Fundamentals of Clinical Research for Radiologists

Randomized Controlled Trials

Harald O. Stolberg[1]
Geoffrey Norman[2]
Isabelle Trop[3]

Received June 14, 2004; accepted after revision July 2, 2004.

Series editors: Nancy Obuchowski, C. Craig Blackmore, Steven Karlik, and Caroline Reinhold.

This is the 12th in the series designed by the American College of Radiology (ACR), the Canadian Association of Radiologists, and the *American Journal of Roentgenology*. The series, which will ultimately comprise 22 articles, is designed to progressively educate radiologists in the methodologies of rigorous clinical research, from the most basic principles to a level of considerable sophistication. The articles are intended to complement interactive software that permits the user to work with what he or she has learned, which is available on the ACR Web site (www.acr.org).

Project coordinator: G. Scott Gazelle, Chair, ACR Commission on Research and Technology Assessment; staff coordinator: Jonathan H. Sunshine, Senior Director for Research, ACR.

[1]Department of Radiology, McMaster University Medical Centre, 1200 Main St. W, Hamilton, ON L8N 3Z5, Canada. Address correspondence to H. O. Stolberg.

[2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON L8N 3Z5, Canada.

[3]Department of Radiology, Hôpital Saint-Luc, 1058 St. Denis St., Montreal, QC H2X 3J4, Canada.

AJR 2004;183:1539–1544

0361–803X/04/1836–1539

Preceding articles in this series have provided a great deal of information concerning research design and methodology, including research protocols, statistical analyses, and assessment of the clinical importance of radiologic research studies. Many methods of research design have already been presented, including descriptive studies (e.g., case reports, case series, and cross-sectional surveys), and some analytical designs (e.g., cohort and case-control studies).

Case-control and cohort studies are also called observational studies, which distinguishes them from interventional (experimental) studies because the decision to seek one treatment or another, or to be exposed to one risk or another, was made by someone other than the experimenter. Consequently, the researcher's role is one of observing the outcome of these exposures. By contrast, in experimental studies, the researcher (experimenter) controls the exposure. The most powerful type of experimental study is the randomized controlled trial. The basic principles of randomized controlled trials will be discussed in this article.

History of Randomized Controlled Trials

The history of clinical trials dates back to approximately 600 B.C. when Daniel of Judah [1] conducted what is probably the earliest recorded clinical trial. He compared the health effects of the vegetarian diet with those of a royal Babylonian diet over a 10-day period. The trial had obvious deficiencies by contemporary medical standards (allocation bias, ascertainment bias, and confounding by divine intervention), but the report has remained influential for more than two millennia [2].

The 19th century saw many major advances in clinical trials. In 1836, the editor of the *American Journal of Medical Sciences* wrote an introduction to an article that he considered "one of the most important medical works of the present century, marking the start of a new era of science," and stated that the article was "the first formal exposition of the results of the only true method of investigation in regard to the therapeutic value of remedial agents." The article that evoked such effusive praise was the French study on bloodletting in treatment of pneumonia by P. C. A. Louis [2, 3].

Credit for the modern randomized trial is usually given to Sir Austin Bradford Hill [4]. The Medical Research Council trials on streptomycin for pulmonary tuberculosis are rightly regarded as a landmark that ushered in a new era of medicine. Since Hill's pioneering achievement, the methodology of the randomized controlled trial has been increasingly accepted and the number of randomized controlled trials reported has grown exponentially. The Cochrane Library already lists more than 150,000 such trials, and they have become the underlying basis for what is currently called "evidence-based medicine" [5].

General Principles of Randomized Controlled Trials

The randomized controlled trial is one of the simplest but most powerful tools of research. In essence, the randomized controlled trial is a study in which people are allocated at random to receive one of several clinical interventions [2]. On most occasions, the term "intervention" refers to treatment, but it should be used in a much wider sense to include any clinical maneuver offered to study participants that may

have an effect on their health status. Such clinical maneuvers include prevention strategies, screening programs, diagnostic tests, interventional procedures, the setting in which health care is provided, and educational models [2]. Randomized controlled trials in radiology can play a major role in the assessment of screening programs, diagnostic tests, and procedures in interventional radiology [6–13].

