Using Data to Inform Debates in International Research Ethics

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Overview

- An obligation to obtain empirical evidence in medical ethics
- The example of placebo controls
- Further opportunities

An Empirical Imperative

- Clinical research is predicated on the notion that we need data to determine ‘truth’ and facilitate sound decision-making
- Ironically, methods of clinical research, including those designed to protect participants such as conclusions about appropriate trial design in particular cases and informed consent, are introduced without data regarding safety or efficacy
- Where relevant we need to evaluate these protections as we would any proposed clinical intervention

Empirical Research in Medical Ethics

- Defined: “ the application of research methods in the social sciences (such as anthropology, epidemiology, psychology, and sociology) to the *direct* examination of issues in medical ethics.”
- Distinguished from other forms of ethics such as *normative ethics* and *metaethics*

Potential Roles for Empirical Research in Medical Ethics

- Purely descriptive studies
- Testing established or new norms
- Descriptions of facts relevant to normative arguments
- Slippery slope arguments
- Assessing likely consequences
- Empirical testing of normative theories
- Case Reports
- Demonstration projects

Examples of Previous Efforts

- The Subject Interview Study and the Advisory Committee on Human Radiation Experiments
- International Perspectives on Protecting Human Research Subjects and the US National Bioethics Advisory Commission
- Designing and evaluating an informed consent process for umbilical blood banking
- Randomized trials in informed consent

Rich Rhetoric

- Chronicles of ‘unethical’ use of placebo controls
  - Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *NEJM* 1994; 331: 394-398
- Subsequent research to decrease vertical transmission of HIV infection
  - US study 076
  - Contemporaneous trials in Africa and Asia
- ‘Tuskegee’ trump card
  - Angell M, The ethics of clinical research in the third world. *NEJM* 1997; 337: 847-849
- A ‘polarized debate’ involving “placebo orthodoxy” and “active-control orthodoxy”
  - Emanuel EJ, Miller FG. The ethics of placebo-controlled trials – a middle ground. *NEJM* 2001; 345: 915-919.

Purpose

- The sole purpose here is to suggest ways empirical research can inform and enlarge conceptual discussions and policy making regarding the use of placebo controls in clinical trials, not to address the range of unsettled ethical questions
- To suggest where empirical efforts may enhance approaches to ensure clinical research is conducted in an ethically appropriate fashion

Overview

- Empirical evaluations concerning placebo controls in hypertension
  - Assessing claims about harm
  - Determining the attitudes of physicians
- Related work
- Further opportunities

The Contentious Nature of Using Placebo-Controls in Studies of Hypertension

- Challenged by Rothman and Michels
  - "despite the established efficacy of many agents in treating mild-to-moderate hypertension."
- Seemingly inconsistent with the Declaration of Helsinki (October 2000, prior to December 2002 clarification)
  - "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods."

Placebo-Controls in Short-Term Clinical Trials of Hypertension

Sana M. Al-Khatib, Robert M. Califf, Vic Hasselblad, John H. Alexander, Douglas C. McCrory, Jeremy Sugarman

Science 2001; 292: 2013-2015

Background

- Short-term placebo-controlled trials for mild to moderate hypertension are common, despite claims that they are ‘unethical’
- ICH would seem to permit such trials, “if withholding the effective treatment leads to no serious harm and if patients are fully informed about available therapies and the consequences of delayed treatment.”

