The National Academies of
SCIENCES • ENGINEERING • MEDICINE

Forum on Neuroscience and Nervous System Disorders

Neuroscience Trials of the Future: A Workshop

March 3–4, 2016

Keck Center
500 5th St., NW | Room 100
Washington, DC 20001

Background: While major strides have been made over the past two decades in basic neurosciences, the pace of translation into more effective treatments has eluded the field. Among the many factors contributing to this reality are the standard clinical trial methods that have barely changed, perhaps with the exception of increased use of electronic data acquisition and analysis.

Clinical trials in neuropsychiatric disorders continue to suffer from high failure rates even with biological targets that are well validated. Even in the hands of experienced investigators, the now commonplace problem of poor assay sensitivity, and attendant trial failure, have adversely affected pharmaceutical and device development. Signal detection in CNS trials is regularly beset by high placebo or non-specific response, intra-subject variability of endpoints, inter-subject and inter-site variability in multicenter trials, poor treatment adherence, and weak patient engagement and retention. The net effect of these challenges has been to simply increase the trial sample size in an attempt to control type II error. Yet, promising early clinical data often are not replicated in larger registration trials, and phase III failure rate in neuroscience randomized controlled trials remain among the highest in medicine. The apparent unsustainability of the current clinical development scenario has driven many large pharmaceutical companies entirely out of investment in neurosciences.

Quite apart from the business perspective, the fact that many early stage clinical trials misleadingly provide a signal (a type I error) raises the question whether volunteering for these trials is in the best interest of trial subjects, in particular, and for the patients with that particular disorder in general.

Better methods, from clinical study design through execution and evaluation, could help restore the integrity, feasibility, acceptability, efficiency and economic viability of clinical neuropsychiatric development. However, in order to use innovative approaches to address these challenges, buy-in and acceptance from the regulatory community will be important. For example, adaptive trials could offer a more efficient means of addressing experimental questions involving multiple uncertainties, although they are often infrequently used. In addition, understanding the utility of wearable and patient monitoring devices (and the data generated) in neuroscience clinical trials is needed. Given the current challenges in neuroscience clinical trials, this public workshop will bring together key stakeholders to discuss opportunities to improve the integrity, efficiency, and validity of clinical trials for nervous system disorders (focusing specifically on Phase II and Phase III trials).

Meeting objectives:

- Examine assay sensitivity challenges in clinical trials for nervous system disorders, including causes of type I error in early trials and poor signal detection and type II error in later stage trials.
- Explore opportunities to improve clinical trial methodology for nervous system disorders, including strategies for:
    - Guiding the selection of patient populations, such as using endophenotyping to increase the yield of responders and using genomics, proteomics, and imaging biomarkers to "stage" nervous system disorders.
    - Increasing patient engagement through all phases of the clinical trial (i.e., recruitment, screening, and post-trial) and improving adherence and retention.
    - Using patient-centric technologies (e.g., wearables) and integrating such real-world, real-time data with traditional clinical data.
    - Improving monitoring during clinical trials.
    - Leveraging recent advances in diagnostics, biomarkers, and endpoints to develop more efficient clinical trials.
    - Using novel trial designs (e.g., adaptive, enrichment, and platform design studies) for nervous system disorders, including associated regulatory challenges and opportunities.

March 3, 2016

8:30 a.m. Opening Remarks

ATUL PANDE, *workshop co-chair*
Chief Medical Officer and Executive Vice President
Tal Medical

RICHARD KEEFE, *workshop co-chair*
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine

Neuroscience Clinical Trials: Challenges and Opportunities

8:45 a.m. STEVEN ROMANO
Senior Vice President and Chief Science Officer
Mallinckrodt Pharmaceuticals

9:05 a.m. SHITIJ KAPUR
Executive Dean and Head of School
Institute of Psychiatry, Psychology & Neuroscience
King's College London

9:30 a.m. Discussion among Speakers and Workshop Participants

9:45 a.m. BREAK

SESSION I: CLINICAL TRIAL DESIGN

Session Objectives: Discuss current challenges to clinical trial design for nervous system disorders. Explore elements of clinical trial protocols that might be improved and lead to more efficient trials. Discuss how novel trial designs (e.g., adaptive, enrichment, and platform design studies) might be used for nervous system disorders.

