Non-Invasive Neuromodulation of the Central Nervous System: A Workshop

March 2 and 3, 2015

Institute of Medicine
500 Fifth St., NW, Room 100
Washington, DC 20001

Background:

Based on advances in biotechnology and neuroscience, neuromodulation devices are poised to gain clinical importance in the coming years and to be of increasing interest to patients, health care providers and payers, and industry. Emerging evidence suggests that the potential therapeutic and non-therapeutic uses of non-invasive neuromodulation devices for the central nervous system are broad and will continue to expand. Along with the growing number of opportunities, there are challenges and open questions associated with the use of these devices. Currently, there is a need for greater understanding of the potential benefits and risks; in particular, of the short- and long-term impact of using these devices. From a regulatory standpoint, there are scientific and clinical questions that are important for regulatory approval and usability for consumers. A third area of consideration is the existing, and appropriate, levels of evidence for reimbursement. Several issues raise ethical questions, including the potential for off-label, over-the-counter, or "do it yourself" uses or for enhancement. Given the growing interest in non-invasive neuromodulation devices for the central nervous system, the goal of this workshop is to explore opportunities, challenges, and ethical questions surrounding the development, regulation and reimbursement of such devices.

Meeting objectives:

- Highlight potential benefits and risks of non-invasive neuromodulation based on known short and long-term central nervous system mechanisms of action
    - Explore the scientific landscape of non-invasive neuromodulation device development for both therapeutic and non-therapeutic uses
        - Consider issues concerning vulnerable populations
- Consider the regulatory landscape for non-invasive neuromodulation devices
    - Discuss potential outcome measures for therapeutic uses in regulatory processes
    - Explore pathways for regulatory approval of therapies utilizing a combination of non-invasive neuromodulation devices and pharmaceuticals
    - Discuss differences in regulatory pathways among countries
- Explore current and potential use reimbursement practices for therapeutic use of non-invasive neuromodulation devices
    - Explore the evidence base and acceptable therapeutic outcome measures utilized in reimbursement decisions
        - Consider economic outcome measures used to determine payer practices

- Examine ethical questions around the use of non-invasive neuromodulation devices
    - Consider ethical issues of off-label and over-the counter use on regulation, reimbursement and patient safety
        - Discuss the use of these devices for enhancement in individuals without an impaired baseline
        - Consider the implications of involuntary or coercive use (e.g., children, court ordered treatment)

March 2, 2015

8:30 a.m. Opening Remarks

ALVARO PASCUAL-LEONE, *workshop co-chair*
Professor of Neurology
Associate Dean for Clinical and Translational Research
Harvard Medical School

JEFFREY NYE, *workshop co-chair*
Vice President Neuroscience Innovation and Scientific Partnership Strategy
Janssen Research and Development, LLC
Johnson and Johnson Innovation

HANK GREELY**,** *workshop co-chair*
Director, Stanford Program in Neuroscience and Society
Stanford University

8:40 a.m. Mechanisms and targets of action

- Provide an overview of what is known about mechanisms and targets of action.
- Discuss what technology is needed to further develop the field.

MARK HALLETT
Chief, Human Motor Control Section
National Institute of Neurological Disorders and Stroke

9:05 a.m. Non-invasive neuromodulation technology

- Provide an overview of non-invasive neuromodulation devices, including electromagnetic devices and other developing devices, such as those involving ultrasound and light.
- Discuss what is known and unknown about engineering neuromodulation devices.
- Discuss how electrical dose and exposure of different brain locations to electric fields can be modeled.

VICTOR KRAUTHAMER
LEONARDO ANGELONE

Division of Biomedical Physics
Office of Science and Engineering Labs
Food and Drug Administration

SESSION I: THERAPEUTIC AND NON-THERAPEUTIC USES

Session Objectives: Discuss potential benefits and risks of non-invasive neuromodulation devices based on known short- and long-term central nervous system mechanisms of action. Explore the scientific landscape of device development for both therapeutic and non-therapeutic uses. Discuss the scientific controversies behind the potential uses. Consider issues concerning vulnerable populations.

Part One: Therapeutic Uses – Current & Developing

- What are common clinical applications of non-invasive neuromodulation devices?
- What are the known benefits and risks associated with use? What are the scientific controversies behind this evidence?
- Are mechanisms and outcomes of use different between adults and children?
- What opportunities and challenges exist around increasing understanding of effects of treatment?
- "In place of current therapeutics": How do non-invasive neuromodulation devices compare to current treatment options?
- "In combination with current therapeutics": What is the potential for use in combination with other therapies, and what is known about interactions?

