Randomized Controlled Trials

Madhukar Pai, MD, PhD
McGill University
Montreal
madhukar.pai@mcgill.ca

What is a randomized controlled trial?

- Simplest definition: Individuals are allocated at random to receive one of several interventions (at least two total).
- RCT's are experimental—the intervention is controlled by the investigator
- RCT's are usually comparative studies ("controlled" in the RCT)

Courtesy: J Colford

What is random allocation?

- Random allocation means that all participants have a defined probability of assignment to a particular intervention
  - Allocation is not determined by the investigator, clinicians, or participants
  - Allocation is not predictable based on a pattern

Courtesy: J Colford

Are these randomized designs if based on…

- Date of birth (odd to group 1; even to group 2)
- Hospital record number (last digit; odd to group 1, even to group 2)
- Day of enrollment (Monday=Rx, Tues=Placebo, etc)
- Alternating (first person=Rx, second person=placebo, etc)

- No, these are called “quasi randomized”

Courtesy: J Colford

What purpose is served by random allocation?

- Covariates are distributed equally across the groups at baseline
  - Not always (especially if N is small)!
- Affects both measured and, more importantly, unmeasured variables
- The risk of imbalance remains even after properly executed randomization
- Table 1 in most RCTs will provide a comparison of treatment and comparison groups, with p-values
  - If randomisation has been performed correctly, chance is the only explanation for any observed difference between groups, in which case statistical tests are considered superfluous

Courtesy: J Colford

Panel 2: **Benefits of randomisation**

Proper implementation of a randomisation mechanism affords at least three major advantages:

It eliminates bias in treatment assignment
Comparisons of different forms of health interventions can be misleading unless investigators take precautions to ensure that their trial comprises unbiased comparison groups relative to prognosis. In controlled trials of prevention or treatment, randomisation produces unbiased comparison groups by avoiding selection and confounding biases. Consequently, comparison groups are not prejudiced by selection of particular patients, whether consciously or not, to receive a specific intervention. The notion of avoiding bias includes eliminating it from decisions on entry of participants to the trial, as well as eliminating bias from the assignment of participants to treatment, once entered. Investigators need to properly register each participant immediately on identification of eligibility for the trial, but without knowledge of the assignment. The reduction of selection and confounding biases underpins the most important strength of randomisation. Randomisation prevails as the best study design for study of small or moderate effects.[6]

It facilitates blinding (masking) of the identity of treatments from investigators, participants, and assessors, including the possible use of a placebo[3]
Such manoeuvres reduce bias after random assignment, and would be difficult, perhaps even impossible, to implement if investigators assigned treatments by a non-random scheme.

It permits the use of probability theory to express the likelihood that any difference in outcome between treatment groups merely indicates chance

Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. Lancet. 2002 Feb 9;359(9305):515-9

What elements of a trial can be randomized?

- Most common unit is individual patient
- Sometimes groups are randomized=cluster randomization
  - Examples: families, schools, towns, hospitals, communities
  - Worry about contamination in cluster randomization
  - Special statistical techniques needed to cope with the loss of independence of the individual units

Courtesy: J Colford

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PLoS NEGLECTED TROPICAL DISEASES

Effects of Deworming on Malnourished Preschool Children in India: An Open-Labelled, Cluster-Randomized Trial

Shally Awasthi[1]*, Richard Peto[2], Vinod K. Pande[1], Robert H. Fletcher[3], Simon Read[2], Donald A. P. Bundy[4]

1 Department of Paediatrics, King George's Medical University, Lucknow, India, **2** Clinical Trial Service Unit, University of Oxford, Oxford, United Kingdom, **3** Harvard Medical School, Harvard University, Boston, Massachusetts, United States of America, **4** Human Development Division, The World Bank, Washington, D.C., United States of America

