

Questions About Sham Neurosurgical Procedures in a Patient-Centered Paradigm

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Nocebo



The Gold Standard for Scientific Evidence

- Prospective, randomized, controlled clinical trial (RCT) – required by FDA law
 - Randomization accounts for all known and unknown factors that determine the outcome
 - Control group provides a comparison for gauging safety and efficacy data
- Double blinded, placebo control-- required by scientific consensus, not law
 - Artificial comparison group to filter psychological 'bias' of patients, providers, and evaluators
 - Blinded to make deception (sham status) equal

Key Issues for Sham Controls

- ❑ **Consistent failure of sham controlled trials in pivotal studies versus substantial, lasting benefits for patients in open label trials**
- ❑ **Possible explanations for failures based on:**
 - 1) **Research on the mechanisms and actions of placebo responses**
 - 2) **Violation of assumptions of the linear statistical experimental model**
 - 3) **Research questions to fill the gaps in knowledge about psychological responses to treatment and the interactions among these factors**
- ❑ **An alternative patient-centered approach that is safer, provides additional information, and is more financially feasible**

Ethical Issues

- The ethical context is important to build trust and collaborative relationships between patients and researchers
- The ethics of sham brain surgery are questionable, for example
 - Deception and Risk
 - Therapeutic misconception

Analysis of Failed Pivotal Trials

- Phase I, open label:
 - 30-50% or more improvement (UPDRS motor off)
 - Lasting 3 or more years for all therapies up to 10 years and counting in some cases
- Phase II, pivotal RCT, sham control
 - Improvements less than half of phase 1 for both groups reflects lower expectations and other factors
 - Little or no separation between treatment & control
 - Later follow-up analysis showed statistically significant differences as early as 18 months

Research on Placebo Response

- What is a placebo response?
- Risk-benefit determination
 - Who decides? Role of individual patient
 - What criteria? Emphasis on type 2 vs type 1 errors
- Strength of placebo response
 - What determines the strength of
 - the placebo response?
 - the treatment response?
 - how do they differ?
 - How long does the placebo effect last?
 - What factors determine the time frame?

Interaction effects

- Interaction effects— assumed to be zero
 - Is the psychological placebo response distinguishable from the biochemical activity of the intervention that works on the same striatal pathway?
 - Does the placebo response substitute for treatment response? Are they additive? Multiplicative?
 - Does the extent of interaction vary with the magnitude of the placebo response?
- What is the value of comparing intentionally artificial treatment and control groups that have been modified to minimize strong psychological effects and without regard unknown interactions between these effects and biologically active interventions?

Alternative to Sham Controls

- DBS study design: Randomized single blind, best medical therapy controlled trial provides:
 - Randomization controls for all other effects on outcomes.
 - Single blind of independent, centralized raters of outcome measures controls for the major source of exogenous bias.
 - A “time limited placebo” effect would define a benchmark time needed for stable improvements to last to be considered a reliable result from the treatment.
 - Added benefit of useful data for safety/efficacy comparisons in a realistic context to inform clinical practice.
- Conditional approval and payment for coverage with evidence development (CED) in expanded follow up for larger phase III and IV protocols to establish longer term safety and efficacy.

Summary of PWP Perspective

- ❑ Risk benefit tradeoffs -- Versus the certainty of progression. The major risk is NOT having access to more effective treatments (type 2 error)
- ❑ Time is not neutral for PWP. To speed up the process, certainty is not required, but full disclosure and honesty are.
- ❑ Assumptions must be verified. The interactions between the treatment and the very powerful placebo response to brain surgery are not known.
- ❑ Placebo responses that are reliable, stable, and durable should not be treated as bias to be eliminated but rather as an important part of the therapeutic process.
- ❑ Activation of PWP both physically and mentally, individually and in groups, at all levels of research and health care is necessary to discover the processes of healing from PD (cure) and is in itself therapeutic.
- ❑ The major challenge for health care in this century is the creation of the infrastructure to support the paradigm shift to patient-centered health care necessary to manage chronic disease in an era of scientific innovation.

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Paradigm shift for medical science:

CURRENT DESIGN

- Provider expertise
- Constituent group interests
- Patient as subject
- Linear model
 - Independent static factors, no interaction
 - Avoid false positive
- Assume distinct biological and psycho-social treatment response
- Blind to eliminate bias from evaluator and to equalize psycho-social effects

PATIENT-CENTERED

- Patient activated
- Patient Interests
- Patient as collaborator
- Dynamic systems model
 - Feedback process and human adaptation
 - Avoid false negative
- Conduct research on confounded treatment and placebo and interactions
- Blind evaluator bias only, Retain beneficial human psycho-social response

Authentic Voice for Patients

The ***Parkinson Pipeline Project*** illustrates the empowerment of grass roots PWP in technology enabled social networks

- linked to peers with complementary skills in online communities
- Ready access to scientific, business, and regulatory data
- Motivated to collaborate with researchers to accelerate 'cures'
- Primarily young and middle age onset, activist PWP
 - Educated professionals and business executives
 - Unique vantage point largely unexplored by science
 - Opinion leaders and active participants in clinical research

Patient Goals and Roles

- A basic premise of this presentation is that only PWP ourselves or care-givers who live with the consequences of PD have the full information on the Patients' interests.
- My role is to point out the differences in the views of patients and other constituencies and persuade the scientific consensus to take a fresh look at the assumptions versus the reality of failed clinical trials.
- Ultimate goal is collaboration between the patient care team and the clinical researcher to support individualized "patient centered" medical research and health services.
- PD has large numbers of talented, educated, accomplished professionals and business at the peaks of their careers, willing and able to make valuable contributions