

NATIONAL INSTITUTES OF HEALTH

Sham Neurosurgical Procedures in Clinical Trials for Neurodegenerative Diseases: Scientific and Ethical Considerations

Hyatt Regency Bethesda Hotel

June 30 - July 1, 2010

The randomized, placebo-controlled clinical trial is generally viewed as the gold-standard in clinical investigation. However, when a trial involves a sham surgical procedure, unique scientific and ethical issues emerge. There are several examples of positive findings in open label studies of cell or gene therapies in Parkinson's disease where subsequent trials which included a sham neurosurgical arm failed to show a difference between treatment arms. While sham neurosurgical arms have often been included in recent gene therapy trials for Parkinson's disease (four of six that have been initiated since 2003) and Alzheimer's disease (one trial started enrolling in November of 2008), their use is not without controversy.

As novel therapies are developed for neurodegenerative diseases, questions will arise about whether to include a sham arm and, if so, at what stage in development. Institutional Review Boards and patients will face complex decisions regarding such studies.

The NIH Office of Biotechnology Activities, Office of the Director and the National Institute of Neurological Disorders and Stroke have developed this conference to explore the scientific and ethical issues regarding sham neurosurgical arms and to provide a foundation for the development of points to consider when designing clinical trials which involve delivery to the central nervous system. The specific goals are to:

- *Increase our understanding of the utility and limitations of sham neurosurgical procedures through a review of the prior clinical trial experience in Parkinson's disease*
- *Address how experiences from trials in Parkinson's disease may inform clinical trial design for other neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease*
- *Discuss the scientific and ethical issues raised by the use of sham neurosurgical procedures, including trial design, subject recruitment, risk assessment, and informed consent*
- *Explore the perspective of patients regarding the design of trials that may involve sham neurosurgical procedures*

Wednesday, June 30, 2010

8:00 AM

Welcome and Opening Remarks

Story Landis, Ph.D., National Institute of Neurological Disorders and Stroke, National Institutes of Health
Jacqueline Corrigan-Curay, M.D., J.D., Office of Biotechnology Activities, National Institutes of Health
Howard J. Federoff, M.D., Ph.D., Conference Co-Chair, Georgetown University Medical Center, Washington, DC
Anthony Lang, M.D., FRCPC, Conference Co-Chair, University of Toronto, Toronto, Ontario, Canada

8:15 AM

Clinical Trial Design: Randomization, Controls and Minimizing Bias

Presenter: Karl Kiebertz, M.D., M.P.H., University of Rochester, Rochester, NY – [Slide Presentation](#)

8:30 AM

Clinical Trial Design: Statistical Challenges in Designing Surgical Trials for Neurodegenerative Diseases

Presenter: Steven Piantadosi, M.D., Ph.D., Cedars-Sinai Medical Center, Los Angeles, CA
[Slide Presentation](#)

8:45 AM

Insights into Understanding the Placebo Response

Presenter: A. Jon Stoessl, M.D., University of British Columbia, Vancouver, British Columbia, Canada
[Slide Presentation](#)

9:05 AM

Review of Parkinson's Disease Trials that Did Not Include a Sham Neurosurgical Arm

Fetal Cell Transplantation Trials for Parkinson's Disease

Presenter: Hakan Widner, M.D., Ph.D., Skane University Hospital, Lund, Sweden
[Slide Presentation](#)

Neurotrophic Factor Trials for Parkinson's Disease

Presenter: John T. Slevin, M.D., University of Kentucky Medical Center, Lexington, KY
[Slide Presentation](#)

9:35 AM

BREAK

9:50 AM

Review of Parkinson's Disease Trials that Included a Sham Neurosurgical Arm

Fetal Cell Transplantation Trials for Parkinson's Disease

Presenter: C. Warren Olanow, M.D., Mount Sinai Medical Center, New York, NY
[Slide Presentation](#)

Neurotrophic Factor Trials for Parkinson's Disease

Presenter: Mark A. Stacy, M.D., Duke University School of Medicine, Durham, NC
[Slide Presentation](#)

10:20 AM

Proposed European Union Trial of Fetal Cell Transplantation for Parkinson's Disease

Presenter: Roger Barker, M.D., University of Cambridge, Cambridge, United Kingdom
[Slide Presentation](#)

10:35 AM

Parkinson's Disease Trials: A Critical Assessment

Presenter: Steven Piantadosi, M.D., Ph.D.
[Slide Presentation](#)

10:55 AM

Questions and Discussion of Parkinson's Disease Clinical Trials (*by presenters*)

- How does one interpret the data from the open trials in light of results of the trials which included a sham neurosurgical arm?

11:30 AM

BREAK for Lunch Distribution

12:00 PM

Panel Discussion I. What Have We Learned from the Parkinson's Disease Trials?

