SPECIAL ETHICAL ISSUES IN RANDOMIZED TRIALS

From the Therapy chapter for the 3rd edition of Clinical Epidemiology, by DL Sackett
17 April 2004 (day 108)

Gordon Guyatt discusses the universal ethical issues in clinical research in Chapter XX. This section will simply identify and expand upon those that are of special interest in RCTs, identifying current controversies along the way.

Ethics Check List for an RCT:

Is your RCT ethical at its inception?	
1 ❍	Have you carried out a systematic review of all relevant prior trials?
2 ❍	Will your RCT's design and execution move us toward a valid determination of the treatment's efficacy and safety?
3 ❍	Will your RCT withhold "established effective therapy" from any or all of its participants?
Will your RCT remain ethical during its execution?	
4 ❍	Will you guarantee potential participants free, informed consent?
5 ❍	Will your participants be free to withdraw without losing care?
6 ❍	Will you preserve participant confidentiality?
7 ❍	Will you identify and act upon adverse treatment effects promptly?
8 ❍	Will you stop your RCT as soon as the better treatment is clearly established?
9 ❍	Are your trial closeout procedures ethical?
Will your sponsors and investigators behave ethically during the trial?	
10 ❍	Will "bounties" be offered for admitting patients to your RCT?
11 ❍	Will your RCT data be protected from distortion by market considerations?
12 ❍	Will your RCT be terminated for market considerations?
Will your RCT's sponsors and investigators behave ethically after the trial is over?	
13 ❍	Will you be free to report your RCT, regardless of its results?
14 ❍	Will your RCT publications be "ghost-written"?
15 ❍	Will your RCT's investigators declare their potential conflicts of interest in subsequent speeches, publications, and guideline committee participations?
16 ❍	Will you make the results of your RCT available for updating all relevant systematic reviews?

1. **Have you carried out a systematic review of all relevant prior trials?**

Before you design your trial, you should pore over any systematic reviews of previous relevant studies. Has your experimental treatment already been definitively shown to benefit or harm the patients (or some subgroup of them) that you were intending to enroll in your trial? Have the doses and durations of treatment you're considering already been shown to be too much or too little? Have any of the clinical measurements or scales you were intending to use been found wanting or superceded by newer, better ones? Would minor adjustments in your protocol permit the inclusion of your trial results in subsequent, even more informative systematic reviews?

2, **Will your RCT's design and execution move us toward a valid determination of the treatment's efficacy and safety?**

We (and every trialist we know) agree with the proposition that an RCT is unethical if it is incapable, at the outset, of moving us toward a valid determination of a treatment's efficacy and safety. To meet this ethical requirement of reducing our therapeutic ignorance, you have to do

two things. First, you must generate a scientifically sound protocol. It must be capable of providing unbiased estimates of efficacy and safety for the patients in your trial.

Second, there has to be a good prospect for combining your results with those of other, similar trials in later systematic reviews. This is especially important if your trial is at risk of being "underpowered" (that is, too small to generate a usefully narrow confidence interval around the effects of treatment).

Some trialists hold that underpowered (too small) trials are unethical and should not be carried out. We disagree, because that attitude perpetuates therapeutic ignorance. However, everything must be done to maximize the accessibility of every trial's results for systematic reviews. To meet this ethical requirement, you must do two things. First, you must register your trial by the time your protocol is funded and its execution is about to begin (as this edition was being written, the best way to register a trial was to obtain an International Standard Randomised Controlled Trial Number, or ISRCTN, from the Current Clinical Trials website at <www.controlled-trials.com/isrctn/introduction.asp>. Better still, publish your protocol, preferably at an Open Access website, such as that supported by BioMed Central www.biomedcentral.com. (Indeed, if you have not yet begun your trial, BMC will send your protocol out for peer review and comment.) Second, you must report the results of your trial in some easily accessible site, regardless of the sample size you achieved. Your report should include a description of the occurrence and reasons for changes that were made in the protocol during the execution of the study.

3. **Will your RCT withhold "established effective therapy" from any or all of its participants?**

It's best to introduce this step with two disclaimers and three definitions. The first disclaimer is that withholding established effective therapy is not about proper food, clean sheets, and competent, caring nurses and doctors in attendance here; those are deserved by any patient, anywhere. The second disclaimer is that this matter is not about "standard" or "traditional" care that is routinely given to patients with the target disorder, regardless of its evidence-base, as long as it is provided equally to experimental and control patients.