Randomized controlled trials are used to examine the effect of interventions on particular outcomes such as death or the recurrence of disease. Some consider randomized controlled trials to be the best of all research designs [14], or "the most powerful tool in modern clinical research" [15], mainly because the act of randomizing patients to receive or not receive the intervention ensures that, on average, all other possible causes are equal between the two groups. Thus, any significant differences between groups in the outcome event can be attributed to the intervention and not to some other unidentified factor. However, randomized controlled trials are not a panacea to answer all clinical questions; for example, the effect of a risk factor such as smoking cannot ethically be addressed with randomized controlled trials. Furthermore, in many situations randomized controlled trials are not feasible, necessary, appropriate, or even sufficient to help solve important problems [2]. Randomized controlled trials are not appropriate for cancer screening, a situation in which the outcome is rare and frequently occurs only after a long delay. Thus, although the test for appraising the ultimate value of a diagnostic test may be a large well-designed randomized controlled trial that has patient outcomes as the end point [16], the trial should presumably be performed after other smaller studies have examined the predictive value of the test against some accepted standard.

An excellent example of the controversies that can arise with randomized controlled trials is an overview of the publications on mammography screening. The most important references concern the article by Miettinen et al. [17] linking screening for breast cancer with mammography and an apparently substantial reduction in fatalities and the responses that it elicited [18–22].

Randomized controlled trials may not be appropriate for the assessment of interventions that have rare outcomes or effects that take a long time to develop. In such instances, other study designs such as case-control studies or cohort studies are more appropriate. In other cases, randomized controlled trials may not be feasible because of financial constraints or because of the expectation of low compliance or high drop-out rates.

Many randomized controlled trials involve large sample sizes because many treatments have relatively small effects. The size of the expected effect of the intervention is the main determinant of the sample size necessary to conduct a successful randomized controlled trial. Obtaining statistically significant differences between two samples is easy if large differences are expected. However, the smaller the expected effect of the intervention, the larger the sample size needed to be able to conclude, with enough power, that the differences are unlikely to be due to chance. For example, let us assume that we wish to study two groups of patients who will undergo different interventions, one of which is a new procedure. We expect a 10% decrease in the morbidity rate with the new procedure. To be able to detect this difference with a probability (power) of 80%, we need 80 patients in each treatment arm. If the expected difference in effect between the two groups increases to 20%, the number of patient required per arm decreases to 40. Conversely, if the difference between the groups is expected to be only 1%, the study population must increase to 8,000 per treatment arm. The sample size required to achieve power in a study is inversely proportional to the treatment effect squared [23]. Standard formulas are available to calculate the approximate sample size necessary when designing a randomized controlled trial [24–26].

Randomization: The Strength of the Randomized Controlled Trial

The randomization procedure gives the randomized controlled trial its strength. Random allocation means that all participants have the same chance of being assigned to each of the study groups [27]. The allocation, therefore, is not determined by the investigators, the clinicians, or the study participants [2]. The purpose of random allocation of participants is to assure that the characteristics of the participants are as likely to be similar as possible across groups at the start of the comparison (also called the baseline). If randomization is done properly, it reduces the risk of a serious imbalance in known and unknown factors that could influence the clinical course of the participants. No other study design allows investigators to balance these factors.

The investigators should follow two rules to ensure the success of the randomization procedure. They must first define the rules that will govern allocation and then follow those rules strictly throughout the entire study [2]. The crucial issue is that after the procedure for randomization is determined, it should not be modified at any point during the study. There are many adequate methods of randomization, but their common element is that no one should be able to determine ahead of time to which group a given patient will be assigned. Detailed discussion of randomization methods is beyond the scope of this article.

Numerous methods are also available to ensure that the sample of patients is balanced whenever a small predetermined number of patients have been enrolled. Unfortunately, the methods of allocation in studies described as randomized are poorly and infrequently reported [2, 28]. As a result, it is not possible to determine, on most occasions, whether the investigators used proper methods to generate random sequences of allocation [2].

Bias in Randomized Controlled Trials

The main appeal of the randomized controlled trial in health care derives from its potential for reducing allocation bias [2]. No other study design allows researchers to balance unknown prognostic factors at baseline. Random allocation does not, however, protect randomized controlled trials against other types of bias. During the past 10 years, randomized controlled trials have been the subject rather than the tool of important, albeit isolated, research efforts usually designed to generate empiric evidence to improve the design, reporting, dissemination, and use of randomized controlled trials in health care [28]. Such studies have shown that randomized controlled trials are vulnerable to multiple types of bias at all stages of their workspan. A detailed discussion of bias in randomized controlled trials was offered by Jadad [2].