10:00 a.m. Session Overview and Objectives

STEPHEN BRANNAN, *session moderator*
Vice President of Clinical Research and Medical Affairs
Forum Pharmaceuticals

Biomarkers

10:10 a.m. ANIL MALHOTRA
Director, Psychiatry Research, Zucker Hillside Hospital
Professor, Molecular Medicine and Psychiatry
Hofstra North Shore-LIJ School of Medicine

10:25 a.m. ALICE CHEN-PLOTKIN
Assistant Professor of Neurology
Perelman School of Medicine, University of Pennsylvania

Diagnosis and Patient Identification

- Discuss alternatives to the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM).

10:40 a.m. SARAH MORRIS
Acting Head, NIMH RDoC Unit
Program Officer, Schizophrenia Spectrum Disorders Research Program
National Institute of Mental Health

10:55 a.m. ROBERT BILDER
Professor-in-Residence, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles
Editor-in-Chief, *Diagnostics in Neuropsychiatry*

11:10 a.m. **Statistical Approaches and Considerations**

MICHAEL PENCINA
Director of Biostatistics, Duke Clinical Research Institute
Professor of Biostatistics and Bioinformatics
Duke University

Novel Clinical Trial Designs

11:25 a.m.

ERIK SNOWBERG
Professor of Economics and Political Science
California Institute of Technology

and

SYLVAIN CHASSANG
Professor of Economics and Public Affairs
Princeton University

11:45 a.m.

JAIDEEP KAPUR
Study Chair, Established Status Epilepticus Treatment Trial (ESETT)
Eugene Meyer III Professor of Neuroscience, Neurology
University of Virginia School of Medicine

12:00 p.m. Panel Remarks

Additional Panelists:

TIFFANY FARCHIONE
Acting Deputy Director
Division of Psychiatry Products
Food and Drug Administration

CARLOS PEÑA
Director, Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

12:30 p.m. Discussion among Speakers and Workshop Participants

1:00 p.m. LUNCH

SESSION II: CLINICAL TRIAL METHODOLOGY

Session Objectives: Explore opportunities to improve clinical trial methodology for nervous system disorders, including strategies for patient selection, engagement, and retention. Examine the extent to which current diagnostic methods contribute to the inherent variability in study populations. Discuss the utility of patient-centric technologies (e.g., wearables) and how such real-world, real-time data might be integrated with traditional clinical data to improve the integrity and efficiency of trials. Consider lessons learned and best practices from other therapeutic areas that might be applied to neuroscience clinical trials.

1:45 p.m. Session Overview and Objectives

AMIR KALALI, *session moderator*
Head, Neuroscience Center of Excellence
Quintiles

2:00 p.m. **Transforming Clinical Trials with Technology (guided panel discussion)**

- Discuss opportunities to improve patient engagement and retention.
- Discuss how to improve patient adherence to assigned treatment.
- Discuss opportunities to improve patient assessments.
- Consider the potential applications of emerging technologies (e.g., wearables) for clinical trials.
    - What are common clinical applications of these technologies?
    - What are the known benefits and risks associated with use? What are the scientific controversies behind this evidence?

CARLOS RODARTE
Chief Executive Officer
Health Rhythms

JOHN REITES
Head, Digital Health Acceleration
Qunitiles

DREW SCHILLER
Chief Technology Officer and Co-Founder
Validic

GLEN DE VRIES
President and Co-Founder
Medidata Solutions, Inc.

KARL KIEBURTZ
Robert J. Joynt Professor in Neurology
Senior Associate Dean for Clinical Research
Director of the Clinical & Translational Science Institute
University of Rochester Medical Center

3:15 p.m. BREAK

Lessons Learned from Other Therapeutic Areas

3:30 p.m. *Oncology*

PERRY NISEN
Chief Executive Officer
Sanford Burnham Prebys Medical Discovery Institute

3:45 p.m. *Cardiology*

ADRIAN FELIPE HERNANDEZ
Professor of Medicine
Duke Clinical Research Institute
Duke University School of Medicine

4:00 p.m. Discussion among Speakers and Workshop Participants

4:45 p.m. Day-One Wrap Up
Workshop Co-chairs

5:00 p.m. ADJOURN DAY ONE

March 4, 2016

8:30 a.m. Day Two Opening

ATUL PANDE, *workshop co-chair*
Chief Medical Officer
Tal Medical

RICHARD KEEFE, *workshop co-chair*
Professor of Psychiatry and Behavioral Sciences
Duke University School of Medicine

KEYNOTE SESSION III: INTERNATIONAL REGULATORY LANDSCAPE

Session Objectives: Consider the regulatory landscape for neuroscience clinical trials. Explore differences in regulatory pathways among countries and consider the impact.