The concern here is much more specific, and the first definition is for "Established Effective Therapy." The definition used in this chapter is: any intervention, for a specific disorder in a specific group of patients, for which the "totality of evidence" documents more good than harm. Integral to this discussion is a decision on who should define "good" and "harm" here: patients, their clinicians, researchers, regulators, or funders? We favor the patient's perspective, and recognize that individual patients' utilities for "good" and "harm" will lead to some of them accepting very risky treatments and others rejecting fairly safe ones.

This leads us to the second definition, this time for the "totality of evidence:" either a positive systematic review (epitomized by a Cochrane review) of one or more high-quality RCTs, or the presence of "all or none" evidence.

The third definition, for "all or none" evidence, means two contrasting but convincing situations. In the first of them, all patients with the condition died in the days before the therapy was introduced and, afterwards, some of them survived. A nice example here would be tuberculous meningitis, a universally fatal disease before the introduction of streptomycin. Other examples would be choriocarcinoma and testicular cancer before the introduction of chemotherapy, and malignant hypertension before the introduction of antihypertensive drugs. The second convincing situation is when many patients with the condition died in the days before the therapy was introduced but afterwards, none (or almost none) of them died. A nice example here would be acute pneumococcal pneumonia in otherwise healthy teen-agers, which exhibited a case-fatality rate as high as xx% before the introduction of penicillin.

Withholding established effective therapy in "me too" trials

Trials that propose withholding "established effective therapy" are of two sorts, and both are contentious as we write this edition[1,2]. The first sort of trial proposes withholding established effective therapy to test an alternative (sometimes a "me too") drug against a placebo. (Here, a "me-too" drug is a promising new but untested drug, often of the same class as the established effective therapy, which requires validation in an RCT to be licensed for sale.) Most often, this sort of RCT is proposed for a condition that is considered "mild" (e.g., acne). Alternatively, the RCT calls for replacing established effective therapy with a placebo in more serious conditions, but for just a short time, during which the investigator contends that there will be no serious or permanent damage from its absence (e.g., mild to moderate depression).

Proponents of withholding established effective therapy in this situation argue that head-to-head trials, whether for superiority or non-inferiority, are just too expensive in view of the tiny risks involved. Opponents of placebo-controlled trials of this sort, including us, argue that they constitute both bad clinical science and bad ethics. We claim that they are bad clinical science because patients and clinicians don't want to know whether the new, promising drug is better than nothing (placebo). We want to know whether the new, promising drug is better than established effective therapy ("superiority"), or as good as established effective therapy ("non-inferior") but safer, cheaper, easier to take, or simply providing them a wider choice. The best way to answer this question is with a head-to-head comparison of the new promising drug against the established effective therapy. Opponents of withholding established effective therapy in "me-too" trials also argue that testing the new, promising drug against placebo is bad ethics because such trials assign half (usually) of their patients to a treatment (placebo) known to be ineffective[1].

When established effective therapy is not available at the trial site

The second situation in which trialists propose to withhold established effective therapy is when it is not available in the town, province, or country where the trial would take place. In Canada, for example, this could apply to urgent high-tech treatments that are hours or even days away from the patients who need them (e.g., immediate angioplasty for patients with threatened heart attacks who live in a Newfoundland outport with no roads, or reside above the Arctic Circle). This situation would also apply to entire countries whose economic or political realities may prohibit access to established effective therapy (e.g., for AIDS in South Africa).

Proponents of this view argue that such trials are good clinical science when established effective therapy is simply not available, and are ethical when three further conditions are met. First, they must be carried out in partnership with researchers, community leaders, and patients at the sites where the RCT is to be done[3]. The prerequisites, strategies, and tactics for creating this vital partnership are developing rapidly, and readers might want to catch up with them by following the reports of the Clinical Bioethics group at the US National Institutes of Health.

The second prerequisite follows from the first: such trials must be approved by local ethics committees at the sites where they are carried out, regardless of where their investigators come from[2]. Third, these trials must test new, promising treatments which, if effective, would be available to all other patients in the location (outports, Arctic Circle, low-income country, or province) where the RCT will be carried out, at least for an agreed period of time. Proponents of this view wouldn't hesitate to label as unethical, any RCT carried out to validate expensive drugs for rich folks in Canada by testing them in poor folks overseas who could never afford them.