In summary, randomized controlled trials are quantitative, comparative, controlled experiments in which a group of investigators studies two or more interventions by administering them to groups of individuals who have been randomly assigned to receive each intervention. Alternatively, each individual might receive a series of interventions in random order (crossover design) if the outcome can be uniquely associated with each intervention, through, for example, use of a "washout" period. This step ensures that the

effects from one test are not carried over to the next one and subsequently affect the independent evaluation of the second test administered. Apart from random allocation to comparison groups, the elements of a randomized controlled trial are no different from those of any other type of prospective, comparative, quantitative study.

Types of Randomized Controlled Trials

As Jadad observed in his 1998 book *Randomised Controlled Trials* [2]:

> Over the years, multiple terms have been used to describe different types of randomized controlled trials. This terminology has evolved to the point of becoming real jargon. This jargon is not easy to understand for those who are starting their careers as clinicians or researchers because there is no single source with clear and simple definitions of all these terms.

The best classification of frequently used terms was offered by Jadad [2], and we have based our article on his work.

According to Jadad, randomized controlled trials can be classified as to the aspects of intervention that investigators want to explore, the way in which the participants are exposed to the intervention, the number of participants included in the study, whether the investigators and participants know which intervention is being assessed, and whether the preference of nonrandomized individuals and participants has been taken into account in the design of the study. In the context of this article, we can offer only a brief discussion of each of the different types of randomized controlled trials.

Randomized Controlled Trials Classified According to the Different Aspects of Interventions Evaluated

Randomized controlled trials used to evaluate different interventions include explanatory or pragmatic trials; efficacy or equivalence trials; and phase 1, 2, 3, and 4 trials.

Explanatory or pragmatic trials.—Explanatory trials are designed to answer a simple question: Does the intervention work? If it does, then the trial attempts to establish how it works. Pragmatic trials, on the other hand, are designed not only to determine whether the intervention works but also to describe all the consequences of the intervention and its use under circumstances corresponding to daily practice. Although both explanatory and pragmatic approaches are reasonable, and even complementary, it is important to understand that they represent extremes of a spectrum, and most randomized controlled trials combine elements of both.

Efficacy or effectiveness trials.—Randomized controlled trials are also often described in terms of whether they evaluate the efficacy or effectiveness of an intervention. Efficacy refers to interventions carried out under ideal circumstances, whereas effectiveness evaluates the effects of an intervention under circumstances similar to those found in daily practice.

Phase 1, 2, 3, and 4 trials.—These terms describe the different types of trials used for the introduction of a new intervention, traditionally a new drug, but could also encompass trials used for the evaluation of a new embolization material or type of prosthesis, for example. Phase 1 studies are usually conducted after the safety of the new intervention has been documented in animal research, and their purpose is to document the safety of the intervention in humans. Phase 1 studies are usually performed on healthy volunteers. Once the intervention passes phase 1, phase 2 begins. Typically, the intervention is given to a small group of real patients, and the purpose of this study is to evaluate the efficacy of different modes of administration of the intervention to patients. Phase 2 studies focus on efficacy while still providing information on safety. Phase 3 studies are typically effectiveness trials, which are performed after a given procedure has been shown to be safe with a reasonable chance of improving patients' conditions. Most phase 3 trials are randomized controlled trials. Phase 4 studies are equivalent to postmarketing studies of the intervention; they are performed to identify and monitor possible adverse events not yet documented.

Randomized Controlled Trials Classified According to Participants' Exposure and Response to the Intervention

These types of randomized controlled trials include parallel, crossover, and factorial designs.

Parallel design.—Most randomized controlled trials have parallel designs in which each group of participants is exposed to only one of the study interventions.

Crossover design.— Crossover design refers to a study in which each of the participants is given all of the study interventions in successive periods. The order in which the participants receive each of the study interventions is determined at random. This design, obviously, is appropriate only for chronic conditions that are fairly stable over time and for interventions that last a short time within the patient and that do not interfere with one another. Otherwise, false conclusions about the effectiveness of an intervention could be drawn [29].

Factorial design.—A randomized controlled trial has a factorial design when two or more experimental interventions are not only evaluated separately but also in combination and against a control [2]. For example, a 2×2 factorial design generates four sets of data to analyze: data on patients who received none of the interventions, patients who received treatment A, patients who received treatment B, and patients who received both A and B. More complex factorial designs, involving multiple factors, are occasionally used. The strength of this design is that it provides more information than parallel designs. In addition to the effects of each treatment, factorial design allows evaluation of the interaction that may exist between two treatments. Because randomized controlled trials are generally expensive to conduct, the more answers that can be obtained, the better.

