

Therapeutic Development, Sham Surgery Controls, and Evidence of Effectiveness

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NIH Conference: Sham Neurosurgical
Procedures in Clinical Trials: Scientific and
Ethical Considerations
Bethesda, Maryland
June 30 – July 1, 2010

Therapeutic Development and Sham Surgery Controls: Outline

- Therapeutic (drug and biologic) Development
 - Objective
 - Process
 - Regulatory requirements
 - “Adequate and well-controlled investigations”
- Sham surgery controls
- Conclusions

Therapeutic Development

- Objective: Drugs (including biologics) that are safe and effective for a given indication
- Process
 - Drug discovery
 - Nonclinical (animal) study objectives:
 - Toxicity, biodistribution, carcinogenicity, proof-of-principle
 - Guide design (including dosing, population, and monitoring) of subsequent Phase 1 study
 - Phase 1 objectives:
 - Safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, feasibility, and activity (efficacy?)
 - Guide dosing and monitoring in subsequent Phase 2 studies
 - Phase 2 objectives:
 - Investigate dose, route, regimen, population, endpoints, and magnitude of effect
 - Determine design of subsequent confirmatory (Phase 3) studies
 - Phase 3 objectives: Evidence of efficacy and safety to support a marketing application (New Drug Application (NDA) or Biologics Licensing Application (BLA))
 - At each step in drug development, reliable data is valuable for “go : no-go” decisions regarding further drug development.

Regulatory requirements for NDA or BLA

- Food, Drug, and Cosmetic Act:
 - a) Section 505(d)(5): Approval of a new drug requires “substantial evidence that the drug will have the effect it purports or is represented to have.”
 - a) Section 505(d)(7): “Substantial evidence” means evidence consisting of “adequate and well-controlled investigations.”

Regulatory Requirements for NDA or BLA

- 21 CFR 314.126: Adequate and well-controlled studies
 - “The purpose of conducting clinical trials is to distinguish the effect of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.”
 - Generally, the following types of controls are recognized:
 - Placebo control
 - Dose-comparison concurrent control
 - No treatment concurrent control: “Where ... placebo effect is negligible ...”
 - Active-treatment concurrent control
 - Historical control: “usually reserved for special circumstances”

Sham Neurosurgical Controls

- Useful to distinguish effect of study drug from placebo effect (i.e., expectation bias)
- May be necessary for blinding of study subject and investigator
 - Blinding decreases risk of biased management and biased outcome assessment, which could produce biased (misleading) study results.
- Useful in Phase 1 and Phase 2 studies to assess effectiveness (and safety)
 - to determine the population most responsive to the study agent, the endpoints that best indicate the study agent activity, and the estimated magnitude of effect, to guide the design of subsequent studies (avoid Phase 3 failures)
 - to guide “go : no-go” decisions (avoid Phase 3 failures)
- May be recommended for Phase 3 studies intended as “well-controlled investigations” to provide the “substantial evidence” necessary to support an NDA or BLA

Sham Neurosurgical Controls: Conclusions

- Sham surgery controls can be useful at every stage of clinical drug development.
 - To provide reliable data to guide the next phase of drug development.
 - For “go : no-go” decisions regarding further clinical development.
- The relative value of sham surgery controls depends on the study objectives (as described above), the specific indication, and the study endpoints.
- The greater the FDA concern regarding expectation bias (i.e., placebo effect), biased management, or biased assessment, the more likely that FDA will ask for sham surgery controls.

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