9:30 a.m. Overview Talk and Session Objectives

ALVARO PASCUAL-LEONE, *moderator*
Professor of Neurology
Associate Dean for Clinical and Translational Research
Harvard Medical School

9:55 a.m. Panel Remarks

ROY HAMILTON
Assistant Professor in Neurology
University of Pennsylvania

SARAH "HOLLY" LISANBY
Professor and Chair
Department of Psychiatry & Behavioral Sciences
Duke University

ALEXANDER ROTENBERG
Associate Professor of Neurology, Harvard Medical School
Senior Associate in Neurology, Boston Children's Hospital

W. JEFFREY ELIAS
Associate Professor of Neurological Surgery and Neurology
Director of Stereotactic and Functional Neurosurgery
University of Virginia School of Medicine

10:35 a.m. Discussion among Speakers and Workshop Participants

11:10 a.m. BREAK

Part Two: Developing Non-Invasive Neuromodulation Devices for Therapeutic Uses

- What is the level of interest in development of these devices?
- What are the opportunities and barriers to development?

11:25 a.m. Session Overview and Objectives

JEFFREY NYE, *moderator*
Vice President Neuroscience Innovation and Scientific Partnership Strategy
Janssen Research and Development, LLC
Johnson and Johnson Innovation

11:30 a.m. Panel Remarks

MARK DEMITRACK
Vice President and Chief Medical Officer
Neuronetics

ATUL PANDE
Chief Medical Officer and Executive Vice President
Tal Medical

ANA MAIQUES
Chief Executive Officer
Neuroelectrics

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

12:30 p.m. LUNCH

Part Three: Non-Medical and Investigational Uses

- What is the type and extent of non-medical use?
- What are the known benefits and risks associated with use?
- What opportunities and challenges exist around non-therapeutic use, including over-the-counter and consumer-initiated use?
- Are mechanisms and outcomes of use different between adults and children?
- How is non-invasive neuromodulation used for diagnostic and investigational purposes?

1:15 p.m. Session Overview and Objectives

FRANCES JENSEN, *moderator*
Professor and Chair of Neurology
Perelman School of Medicine
University of Pennsylvania

1:20 p.m. Overview Talk

ROBERT CHEN
Professor of Neurology
University of Toronto

1:40 p.m. Panel Remarks

DYLAN EDWARDS
Director, Laboratory for Non-Invasive Brain Stimulation and Human Motor Control
Burke Medical Research Institute
Associate Professor, Department of Neurology
Weill Cornell Medical College

ROI COHEN KADOSH
Wellcome RCD Fellow and University Research Lecturer
University of Oxford

DANIEL WETMORE
Director, IP and Usability
Thync

MICHAEL FOX
Assistant Professor of Neurology
Harvard University

2:20 p.m. Discussion among Speakers and Workshop Participants

2:45 p.m. BREAK

SESSION II: REGULATORY

Session Objectives: Consider the regulatory landscape for non-invasive neuromodulation devices. Discuss potential outcome measures for therapeutic uses in regulatory processes, pathways for regulatory approvals for therapies using a combination of non-invasive neuromodulation devices and pharmaceuticals, and differences in regulatory pathways among countries and consider the impact.

3:00 p.m. Session Overview and Objectives

JEFFREY NYE, *session moderator*
Vice President Neuroscience Innovation and Scientific Partnership Strategy
Janssen Research and Development, LLC
Johnson and Johnson Innovation

Regulatory Pathways for Non-Invasive Devices

- How does the regulatory landscape contrast for non-invasive devices vs. other medical devices?
- What is the current regulatory position regarding the balance between risk-benefit standard of evidence and fostering innovation?
- How are medical devices defined in the context of regulatory approval?
- When do pre-existing device-based indications (e.g., pre-surgical mapping) impact other potential uses?
- What regulatory oversight exists for over-the-counter use?
- What are the regulatory issues regarding combination non-invasive neuromodulation devices and pharmaceutical therapies?
- Consider country differences in regulatory pathways, including:
    - How are regulatory pathways for non-invasive neuromodulation devices different?
    - What challenges exist for companies targeting domestic and foreign markets?
    - What is the impact of differences in regulations?
    - How does the FDA coordinate with overseas regulatory agencies?

3:05 p.m. TIMOTHY MARJENIN
Chief, Neurostimulation Devices Branch
Food and Drug Administration

3:25 p.m. IBIM TARIAH
Technical Director
BSI

3:40 p.m. Conducting Clinical Trials

- What levels of evidence are needed to warrant clinical use?
- What considerations are important when designing clinical trials (e.g., timing, length, magnitude)?
- What challenges exist for developing clinical trials for non-invasive neuromodulation devices?
- How can clinical trials be conducted effectively?

