</th>
<th>Multiple Rehabilitation specialties</th>
<th>All Rehabilitation applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physician specialties</td>
<td>86</td>
<td>83%</td>
<td>16%</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>62%</td>
<td>40%</td>
<td>5%</td>
<td>38%</td>
<td>40%</td>
<td>29%</td>
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<tr>
<td>2. Physical Therapist</td>
<td>29</td>
<td>66%</td>
<td>55%</td>
<td>10%</td>
<td>0%</td>
<td>14%</td>
<td>38%</td>
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<td>21%</td>
<td>38%</td>
<td>31%</td>
<td>45%</td>
</tr>
<tr>
<td>3. Occupational Therapist</td>
<td>6</td>
<td>1%</td>
<td>10%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>4. Speech language pathologist</td>
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<td>0%</td>
<td>0%</td>
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</tr>
<tr>
<td>5. Rehabilitation nurse or nurse (general)</td>
<td>7</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6. Rehabilitation psychologist, neuropsychologist or psychologist</td>
<td>193</td>
<td>52%</td>
<td>3%</td>
<td>4%</td>
<td>6%</td>
<td>5%</td>
<td>83%</td>
<td>27%</td>
<td>2%</td>
<td>30%</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>7. Bioengineer or Rehabilitation engineer</td>
<td>302</td>
<td>36%</td>
<td>14%</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
<td>17%</td>
<td>79%</td>
<td>7%</td>
<td>19%</td>
<td>22%</td>
<td>18%</td>
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<tr>
<td>8. Kinesiologist</td>
<td>1</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>9. Neuroscience</td>
<td>29</td>
<td>41%</td>
<td>0%</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>41%</td>
<td>52%</td>
<td>3%</td>
<td>52%</td>
<td>28%</td>
<td>24%</td>
</tr>
<tr>
<td>10. Neurosurgery / Neurobiology / Neurophysiology</td>
<td>28</td>
<td>32%</td>
<td>14%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>39%</td>
<td>36%</td>
<td>0%</td>
<td>46%</td>
<td>50%</td>
<td>29%</td>
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<tr>
<td>11. Physiology</td>
<td>28</td>
<td>46%</td>
<td>32%</td>
<td>7%</td>
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<td>11%</td>
<td>39%</td>
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<td>32%</td>
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<td>Other Specialty</td>
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<td>6%</td>
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<td>14%</td>
<td>63%</td>
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<td>32%</td>
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<td>Multiple Rehabilitation specialities</td>
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<td>91%</td>
<td>20%</td>
<td>8%</td>
<td>8%</td>
<td>14%</td>
<td>94%</td>
<td>74%</td>
<td>10%</td>
<td>51%</td>
<td>46%</td>
<td>47%</td>
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<tr>
<td>All Rehabilitation applications</td>
<td>1,178</td>
<td>50%</td>
<td>12%</td>
<td>5%</td>
<td>4%</td>
<td>6%</td>
<td>52%</td>
<td>50%</td>
<td>6%</td>
<td>29%</td>
<td>26%</td>
<td>24%</td>
</tr>
</tbody>
</table>
Challenges

• Some ICs with items in the portfolio did not participate in the development of the plan
  ■ Will require additional work with respect to outreach, education and buy-in
  ■ NICHD assisting with this process (Thanks!)

• Categorical definitions and weighting can change each year or could be revisited as a result of this analysis

• Category does not include all projects that have a rehabilitation focus and may include some that are not rehabilitation-related

• Changes in overarching NIH budget could have impacts on all portfolios
Questions
21st Century Cures Act

• Passed the House on November 30, 2016, by vote of 392-26
• Passed the Senate on December 5 by a vote of 94-5
• President signed the bill on December 13
P.L. 114-255

Purpose:

• To accelerate the discovery, development, and delivery of new cures and treatments

• Provide additional funding for the NIH and FDA
Cures – NIH Funding Provisions

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>BRAIN</th>
<th>PMI</th>
<th>Cancer Moonshot</th>
<th>Regenerative Medicine</th>
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<tr>
<td>2017</td>
<td>10</td>
<td>40</td>
<td>300</td>
<td>2</td>
</tr>
<tr>
<td>2018</td>
<td>86</td>
<td>100</td>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>2019</td>
<td>115</td>
<td>186</td>
<td>400</td>
<td>10</td>
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<td>2020</td>
<td>140</td>
<td>149</td>
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<td>2021</td>
<td>100</td>
<td>109</td>
<td>195</td>
<td></td>
</tr>
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<td>2022</td>
<td>152</td>
<td>150</td>
<td>194</td>
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</tr>
<tr>
<td>2023</td>
<td>450</td>
<td>419</td>
<td>216</td>
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<td>2024</td>
<td>172</td>
<td>235</td>
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<tr>
<td>2025</td>
<td>91</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2026</td>
<td>195</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-Yr total</td>
<td>1,511</td>
<td>1,455</td>
<td>1,800</td>
<td>30</td>
</tr>
</tbody>
</table>

* BRAIN denotes Brain Research through Advancing Innovative Neurotechnologies, and PMI Precision Medicine Initiative.
New/Revised Programs

• Precision Medicine Initiative (now “All of Us”)
• Next Generation Researchers Initiative
• Raises NIH’s Loan Repayment Program cap from $35,000 to $50,000 – includes clinical and pediatric programs for now
• EUREKA Prize Competitions and encourages high-risk, high-reward research
Inclusion in Research

- Ensure women, children, and racial/ethnic minorities are appropriately represented in clinical research
- Assemble clinical research data on women, minorities, and “relevant” age categories including pediatric and older populations
- Requires the NIH Director to hold a workshop regarding appropriate age groups in research and update policies, as appropriate
- Improve research related to sexual and gender minority populations
Relieves Burdens and Increases Access

• Exempts NIH from conference and travel requirements
• HHS must examine financial conflicts of interest & financial expenditure reporting
• NIH must consider ways to reduce burden relating to sub-recipient monitoring
• Clinical Trials – requires reporting on status in CT.gov
• Data Access and Privacy
  • Requires HHS to issue Certificates of Confidentiality and enhances protections for certain types of research
  • Authorizes the NIH Director to require funding recipients to share data
Cures Act Provisions – NICHD

NICHD has role in each of the following:

- National pediatric research network
- Global pediatric research
- Inclusion of children in clinical research
- Task Force on Research Specific to Pregnant Women and Lactating Women
- Medical Rehabilitation Research
Cures Act – Pediatric Provisions

- Pediatric Research Network – IDeA States Pediatric Clinical Trials Network underway
- Global Pediatric Network – led by FDA/private industry
- Pediatric Inclusion
  - Requires the NIH Director to include in clinical research, and collect data on, children and older populations
  - Requires workshop to obtain input from stakeholders; scheduled for June 1-2, 2017
  - Request for Information to gain additional input
  - Report findings and update policies as appropriate
Task Force – Medications Used in Pregnancy and Postpartum

• Purpose: “to identify and make recommendations to address gaps in knowledge and research about safe and effective therapies used during pregnancy and for lactating women”

• Report to HHS Secretary and Congress by September 2018

• Sunsets after two years unless extended
Task Force - Implementation

- Authority delegated to NIH Director January 19, 2017
- Director asks NICHD to lead – Cathy Spong spearheading the effort
- Charter establishing Task Force filed March 13 (FACA Committee)
- Slate of nominees prepared for Secretary’s approval – including required Federal members
- Analysis of currently supported research underway
Task Force – Next Steps

• First two meetings open to the public (posted in the *Federal Register*
  
• August 21-22, 2017
• November 6-7, 2017

Web page created: https://www.nichd.nih.gov/about/advisory/PRGLAC/Pages/index.aspx
Improving Medical Rehabilitation Research at the NIH

