THE ETHICS AND SCIENCE OF PLACEBO-CONTROLLED TRIALS

Susan S. Ellenberg, Ph.D.
Director, Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research, FDA

National Institutes of Health
Ethical/Regulatory Aspects of Human Subject Research
November 12, 2003

BACKGROUND

- Scientific rationale for placebo controls is well understood and widely accepted
- Ethical concerns about use of placebo controls in specific settings regularly arise
  - deception
  - desperate need situations
- Two events in 1990's raised new issues

"THE CONTINUING UNETHICAL USE OF PLACEBO CONTROLS"

- Ken Rothman and Karen Michels, *New England Journal of Medicine*, 1994
- Asserted that placebo-controlled trials were always unethical unless no effective treatment was known for condition under study
- Assertion based on their interpretation of the Declaration of Helsinki
- Noted that many trials violate this standard
- Argued that FDA policies requiring placebo-controlled trials foster unethical research

TRIALS TO PREVENT PERINATAL TRANSMISSION OF HIV IN DEVELOPING COUNTRIES

- Paper by Public Citizen's Sidney Wolfe and Peter Lurie (*NEJM*, 1997) attacked ethics of NIH-sponsored studies of short-course AZT treatment to prevent transmission of HIV from mother to newborn
- Asserted that more intensive regimen already demonstrated to be effective ("076 regimen") should have been used as control

DIFFERING PERSPECTIVES

- Clinical trialists studying treatments for serious/life-threatening diseases
- Drug developers and regulators focusing on treatments to relieve symptoms
- Bioethicists and public advocates concerned about exploitation in third world countries
- Public Health authorities trying to identify effective and affordable regimens for third world

NEW ISSUES

- Can active control always be a scientifically acceptable substitute for placebo control?
- Do the ethics of a placebo-controlled trial depend on the consequence of remaining untreated?
- Must a known effective agent be used as a control, even if it cannot be implemented for financial and logistical reasons in studying a new agent?

(TERMINOLOGY)

- Untreated controls in non-blinded studies raise same issues as placebo controls in blinded studies

- Placebos are used in many studies that do not raise the usual ethical issues
  - "Add-on" studies (A+B vs. A+placebo)
  - "Double dummy" studies (A+placebo (B) vs. B+placebo (A)

THE PURPOSE OF MOST CLINICAL TRIALS IS TO DETERMINE WHETHER A TREATMENT IS EFFECTIVE AND "SAFE ENOUGH"

WAYS TO SHOW A TREATMENT IS EFFECTIVE

- Show superiority to placebo
- Show superiority to known effective treatment ("active control")
- (Show equivalence/noninferiority to active control)

DRUG DEVELOPMENT 101

- Most new drugs developed to compete with existing drugs are not expected to be more effective than those already on market
  - may have a secondary advantage: more favorable toxicity profile, more convenient dosing regimen, more desirable formulation or route of administration
  - primary goal will be to show equivalent or noninferior efficacy to competing product
- Equivalence/noninferiority studies are frequently inadequate to support conclusion that a new drug is effective

THE PROBLEM WITH NONINFERIORITY STUDIES

- Treatment X has been compared to placebo in 5 studies, with effects of 10, 4, 16, 0 and 8. The 3 highest effect sizes were significant; drug was approved. Trials all designed similarly, with adequate power, and performed in apparently similar populations.

THE PROBLEM WITH NONINFERIORITY STUDIES

- Treatment X has been compared to placebo in 5 studies, with effects of 10, 4, 16, 0 and 8. The 3 highest effect sizes were significant; drug was approved. Trials all designed similarly, with adequate power, and performed in apparently similar populations.
- New treatment Y is compared to treatment X. Outcomes are similar. Is treatment Y effective?

