

# Choice of Control Group

Robert M. Nelson, M.D., Ph.D.  
Pediatric Ethicist, Office of  
Pediatric Therapeutics, Food and  
Drug Administration



Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, June 9, 2008

1

# Choice of Control Group

- The selection of an appropriate control group is a critical decision which impacts on the scientific validity and ethical acceptability of a clinical investigation.
- The proper control group allows for discrimination between patient outcomes caused by the test treatment, and outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.



E-10 Choice of Control Group and Related Issues in Clinical Trials, May 2001

2

## Types of Control Groups

- **Concurrent Control** (control/test groups chosen from same population, usually by randomization, and treated concurrently)
  - Placebo (e.g., two or three-arm study)
  - Active (Positive)
  - Dose-Response (different dose or regimen of study treatment)
  - No treatment (not blinded)
- **External (including historical) Controls**, regardless of comparator treatment



## Assay Sensitivity

- **Definition:** the ability of a clinical trial to distinguish effective treatment from less effective or ineffective treatment.
- Adding a known positive and/or negative (placebo) control group as a third study arm can serve as a measure of the assay sensitivity of a clinical trial, especially in the absence of observed differences between the study drug and the other control interventions.



## Concept of Equipoise

- Combines two principles: scientific and ethical
  - Scientific: genuine uncertainty (or indifference) about the relative merits of the interventions being compared in a clinical investigation.
  - Ethical: no patient-subject should be randomized to an intervention known to be inferior either to the study intervention or to known effective treatment.
- The requirement for scientific uncertainty and an ethical obligation to provide proven effective therapy are separate claims. One should carefully distinguish between these two senses when using the concept of equipoise.



5

## Debate over Placebo Controls: Paragraph 29. WMA Declaration of Helsinki (2000)

- “The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”



<http://www.wma.net/e/policy/b3.htm>

6

## Note of Clarification on Paragraph 29

- “The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances...”



Added by the WMA General Assembly, Washington 2002 (<http://www.wma.net/e/policy/b3.htm>)

7

## Note of Clarification on Paragraph 29

- “However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
  - “Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or [currently under revision]
  - “Where a prophylactic, diagnostic or therapeutic method is being investigated for a *minor condition* and the patients who receive placebo will *not be subject to any additional risk of serious or irreversible harm.*”



Added by the WMA General Assembly, Washington 2002 (<http://www.wma.net/e/policy/b3.htm>)

8

## Choice of control in clinical trials

- “As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".



## Choice of control in clinical trials

- “Placebo may be used:
  - “When there is no established effective intervention;
  - “When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;
  - “When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.”



## Component Analysis

- “To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively, as is done in clinical practice. Research protocols meeting the criteria [of 21 CFR 50.52] regarding risk and benefit may be conducted or supported provided the conditions of [21 CFR 56.111] and the requirements [of 21 CFR 50.55] will be met. If the research also includes a purely investigative procedure presenting more than minimal risk, the research should be reviewed under [21 CFR 50.53] with respect to such procedure.”

– The National Commission 1978



11

## General Ethical Principles of Subpart D

- Research involving children either must present a balance of risks and potential benefits comparable to the available alternatives (21 CFR 50.52), or be restricted to “minimal (or low) risk” absent direct benefit to child (21 CFR 50.51 or 53).
- Under 21 CFR 50, Subpart D, withholding known effective treatment from children enrolled in a control group must present no more than a “minor increase over minimal risk.”



12