New Provisions:
• Augments requirements for Research Plan
• Requires development of objectives and benchmarks
• Requires scientific workshop every five years
• Enhances coordination within NIH and across the Federal government
• Defines “medical rehabilitation research”
<table>
<thead>
<tr>
<th>1990 Law</th>
<th>Cures Act - 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NCMRR established within NICHD</td>
<td>• NCMRR established within NICHD</td>
</tr>
<tr>
<td>• Supports peer-reviewed research</td>
<td>• Supports peer-reviewed research</td>
</tr>
<tr>
<td>• Research plan required within 18 months, with updates as appropriate</td>
<td>• Revised research plan not less than every five years</td>
</tr>
<tr>
<td></td>
<td>• NCMRR Director annually reports to Coordinating Committee and Advisory Board, identifying resources for research</td>
</tr>
</tbody>
</table>
1990 Law
• Coordinating Committee makes recommendations for research priorities

Cures Act - 2016
• Coordinating Committee makes recommendations for research priorities
• Committee periodically hosts scientific workshop
1990 Law
• Establishes Advisory Board with specified membership

Cures Act - 2016
• Reauthorizes Advisory Board with updated, specified membership
• Adds DPCPSI Director
• Review and coordination/prevent duplication
• Secretary may enter into IAAs
• New definition of medical rehabilitation research
21st Century Cures – Next Steps

• Legislative Implementation Work Group
  • Formal process with designated members from across NIH
  • Assigns implementation plans to the appropriate IC/OD Office
    • Plans contain actions required to implement provisions, address significant policy, procedural or legal issues, describes new or revised regulations, guidelines or delegations needed, notes required deadlines
  • Final plans submitted to NIH Director
  • Task Force and Rehab plans submitted by NICHD
Ahead of the Game

✓ Scientific Conference
✓ Research Plan
✓ Increased Coordination
✓ Annual Report
Thank you!

Questions?

kaeserl@mail.nih.gov
NCMRR: Why is it a Center?

Alison Cernich
Lisa Kaeser
NCMRR was created in 1990 following the passage of the American with Disabilities Act

NICHD leadership makes case to NIH Director for incorporating NCMRR into NICHD
  • Center Director reports to the Director of the Institute

The Center was provided the role of coordinating within and outside NIH

Required first research plan within 18 months of passage

Created a federal advisory committee
Blue Ribbon Panel

- 2006 NIH Reauthorization Bill left NCMRR language as is
- In 2012, Dr. Collins and Dr. Guttmacher convened a Blue Ribbon Panel to evaluate rehabilitation research at NCMRR, NICHD, and across the NIH
- Provided a number of recommendations that NIH is working to address
- Structural recommendations included
  - Independent Institute/Center
  - Office in the NIH Director’s Office
Current Status

- 2016 – Cures Act revised NCMRR Authorizing Language
  - Left structure large in place but added new requirements for coordination, scientific workshops, and regularly updating the research plan
- Center in NICHD at the level of the Office of the Director
  - Dedicated budget
  - Full granting authority
  - Ability to enter into agreements
  - Build collaborations
  - Coordinate internal and external to NIH
  - Develop a research plan
  - Plan and host conferences and workshops
- Moved quickly to address both Blue Ribbon Panel Recommendations and Cures Act Implementation
Medical Rehabilitation Research Infrastructure Network

Ralph Nitkin, Ph.D.
May, 2017
Phase 1: 2000-2005

• Originally developed in response to Advisory Board
• Need to build research infrastructure in medical rehabilitation
• Enhance research capacity through scientific cores, information technology, and networking activities
• NICHD committed almost $4 million per year to support four, geographically distinct networks: West, South, Midwest, Northeast

Focus on mentoring over research expertise per se
Phase 2: 2005-2010

- No longer have regional constraints
- Provide access to expertise in specific domains relevant to rehabilitation research
  - Courses and workshops
  - Mentorship and consultations
  - Pilot grants
  - Other collaborative opportunities (sabbaticals?)

- Proposed expertise must be: rehab-relevant, not readily available elsewhere, teachable
- Got 13 applications; with additional support from NINDS and NIBIB, able to stretch funding to support 6 networks
Results of Phase 2 competition

- Access to expertise in:
  - neurorehabilitation and robotics
  - cognitive rehabilitation and brain imaging
  - neurosciences and functional regeneration
  - proteomic and genomic analysis
  - muscle physiology
- Trans-center cooperation, esp at national research meetings
- Many contacts; dozens of productive collaborations
- Growing number of good applications for pilot funding
- Increased submission of NIH research applications - including some that resulted in funded grants
- Stimulated Rehab applications to other NIH Institutes!
Evolving Model for Research Infrastructure

Common resources across centers (relative emphasis depends on research domain):

- State-of-the art research cores
- Workshops, symposia, webinars
- On-Line Information and consultation services
- Collaborations and Mentorship
- Sabbaticals, Mini-sabbaticals, Visiting scholars
- Pilot grants
- Collaborative activities across centers
Phase 3 Competition

- Encouraged applications to more adequately cover full range of ICF (e.g. Disability, Psycho-social, Environmental, Outcomes, Health services)
- Received 23 applications
- With continued support from NINDS and NIBIB stretched funding to support 7 centers (50% turn-over from previous phase)
Phase 3 Funded Rehabilitation Research Infrastructure Networks, 2010-2015

- 7 Networks, across the ICF spectrum:
  - Genomics, gene expression, and proteomics
  - Muscle physiology, imaging, and function
  - Bioengineering and robotics
  - Modeling and simulation of movement
  - Assessment and outcomes
  - Analysis of large datasets
  - Technology assessment and product development; commercialization and regulations

Accessible through common portal: WWW.NCMRR.ORG
2014: Network-Enabled Submission of Research Applications across the ICs

- HD 19
- AR 15
- DK 9
- NS 8
- AG 7
- HL 5
- TR 3
- NR 3
- OD 2
- AT 2

- EY 1
- CA 1
- DE 1
- GM 1

Beyond NIH
- VA 1
- AHRQ 1
- NSF 1
- NIDRR 1
Phase 4: 2015-2020

• Especially requested expertise in these domains:
  • Clinical Trial Design
  • Engineering and the Environment
  • Individualized Medical Rehabilitation and Dynamic Reassessment
  • Applied Behavioral Supports for Rehab Research and Healthy Outcomes

Or any other appropriate research domain

• Forced to switch to the “P2C” mechanism
Phase 4 Applications

• Received 20 applications, but only partial response to targeted domains:
  • Clinical trials: 5
  • Engineering and the Environment: 4
  • Individualized Rehab and Dynamic Reassessment: 2
  • Applied Behavioral Supports & Healthy Outcomes: 0

• With continued support from NINDS and NIBIB funding to support 6 centers – but still no other ICs

• 50% turn-over from previous phase
Phase 4 Funding: 2015-2020 (current)

- 6 Networks, across the ICF spectrum:
  
  **COMPETITIVE RENEWAL**
  - Modeling and simulation of movement
  - Analysis of large datasets
  - Technology assessment, product development, commercialization, and regulations

  **NEW NETWORKS**
  - Clinical trial design
  - Regenerative Medicine
  - Neuromodulation: clinical applications

NCMRR also funded a supplemental “coordinating center”; this was awarded to Univ Alabama
## Distribution of NCMRR Resources (FY 2016)