---

[1] If you are hung up about the so-called "placebo effect" at this point, try page xx on placebos, or study the letters that followed Kenneth Rothman's commentary in reference 1.

[2] If no local ethics committee exists, this review should be carried out by some other group that is both competent and independent of the trial.

Opponents of performing RCTs that withhold established effective therapy in places that prohibit or can't afford it argue that such trials invoke an ethical "double-standard."[4] For example, when we wrote this edition, the hotly-debated 5th revision of the Declaration of Helsinki read: "a placebo may be used as the control treatment in a clinical trial [when] effective treatment is not available to patients due to cost constraints or short supply." That declaration appeared quite clear. However, it then added, in our view, an impossible condition: "This may only be applied when background conditions of justice prevail within the health care system in question; for example, a placebo-controlled trial is not permissible when effective but costly treatment is made available to the rich but remains unavailable to the poor or uninsured." This appeared to deny the former permission, because a major reason for conducting such trials is precisely because established effective therapy is available only to the rich. Indeed, one can argue that no country, including Canada, meets this condition. Updates on this debate may be found on the World Medical Association website[5], and general developments on the WebPages of the international Science and Development Network[6].

The next three items are a familiar but vital trilogy in any research involving human participants:

4. **Will you guarantee potential participants free, informed consent?**

5. Will your participants be free to withdraw without losing care?

6. Will you preserve participant confidentiality?

You have to tell potential study patients, in ways that they understand, everything that might reasonably be expected to affect their decisions to accept or refuse an invitation to enter your RCT. They must be told who is going to do what to them, when and how often, with what immediate and long-term prospects for good and harm. They must be able to quit the RCT whenever they want without sacrificing their access to care. Moreover, they must be assured that their anonymity will be preserved in any public reporting of the trial or its results.

As this chapter was being written, a systematic review was underway of cohort studies that compared the outcomes of patients treated within RCTs with those of similar patients treated outside these trials[7]. An earlier, small review found that patients treated inside trials (even with placebos) usually fared a little or a lot better, and often even enjoyed lower mortality[8]. [Author's note: The big "TROUT" review is just being completed, and I'll summarize it here when it's out.]

The next three items concern the trial once it is underway.

7. **Will you identify and act on adverse treatment effects promptly?**

The side-effects and toxicity of the established effective therapy given in an RCT are usually well-known and even anticipated (bleeding on warfarin and the like). Appropriate responses to their occurrence should be built right into the follow-up protocol. The frequency and severity of side-effects and toxicity of the experimental treatment often are less well-known. Study patients on these treatments should be monitored for their occurrence and treated accordingly (such as the search for, and treatment of, agranulocytosis among patients assigned to ticlopidine). Special attention must be given to "Serious Unanticipated Adverse Events" (SUAEs) that befall trial patients. If they occur at rates greater than chance, it can become imperative to stop the RCT. A mechanism must be in place for immediately notifying a monitor of their occurrence. For example, when I chair a Data Safety and Monitoring Board, I am informed of SUAEs within 24 hours of their recognition. You may need lots of resources to meet this obligation, especially when sponsors and regulators seek lots of "Not-very-serious-and-already-anticipated" adverse events (NVSAAAAE).

8. **Will you stop your RCT as soon as the better treatment is clearly established?**

In many RCTs, all the patients are admitted and treated before even minor trends in their outcome-differences emerge. In other RCTs, however, efficacy or futility become apparent during the enrollment phase. This is why we advised statistical warning rules for the latter trials back in the section on analysis. The ethical imperative here is to offer all patients the better treatment as soon as it is clearly identified.

This question is answered slightly differently when an on-going "non-inferiority" trial is showing equivalence, but with a wide confidence interval, that still includes superiority, inferiority, or both. This trial should continue to a definitive result.