THE PROBLEM WITH NONINFERIORITY STUDIES

- Treatment X has been compared to placebo in 5 studies, with effects of 10, 4, 16, 0 and 8. The 3 highest effect sizes were significant; drug was approved. Trials all designed similarly, with adequate power, and performed in apparently similar populations.
- New treatment Y is compared to treatment X. Outcomes are similar. Is treatment Y effective?
  - maybe yes, if X had effect of 8 or more
  - maybe no, if X had effect of 4 or less

THE PROBLEM WITH NONINFERIORITY STUDIES

- Treatment X has been compared to placebo in 5 studies, with effects of 10, 4, 16, 0 and 8. The 3 highest effect sizes were significant; drug was approved. Trials all designed similarly, with adequate power, and performed in apparently similar populations.
- New treatment Y is compared to treatment X. Outcomes are similar. Is treatment Y effective?
  - maybe yes, if X had effect of 8 or more
  - maybe no, if X had effect of 4 or less
- Without placebo, don't know effect of X in trial

THE PROBLEM WITH NONINFERIORITY STUDIES

- Conclusion of noninferiority requires a critical assumption: that the effect of the active control in this study is as good or better as in earlier studies
- Similar to assumptions made in historically controlled studies
- Validity of conclusion rests on unverifiable assumption of consistency of effect across studies (and over time)

CONSISTENCY ASSUMPTION DOES NOT HOLD IN MANY DISEASE AREAS

- Pain
- Depression
- Anxiety
- Allergic Rhinitis
- GERD
- Hypertension

VARIABILITY OF RESULTS IS MULTIFACTORIAL

In studies of symptom-relieving treatment, non-inferiority trials are often unreliable, for many reasons

- symptoms wax and wane
- widely varying response rates
- modest effect sizes
- high placebo response rates
- effect measures are variable

If effect size of standard drug is moderate to large, and consistent from study to study, new drug can be reliably evaluated in noninferiority study (vaccines, most antibiotics, many cancer drugs)

If effect size is modest and varies substantially from study to study, drug cannot be reliably evaluated in noninferiority studies (most drugs for symptom relief)

If effect size is modest but consistent, new drugs can potentially be reliably evaluated in noninferiority studies, but these studies might need to be very large

INTEGRATING ETHICAL AND SCIENTIFIC CONSIDERATIONS INTO DRUG DEVELOPMENT POLICY

- In evaluating new drugs, placebo controls should be used when possible because of
  - Difficulties in interpreting results of active control trials
  - Increased efficiency of placebo-controlled trials
- There are cases, however, in which placebo controls are not acceptable

WHEN ARE PLACEBOS UNETHICAL?

- Depends on consequence of going untreated
- If available treatment is known to
  - prevent or delay death
  - prevent or delay irreversible disease progression
  - prevent or delay any other major harm to long-term health

  Then placebo treatment is generally not ethical
- If available treatment has no expected impact on long-term health, placebo treatment may be acceptable provided patient is fully informed of
  - potential consequences of being untreated
  - availability of treatment outside the trial

EASY CASES

- Clear impact on mortality or major morbidity
  - chemotherapy for many cancers
  - thrombolytics post-MI
  - antiviral drugs for HIV

EASY CASES

- Clear impact on mortality or major morbidity
  - chemotherapy for many cancers
  - thrombolytics post-MI
  - antiviral drugs for HIV
- No impact on mortality or major morbidity
  - analgesics
  - hair growth promoters
  - anti-acne drugs
  - anti-impotence drugs

ROOM FOR DEBATE: HARDER CASES

- No evidence of harm from remaining untreated, but concern that harm is possible
  - antidepressants: increased suicides?

OBLIGATION TO MONITOR SAFETY

- Safety monitoring is expected of sponsors in any trial of medical intervention
- In trials comparing new agent to placebo, when known effective agents exist, need to establish monitoring plan that can identify quickly anyone whose condition requires immediate active therapy
  - Anti-asthma treatments
  - Antipsychotics
  - Antidepressants

ROOM FOR DEBATE: HARDER CASES

- No evidence of harm from remaining untreated, but concern that harm is possible
  - antidepressants: increased suicides?
- Known harm from long-term nonuse of therapy but no known harm from short-term nonuse (as in a study)
  - antihypertensives
  - lipid-lowering drugs

ROOM FOR DEBATE: HARDER CASES

- No evidence of harm from remaining untreated, but concern that harm is possible
  - antidepressants: increased suicides?
- Known harm from long-term nonuse of therapy but no known harm from short-term nonuse (as in a study)
  - antihypertensives
  - lipid-lowering drugs
- Different views on benefit or risk-benefit ratio
  - treatment for sepsis
  - pertussis vaccines