<table>
<thead>
<tr>
<th>Category</th>
<th>Dollars</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training &amp; Career Development</td>
<td>$9,872,764</td>
<td>14%</td>
</tr>
<tr>
<td>Research Infrastructure</td>
<td>$4,750,608</td>
<td>6.7%</td>
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<tr>
<td>(20% pass through to pilot grants)</td>
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<tr>
<td>Centers</td>
<td>0</td>
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<tr>
<td>Clinical Trial Networks</td>
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<tr>
<td>Research Grants</td>
<td>$49,030,115</td>
<td>79.3%</td>
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<td>Total</td>
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<td>NCSRR</td>
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<tr>
<td># Website Contacts</td>
<td>20,000</td>
<td>200,000</td>
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<tr>
<td># Substantive Collaboration</td>
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<td>100</td>
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<tr>
<td>Presentations (Local, National)</td>
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<td>13</td>
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<td>Webinars</td>
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<td>10</td>
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<td>Pilot Grant Requests Received</td>
<td>42</td>
<td>40</td>
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<tr>
<td>Pilot awards made</td>
<td>13</td>
<td>4</td>
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<td>Pilots to Less Resourced</td>
<td>4</td>
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<tr>
<td>Institutions</td>
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<tr>
<td>Visiting Scholars from</td>
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<tr>
<td>Less Resourced Institutions</td>
<td></td>
<td></td>
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</tbody>
</table>
Outcomes: Activities and Other Products

• Presentations locally, regionally, national meetings:
  • Joint presentations with other P2C programs (e.g., NIH conferences, ACRM, SfN)

• Webinars (mostly archived)

• Other “products”:
  • databases, directories, lists of resources
  • Workshops, tutorials, webinars
  • software, simulation videos
  • Newsletters, research forums
Each network also supports a handful of visiting scholars and mini-sabbaticals; Small travel awards to attend workshops
Outreach to Less-Resourced Institutions

• Adding to mailing lists and newsletters
• Targeted solicitations to minority institutions
• Free workshops; providing remote access
• Poster competitions for annual symposium
• Travel awards
• Expertise on their institutional advisory panel
Resultant Research Applications

- Networks just entering their third year of funding, so resulting research applications are just starting to be submitted: 5-20 per center

- Majority apply to the NIH
  - Including NIAMS, NICHD, NINDS, NIA, NHLBI, NIBIB
  - Mechanisms include R01 and R21, and even Ks, Fs
  - A few have already been successful others in revision

- Applications to other agencies:
  - VA, DoD, NSF, NIDILRR, FDA, CDC, AHRQ
  - Also a few to research foundations
Annual Publications citing the Medical Rehabilitation Infrastructure Networks

- 2007: 13
- 2008: 16
- 2009: 24
- 2010: 27
- 2011: 49
- 2012: 70
- 2013: 79
- 2014: 88
- 2015: 99
- 2016: 59
An Update on the Draft NIH Strategic Plan for Cerebral Palsy Research

Jim Koenig, Ph.D.
Program Director
NINDS

May 2, 2017
The Committee urges NIH to work with scientists and stakeholders to develop a 5-year strategic plan for CP prevention, treatment, and cure through the lifespan with the goal of reducing the number of people impacted by CP overall, as well as improving the opportunity for recovery of those already diagnosed.
Research gaps and opportunities identified through two workshops provided input for the strategic plan.

November 12-13, 2014

*State-of-the-Science and Treatment Decisions in Cerebral Palsy*
(see Lungu, et al., Neurology 2016; 87:1293-1298)

March 24-25, 2016

*Basic and Translational Research in Cerebral Palsy*

Partners with NICHD and NINDS included AACPDM, CP Foundation and Reaching for the Stars.
Team involved in constructing draft Plan

- **NINDS Extramural Staff**
  - Walter Koroshetz
  - Jim Koenig
  - Codrin Lungu
  - Adam Hartman
  - Deborah Hirtz

- **NICHD Extramural Staff**
  - Diane Bianchi
  - Alison Cernich
  - Ralph Nitkin
  - Tonse Raju

- **NINDS Office of Science Policy and Planning**
  - Paul Scott
  - Ling Wong
  - Cara Long
The draft Strategic Plan for Cerebral Palsy Research

• Priority Area 1 – Basic and Translational Research
  – Enhance understanding of the fundamental mechanisms of the developing brain-spine-muscle axis
    • Create and evaluate animal models to study the complex dynamic created when environmental perturbations impinge upon development.
    • Empirically evaluate cellular and molecular pathways of injury and repair.
    • Investigate cell-based therapies.
    • Include study of maternal factors especially placental function.
  – Integrate state-of-the-art neuroimaging
    • Broaden application of current advanced imaging techniques to study the at-risk fetus and infant as well as affected child.
    • Develop new technologies for fetal and perinatal brain evaluation as well as placental function.
    • Integrate imaging throughout basic and clinical investigations.
The draft Strategic Plan for Cerebral Palsy Research

• Priority Area 1 – Basic and Translational Research

  – Clarify mechanisms and establish biomarkers
    • Identify mechanistic basis of genetic, structural and functional factors driving impairment and recovery.
    • Understand how injuries underlying CP lead to hydrocephalus.
    • Develop human biomarkers to improve diagnosis, explain heterogeneity and predict treatment outcomes.

  – Understand and utilize neuroplasticity
    • Identify brain and motor system critical periods and how their identification can translate to clinical applications.
    • Consider neuroplasticity-promoting interventions from other fields.
    • Explore the biology underlying the resilient phenotype.
The draft Strategic Plan for Cerebral Palsy Research

• Priority Area 2 – Clinical Research

  – Consider the entire lifespan
    • Improve precision of individual diagnosis.
    • Guide newly affected families.
    • Develop rehabilitative strategies that enhance beneficial neuroplasticity.
    • Consider needs of adults with CP.

  – Enhance treatment options
    • Consider combination therapies targeting different pathways; i.e., non-invasive neuromodulation, pharmacological, physical and occupational therapy.
    • Accelerate bench-to-bedside strategies by incentivizing translation
The draft Strategic Plan for Cerebral Palsy Research

• Priority Area 2 – Clinical Research

  – Revisit and update study designs in the field
    • Consider innovative study designs to complement RCTs in comparative effectiveness research.

  – Maximize potential of existing registries and databases
    • Consolidate patient registries and databases.
    • Enhance public-private partnerships.
    • Enhance communication between patients and researchers to generate and share data.

  – Develop better data metrics
    • Develop common data elements.
    • Increase quality and availability of patient-reported outcomes.
Priority Area 3 – Workforce Development

- Enhance training of next generation investigators.
- Attract researchers to the field.
- Leverage expertise across specialties; 
  ie., add bioengineers, computational scientists, trialists, placental scientists, etc. to current workforce.
Accomplishments

• Establishment of the Cerebral Palsy Research Network (CPRN) to address the need of maximizing the potential of databases and registries. Headed by Paul Gross, former NINDS Council Member.

• NINDS working with AACPDM developed and published CP common data elements in September, 2016 (available at https://www.commondataelements.ninds.nih.gov/CP.aspx #tab=Data_Standards).

• To address the needs of families with a newly diagnosed individual, a CP Tool Kit has been developed by CP NOW Foundation (https://cpnowfoundation.org/).
Accomplishments

• The draft Strategic Plan was posted on the NICHD/NINDS websites in March, 2017 and feedback was requested by early April.
• There were approximately 30 comments about the Plan.
• Generally, comments were positive.
• Major themes were:
  – Enhance emphasis on early diagnosis
  – Placental involvement
  – Treatment
  – Patient oriented research
The plan for moving forward

✓ Step 1 – Seek input from workshop sponsors and organizers.
✓ Step 2 – Post draft Plan on NINDS/NICHD websites and invite comment from workshop participants and the public.
➢ Step 3 – Revise and finalize Plan based on feedback.
  • Step 4 – Share final Strategic Plan with community.
  • Step 5 – Look to develop research initiatives to fill knowledge gaps.
  • Step 6 – Bring final Plan and proposed initiatives to a future Council meeting for approval.
For Discussion

• Are there gaps in the Strategic Plan that should be filled?

• Recommendations for high impact areas to incentive/prioritize?
StrokeNet update

Scott Janis

NINDS

May 2, 2017
Stroke is the Fifth Leading Cause of Death in the U.S.