Randomized Controlled Trials Classified According to the Number of Participants

Randomized controlled trials can be performed in one or many centers and can include from one to thousands of participants, and they can have fixed or variable (sequential) numbers of participants.

"N-*of-one trials.*"—Randomized controlled trials with only one participant are called "*n*-of-one trials" or "individual patient trials." Randomized controlled trials with a simple design that involve thousands of patients and limited data collection are called "megatrials." [30, 31]. Usually, megatrials require the participation of many investigators from multiple centers and from different countries [2].

Sequential trials.—A sequential trial is a study with parallel design in which the number of participants is not specified by the investigators beforehand. Instead, the investigators continue recruiting participants until a clear benefit of one of the interventions is observed or until they become convinced that there are no important differences between the interventions [27]. This element applies to the comparison of some diagnostic interventions and some procedures in interventional radiology. Strict rules govern when trials can be

stopped on the basis of cumulative results, and important statistical considerations come into play.

Fixed trials.—Alternatively, in a fixed trial, the investigators establish deductively the number of participants (sample size) that will be studied. This number can be decided arbitrarily or can be calculated using statistical methods. The latter is a more commonly used method. Even in a fixed trial, the design of the trial usually specifies whether there will be one or more interim analyses of data. If a clear benefit of one intervention over the other can be shown with statistical significance before all participants are recruited, it may not be ethical to pursue the trial, and it may be prematurely terminated.

Randomized Controlled Trials Classified According to the Level of Blinding

In addition to randomization, the investigators can incorporate other methodologic strategies to reduce the risk of other biases. These strategies are known as "blinding." The purpose of blinding is to reduce the risk of ascertainment and observation bias. An open randomized controlled trial is one in which everybody involved in the trial knows which intervention is given to each participant. Many radiology studies are open randomized controlled trials because blinding is not feasible or ethical. One cannot, for example, perform an interventional procedure with its associated risks without revealing to the patient and the treating physician to which group the patient has been randomized. A single-blinded randomized controlled trial is one in which a group of individuals involved in the trial (usually patients) does not know which intervention is given to each participant. A double-blinded randomized controlled trial, on the other hand, is one in which two groups of individuals involved in the trial (usually patients and treating physicians) do not know which intervention is given to each participant. Beyond this, triple-blinded (blinding of patients, treating physicians, and study investigators) and quadruple-blinded randomized controlled trials (blinding of patients, treating physicians, study investigators, and statisticians) have been described but are rarely used.

Randomized Controlled Trials Classified According to Nonrandomized Participant Preferences

Eligible individuals may refuse to participate in a randomized controlled trial. Other eligible individuals may decide to participate in a randomized controlled trial but have a clear preference for one of the study interventions. At least three types of randomized controlled trials take into account the preferences of eligible individuals as to whether or not they take part in the trial. These are called preference trials because they include at least one group in which the participants are allowed to choose their preferred treatment from among several options offered [32, 33]. Such trials can have a Zelen design, comprehensive cohort design, or Wennberg's design [33–36]. For a detailed discussion of these designs of randomized controlled trials, the reader is directed to the excellent detailed discussion offered by Jadad [2].

The Ethics of Randomized Controlled Trials

Despite the claims of some enthusiasts for randomized controlled trials, many important aspects of health care cannot be subjected to a randomized trial for practical and ethical reasons. A randomized controlled trial is the best way of evaluating the effectiveness of an intervention, but before a randomized controlled trial can be conducted, there must be equipoise—genuine doubt about whether one course of action is better than another [16]. Equipoise then refers to that state of knowledge in which no evidence exists that shows that any intervention in the trial is better than another and that any intervention is better than those in the trial. It is not ethical to build a trial in which, before enrollment, evidence suggests that patients in one arm of the study are more likely to benefit from enrollment than patients in the other arm. Equipoise thus refers to the fine balance that exists between being hopeful a new treatment will improve a condition and having enough evidence to know that it does (or does not). Randomized controlled trials can be planned only in areas of uncertainty and can be carried out only as long as the uncertainty remains. Ethical concerns that are unique to randomized controlled trials as well as other research designs will be addressed in subsequent articles in this series. Hellman and Hellman [37] offered a good discussion on this subject.