Moderator: Christopher Goetz, M.D., Rush University,
Chicago, IL

Panelists: Anders Bjorklund, M.D., Ph.D., Lund University,
Lund, Sweden
Stanley Fahn, M.D., Columbia University, New
York, NY
Thomas B. Freeman, M.D., University of South
Florida College of Medicine, Tampa, FL
Don Gash, Ph.D., University of Kentucky,
Lexington, KY
Ivar Mendez, M.D., Ph.D., Halifax Infirmary,
Halifax, Nova Scotia, Canada
Steven Piantadosi, M.D., Ph.D.
Hakan Widner, M.D., Ph.D., Skane University
Hospital, Lund, Sweden

- From a neurosurgical standpoint, what does the surgical delivery of cells or other factors to the brain entail? How does one quantify the medical and surgical risks of a sham neurosurgical arm with the following interventions, and do the risks differ by neurodegenerative disease?
 - Partial burr hole
 - Stereotactic frames
 - Conscious sedation
 - General anesthesia
 - Imaging
 - Immunosuppression
- How does one distinguish the absence of benefit from a failed trial?
- Are there specific questions that can only be answered by including sham neurosurgical procedures?
- At what stage in therapeutic development is inclusion of a sham neurosurgical arm warranted/not warranted?
- How does the placebo response seen in these trials impact the design of future trials?
 - Are there alternative clinical trial designs that could be employed when a study is conducted without a sham neurosurgical arm and a significant placebo effect is anticipated?
 - Are there validated outcome measures for Parkinson's disease that are reliable, objective,

and not influenced by a placebo response that can be used to evaluate disease progression without the inclusion of a sham neurosurgical arm?

- What measures can be taken to minimize (1) the placebo effect and (2) investigator bias, including impact on assessment of endpoints?
- Given that a new therapy may be either added to or substituted for standard medical therapy, should these trials include a “best medical management” arm as well as a sham neurosurgical arm?

2:30 PM

BREAK

2:45 PM

Panel Discussion II: How do the Considerations for Inclusion of a Sham Neurosurgical Arm Differ for Other Neurological Disorders?

Moderator: Karl D. Kieburtz, M.D., M.P.H.

Panelists: Marc Peschanski, M.D., Ph.D., Institute for Stem Cell Therapy and Exploration of Monogenic Diseases, Evry, France
Steven Piantadosi, M.D., Ph.D.
Jeffrey Rothstein, M.D., Ph.D., Johns Hopkins School of Medicine, Baltimore, MD
Joao Siffert, M.D., Ceregene, Inc., San Diego, CA

- For Alzheimer’s disease, ALS, and Huntington’s disease, are there validated outcome measures that are reliable, objective and not influenced by a placebo response that can be used to evaluate disease progression without the inclusion of a sham neurosurgical arm?
- How does the limited sample size encountered in rare disorders such as ALS and HD impact trial design?
- Are there circumstances when standard medical therapy may be a more appropriate control than a sham neurosurgical arm?
 - What criteria would determine this?
 - Does the delay of an anticipated therapeutic response mitigate the need for a sham arm?

- Are there validated measures to assess capacity to give informed consent in disorders in which there may be impaired cognitive function or judgment?
 - What issues are encountered during the consent process when a subject has impaired cognitive function or judgment?
 - How does the inclusion of a sham arm in a trial impact this process when the subject is impaired?
- How might the placebo response differ in these diseases, and how would trial design be impacted?
- Do the absence of alternate therapeutic approaches and/or the severity of a disease impact the decision to include a sham neurosurgical arm?

3:45 PM

BREAK

4:00 PM

Patient Perspectives on Sham Neurosurgical Procedures

Research Studies on Patient Perspectives

Presenter: Scott Kim, M.D., Ph.D., University of Michigan,
Ann Arbor, MI [Slide Presentation](#)

4:20 PM

One Patient's Perspective

Discussant: Pat Lyons with Mark Stacy, M.D.

- Did you expect there would be a clinical benefit?
- What did you understand about the potential for a placebo effect?
- Was there information that you did not have at the beginning of the trial that would have been helpful to you in making your decision to enroll?

Foundation Perspective

Discussant: Robin Elliott, Parkinson's Disease Foundation,
New York, NY
[Slide Presentation](#)

- In your conversations with people with Parkinson's disease, do you think the reasons for inclusion of sham neurosurgical procedures in clinical trials are understood?

- In your conversations with people with Parkinson’s disease, has the inclusion of a sham neurosurgical arm influenced their decision to enroll in a trial?
- Is there information about trial designs that potential subjects feel could be more clearly articulated?

Advocacy Perspective

Discussant: Amy Comstock Rick, J.D., Parkinson's Action Network, Washington, DC

- What role do advocacy groups and people with Parkinson’s or other neurodegenerative diseases have in shaping trial design?
- How can the inclusion of patients in this process be implemented most effectively?

5:00 PM **Public Comment**

5:30 PM **Adjourn**

Thursday, July 1, 2010

8:00 AM **Opening Remarks**

Howard J. Federoff, M.D., Ph.D., Co-Chair
Anthony Lang, M.D., FRCPC, Co-Chair

8:20 AM **A Patient’s Perspective on the Use of Sham Neurosurgical Procedures**

Moderator: Howard Federoff, M.D., Ph.D.