Methods

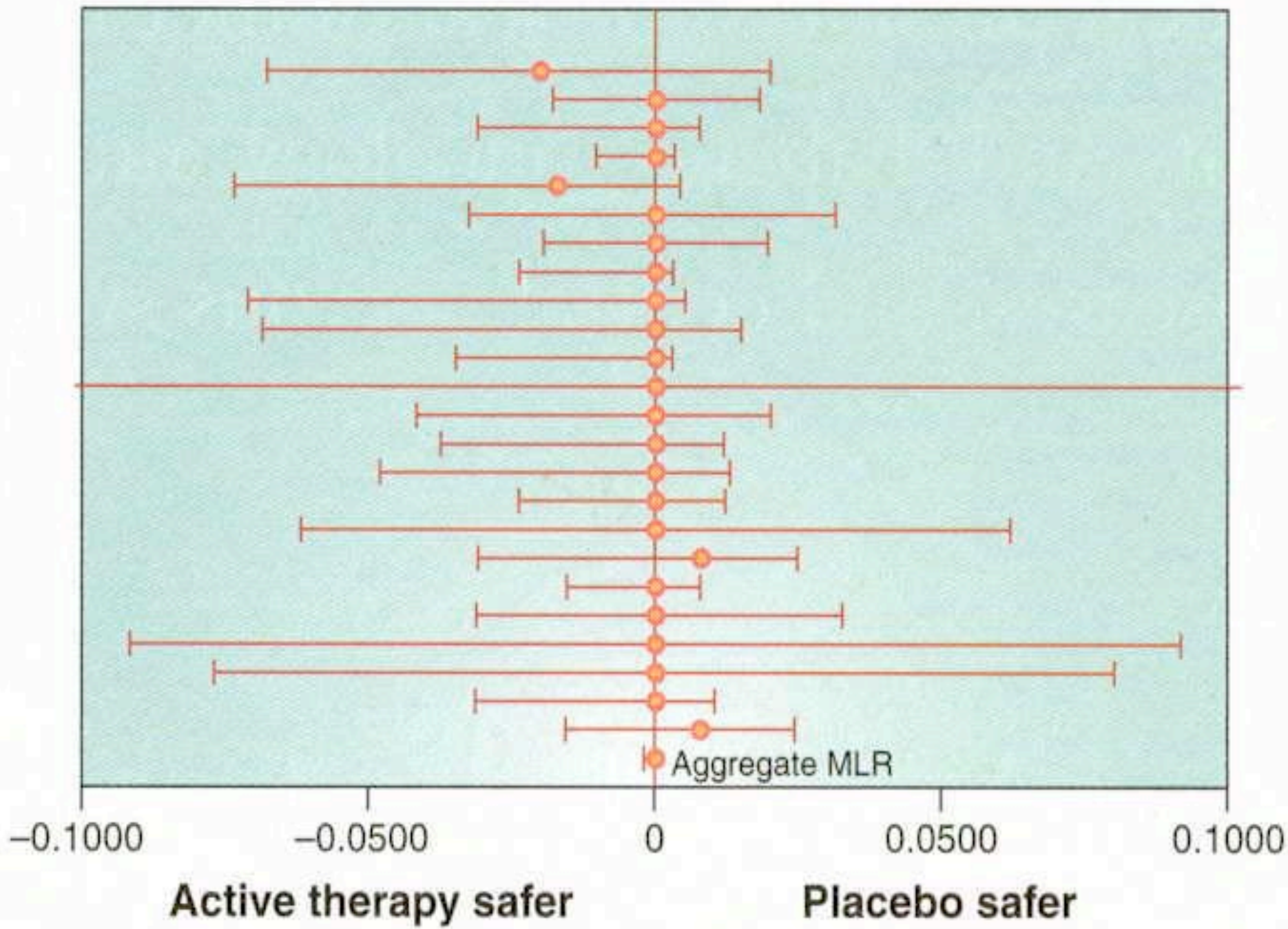
- Medline search, 1/97-12/98
- Inclusion criteria
  - RCTs
  - Mild to moderate hypertension
  - Non-pregnant adults
  - Placebo use
  - Trial duration <20 weeks
  - Primary data
- Articles abstracted

Results

- 267 postings
- 80 met inclusion criteria
- 25 provided adequate data for abstraction
- Sample sizes 20-734
- Total sample of 6409
- Power to detect 2.5 in 1000 difference in treatment arms