- 6.8 million Americans have had a known stroke; almost 800,000 new strokes each year (~23% are recurrent strokes).
- The aging of the US population is on course to lead to a 21.9% increase in prevalence of stroke by 2030.
- Hypertension and atherosclerosis are the most common treatable risk factors for stroke, cognitive decline and dementia.
- “Silent strokes” can be seen in 6% - 28% of older people, and are associated with cognitive decline and dementia.
- White matter disease can be seen in 40-80% of older people, and are associated with hypertension and risk of cognitive decline and dementia.
- Nearly half of people ≥65 years old have cognitive deficits 6 months after an ischemic stroke.
NIH Investment in Stroke Research

Overall NIH invested $288M in Stroke research FY 2015

- NINDS - stroke and cerebrovascular biology: 188,000
- NHLBI: 22,000
- NICHD: 19,000
- NIA: 15,000
## Research Priority Setting
A Summary of the 2012 NINDS Stroke Planning Meeting Report

Barbara G. Vickrey, MD, MPH; Thomas G. Brott, MD; on behalf of the Stroke Research Priorities Meeting Steering Committee and the National Advisory Neurological Disorders and Stroke Council; Walter J. Koroshetz, MD; on behalf of the National Institute of Neurological Disorders and Stroke

### Prevention
1. Prevention of Vascular Cognitive Impairment (VCI)
2. Imaging Biomarkers in Stroke Prevention: From Bench to Bedside
3. Expediting High Priority Comparative Effectiveness Research (CER) Trials in Stroke Prevention

### Treatment
1. Preclinical and Clinical Studies to Improve Early Reperfusion Therapy and Establish Limitations of Late Reperfusion Therapy
2. Preclinical and Clinical Studies to Achieve Robust Brain Protection
3. Expand and Integrate Existing Stroke Trial Networks to Accelerate Translation

### Recovery
1. Translational Research Using Neural Interface Devices for Stroke and Other Neurologic Disorders
2. Program for Translational Research Targeting Early Recovery after Stroke in Humans

### Cross-cutting
Accelerate the Translation of Stroke Research in Preclinical Animal Models into Clinical Studies of Highly Promising Treatments
• Established in 2013
• 25 regional centers with 350 satellite stroke hospitals, a coordinating center, and a data coordinating center
• Small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention, and recovery and rehabilitation.
• $50k/year/hub for training
• Infrastructure Total Cost-~$11million/year

http://nihstroke.net.org/
The Stroke Network Vision:

- Increased trial efficiency
- Balanced, prioritized set of early phase and phase 3 trials in prevention, treatment and recovery
  - Provides an efficient path for phase 2 moving to phase 3
  - Allows the logical ordering of trials that enter into network and create a pipeline of future trials for the network
- Stable infrastructure and research capacity
  - Improved team research among different subspecialties
  - Stable funding for research effort, fellowship training
- Improved data sharing
  - Single data center with uniform governance for data access
  - Fosters the use of CDEs
- Coordination and public-private partnerships with non-profits, industry, and international partners
- Manages trials that compete for the same patient groups
  - Established upon the commitment to consider ALL eligible stroke patients for a trial
- Trains the next generation of Stroke clinical researchers
Teamwork is the Solution

- Stroke Coordinators
- Industry
- Non-profit Stroke Associations
- PCORI/AHRQ
- Translational Stroke Science
- Informatics
- Health Technology
- International partners
- FDA
- New Investigators
- Pediatratics
- Statisticians
- Neuroimaging
- NeuroSurgery
- Stroke recovery
- Neurointerventional
- Vascular Neurology
- Emergency care
- Epidemiology
- Neuropathology
- Pediatrics
- Epidemiology
- Neuroimaging
- NeuroSurgery
- Stroke recovery
- Neurointerventional
- Vascular Neurology
- Emergency care
- Epidemiology
- Neuropathology
- Pediatrics
Goal of the Network

• To be the leading platform for stroke trials in the U.S. and globally

• To reduce the burden of stroke in the U.S and globally
25 Regional Coordinating Centers (RCCs) have fully executed MTAs, 159 Satellite MTAs are fully executed (including with 5 VA sites). This represents 353 clinical performance sites. 212 fully executed CIRB Reliance Agreements have been completed on behalf of StrokeNet.
StrokeNet Hospitals
StrokeNet Population Coverage by Group and Distance

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Distance from StrokeNet Center</th>
<th>Total (50 States)</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 Mile Radius</td>
<td>% of Total</td>
<td>40 Mile Radius</td>
</tr>
<tr>
<td>Total Population</td>
<td>120,758,537</td>
<td>38.3%</td>
<td>157,727,442</td>
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<tr>
<td>Male (adult)</td>
<td>44,518,863</td>
<td>38.1%</td>
<td>58,121,547</td>
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<tr>
<td>RACE</td>
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<td></td>
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<tr>
<td>White</td>
<td>80,374,323</td>
<td>34.5%</td>
<td>109,783,225</td>
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<tr>
<td>Hispanic/Latino</td>
<td>24,695,940</td>
<td>44.6%</td>
<td>29,719,245</td>
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<tr>
<td>Black</td>
<td>18,115,454</td>
<td>45.9%</td>
<td>21,868,666</td>
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<tr>
<td>Asian</td>
<td>9,952,233</td>
<td>65.3%</td>
<td>11,108,254</td>
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<tr>
<td>Other</td>
<td>8,048,767</td>
<td>53.3%</td>
<td>9,567,560</td>
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<tr>
<td>American Indian</td>
<td>509,505</td>
<td>20.0%</td>
<td>675,804</td>
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<tr>
<td>Pacific Islander</td>
<td>197,664</td>
<td>37.6%</td>
<td>235,546</td>
</tr>
<tr>
<td>AGE</td>
<td></td>
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<tr>
<td>Age 20 - 29</td>
<td>17,545,069</td>
<td>40.0%</td>
<td>22,223,717</td>
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<tr>
<td>Age 30 - 39</td>
<td>16,643,178</td>
<td>40.8%</td>
<td>21,216,296</td>
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<tr>
<td>Age 40 - 49</td>
<td>17,146,444</td>
<td>39.3%</td>
<td>22,493,618</td>
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<tr>
<td>Age 50 - 59</td>
<td>16,569,263</td>
<td>40.1%</td>
<td>21,454,193</td>
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<td>Age 60 - 69</td>
<td>11,115,483</td>
<td>35.8%</td>
<td>14,770,368</td>
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<tr>
<td>Age 70 - 79</td>
<td>6,019,004</td>
<td>34.5%</td>
<td>8,021,282</td>
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<tr>
<td>Age 80 and over</td>
<td>4,271,337</td>
<td>36.8%</td>
<td>5,616,526</td>
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<tr>
<td>Age &gt; 65</td>
<td>14,950,815</td>
<td>35.2%</td>
<td>19,866,025</td>
</tr>
</tbody>
</table>
Infrastructure Work Scope

- **Network Development**
  - SOPs
  - Working Groups
  - RCC Site Visits
  - Interaction with Global Networks

- **Project Development and Execution**
  - Feasibility and budgeting
  - Project Development advice and trial designs
  - Protocol finalization
  - Project management

- **Information Management**
  - Network, RCC, Sites, Investigators
  - Regulatory project management
  - cIRB and patient reimbursement
  - Neuroimaging repository
NCC Organizational Chart

Contact PI (Broderick)
Co-PIs (Khatri, Chimowitz, Cramer)

Trial Design,
Feasibility
Assessment,
Scientific and Clinical
Expertise

Operational
Infrastructure

Educational Core
(Kleindorfer, Marshall)

Working Groups
Imaging Core
Feasibility
Advisory Groups
# STROKENET: Working Group