9. **Are your trial close-out procedures ethical?**

At the end of an RCT, trial patients, their clinicians, and perhaps, in low-access places, the community, should be notified of its results and of the treatment they received during it. In the RRPCE trial, we sent this information to the clinician, who then saw the patient, explained the trial result and their assignment to them, and offered to help them start or stay on aspirin. This is often not the case. Zelda Di Blasi and colleagues surveyed investigators of placebo-controlled trials published in major journals in 2000 or in a national research register, and found that only 45% of them informed all or most of their participants about their allocation at trial closure[9]. Although some justified withholding this information because a further blind follow-up was underway, about half of those who didn't tell patients their treatment stated that they never thought of it. Fortunately, 75% of this latter group said they would inform their patients in future trials.

After a positive trial, a major ethical problem arises if investigators and sponsors stop supplying the newly established effective therapy to experimental patients and fail to offer it to control patients. It is now common practice to supply drugs at no cost to both groups for 6-12 months after a positive trial closes. Similarly, in a surgical trial, it is important to offer an efficacious operation to control (unoperated) patients as soon as its efficacy is established. For example, we gave the results of a scheduled interim analysis to the monitors, Principal Investigator, and Steering Committee for the NASCET endarterectomy trial on a Thursday. All of them decided that afternoon that the trial should be terminated, and a control (unoperated) patient underwent endarterectomy the next day.

The next three items consider certain actions of trialists and sponsors during the RCT. All deserve and receive prominent negative publicity when they are exposed.

10. **Will "bounties" be offered for admitting patients to your RCT?**

Entering and following trial patients means less time to see other patients. The "opportunity cost" of not seeing, and not billing for, these other patients translates to a loss of clinician-income. Similarly, complex admission and follow-up procedures often require additional laboratory services, specially-trained study nurses, and data clerks. Most hospitals insist that all their research costs be recovered. Trialists like us maintain that it is both appropriate and ethical to replace this lost income and pay for these extra services. For this reason, we typically pay our study clinicians a "fee-for-service" when they admit and follow RCT patients. The amount of this fee is set to maintain their net incomes. Similarly, we pay the salaries of the additional support staff and the local costs of running the trial.

The Canadian Medical Association agrees with us and, like many other professional groups, has issued specific policies in support of these practices, including institutional reimbursement[10]. To protect against exploitation, however, they require the approval of these financial arrangements by local ethics committees. Moreover, they require that "Research subjects must be informed if their physician will receive a fee for enrolling them in a study."

Alas, in many RCTs designed and sponsored by pharmaceutical companies, this "cost recovery fee" is replaced by a "bounty" that vastly exceeds the cost of the trial. Bounties of a thousand or more dollars per patient are common, as are bonuses of several thousand additional dollars if some preset number of patients is entered. This means that clinicians in poor countries can earn more in a day from performing a "me-too" trial than they can in a month from caring for the sick. Trialists like us decry this use of patients for personal financial gain. So do groups like the Canadian Medical Association, who have clearly stated: "This remuneration should not constitute enticement."

Bounties can also destroy the validity of an RCT when they become a financial incentive to fake the entry patients and falsify missing follow-up data.

Bounties may be harming academic centers as well, where sponsor-initiated trials can buy the talents and efforts of academic staff away from investigator-initiated research and teaching. Sadly, this subversion is often encouraged by the cash-strapped leadership of these academic centers, even to the point of exhorting academic scientists to apply business principles to the conduct of clinical research. One such leader boasts of an institution where: "Four basic business concepts have been implemented: *viewing the research protocol as a commodity* [italics ours], seeking payment for services rendered, *tracking investments* [italics ours again], and assessing performance.[11]"

11. **Will your RCT data be protected from distortion by market considerations?**

All of my RCTs of drugs have been sponsored in part (but never in whole) by their manufacturers. Their support typically comprises providing the study drug and its placebo, plus a cash grant administered entirely by us. From this grant, we pay for vital activities when their budget-lines are rejected by traditional research agencies. Chief among these are repeated investigators' meetings and frequent visits to study centers to solve problems and to maintain accrual rates and protocol adherence. This support has greatly improved the quality of our trials.

Moreover, these manufacturers' pharmacological expertise has been highly valuable in designing and monitoring trial drug regimens, including alerting study staff to side-effects and toxicity. Often, we have invited them to sit on a trial's "Steering Committee," the people who administer the trial while remaining blind to its emerging results.

Note that all of these activities are at arms-length from the data. Our industry colleagues never receive raw data from the field, nor do they carry out any of the primary data analyses. They don't learn the results of our trials until after the Trial Monitoring Committee has unblinded the Principal Investigator and that person, in turn, has unblinded the Steering Group. In our case this data prohibition has never arisen from a lack of trust; we've never worried that our sponsors would distort the data analysis to sell an inferior drug. Rather, we've been concerned about the credibility of the trial result.