NEW SEPSIS TREATMENT

- Activated protein C (drotrecogin alfa) approved in November 2001; first biologic agent for this indication (many previous failures)
- Data presented at FDA Advisory Committee meeting, October 2001: reduced mortality Commiftee split 10-10 on approval
- Dissenters published article detailing concerns (*NEJM* 10/26/02)
  - Risk of serious hemorrhage
  - Adequacy of efficacy data
- Ongoing issues
  - Defining population in which benefits exceed risks
  - Cost-effectiveness

PERTUSSIS VACCINES

- Pertussis (whooping cough) is a serious childhood disease that can cause death and brain damage in infants
- Until 1990's, whole-cell pertussis vaccine routinely used in U.S. and elsewhere, but not everywhere
  - Fairly reactogenic (fevers, extended crying)
  - Some believed vaccine could cause permanent damage
- Placebo-controlled studies of acellular vaccine, expected to be safer, performed in Sweden and Italy where whole-cell vaccine not used

ROOM FOR DEBATE: HARDER CASES

- No evidence of harm from remaining untreated, but concern that harm is possible
  - antidepressants: increased suicides?
- Known harm from long-term nonuse of therapy but no known harm from short-term nonuse (as in a study)
  - antihypertensives
  - lipid-lowering drugs
- Different views on benefit or risk-benefit ratio
  - treatment for sepsis
  - pertussis vaccines
- Non-availability of proven therapy
  - prevention of perinatal transmission of HIV in developing countries

MALARIA PREVENTION

- CDC wished to test effectiveness of treated mosquito netting in settings of high malaria prevalence
- Best way to keep mosquitos away: air-conditioned houses in which windows can be kept closed
- Obligation of CDC to provide air-conditioned houses to control group?
  - Even if they did, would probably prove more effective than mosquito netting
  - Usefulness of such a result to the community?

WHAT ABOUT SEVERE DISCOMFORT?

- Products that effectively treat/prevent severe symptoms are often highly effective
  - anesthesia
  - treatment for acute asthma
- Active control trials can usually be conducted with reasonable reliability and efficiency when control is known to be highly effective
- When effect is modest, may have a dilemma
  - placebo-controlled trials may be infeasible
  - active control trials may not be informative
  - "add-on" study may be best option if most do not get full relief with standard treatment

WHY WOULD ANYONE WANT TO ENTER A PLACEBO-CONTROLLED TRIAL INSTEAD OF TAKING ACTIVE TREATMENT?

- Depression as an example
  - A is functioning well on current drug, may have no interest in study of a new drug
  - B doesn't feel adequately treated with current drug, has tried several other drugs, may be very interested in new drug study
  - C is considering whether to try drug therapy

WHY STUDY NEW DRUGS THAT ARE NOT EXPECTED TO BE BETTER THAN EXISTING DRUGS?

- Many therapeutic advances provide no increased efficacy, but reduce toxicity, increase convenience or offer other advantages
- Having multiple products available increases chances of successfully individualizing therapy
  - not all drugs work in all recipients
  - a drug that is less effective overall may work for a patient who does not respond to the "more effective" drug
  - similarly effective drugs may have different toxicity profiles that may be differentially tolerable
  - interaction with other commonly used drugs may vary

BETTER DRUGS, SIMILAR EFFICACY

Drug Class	Old/New	Advance
ntidepressant	Tricyclics/SSRIs	Different (better accepted) side effects
ntipsychotic	Phenothiazines/ atypical antipsychotics	Decreased extrapyramidal effects
ntihistamine	Sedating/Nonsedating	Lack of sedation
nti-inflammatory	NSAIDs/COX-2-selective NSAIDs	Decreased risk of GI bleeding
ntihypertensive	High-dose diuretics/Low-dose diuretics, ACE inhibitors, calcium channel blockers	Decreased hypokalemia and depression

DECLARATION OF HELSINKI

- International statement of fundamental ethical principles for biomedical research
- Initially adopted by World Medical Association in 1964
- Revisions made in 1975, 1983, 1989, 1996, 2000
- Proposed clarification 2001

DH POSITION ON PLACEBOS: OCTOBER 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.