<table>
<thead>
<tr>
<th>Acute Stroke</th>
<th>Primary and Secondary Prevention</th>
<th>Recovery and Rehabilitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair: Pooja Khatri University of Cincinnati</td>
<td>Chair: Marc Chimowitz Medical University of South Carolina</td>
<td>Chair: Steve Cramer UC Irvine</td>
</tr>
<tr>
<td>Co-chair: Jeff Saver UCLA</td>
<td>Co-chair: Ralph Sacco University of Miami School of Medicine</td>
<td>Co-chair: Steve Wolf PhD Emory University</td>
</tr>
<tr>
<td>Scott Janis, NINDS</td>
<td>Claudia Moy, NINDS</td>
<td>Daofen Chen, NINDS</td>
</tr>
<tr>
<td>Renee’ Martin NDMC</td>
<td>Sharon Yeatts NDMC</td>
<td>Sue Marden, NICHD</td>
</tr>
<tr>
<td>Greg Albers Imaging Core</td>
<td>Colin Derdeyn Imaging Core</td>
<td>Caitlyn Ellerbe NDMC</td>
</tr>
<tr>
<td>David Liebeskind Imaging Core</td>
<td>Steve Warach Imaging Core</td>
<td>Max Wintermark Imaging Core</td>
</tr>
<tr>
<td>TBD Minority Recruitment and Retention</td>
<td>Bernadette Boden-Albala PhD. Mt. Sinai School of Medicine/New York City Collaborative</td>
<td>Dorothy Edwards, PhD Minority Recruitment and Retention</td>
</tr>
<tr>
<td>Bill Barsan Univ of Michigan (ad hoc NETT member)</td>
<td>Amy Towfighi USC/UCLA</td>
<td>Alex Dromerick The Medstar Research Institute</td>
</tr>
<tr>
<td>Natalia Rost Massachusetts General</td>
<td>Scott Kasner University of Pennsylvania</td>
<td>Larry Wechsler University of Pittsburgh</td>
</tr>
<tr>
<td>Ed Jauch Medical University of South Carolina</td>
<td>Kamakshi Lakshminarayan University of Minnesota</td>
<td>Sean Savitz University of Texas at Houston</td>
</tr>
<tr>
<td>Brett Meyer UC San Diego</td>
<td>David Tirschwell University of Washington</td>
<td>Lorie Gage Richards University of Utah</td>
</tr>
<tr>
<td>Phil Scott University of Michigan</td>
<td>Shyam Prabhakaran Northwestern University</td>
<td>Maarten Lansberg Stanford University</td>
</tr>
<tr>
<td>Jay Mocco Mt. Sinai School of Medicine</td>
<td>Howard Kirschner Vanderbilt University</td>
<td>Andrew Grande University of Minnesota</td>
</tr>
<tr>
<td>Cathy Sila Case Western Reserve University School of Medicine</td>
<td>Tanya Turan Medical University of South Carolina</td>
<td>Steven Page Ohio State University</td>
</tr>
<tr>
<td>Wade Smith UC San Francisco</td>
<td>Max Hammer University of Pittsburgh</td>
<td>Carolee Winston USC/UCLA</td>
</tr>
<tr>
<td>Robert Dempsey University of Wisconsin</td>
<td>Jose Romano, University of Miami</td>
<td>Randy Marshall Columbia University</td>
</tr>
<tr>
<td>Enrique Leira University of Iowa</td>
<td>Coordinator: Heena Olalde University of Iowa</td>
<td>Coordinator: Aimee Reiss, Emory University</td>
</tr>
<tr>
<td>Coordinator: Kiva Schindler Emory University</td>
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</tr>
</tbody>
</table>
Advisory Committees

1) **Ethics and Competing Trials Committee** (Dr. Jennifer Majersik) – written guideline

2) **The Minority Recruitment and Retention Advisory Committee** under the direction of B. Boden Albala and Dawn Kleindorfer to assist in the development of strategies to address women and minority recruitment needs in SN grant proposals.

3) **The Interventional Advisory Committee** under the direction of Colin Derdeyn and Sam Zaidat to assist in addressing the changes in clinical practice and potential trial design necessitated by the positive findings in the recent endovascular trials.

4) **Pediatric Stroke Committee** under direction of Heather Fullerton and Catherine Amlie-LeFlond
* In conjunction with the NCC
WebDCU™ – an Integrated CTMS
Project assistance

- **Pre-Implementation**
  - Protocol, CRF, and SAP development
  - Study database setup in WebDCU™
  - Integration of randomization into WebDCU™

- **Implementation**
  - Data management and QA
  - Site Monitoring
  - Neuroimaging tracking
  - Interim reports and analyses
  - Interaction with DSMB as unblinded statistician
  - Blinded statistical input (if needed)

- **Post-Implementation**
  - Database lock
  - Analyses and publications
  - Submission of Public Use Data Sets (PUDS)
Pictured from left to right:
Dawn Kleindorfer, Chair, UC, Randy Marshall, Co-Chair, Columbia, Scott Janis, Project Scientist, NINDS, Barbara Bregman, Faculty, Georgetown, David Liebeskind, Faculty, UCLA, David Tirschwell, Faculty, Washington, Cemal Sozener, Former Trainee, Michigan, Farhaan Vahidy, Former Trainee, UTH, Heena Olalde, Coordinator, Iowa, Jeanne Sester, Coordinator, UC, Kristy Yuan, Trainee, UCSF, Laura Stein, Trainee, UPenn
Current Trainees

- 28 trainees, 64% female
- 4 Minority/Underrepresented
- 11/28 are faculty members

Degrees
- MD 22
- PhD 4
- MPH - PhD 1
- MPH 1
## Disciplines of Trainees

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Number</th>
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<tbody>
<tr>
<td>Vascular Neurology</td>
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<tr>
<td>Neurology</td>
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<tr>
<td>Neurology/NSG Neurocritical Care</td>
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<tr>
<td>Neurosurgery</td>
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<tr>
<td>Stroke Rehabilitation</td>
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<tr>
<td>Stroke Epidemiology</td>
<td>2</td>
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<tr>
<td>Emergency Medicine</td>
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<tr>
<td>Vascular Physiology</td>
<td>1</td>
</tr>
<tr>
<td>Occupational Therapy/Rehabilitation Psychology</td>
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<tr>
<td>Date</td>
<td>Topic</td>
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<tr>
<td>July 28</td>
<td>Atrial Cardiopathies and Cryptogenic Stroke</td>
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<tr>
<td>Aug 25</td>
<td>Genetics in Stroke</td>
</tr>
<tr>
<td>Oct 11</td>
<td>Minority Recruitment and Retention</td>
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<tr>
<td>Oct 27</td>
<td>Wake-up Strokes/Unknown Onset</td>
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<tr>
<td>Nov 17</td>
<td>Moyamoya and other Arterio – Pediatric treatment and complications</td>
</tr>
<tr>
<td>Jan 26</td>
<td>Pharmacology and mHealth to improve Rehabilitation Outcomes</td>
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<tr>
<td>Feb 23</td>
<td>Post-Stroke Outcome Measures</td>
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<tr>
<td>Mar 23</td>
<td>Gloves Off for Acute Stroke Management; Fellow Case Presentations</td>
</tr>
<tr>
<td>April 20</td>
<td>Cancer and Stroke</td>
</tr>
<tr>
<td>May 25</td>
<td>Big Data and our Understanding of Stroke Population Outcomes</td>
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</table>
## NIH StrokeNet Professional Development Webinar Schedule

**All Times are Eastern Time**

2016 – 2017

To join the meetings: [https://nihstrokenet.adobeconnect.com/pdw/](https://nihstrokenet.adobeconnect.com/pdw/)