Reporting of Randomized Controlled Trials

The Quality of Randomized Controlled Trial Reporting

Awareness concerning the quality of reporting randomized controlled trials and the limitations of the research methods of randomized controlled trials is growing. A major barrier hindering the assessment of trial quality is that, in most cases, we must rely on the information contained in the written report. A trial with a biased design, if well reported, could be judged to be of high quality, whereas a well-designed but poorly reported trial could be judged to be of low quality.

Recently, efforts have been made to improve the quality of randomized controlled trials. In 1996, a group of epidemiologists, biostatisticians, and journal editors published "CONSORT (Consolidated Standards of Reporting Trials)" [38], a statement that resulted from an extensive collaborative process to improve the standards of written reports of randomized controlled trials. The CONSORT statement was revised in 2001 [39]. It was designed to assist the reporting of randomized controlled trials with two groups and those with parallel designs. Some modifications will be required to report crossover trials and those with more than two groups [40]. Although the CONSORT statement was not evaluated before its publication, it was expected that it would lead to an improvement in the quality of reporting of randomized controlled trials, at least in the journals that endorse it [41].

Recently, however, Chan et al. [42] pointed out that the interpretation of the results of randomized controlled trials has emphasized statistical significance rather than clinical importance:

> The lack of emphasis on clinical importance has led to frequent misconceptions and disagreements regarding the interpretation of the results of clinical trials and a tendency to equate statistical significance with clinical importance. In some instances, statistically significant results may not be clinically important and, conversely, statistically insignificant results do not completely rule out the possibility of clinically important effects.

Limitations of the Research Methods Used in Randomized Controlled Trials

The evaluation of the methodologic quality of randomized controlled trials is central to the appraisal of individual trials, the conduct of unbiased systematic reviews, and the performance of evidence-based health care. However, important methodologic details may be omitted from published reports, and the quality of reporting is, therefore, often

used as a proxy measure for methodologic quality. High-quality reporting may hide important differences in methodologic quality, and well-conducted trials may be reported badly [43]. As Devereaux et al. [41] observed, "[h]ealth care providers depend upon authors and editors to report essential methodological factors in randomized controlled trials (RCTs) to allow determination of trial validity (i.e., likelihood that the trials' results are unbiased)."

The most important limitations of research methods include the following:

Insufficient power.—A survey of 71 randomized controlled trials showed that most of these trials were too small (i.e., had insufficient power to detect important clinical differences) and that the authors of these trials seemed unaware of these facts [44].

Poor reporting of randomization—A study of 206 randomized controlled trials showed that randomization, one of the main design features necessary to prevent bias in randomized controlled trials, was poorly reported [45].

Other limitations.—Additional limitations identified by Chalmers [46] were inadequate randomization, failure to blind the assessors to the outcomes, and failure to follow up all patients in the trials.

Intent to Treat

A method to correct for differential dropout rates between patients from one arm of the study and another is to analyze data by the intent to treat—that is, data are analyzed in the way patients were randomized, regardless of whether or not they received the intended intervention. The intent to treat correction is a form of protection against bias and strengthens the conclusions of a study. A detailed discussion of the assessment of the quality of randomized controlled trials was offered by Jadad [2].

In the appraisal of randomized controlled trials, a clear distinction should be made between the quality of the reporting and the quality of methodology of the trials [43].

Recent Randomized Controlled Trials in Radiology

In recent years, randomized controlled trials have become increasingly popular in radiology research. In 1997, for instance, there were only a few good randomized studies in diagnostic imaging, such as the one by Jarvik et al. [47]. Since 2000, the number of good randomized controlled trials has significantly increased in both diagnostic and interventional radiology. Examples of randomized controlled trials in diagnostic imaging include the works of Gottlieb et al. [48] and Kaiser et al. [49]. Examples of interventional randomized controlled trials are the studies by Pinto et al. [50] and Lencioni et al. [51].

Randomized controlled trials are equally important in screening for disease. Our initial experience with breast screening was unfortunate, and controversy over this issue continues to this day [52, 53]. On the other hand, positive developments have occurred, such as the work of the American College of Radiology Imaging Network. Writing for this group, Berg [54] has offered a commentary on the rationale for a trial of screening breast sonography.

Radiologists have a great deal to learn about randomized controlled trials. Academic radiologists who perform research and radiologists who translate research results into practice should be familiar with the different types of these trials, including those conducted for diagnostic tests and interventional procedures. Radiologists also must be aware of the limitations and problems associated with the methodologic quality and reporting of the trials. It is our hope that this article proves to be a valuable source of information about randomized controlled trials.