However, other industry-sponsored trials have been accused of distorting trial data for market considerations. In some trials, the data are held by the Contract Research Organization or sponsoring company and not released to the investigators. Thomas Bodenheimer interviewed a wide array of trialists, pharmaceutical executives, administrators, CRO physicians, and professional medical writers[12]. One of the trialists feared that industry control over data allows companies to "provide the spin of the data that favors them." Thomas Bodenheimer also pointed

out that “In the commercial sector, where most investigators are more concerned with reimbursement than with authorship, industry can easily control clinical-trial data.” He identified one senior trialist who had refused to place his name on the published results of a study because the sponsor “was attempting to wield undue influence on the nature of the final paper. The effort was so oppressive that we felt it inhibited academic freedom.”

Given the risks to validity and credibility arising from sponsors controlling RCT data, major medical journals have issued strict rules of authorship and accountability[13]. These are nicely illustrated in *The Lancet*, where the “Role of the Funding Source” must be spelled out in any RCT report. These disclosures are of great assistance to readers, and often provide striking contrasts in credibility. Compare the following two examples:

i. “The sponsors of the two trials had no role in study design, data collection, data analysis, data interpretation, or writing of the report.[14]”

ii. “Employees and consultants of the sponsor developed the protocol, enrolled patients, and coordinated the trial. The study sponsor was responsible for data collection and analysis. . . .[15]”

12. <u>Will your RCT be terminated for market considerations?</u>

Once an RCT begins, trialists like us consider it unethical to stop it until there is clear evidence of:

- superiority (one treatment is clearly superior to the other, or to placebo),
- non-inferiority (one treatment is clearly not inferior to the other active treatment),
- harm (one treatment is clearly inferior, or harmful side-effects outweigh any benefit from it), or
- futility (too slow accrual or too few events to ever be able to answer the study question[3]).

Stopping for other reasons may treat study patients as objects, and places them at risk with no prospect of a valid answer to the study question. In our own RCTs, our sponsors have always agreed with this view.

Unfortunately, the funding of other RCTs has been cut-off when sponsors decide that their money is better spent elsewhere. For example, the Steering Committee of an RCT of fluvastatin (to reduce cardiovascular risk and preserve cognitive function in the elderly) was told that their funding was being cut off “because it was feared that a similar trial of pravastatin . . . would reach its conclusion before the fluvastatin trial” and that the sponsor said it was necessary “to reallocate resources from Lescol [fluvastatin] to the newer growth assets.[16]” And in 2003, funding for a trial of verapamil (to reduce cardiovascular risk for hypertensive patients) was stopped 2 years early by its sponsors “with no written rationale or further details about the decision” given to the investigators[17]. As this book was being written, Bruce Psaty and Drummond Rennie documented six cases of what they labelled “a broken pact with researchers and patients.[18]”

The final three items raise ethical issues following the completion of an RCT.

13. <u>Will you be free to report your RCT, regardless of its results?</u>

RCTs with indeterminate (often mis-labelled “negative”) results are both slower[19] and less likely[20] to be published. Although both these behaviors are understandable, we believe that they (especially the latter) are unethical on the bases of both transparency and accountability. The failure to publish indeterminate trial results is all the more unethical with the advent of the systematic review, which can only meta-analyze what it can find. This latter conviction has been

[3] Nonetheless, these indeterminate results should be registered, published, and made available to subsequent systematic reviews.

well-put by Iain Chalmers: “All unbiased comparative studies should be published, so that the totality of the relevant evidence can be evaluated in the systematic reviews that are needed by those making choices and decisions in health care and about further research.[21]”

Sometimes, RCT sponsors make this problem much worse by suppressing publications that threaten profits. Thomas Bodenheimer documented several examples in which funding companies stopped the publication of trial results[22]. In others, they delayed publication while they prepared (sometimes in secret) competing papers on the same topic that were favorable to the company’s viewpoint.