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Speaker</th>
<th>Time</th>
<th>Institution</th>
<th>Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 1</td>
<td>Writing your CV &amp; Biosketch</td>
<td>Dawn Kleindorfer</td>
<td>3:00 EDT</td>
<td>Cincinnati</td>
<td>None Needed</td>
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<tr>
<td>Monday</td>
<td></td>
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<tr>
<td>Aug 16</td>
<td>Grant Writing</td>
<td>Steve Greenberg</td>
<td>2:00 EDT</td>
<td>MGH</td>
<td>Randy Marshall</td>
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<tr>
<td>Tuesday</td>
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<tr>
<td>Sept 22</td>
<td>How to Present your Data</td>
<td>Enrique Leira</td>
<td>2:00 EDT</td>
<td>Iowa</td>
<td>Farhaan Vahidy</td>
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<tr>
<td>Thursday</td>
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<tr>
<td>Oct 19</td>
<td>Creating a Study Budget</td>
<td>Joe Broderick</td>
<td>2:00 EDT</td>
<td>Cincinnati</td>
<td>David Liebeskind</td>
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<tr>
<td>Wednesday</td>
<td></td>
<td>Judith Spilker</td>
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<tr>
<td>Nov 10</td>
<td>Approval Process for Medical Devices in Stroke</td>
<td>Wade Smith</td>
<td>2:00 EST</td>
<td>UCSF</td>
<td>Dawn Kleindorfer</td>
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<tr>
<td>Thursday</td>
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<tr>
<td>TBA - Trainee Presentations</td>
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<td>TBA - Trainee Presentations</td>
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</table>

**NIH StrokeNet Professional Development Webinar Schedule**

**2016 – 2017**

To join the meetings: [https://nihstrokenet.adobeconnect.com/pdw/](https://nihstrokenet.adobeconnect.com/pdw/)
Where do StrokeNet Trainees Go Next?
What are they doing related to research?

- Conducting research
- Submitting grants
- Enrolling in trials

Year:
- 2013-14
- 2014-15
- 2015-16
Network Trial Activity
Process of Trial Concept to Trial Start

- Trials can arise from Working Groups within StrokeNet or from outside StrokeNet
- Process involves interaction with Protocol PIs along the entire way but with the bulk of the focus of the Working Groups and Executive Committee on scientific input (not review) and trial feasibility within the network
StrokeNet Trial Development Process

1. Applicant submits protocol concept to NINDS
2. Applicant discusses concept with working Group
3. ESC Approval
4. Feasibility review and development of budget
5. Scientific Peer Review
6. Council Review
7. Final Protocol development with Network
8. cIRB approval
9. GO!!
StrokeNet Trial Development Process

1. Investigator contact w/ initial concept 40
2. Discuss w/ StrokeNet working group
3. Submit concept proposal to NINDS 29
4. Extra. Science Committee Approval 19
5. Feasibility survey and budget
6. Submit application to NINDS 16 (23)
7. NINDS Scientific Peer Review
8. NINDS Council Approval 2 of 12 reviewed
10. StrokeNet CIRB approval protocol 2
11. Trial started within StrokeNet 1
## Trial Process – DEFUSE III As Example

<table>
<thead>
<tr>
<th>Step</th>
<th>Date</th>
<th>Step</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval NINDS Exec</td>
<td>5/7/2014</td>
<td>Working Group Summary</td>
<td>2/6/2015</td>
</tr>
<tr>
<td>Acute Working Group</td>
<td>5/7/2014</td>
<td>Executive Committee Summary</td>
<td>2/9/2015</td>
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<tr>
<td>Executive Committee Summary</td>
<td>6/18/2014</td>
<td>Notice of Award</td>
<td>9/30/2015</td>
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<tr>
<td>Submission for NIH Review</td>
<td>7/5/2014</td>
<td>First patient enrolled</td>
<td>4/1/2016</td>
</tr>
<tr>
<td>NIH Review</td>
<td>11/10/2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second Feasibility Assessment Begun</td>
<td>1/16/2015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Feasibility Survey/Population Assessment – ARCADIA Trial as Example

**Feasibility Survey**
- Feasibility recommendation to StrokeNet Exec Committee: 122 clinical sites willing to participate and provide approximately 5 subjects per year.

**Population Assessment**
- Summary of Eligibility Analysis Within a Population: 10.7% of ischemic stroke patients were eligible for this trial within a population.
- Estimation does not include the proportion of patients with atrial cardiopathy, a less common and extremely important inclusion requirement for this study.
- 24% of all ischemic stroke patients had any left atrial enlargement described (which may include the excluded “mild” LAE), of which 46 (2% of all stroke cases) were otherwise eligible for the study.
### cIRB Review Activity (27-Sep-2015 thru 24-Jan-2017)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sites</th>
<th>Reliance Agmts executed</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Protocol (Prime) approval</th>
<th>Study wide protocol amendments processed</th>
<th>All Performance Site Amendments processed</th>
<th>Prompt Reportable Events processed</th>
<th>Annual Continuing Reviews/# of sites reviewed</th>
<th>Closeouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREST II</td>
<td>67</td>
<td>22</td>
<td>30-Sep-2014</td>
<td>21</td>
<td>400 (30% personnel changes)</td>
<td>4</td>
<td>(2) 57</td>
<td>4</td>
</tr>
<tr>
<td>TeleRehab</td>
<td>11</td>
<td>1</td>
<td>18-Mar-2015</td>
<td>3</td>
<td>75 (28% personnel changes)</td>
<td>3</td>
<td>(1) 8</td>
<td>0</td>
</tr>
<tr>
<td>DEFUSE III</td>
<td>40</td>
<td>12</td>
<td>16-Oct-2015</td>
<td>6</td>
<td>300 (45% personnel changes)</td>
<td>12</td>
<td>(1) 37</td>
<td>0</td>
</tr>
<tr>
<td>ARCADIA</td>
<td>(120)</td>
<td>Planned</td>
<td>10-Mar-2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>118</td>
<td>34</td>
<td>30</td>
<td>775</td>
<td>19</td>
<td>102</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
Interactions with Other Networks

• NETT – collaborations on trials (POINT and SHINE)
• NeuroNEXT – supportive enrollment in Rhapsody trial
• cIRB
  ▪ Works with VA cIRB for those StrokeNet satellite sites who are part of StrokeNet – first of its kind
  ▪ Collaborations with NeuroNEXT, CTSA, and other cIRBs
• AHA
  ▪ GWTG database – incorporate these data as part of data for feasibility survey of StrokeNet sites (Lee Schwamm, Joe Broderick, Dawn Kleindorfer)
• Global Stroke Alliance (GAINS)
  ▪ 4 meetings in person of national stroke networks leadership. Quarterly meetings by phone
Trials currently underway in the Network

**The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study**
Health and Hope for Patients at Risk for Stroke

**MISTIE III**
MISTIE INTRACEREBRAL HEMORRHAGE TRIAL
Does faster clot removal in ICH give better patient outcomes?

**Diffusion and Perfusion Weighted Imaging Evaluation for Understanding Stroke Evolution TRIAL**
DEFUSE III

Treatment Trials

iDEF

As of 4/24/17
Recruitment

- Total enrolled: 456/500 (91%)
- Date first subject enrolled: 12/30/2013
- Total number of sites opened to enrollment (in 9 countries): 101
- Total number of sites currently active: 72/101 (71%)
- Total number of sites enrolling: 77/101 (76%)

MISTIE III enrollment projection as of 31-Dec-2016
Comparison of Activated StrokeNet vs. All Non StrokeNet Sites

<table>
<thead>
<tr>
<th></th>
<th>Total Sites (n=101)</th>
<th>% of Sites</th>
<th>% of Randomizations (n=450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>StrokeNet Hub</td>
<td>10</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>StrokeNet Spoke</td>
<td>20</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>Non StrokeNet</td>
<td>71</td>
<td>70%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>101</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

*Includes sites on administrative hold and closed sites*
CREST 2 Cumulative Enrollment (Final N=2480)

As of April 24, 2017

n=583
Telerehabilitation in the Home versus Therapy in-Clinic for Patients with Stroke – Thru 4/4/2017

Project Period 09/15/2014-07/31/2018
TeleRehab – Study Time line (first wave focus)