Acknowledgments

We thank Alejandro Jadad for his support and Monika Ferrier for her patience and support in keeping us on track and for preparing the manuscript.

References

1. Book of Daniel 1:1–21
2. Jadad AR. *Randomised controlled trials: a user's guide*. London, England: BMJ Books, 1998
3. Louis PCA. Research into the effects of bloodletting in some inflammatory diseases and on the influence of tartarized antimony and vesication in pneumonitis. *Am J Med Sci* 1836;18:102–111
4. Hill AB. The clinical trial. *N Engl J Med* 1952; 247:113–119
5. Cochrane Library Web site. Available at: www.update-software.com/cochrane. Accessed September 10, 2004
6. Bree RL, Kazerooni EA, Katz SJ. Effect of mandatory radiology consultation on inpatient imaging use. *JAMA* 1996;276:1595–1598
7. DeVore GR. The routine antenatal diagnostic imaging with ultrasound study: another perspective. *Obstet Gynecol* 1994;84:622–626
8. Fontana RS, Sanderson DR, Woolner LB, et al. Screening for lung cancer: a critique of the Mayo Lung Project. *Cancer* 1991;67[suppl 4]:1155–1164
9. [No authors listed]. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients: a multicenter randomized controlled trial—the GIVIO Investigators. *JAMA* 1994;271:1587–1592
10. Jarvik JG, Maravilla KR, Haynor DR, Levitz M, Deyo RA. Rapid MR imaging versus plain radiography in patients with low back pain: initial results of a randomized study. *Radiology* 1997;204:447–454
11. Kinnison ML, Powe NR, Steinberg EP. Results of randomized controlled trials of low-versus high-osmolality contrast media. *Radiology* 1989;170: 381–389
12. Rosselli M, Palli D, Cariddi A, Ciatto S, Pacini P, Distante V. Intensive diagnostic follow-up after treatment of primary breast cancer. *JAMA* 1994; 271:1593–1597
13. Swingler GH, Hussey GD, Zwarenstein M. Randomised controlled trial of clinical outcome after chest radiograph in ambulatory acute lower-respiration infection in children. *Lancet* 1998;351: 404–408
14. Cochrane Library Web site. Available at: www.update-software.com/abstracts/ab001877.htm. Accessed September 10, 2004
15. Nystrom L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. *Lancet* 1993;341: 973–978
16. Duffy SW. Interpretation of the breast screening trials: a commentary on the recent paper by Gotzsche and Olsen. *Breast* 2001;10:209–212
17. Miettinen OS, Henschke CI, Pasmantier MW, Smith JP, Libby DM, Yankelevitz DF. Mammographic screening: no reliable supporting evidence? *Lancet* 2002;359:404–405
18. Tabar L, Vitak B, Chen HHT, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001; 91:1724–1731
19. Hoey J. Does mammography save lives? *CMAJ* 2002;166:1187–1188
20. Norman GR, Streiner DL. *Biostatistics: the bare essentials*, 2nd ed. Hamilton, ON, Canada: B. C. Decker, 2000
21. Silerman WA. Gnosis and random allotment. *Control Clin Trials* 1981;2:161–164
22. Gray JAM. *Evidence-based health care*. Edinburgh, Scotland: Churchill Livingstone, 1997
23. Rosner B. *Fundamentals of biostatistics*, 5th ed. Duxbury, England: Thomson Learning, 2000
24. Norman GR, Streiner DL. *PDQ statistics*, 2nd ed. St. Louis, MO: Mosby, 1997
25. Altman DG, Machin D, Bagant TN, Gardner MJ. *Statistics with confidence*, 2nd ed. London, England: BMJ Books, 2000
26. Moher D, Dulberg CS, Wells GA. Statistical power, sample size, and their reporting in randomized controlled trials. *JAMA* 1994;22:122–124
27. Altman DG. Practical statistics for medical research. London, England: Chapman & Hall, 1991
28. Jadad AR, Rennie D. The randomized controlled