8:50 a.m. Session Overview and Objectives

THOMAS LAUGHREN, *session moderator*
Director
Laughren Psychopharm Consulting, LLC

Key Regulatory Opportunities for Neuroscience Clinical Trials

9:00 a.m. *Regulatory Opportunities and Challenges in the US*

ROBERT CALIFF
Commissioner of Food and Drugs
Food and Drug Administration

9:20 a.m. *Regulatory Opportunities and Challenges in Europe*

LUCA PANI
Director General
Italian Medicines Agency (AIFA)

9:40 a.m. Discussion among Speakers and Workshop Participants

10:45 a.m. BREAK

SESSION IV: ETHICAL CONSIDERATIONS

Session Objectives: Examine ethical, legal, and social questions around neuroscience clinical trials. Consider potential data protection and human subjects' issues that might arise as clinical trials continue to transform.

11:00 a.m. Session Overview and Objectives

PETRA KAUFMANN
Director, Office of Rare Diseases Research and Division of Clinical Innovation
National Center for Advancing Translational Sciences

11:10 a.m. **Data Protection**

FRANK ROCKHOLD
Senior Vice President, Global Clinical Safety and Pharmacovigilance
GlaxoSmithKline
Professor of Biostatistics and Bioinformatics (*starting March 2016*)
Duke University School of Medicine

Human Subjects Protection

11:25 a.m. GREG KOSKI
President and Co-Founder
Alliance for Clinical Research Excellence and Safety (ACRES)

11:40 a.m. EMIL CHIAUZZI
Research Director
PatientsLikeMe

12:00 p.m. Discussion among Speakers and Workshop Participants

12:30 p.m. LUNCH

SESSION V: REIMBURSEMENT

Session Objectives: Consider how data collected by payers are used to inform reimbursement decisions and influence the long-term translation of products in the marketplace. Consider economic outcome measures used to determine payer practices. How will and should these measures be worked into future clinical trials?

1:15 p.m. Session Overview and Objectives

DANIEL BURCH, *session co-moderator*
Vice President and Global Therapeutic Area Head for Neuroscience
Pharmaceutical Product Development (PPD)

MICHAEL POLLOCK, *session co-moderator*
Vice President, Real World Outcomes
Pharmaceutical Product Development (PPD)

1:25 p.m. **Improving the Evidence Base for Reimbursement**

- What evidence is needed from research to align with insurance policies and evidence criteria?

RHONDA ROBINSON BEALE *via teleconference*
Senior Vice President and Medical Officer
Blue Cross of Idaho

1:40 p.m. **Challenges of Generating the Required Evidence: An Industry Perspective**

PAUL STANG
Vice President, Global R&D Epidemiology
Janssen Research and Development

1:55 p.m. **Pragmatic Trials: Challenges and Opportunities for Neuroscience Trials**

MARK CZIRAKY
Co-Founder and Vice President of Research
HealthCore, Inc.

2:10 p.m. Discussion among Speakers and Workshop Participants

2:45 p.m. BREAK

SESSION VI: MOVING FORWARD

Session Objectives: A panel will synthesize and discuss key highlights from the workshop presentations and discussions, including identifying next steps and promising areas for future action and research.

3:00 p.m. Panel Discussion: Session Moderators

ATUL PANDE, *workshop co-chair*
RICHARD KEEFE, *workshop co-chair*
STEPHEN BRANNAN, *session I moderator*
AMIR KALALI, *session II moderator*
THOMAS LAUGHREN, *session III moderator*
PETRA KAUFMANN, *session IV moderator*
DANIEL BURCH & MICHAEL POLLOCK, *session V moderators*

3:45 p.m. Discussion among Session Moderators and Workshop Participants

4:15 p.m. Closing Remarks from the Workshop Co-Chairs

4:30 p.m. ADJOURN WORKSHOP