UC Irvine NOA  
15-Sep-2014

Regulatory Documents sent to sites  
24-Mar-2015

NCC Subaward Executed  
9-Jun-2015

First subject Randomized  
23-Sep-2015

3-18-2015  
CIRB Parent Protocol Approval

13-Apr-2015  
TELEREHAB Investigators and Training Meeting

3-Aug-2015  
Final PTA Completed
## Site variations in start-up

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Date of Email Site Notification of Study Requirements including PTA</th>
<th>PTA Execution</th>
<th># Days</th>
<th>CIRB approval</th>
<th># Days</th>
<th>Receipt and completion of all training and regulatory requirements</th>
<th># Days</th>
<th>Equipment Shipped from UCI*</th>
<th># Days</th>
<th>Site Visit NCC or UCI*</th>
<th># Days</th>
<th>Site Activation</th>
<th>Days from Initial Site Notification to Activation</th>
<th>Enrollment</th>
<th>Working days until enrollment</th>
<th>Current enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSD Hillcrest</td>
<td>10/26/2016</td>
<td>11/2/2016</td>
<td>7</td>
<td>11/29/2016</td>
<td>34</td>
<td>1/10/2017</td>
<td>76</td>
<td>11/29/16</td>
<td>34</td>
<td>1/9/2016</td>
<td>1/10/2017</td>
<td></td>
<td>76 Minimum</td>
<td>pending</td>
<td>pending</td>
<td>0</td>
</tr>
<tr>
<td>RCC 12 UCSD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCC 2 Columbia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RCC 8 Northwestern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All # days are calculated from initial site notification of study requirements
* University of California Irvine is the TeleRehab sponsor and prime award site
Issues Affecting site start-up in TeleRehab Trial

• Added time
  – Complicated award requiring budget revisions
  – Device purchasing and system programming at prime site, breakage during shipping
  – Assembly of trial device at sites-practice with devices at sites
  – Completion and posting of trial required training/regulatory documents
  – Lack of familiarity with CIRB process

• Speed Up the process
  – Experienced site personnel when available
  – RCC involvement
  – Enthusiasm for the project (completion of required documents)
Challenges

- The field and culture of stroke recovery and rehabilitation is new to multicenter clinical trials. Lack of experienced leadership, inclusion of other non-neurology specialties, impact upon variable reimbursement for PT/OT/speech.
Ongoing Clinical Trials in RCCs in 2/2014 (n=245*)

Number of Trials

- Acute: 33
- Prevention: 21
- Biomarker: 24
- Recovery and Rehabilitation: 167

* 2/2014: Out of the 669 ongoing ‘Stroke Trials’ listed on clinicaltrials.gov
Single RCC Studies versus Multi-Center Studies (n=245)
How are we responding?

• Representation at non-neurology national meetings about StrokeNet

• White paper published about stroke recovery/rehab – StrokeNet

• 3 additional rehabilitation trials submitted. Additional one in June. Mentoring of PIs regarding submissions.

• Communicating on proposals across working groups. Looking for opportunities to build recovery questions into prevention or acute trials (possibly as secondary or tertiary aims).

• Organizing NINDS/NCMRR Stroke Rehabilitation workshop in the Fall to discuss opportunities and priorities in recovery trials.
“A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”

Max Planck
Thank you
Goals for today

• Updates on clinical trials-related policies
• Impact of policies and updates on extramural community
Reforms over the clinical trial lifecycle

NIH Stewardship Reforms

- Good Clinical Practice Training
- Clinical Trial RFA/FOA
- Single IRB Policy
- Protocol Template
- ClinicalTrials.gov Registration
- ClinicalTrials.gov Results Submission

NIH Clinical Trial Decision Tree

**NIH Definition of Clinical Trial Decision Tree**

- **Does the study involve one or more human subjects?**
  - No
  - **Does the study involve the use of one or more interventions?**
    - Yes
      - **Does the study prospectively assign human subject(s) to an intervention(s)?**
        - Yes
          - **Does the study have a health-related biomedical or behavioral outcome(s)?**
            - Yes
              - The study is a clinical trial.
            - No
              - The study is not a clinical trial.
        - No
          - The study is not a clinical trial.
  - No
    - The study is not a clinical trial.

**Bottom Line:**
- Breadth of the definition
- Consulting with program staff prior to submission to find the right FOA

Policy on Good Clinical Practice (GCP) Training for NIH Awardees

- **NOT-OD-16-148**
- Issued September 16, 2016
- Effective January 1, 2017
- Complement to other required training on human subjects protections
- Required of all NIH-funded investigators and clinical trial site staff responsible for the conduct, management, and oversight of NIH-funded clinical trials
- Several acceptable courses
- **What’s new?**
  - A new course targeting behavioral/social science is also available
Policy on Funding Opportunity Announcements (FOA) for Clinical Trials

• **NOT-OD-17-043, NOT-OD-16-147**

• Clinical trial applications will be required to:
  • Submit to an FOA that allows clinical trials
    • NIH Parent Announcements will NO longer accept applications that include clinical trials
  • Provide specific information about protocols, specific review criteria, terms and conditions in Notices of Grant Awards

• **What’s new?**
  • Revised notice issued September 16, 2016
  • Effective date: January 25, 2018
  • A new form consolidating human subjects, inclusion, and trial information is being developed by the NIH Office of Extramural Research (OER)
NIH Policy on the Use of a Single Institutional Review Board (IRB) for Multi-Site Research

- **NOT-OD-17-027, NOT-OD-16-094**
- Applies to all domestic sites in multisite clinical research, not just clinical trials
- Improve efficiency
- Minimize duplicative reviews
- **NOT-OD-16-109** Direct and indirect cost scenarios
- **What’s new?**
  - Revised notice issued December 16, 2016
  - Changed effective for applications received on or after September 25, 2017
NCATS SMART IRB Reliance Platform

Through its Clinical and Translational Science Awards (CTSA) Program, NCATS is developing a single institutional review board (IRB) reliance platform for multisite clinical studies: the NCATS Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB Reliance Platform. The goal is to provide flexible resources that investigators nationwide can use to harmonize and streamline IRB review for their own multisite studies.

The process of obtaining ethical approval by multiple IRBs is a longstanding challenge that can lead to significant delays in study activation. One way to streamline the IRB review process and provide more consistent, high-quality reviews is for all sites participating in a multisite clinical study to rely on the ethical review of a single IRB. This concept is called a single IRB reliance model.

NCATS intends for its SMART IRB Reliance Platform to serve as a roadmap to help implement the NIH policy released on June 21, 2016, that requires all NIH-funded multisite clinical studies to use a single IRB.

There are different types of single IRB models, including the following:

Contact

NCATS SMART IRB Reliance Platform Staff

SMART IRB Authorization Agreement

Download the authorization agreement (PDF - 436KB)
Review the joinder agreement checklist (PDF - 116KB)

Join SMART IRB

Visit SMARTIRB.org to join and get started.

Learn More About SMART IRB

View SMART IRB resources, including standard operating procedures.

https://ncats.nih.gov/expertise/clinical/smartirb
NIH/FDA Protocol Template for Phase 2 and 3 IND/IDE Studies

- **NOT-OD-16-043**
- Issued March 17, 2016
- Developed by FDA and NIH
- Target available date: May 2017
- Corresponds to GCP
- Review of comments underway
- Development of an online tool
- Plans to adapt template for Phase 1 trials as well as social/behavioral intervention trials

Sharing and Reporting the Results of Clinical Trials

The principle of data sharing dates to the dawn of scientific discovery—it is how researchers from different disciplines and countries form collaborations, learn from others, identify new scientific opportunities, and work to turn newly discovered information into shared knowledge and practical advances. When research involves human volunteers who agree to participate in clinical trials to test new drugs, devices, or other interventions, this principle of data sharing properly assumes the role of an ethical mandate. These participants are often be blamed entirely. A recent analysis of 400 clinical studies revealed that 30% had not shared results through publication or through results reporting in ClinicalTrials.gov within 4 years of completion.4 This is a serious issue and the proposed rule underscores the intent of NIH to take strong action to promote timely dissemination of clinical trial results.