Discussant: Perry Cohen, Ph.D., Parkinson Pipeline Project, Washington, DC

[Slide Presentation](#)

- Do you see a role for sham neurosurgical arms in clinical trials? Why or why not?

8:35 AM

An Ethical Framework for Evaluating the Use of Sham Neurosurgical Procedures

Presenter: Edmund Pellegrino, M.D., Georgetown University,
Washington, DC
[Slide Presentation](#)

8:55 AM

Ethical Considerations in the Use of Sham Neurosurgical Procedures

Moderator: Jeffrey P. Kahn, Ph.D., M.P.H., University of
Minnesota, Minneapolis, MN

Panelists: Herbert Gottweis, Ph.D., University of Vienna,
Vienna, Austria
Jason H. Karlawish, M.D., University of
Pennsylvania, Philadelphia, PA
Scott Kim, M.D., Ph.D.
Jonathan Kimmelman, Ph.D., McGill University,
Montreal, Quebec City, Canada
[Slide Presentation:](#)
Edmund Pellegrino, M.D.

Dorothy E. Vawter, Ph.D., Minnesota Center for
Health Care Ethics, St. Paul, MN

Balancing Science and Ethics

- Is the scientific evidence supporting the use of a sham neurosurgical arm to answer the study questions sufficiently robust to justify the risks from an ethical perspective?

Discussion of Risk

- Given the previous discussion of the risks of partial burr holes and stereotactic frames, conscious sedation versus general anesthesia, and additional procedures, e.g., imaging, is the stage of the research (e.g. Phase I versus Phase II) determinative in deciding whether it is ethically appropriate to include a sham neurosurgical arm?
- Does the ethical analysis regarding subject selection for a trial that uses a sham neurosurgical arm change depending upon disease stage or severity?
- If previous trials have established that a placebo response to a sham neurosurgical procedure is likely and often sustained, does this potential for a benefit from the sham neurosurgery itself justify an increased level of risk?

- How do trials with open-label extension studies alter the ethical analysis?
- In study designs without cross-over, is there an obligation to offer access to the active agent to those in the sham arm?

10:10 AM

BREAK

10:20 AM

Discussion of Informed Consent

- What strategies can be used to minimize therapeutic misconception?
- How can discussions of risks and benefits be conducted in order to provide realistic expectations of potential harms and side effects?
- What role does investigator bias play in fostering therapeutic misconception, and how can such bias and its effects be minimized?
- What special considerations should the informed consent process address in patients with neurodegenerative diseases where there may be cognitive impairment and/or impaired decision-making capacity?
- If a subject's capacity to give informed consent is impaired, under what circumstances should they still have access to trials involving the use of sham neurosurgical procedures? What is the role of caregivers in this setting?

11:35 AM

Pediatric Trials and Sham Neurosurgical Procedures: Unique Ethical Considerations

Presenter: David Wendler, Ph.D., Department of Bioethics,
National Institutes of Health
[Slide Presentation](#)

Discussants: Ronald G. Crystal, M.D., Weill Cornell Medical
College, New York, NY
[Slide Presentation](#)

Eric Kodish, M.D., The Cleveland Clinic
Foundation, Cleveland, OH

12:45 PM

LUNCH

1:45 PM

Public Comment

2:15 PM

Therapeutic Development, Sham Surgery Controls, and Evidence of Effectiveness

Presenter: Wilson W. Bryan, M.D., Food and Drug Administration, Rockville, MD
[Slide Presentation](#)

2:35 PM

Summary Discussion of the Science and Ethics of the Use of Sham Neurosurgical Procedures in Neurodegenerative Diseases

Moderators: Howard J. Federoff, M.D., Ph.D.
Anthony Lang, M.D., FRCPC

- Are there questions that can only be answered by including a sham neurosurgical arm? At what stage of therapeutic development is inclusion of a sham neurosurgical arm warranted/not warranted?
- How does the selection of the primary or secondary clinical outcome measures affect the need for a sham procedure?
- What alternative controls may be considered in lieu of a sham neurosurgical arm?
- What is the role of a “standard of care” arm and what factors should be considered in using “standard of care” as a control arm either alone or with a sham neurosurgical arm?
- What are the key ethical considerations when including a sham neurosurgical arm versus another type of control?
- How does the evaluation of the risk of the sham neurosurgical procedure differ in the context of different neurological diseases?
- If a sham neurosurgical arm is to be used, what is the optimal study design when a placebo effect is anticipated?
 - Degree of invasiveness
 - Anesthesia: conscious sedation vs. general
- Are there measures which can be taken to minimize placebo effects associated with a surgical intervention?
- For Alzheimer’s disease, ALS, and Huntington’s disease, are there validated, objective disease progression measures that

can be used as clinical endpoints in a trial in place of a sham neurosurgical arm?

- What special considerations should the informed consent process address in subjects with impaired capacity?
- How can potential subjects be better educated and engaged regarding the role of sham neurosurgical procedures in trials for neurodegenerative disorders?

5:00 PM

Closing Remarks

5:15 PM

Adjourn