Serious Adverse Events by Treatment Group

SAE	Active	Placebo
N	4,878	1,604
Death	2	2
Stroke	2	0
MI	2	3
CHF	0	0
Total	6	5


Aggregate MLR
–0.1000
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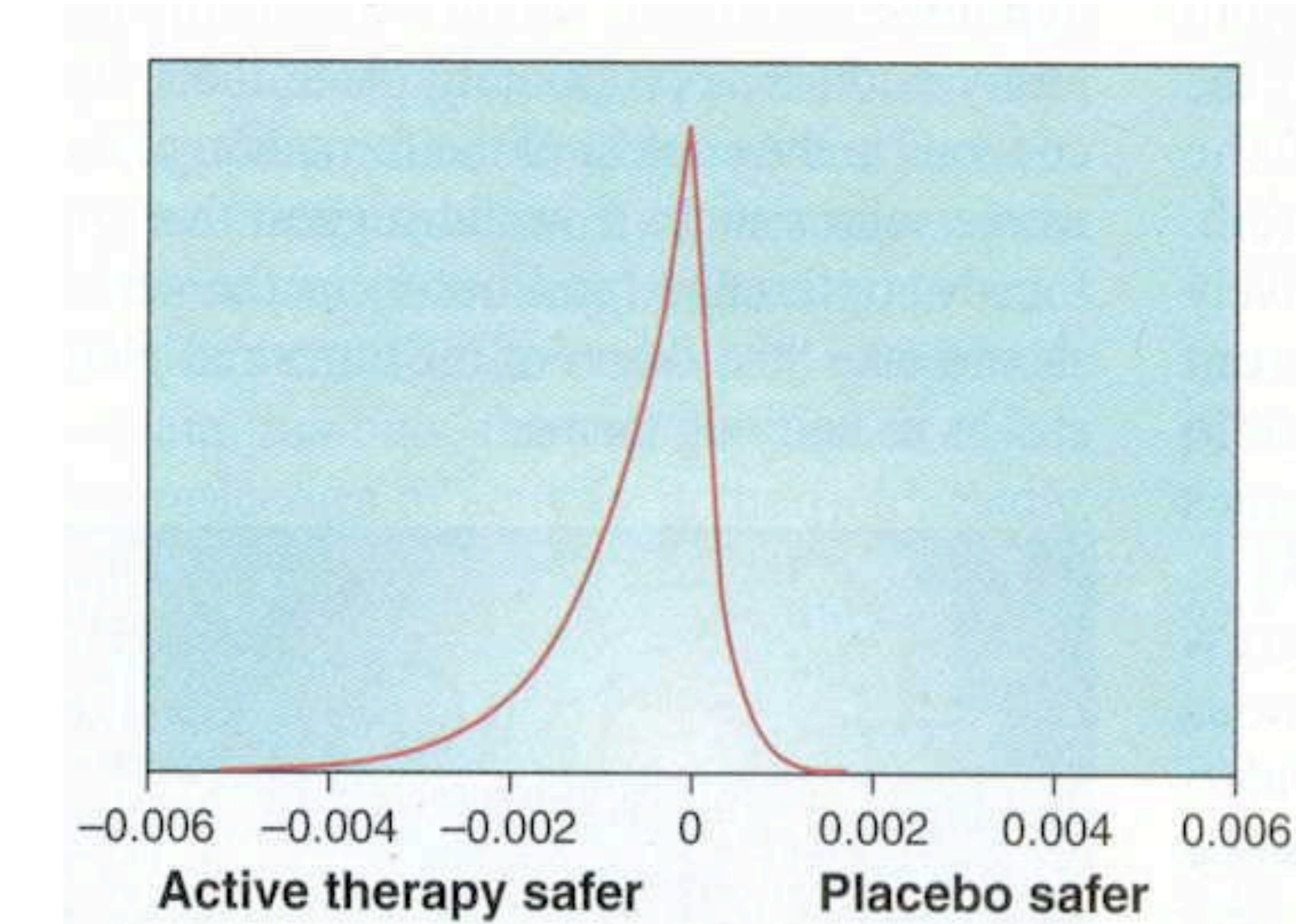
Active therapy safer
Placebo safer