Without access to complete information about a particular scientific question, including negative or incon-

Trial Reporting in ClinicalTrials.gov — The Final Rule

Deborah A. Zarin, M.D., Tony Tse, Ph.D., Rebecca J. Williams, Pharm.D., M.P.H., and Sarah Carr, B.A.

Registration and Results Submission on ClinicalTrials.gov – Final Rule and NIH Policy

- **Final Rule** issued September 21, 2016
- Effective January 18, 2017
- Compliance date: April 18, 2017
- Visit [https://prsinfo.clinicaltrials.gov/](https://prsinfo.clinicaltrials.gov/) for more information
- NIH Policy applies to all NIH-funded clinical trials (not just FDA-regulated trials) regardless of study phase, type of intervention, or whether they are subject to the regulation
- **What’s new?**
  - Nothing new
  - Important to reiterate ramifications of non-compliance with the rule or the NIH policy
  - Funding for any new clinical trials at an institution will be withheld
Much activity underway

- NICHD-specific FOAs that will accept clinical trials
- NIH creation of a consolidated human subjects and clinical trials form as part of the application package
- Information systems in Commons/eRA under development
- Good Clinical Practice (GCP) training for NIH staff as well
- Staff and community training and outreach
- Communications
- Evaluation plans to assess policy change outcomes
Discussion/Questions

Stay tuned….!
PROMOTING MOTOR RECOVERY IN STROKE
FROM VERMICELLI TO NEUROPROSTHETICS

RANDOLPH J. NUDO, PHD
DISTINGUISHED UNIVERSITY PROFESSOR AND VICE CHAIR OF RESEARCH
DEPARTMENT OF REHABILITATION MEDICINE
DIRECTOR, LANDON CENTER ON AGING
DIRECTOR, INSTITUTE FOR NEUROLOGICAL DISCOVERIES

VISION FOR REHABILITATION RESEARCH AT KUMC
Neuroscience
Musculoskeletal Disorders
Outcomes Research
Cancer Rehabilitation
Gait & Balance

DISCLOSURES
- Consultant, Microtransponder, Inc.
- Consultant, St. Jude Medical
- CEO/Co-founder, NeuroBond, LLC (formerly NeuraLink Technologies, LLC)
- Research grants: NIH, Dept. Defense, Paralyzed Veterans of America,
  Ronald D. Deffenbaugh Family Foundation

PREDICTING RECOVERY AFTER STROKE

Winters, et al, 2015, Neurorehab Neural Rep

THEORIES OF RECOVERY

THEORIES OF RECOVERY
REVERSAL OF DIASCHISIS

THEORIES OF RECOVERY
COMPENSATION
THEORIES OF RECOVERY

NEURAL PLASTICITY

Axonal connectivity
Gene expression
BOLD response
Functional connectivity
Tractography
Motor maps
Subcellular morphology
Action potentials (spikes)
Motor evoked potential

EFFECTS OF M1 INFARCT ON ICMS MAPS

POST-INJURY RETRAINING PROMOTES PLASTICITY IN PERI-INFARCT MOTOR CORTEX

ANIMAL MODELS OF FOCAL ISCHEMIA

EFFECTS OF M1 INFARCT ON PREMOTOR MAPS AND ANATOMICAL CONNECTIONS
TEMPORAL MISMATCH CONUNDRUM

EXAMINING REMOTE PLASTICITY IN RATS AFTER MOTOR CORTEX INJURY

RAPID BEHAVIORAL IMPROVEMENT; DELAYED MAP EXPANSION

DOES CORTICAL REORGANIZATION REPRESENT VICARIOUS FUNCTIONING OF SPARED REGIONS TO SUPPORT “TRUE RECOVERY”??
**CHANGES IN LOCAL FIELD POTENTIALS POST-INJURY**

Bundy et al., in preparation

**NEUROMODULATION AFTER STROKE**

iTMS  
TDCS  
epidural stimulation  
Stimulation + behavioral experience

**EARLY INVESTIGATIONAL STUDIES**

- Alzheimer’s disease
- ADHD
- OCD
- Panic Disorder
- ALS
- Bulimia Nervosa
- Chronic Pain
- Epilepsy
- Fibromyalgia
- Migraine
- Parkinson’s disease
- Postpartum Depression
- Posttraumatic Stress Disorder
- Schizophrenia
- Stroke
- Substance Abuse and Craving

**RTMS IN STROKE**

- 2013 Cochrane review: 19 RCTs, 588 participants  
  - Two largest trials showed rTMS did not improve Barthel Index.  
  - Four trials showed no significant effect on motor function.
- 2014 meta-analysis of rTMS on hand function and excitability: 8 RCTs, 273 participants  
  - Positive effect on finger motor ability (4 studies, n = 79) and hand function (3 studies; n = 74). No difference in MEP or MT (n = 62).
- 2015 meta-analysis of rTMS in post-stroke aphasia: (4 studies, n = 137  
  - Medium effect for naming  
  - Trend for benefit on repetition  
  - No effect for comprehension

**CLOSED-LOOP NEUROMODULATION**

Combines neural recording, signal processing and microstimulation in a single device for closed-loop operation

**ADAPTIVE DBS**

Adaptive Deep Brain Stimulation in Advanced Parkinson Disease  
Unified Parkinson’s Disease Rating Scale  
N = 8  
LG-drivem stimulation
SPIKE-TIMING DEPENDENT STIMULATION

“Cells that fire together, wire together.” – Carla Schatz

PATHWAY-SPECIFIC NEUROMODULATION

Fetz NeuroChip

DEVELOPMENT OF ASIC FOR SPIKE-DRIVEN STIMULATION IN RATS

Collaboration with Pedram Mohseni, PhD, Dept. Electrical Engineering and Computer Science, Case Western Reserve University.

MINIATURIZED SYSTEM ASSEMBLY

PROOF-OF-CONCEPT STUDY IN RAT TRAUMATIC BRAIN INJURY MODEL

1. Create TBI in motor cortex (CFA) using CI model.
2. Implant microdevice, record spikes at FPA, stimulate S1 forelimb area.
3. Spike-driven (activity-dependent); 28.5 Hz/duty cycle 27.3 ms; 78.5 ms.
4. No behavioral training; periodic behavioral testing.
5. Compare to “no stimulation”; “open-loop stimulation”.

EFFECTS OF SPIKE-DRIVEN STIMULATION ON MOTOR PERFORMANCE

Guggenmos et al., PNAS, 2013

Guggenmos et al., PNAS, 2013
EVIDENCE FOR ENHANCED FUNCTIONAL CONNECTIVITY

CHALLENGES TO TRANSLATION

Daly & Wolpaw, Lancet Neurology, 2008

THE NEUROSCIENCE OF BRAIN REPAIR

Control - No Stimulation
8 Days Post-Lesion

$20M

FUNDING ACADEMIC RESEARCH

New Medical Breakthroughs

THE NEUROTECHNOLOGY STAR IS RISING

NEXT STEPS FOR: BIOENGINEERING

Invasive Brain Robot Interface
Brain Computer Interface Speller

Next steps: Facebook is working on a brain interface that lets you "Communicate Unclearly Your Mind"
April 18, 2017
SUMMARY

- Neuroplasticity after stroke provides a logical mechanistic basis for recovery of function.
- Neuroplasticity biomarkers can be examined at various levels of analysis.
- Neuroplastic changes are time-dependent.
- Neuromodulatory approaches, both open- and closed-loop, are providing new insights into potential avenues for repair.

ACKNOWLEDGEMENTS

Ronald D. Deffenbaugh Family Foundation
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Alberto Alverno, PhD candidate (IIT)