trial gets a middle-aged checkup. *JAMA* 1998; 279:319–320
29. Louis TA, Lavori PW, Bailar JC III, Polansky M. Crossover and self-controlled designs in clinical research. In: Bailar JC III, Mosteller F. eds. *Medical uses of statistics*, 2nd ed. Boston, MA: New England Medical Journal Publications, 1992:83–104
30. Woods KL. Megatrials and management of acute myocardial infarction. *Lancet* 1995;346:611–614
31. Charlton BG. Megatrials: methodological issues and clinical implications. *Coll Phys Lond* 1995; 29:96–100
32. Till JE, Sutherland HJ, Meslin EM. Is there a role for performance assessments in research on quality of life in oncology? *Quality Life Res* 1992; 1:31–40
33. Silverman WA, Altman DG. Patient preferences and randomized trials. *Lancet* 1996;347:171–174
34. Zelen M. A new design for randomized clinical trials. *N Engl J Med* 1979;300:1242–1245
35. Olschewski M, Scheurlen H. Comprehensive Cohort Study: an alternative to randomized consent design in a breast preservation trial. *Methods Inf Med* 1985;24:131–134
36. Brewin CR, Bradley C. Patient preferences and randomized clinical trials. *BMJ* 1989;299:684–685
37. Hellman S, Hellman DS. Of mice but not men: problems of the randomized trial. *N Engl J Med* 1991;324:1585–1592
38. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;276:7–9
39. Moher D, Schulz KF, Altman DG, CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987–1991
40. Altman DG. Better reporting of randomized controlled trials: the CONSORT statement. *BMJ* 1996;313:570–571
41. Devereaux PJ, Manns BJ, Ghali WA, Quan H, Guyatt GH. The reporting of methodological factors in randomized controlled trials and the association with a journal policy to promote adherence to the Consolidated Standards of Reporting Trials (CONSORT) checklist. *Control Clin Trials* 2002;23:380–388
42. Chan KBY, Man-Son-Hing M, Molnar FJ, Laupacis A. How well is the clinical importance of study results reported? an assessment of randomized controlled trials. *CMAJ* 2001;165:1197–1202
43. Huwiler-Müntener K, Jüni P, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodologic quality. *JAMA* 2002;287:2801–2804
44. Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of Beta, the type 2 error, and sample size in design and interpretation of randomized controlled trials. *N Engl J Med* 1978;299:690–694
45. Schulz KF, Chalmers I, Hayes RJ, Altman DJ. Empirical evidence of bias: dimensions of the methodologic quality associated with estimates of treatment efforts in controlled trials. *JAMA* 1995;273:408–412
46. Chalmers I. Applying overviews and meta-analysis at the bedside: discussion. *J Clin Epidemiol* 1995;48:67–70
47. Jarvik JG, Maravilla KR, Haynor DR, Levitz M, Deyo RA. Rapid MR imaging versus plain radiography in patients with low back pain: initial results of a randomized study. *Radiology* 1997;204: 447–454
48. Gottlieb RH, Voci SL, Syed L, et al. Randomized prospective study comparing routine versus selective use of sonography of the complete calf in patients with suspected deep venous thrombosis. *AJR* 2003;180:241–245
49. Kaiser S, Frenckner B, Jorulf HK. Suspected appendicitis in children: US and CT–a prospective randomized study. *Radiology* 2002;223:633–638
50. Pinto I, Chimeno P, Romo A, et al. Uterine fibroids: uterine artery embolization versus abdominal hysterectomy for treatment—a prospective, randomized, and controlled clinical trial. *Radiology* 2003;226:425–431
51. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. *Radiology* 2003;228:235–240
52. Dean PB. Gotzsche's quixotic antiscreening campaign: nonscientific and contrary to Cochrane principles. *JACR* 2004;1:3–7
53. Gotzsche PC. The debate on breast cancer screening with mammography is important. *JACR* 2004;1:8–14
54. Berg WA. Rationale for a trial of screening breast ultrasound: American College of Radiology Imaging Network (ACRIN) 6666. *AJR* 2003;180: 1225–1228

The reader's attention is directed to earlier articles in the Fundamentals of Clinical Research series:

1. Introduction, which appeared in February 2001
2. Framework, April 2001
3. Protocol, June 2001
4. Data Collection, October 2001
5. Population and Sample, November 2001
6. Statistically Engineering the Study for Success, July 2002
7. Screening for Preclinical Disease: Test and Disease Characteristics, October 2002
8. Exploring and Summarizing Radiologic Data, January 2003
9. Visualizing Radiologic Data, March 2003
10. Introduction to Probability Theory and Sampling Distributions, April 2003
11. Observational Studies in Radiology, November 2004