–0.006
–0.004
–0.002
0
0.002
0.004
0.006
Active therapy safer
Placebo safer

Analyses

- Maximum-likelihood method
  - difference=0, 95% CI: –0.002 to 0.0006
- Bayseian posterior analysis
  - 50th percentile for the posterior distribution of the difference = –0.0004; 95% credible set limits: –0.003 to 0.0006

Explanation of Findings

- Trials are of short duration
- Only patients with mild or moderate disease
- Patient-subjects closely monitored

Lessons

- When medical treatments involve long-term benefits, determining whether placebo-controls are appropriate involves understanding the duration of treatment to confer such benefits – this is an empirical question
- General edicts concerning placebo use need to be sensitive to the real risks and benefits involved

FOOTNOTE:
NOTE OF CLARIFICATION ON PARAGRAPH 29 of the WMA DECLARATION OF HELSINKI

- 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:

  - 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
  - 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.

- All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

http://www.wma.net/e/policy/17-c_e.html

Physicians' Preferences for Active-controlled versus Placebo-controlled Trials of New Antihypertensive Drugs

Scott D. Halperin, Peter A. Ubel, Jesse A. Berlin, Raymond R. Townsend, and David A. Asch

J Gen Intern Med 2002; 17: 689-695

Synopsis

- Nationwide mailed survey in the US
- Designed to evaluate physicians' preferences for active-controlled trials (ACTs) versus placebo-controlled trials (PCTs) of new antihypertensive drugs
- 651 respondents (response rate = 56.4%)

Findings

- Physicians more likely to enroll patients in ACTs than PCTs ($p<.0001$)
- Physicians thought:
  - ACTs provided more valuable information for their practices
  - ACTs more likely to lead to a public health benefit
  - ACTs offered enrolled patients greater opportunity for personal benefit
  - ACTs were less likely to expose patients to unnecessary risks

Conclusions

- Physicians preferred ACTs
- Using ACTs may enhance trial efficiency with respect to recruitment
- ACTs may have a strong influence on prescribing practices

Unanswered Questions

- "Why are clinicians not only uninterested in placebo trials but also suspicious of the benefits and morality of these trials?"
  - Knowledge of evidence for current treatments
  - Attitudes about placebo-controls
- "Are clinicians' concerns about stopping therapy…ill founded?"

Boisaubin EV. Practitioners and clinical trials: true to your patients – or science? *J Gen Intern Med* 2002; 17: 738-739.

Lessons

- The reason(s) why physicians who refer patients to clinical trials prefer ACTs needs to be better understood
- Educational efforts for clinicians as well as potential participants ought to focus on this group especially with respect to the goals of clinical research in this setting

Enlarging the Debate

- Assessing safety of active-controls in psychiatric trials
- Reviewing the power of placebos

Assessing Safety in Antidepressant Trials

- Review of FDA data
- Relative suicide rates higher with ACTs than placebos, raising questions about proprietary data and the influence on the use of placebo controls

Healy D. Are concerns about the ethics of placebos a stalking horse for other issues? *Am J Bioethics* 2002; 2: 17-19.

Reviewing the Power of Placebos

- Systematic review of clinical trials using placebo compared to no treatment
- 130 trials; 114 with adequate data
- Compared to no treatment, placebo had no significant effect on binary outcomes and a beneficial effect on continuous outcomes (that decreased with increasing sample size)
- Significant differences found for subjective, but not objective outcomes
- Authors still suggest use in clinical trials, but not clinical practice

Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *New Engl J Med* 2001; 344: 1594=1602.

Further Opportunities

- Introduce empirical findings into conceptual and policy discussions as well as research ethics review
- Conduct similar work in other fields of clinical investigation
- Develop a research agenda for future work based upon the relevant conceptual and policy questions