Before you even begin your trial, you need to have a written understanding with all your sponsors about the ownership and reporting of its results. For example, the agreement between the manufacturer and investigators in a trial I am presently monitoring is crystal clear:

i. The manufacturer retains sole property rights to the drug’s formula, method of manufacture, and related scientific data.
ii. The investigator reserves the right to publish the results as he sees fit
iii. The investigator must give the manufacturer 15 working days to review and comment on (but not censor) the draft report.
iv. The investigator must give the manufacturer an additional 90 days if the sponsor needs to file a patent or otherwise protect its proprietary rights.
v. These15-day and 90-day rules are waived if there are concerns related to participant safety.

Finally, given the availability of web-based resources for registering trials, posting protocols, and publishing results, the excuses for delayed and absent publication have vanished.

14. **Will your RCT publications be “ghost-written”?**

Sometimes pharmaceutical firms hire “ghost writers” to convert trial results into manuscripts, and encourage investigators to substitute their names for that of the ghost. Annette Flanigin led a team at JAMA who surveyed 809 corresponding “authors” of articles published in major general medical journals in 1996[23]. They found that 11% of these articles had evidence of being ghostwritten, with the true author’s name excluded from the paper. They also found that 19% of these articles had evidence of “honorary authorship,” with a person who didn’t contribute of the writing of the paper listed as an author. Two percent of papers had apparently committed both offences.

Ghostwriters, paid by their industry employers, shouldn’t surprise us if they follow the lyrics of the Johnny Mercer[24] standard: “accentuate the positive, eliminate the negative, and don’t mess with Mr. In-Between.” In commenting on ghost writing, Drummond Rennie, an editor at JAMA, was quoted[25] as saying: “The practice is well-known, scandalous, and outrageous. It is a perfect illustration of deceptive authorship practices for commercial reasons.” Trialists like me agree, and consider ghostwriting unethical.

15. **Will your RCT’s investigators declare their potential conflicts of interest in subsequent speeches, publications, and guideline committee participations?**

Clinicians and patients must be able to trust the guidelines that are produced by governments and voluntary health agencies. The credibility, if not validity, of these therapeutic recommendations and guidelines is destroyed when their “expert” authors fail to declare potential conflicts of interest. For example, based on recommendations from a committee of experts, the American Heart Association (AHA) upgraded its recommendation for using alteplase (a patented thrombolytic) for stroke from “optional” to “definitely recommended.” Afterward, two potential conflicts of interest were charged by Jeanne Lenzer, a medical investigative journalist[26]. First, on

the 9-member "expert" AHA panel, she reported that six of the eight "experts" who recommended the drug had financial ties to its manufacturer (as paid lecturers, consultants, and even grant-holders). Second, she reported that the drug's manufacturer had contributed $2.5 million to new AHA buildings. As this chapter was being written, the US National Institute of Neurological Disease and Blindness was assembling an independent committee to re-analyze the study's data.

This is not an isolated case. Niteesh Choudhry and colleagues quantified the extent and nature of interactions between the authors of guidelines and the pharmaceutical industry[27]. Among those who responded to their survey, 87% had ties to industry (58% as grantees and 38% as consultants or employees), and over half had relationships with firms whose drugs were considered in their guideline. Furthermore, over half reported that their committees had no formal process for declaring financial ties. This team made three recommendations for the authors of clinical practice guidelines:

i. disclosure of potential conflicts of interest to other participants at the beginning of the guideline creation process
ii. exclusion of authors with financially substantial conflicts
iii. complete disclosure of each author's potential conflicts to readers of guidelines.

To close this section on a brighter note, the Steering Committee of the GUSTO trial, testing a thrombolytic drug with enormous potential sales, took this ethical concern one step further[28]. As part of their trial planning, their Steering Committee "unanimously voted to prohibit any honoraria for speaking engagements, payment for consultancy or travel or reimbursement of any kind from any of the five corporate sponsors until 1 year after the publication of the results."

16. **Will you make the results of your RCT available for updating all relevant systematic reviews?**

We've come full circle. If the trialist who follows you is to stop before she designs her trial to pore over any systematic reviews of previous relevant studies, yours had better be there.

REFERENCES

[1] Rothman KJ: The continuing unethical use of placebo controls. N Engl J Med 1994;331:394-8. (plus the subsequent correspondence and rebuttals)

[2] Angell M: Investigators' responsibilities for human subjects in developing countries. N Engl J Med 2000;342:967-9 (plus the subsequent correspondence and rebuttals).