JASON CONNOR
Adaptive Clinical Trial Designer
Berry Consultants

3:55 p.m. Discussion among Speakers and Workshop Participants

5:00 p.m. Day-One Wrap Up

Workshop Co-chairs

5:15 p.m. ADJOURN DAY ONE

March 3, 2015

8:30 a.m. Day Two Opening

Workshop Co-Chairs

SESSION III: ETHICAL CONSIDERATIONS

Session Objectives: Examine ethical questions around the use of non-invasive neuromodulation devices. Consider ethical issues of off-label and over-the-counter use on regulation, reimbursement and patient safety. Discuss the use of these devices for enhancement in individuals without an impaired baseline. Consider the implications of involuntary or coercive use.

8:35 a.m. Session Overview and Objectives

HANK GREELY, *session moderator*
Director, Stanford Program in Neuroscience and Society
Stanford University

8:40 a.m. Neuromodulation, the Self, and Enhancement

- Explore questions about the use of these devices and the impact on "self".
- Consider the impact of use of these devices for enhancement in individuals without an impaired baseline.
- Identify ways of incorporating these considerations into the development and use of non-invasive neuromodulation devices.

ERIK PARENS
Senior Research Scholar
The Hastings Center

MARTHA FARAH
Walter H. Annenberg Professor of Natural Sciences
University of Pennsylvania

9:20 a.m. Neuromodulation and Unsupervised Use

- What are considerations when using non-invasive neuromodulation devices outside of therapeutic use?
- What are potential risks for use of these devices by consumers? Are there differences in risks/benefits between clinical oversight and non-clinical settings?
- How well are users protected from potential malfunctions?

HANNAH MASLEN
Postdoctoral Research Fellow in Ethics
Oxford Center for Neuroethics

9:40 a.m. Neuromodulation and Coercion

- Consider the impact of use in vulnerable populations (e.g., in children or individuals with mental illness) or involuntary use of these devices (e.g., court-ordered or psychiatrist-ordered).

JENNIFER CHANDLER
Professor of Law
University of Ottawa

10:00 a.m. Discussion among Speakers and Workshop Participants

10:30 a.m. Break

SESSION IV: REIMBURSEMENT

Session Objectives: Explore current and potential use reimbursement practices for therapeutic uses of non-invasive neuromodulation devices. Explore the evidence base and acceptable therapeutic outcome measures used in reimbursement decisions. Consider economic outcome measures used to determine payer practices.

10:45 a.m. Session Overview and Objectives

RHONDA ROBINSON BEALE, *session moderator*
Senior Vice President and Medical Officer
Blue Cross of Idaho

10:50 a.m. Current Reimbursement Practices

- Are payors currently reimbursing for these treatments?
- How are insurance companies currently evaluating these treatments in comparison to other options?
- Are there state differences in reimbursement practices?
- What is the impact of non-reimbursement?

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

OSCAR MORALES
Founding Director, Transcranial Magnetic Stimulation Service
McLean Hospital

11:20 a.m. Improving the Evidence Base for Reimbursement

- What is the current evidence base used for reimbursement?

- What evidence is needed from research to align with insurance policies and evidence criteria?
- How might greater information of comparative effectiveness between these devices and other therapeutics impact reimbursement practices?

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

BRADLEY GAYNES
Professor of Psychiatry
Associate Chair of Research Training and Education
UNC School of Medicine

11:50 a.m. Industry Panel

- What is the impact of non-reimbursement or of reimbursement that is fragmented regionally or internationally?
- How do reimbursement decision-making processes differ for pharmaceutical products and medical devices, given the differences in safety profile (i.e., the view of regulators)?
- How different do devices need to be for independent assessments and how important are pooling of studies of devices with a similar mechanism?

MARY HAILEY
Vice President of Health Policy and Government Relations
Neuronetics

ERIC LIEBLER
VP, Scientific, Medical, and Governmental Affairs
electroCore

JOHN REPPAS
Director of Public Policy
Neurotechnology Industry Organization

12:20 p.m. Discussion among Speakers and Workshop Participants

12:45 p.m. LUNCH

1:15pm Non-Invasive Neuromodulation: A Venture Capitalist's Perspective

ROSS JAFFE
Managing Director
Versant Ventures

SESSION V: 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.

1:35 p.m. Panel Discussion: Session Moderators

ALVARO PASCUAL-LEONE, *workshop co-chair*
Professor of Neurology
Associate Dean for Clinical and Translational Research
Harvard Medical School

JEFFREY NYE, *workshop co-chair*
Vice President Neuroscience Innovation and Scientific Partnership Strategy
Janssen Research and Development, LLC
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FRANCES JENSEN
Professor and Chair of Neurology
Perelman School of Medicine
University of Pennsylvania

HANK GREELY**,** *workshop co-chair*
Director, Stanford Program in Neuroscience and Society
Stanford University

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

2:25 p.m. Discussion among Speakers and Workshop Participants

2:45 p.m. Closing Remarks from the Workshop Co-Chairs

3:00 p.m. ADJOURN WORKSHOP