CORRECTIVE ACTION

- Clarification issued 2001
  - OK if scientifically necessary
  - OK if no risk of serious or irreversible harm

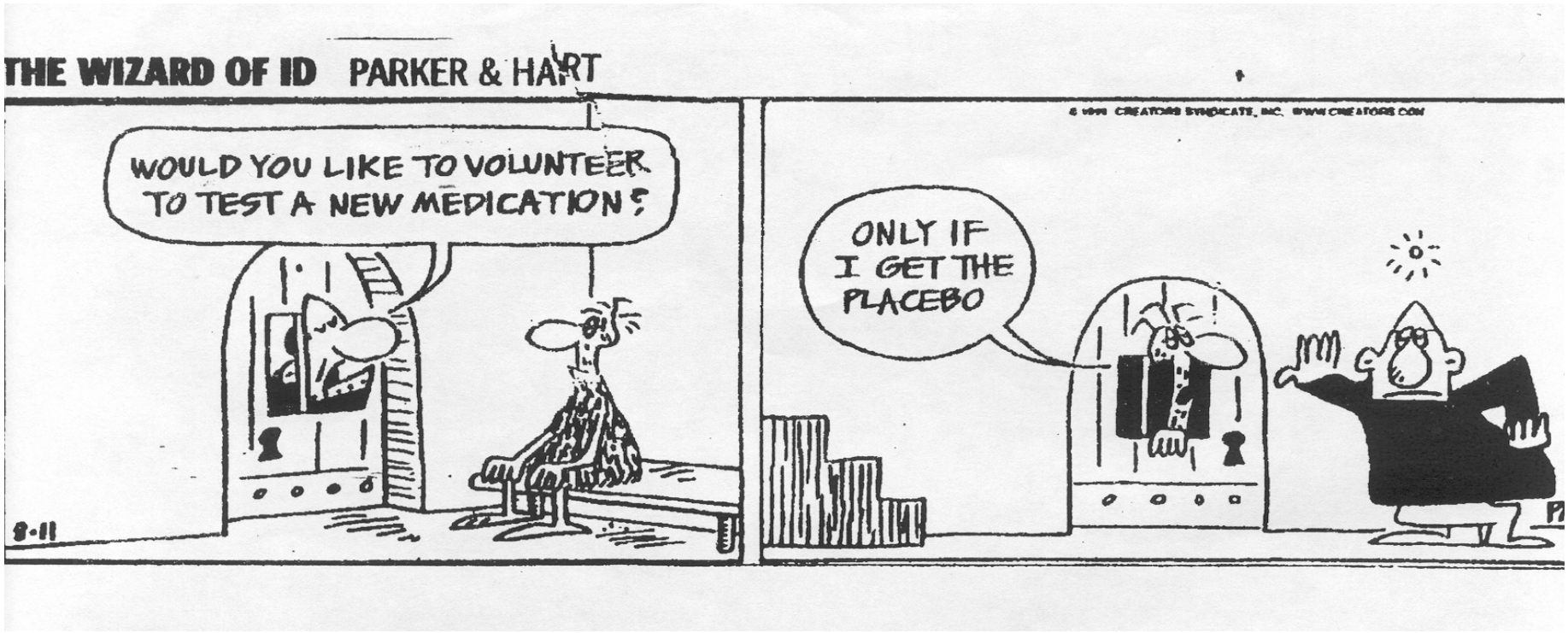
COUNCIL FOR ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS)

- International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)
- Placebos may be used when
  - No established effective intervention
  - Withholding established intervention would expose subjects at most to temporary discomfort or delay in relief of symptoms
  - Use of active control would not yield scientifically reliable results and subjects would not be put at risk of serious or irreversible harm

INTERNATIONAL CONFERENCE ON HARMONIZATION

- Collaboration of industry and regulatory scientists in U.S., Europe and Japan
- Guidance document issued on choice of control groups in clinical trials (ICH E10)
- Addresses scientific and ethical issues
- Supports use of placebo controls, regardless of available therapy, as long as no risk of serious/irreversible harm


HIRAM S. DUDSON
1930 - 1993
Member,
Placebo Group
D. Reilly


THE WIZARD OF ID PARKER & HART
WOULD YOU LIKE TO VOLUNTEER TO TEST A NEW MEDICATION?
9-11
ONLY IF I GET THE PLACEBO

SUMMARY

- Diminishing support for position that placebos are always unethical when treatment alternatives are available
- Placebo controls are essential for studying many types of medical products
- Interpretive difficulties with active control trials remain poorly understood
- Debate on specific cases is inevitable and probably healthy