[3] Lo B, Bayer R, and the Ethics Working Group of the HIV Prevention Trials Network. Establishing ethical trials for treatment and prevention of AIDS in developing countries. BMJ 2003;327:337-9.

[4] Angell M: Investigators' responsibilities for human subjects in developing countries. N Engl J Med 2000;342:967-9 (plus the subsequent correspondence and rebuttals).

[5] http://www.wma.net/e/

[6] http://www.scidev.net/

[7] Vist GE, Hagen KB, Devereaux PJ, Dianne Jackowski, Oxman AD. Outcomes of patients who participate in randomised controlled trials versus those of similar patients who do not participate (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.

[8] Braunholtz DA, Edwards SJL, Lilford RJ: Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect." J Clin Epid 2001;54:217-24.

[9] Di Blasi Z, Kaptchuk TJ, Weinman J, Kleijnen J. Informing participants of allocation to placebo at trial closure: postal survey. BMJ 2002;325:1329-31.

[10] Canadian Medical Association Policy. Physicians and the pharmaceutical industry (Update 2001). CMAJ 2001;164:1339-41.

[11] Marnocha RM. Clinical research: business opportunities for pharmacy-based investigational drug services. Am J Health Syst Pharm 1999;56:249-52.

[12] Bodenheimer T. Uneasy alliance – clinical investigators and the pharmaceutical industry. N Engl J Med 2000;342:1539-44.

[13] Davidoff F, DeAngelis C, Drazen JM, Hoey J, Hojharrd L, Horton R. Sponsorship, authorship, and accountability. Lancet 2001;358:854-6.

[14] Angelini G, Taylor FC, Reeves BC, Ascoine R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 2002;359:1194-99.

[15] Waksman R, Raizner AE, Yeung AC, Lansky AJ, Vandertie L, on behalf of the INHIBIT Investigators. Use of localized intracoronary ß radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. Lancet 2002;359:551-57.

[16] Lievre M, Menard J, Brucket E, Cogneau J, Delahaye F, Giral P, Leitersdorf E, Luc G, Masana L, Moulin P, Passa P, Pouchain D, Siest G. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. BMJ 2001;322:603-6.

[17] Black HR, Elliott WJ, Grandits G, Grambsch P, Lucente T, White WB, Neaton JD, Grimm RH Jr, Hansson L, Lacourciere Y, Muller J, Sleight P, Wevber MA, Williams G, Wittes J, Zanchetti A, Anders RJ, for the CONVINCE Research Group. Principal results of the controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial. JAMA 2003;289:2073-82.

[18] Psaty BM, Rennie D. Stopping medical research to save money. A broken pact with researchers and patients. JAMA 2003;289:2128-31.

[19] Hopewell S, Clarke M, Stewart L, Tierney J.. Time to publication for results of clinical trials (Cochrane Methodology Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

[20] Scherer RW, Langenberg P. Full publication of results initially presented in abstracts (Cochrane Methodology Review). In: *The Cochrane Library*, Issue 2, 2003. Oxford: Update Software.

[21] Chalmers I. All unbiased comparative studies should be published. BMJ 2002;324:483.

[22] Bodenheimer T. Uneasy alliance – clinical investigators and the pharmaceutical industry. N Engl J Med 2000;342:1539-44.

[23] Flanigin A, Carey LA, Fontanarosa PB, Phillips SG, Pace BP, Lundberg GD, Rennie D. Prevalence of articles with honorary authors and ghost authors in peer-reviewed medical journals. JAMA 1998;280:222-4.

[24] Arlen H, Mercer J. "Ac-Cent-Tchu-Ate the Positive." Circa 1945. http://www.leoslyrics.com/listlyrics.php?id=8492

[25] Larkin M. Whose article is it anyway? Lancet 1999;354:136.

[26] Lenzer J: Alteplase for stroke: money and optimistic claims buttress the "brain attack" campaign. BMJ 2002;324:723-9. (The rapid electronic responses make for lively reading!)

[27] Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. JAMA 2002;287:612-7.

[28] Topol EJ, Armstrong P, Van de Werf F, Kleiman N, Lee K, Morris D, Simoons M, Barbash G, White H, Califf RM. Confronting the issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion. Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) Steering Committee. J Am Coll Cardiol 1992;19:1123-8.