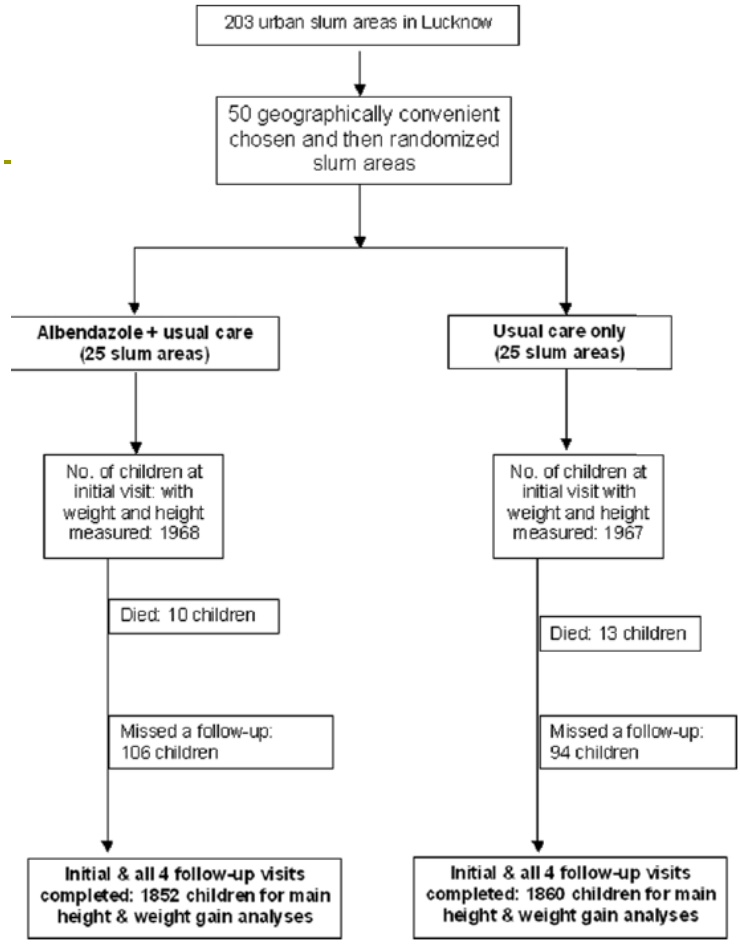
Abstract

Background: More than a third of the world's children are infected with intestinal nematodes. Current control approaches emphasise treatment of school age children, and there is a lack of information on the effects of deworming preschool children.

Methodology: We studied the effects on the heights and weights of 3,935 children, initially 1 to 5 years of age, of five rounds of anthelmintic treatment (400 mg albendazole) administered every 6 months over 2 years. The children lived in 50 areas, each defined by precise government boundaries as urban slums, in Lucknow, North India. All children were offered vitamin A every 6 months, and children in 25 randomly assigned slum areas also received 6-monthly albendazole. Treatments were delivered by the State Integrated Child Development Scheme (ICDS), and height and weight were monitored at baseline and every 6 months for 24 months (trial registration number NCT00396500). p Value calculations are based only on the 50 area-specific mean values, as randomization was by area.

Findings: The ICDS infrastructure proved able to deliver the interventions. 95% (3,712/3,912) of those alive at the end of the study had received all five interventions and had been measured during all four follow-up surveys, and 99% (3,855/3,912) were measured at the last of these surveys. At this final follow up, the albendazole-treated arm exhibited a similar height gain but a 35 (SE 5) % greater weight gain, equivalent to an extra 1 (SE 0.15) kg over 2 years (99% CI 0.6–1.4 kg, $p = 10^{-11}$).

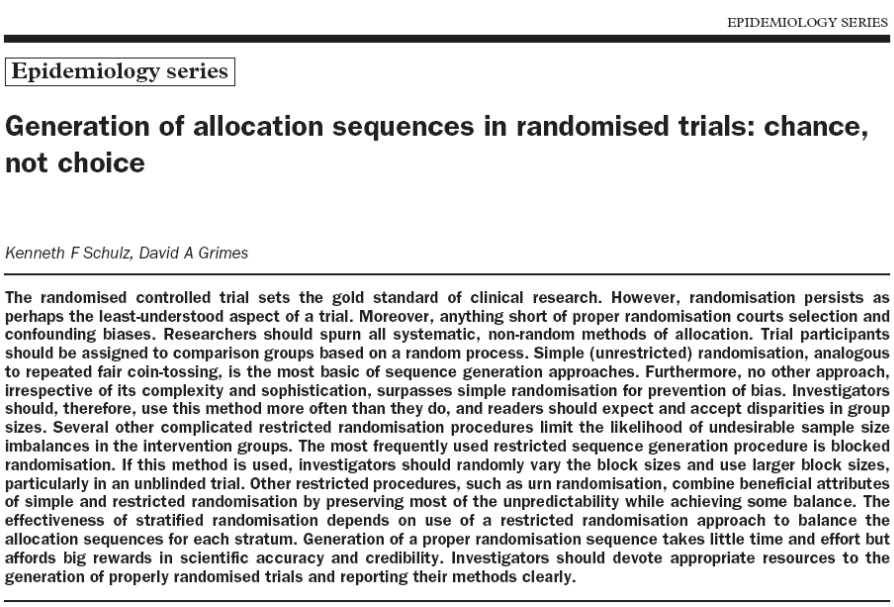
Conclusions: In such urban slums in the 1990s, five 6-monthly rounds of single dose anthelmintic treatment of malnourished, poor children initially aged 1–5 years results in substantial weight gain. The ICDS system could provide a sustainable, inexpensive approach to the delivery of anthelmintics or micronutrient supplements to such populations. As, however, we do not know the control parasite burden, these results are difficult to generalize.



Example of a cluster randomized trial

How is randomization achieved?

- Two steps involved:
  - Generation of allocation sequence
  - Implementation of allocation (concealment of allocation)
- While both are important, there is evidence that concealment of allocation is more critical



EPIDEMIOLOGY SERIES

Epidemiology series

Generation of allocation sequences in randomised trials: chance, not choice

Kenneth F Schulz, David A Grimes

The randomised controlled trial sets the gold standard of clinical research. However, randomisation persists as perhaps the least-understood aspect of a trial. Moreover, anything short of proper randomisation courts selection and confounding biases. Researchers should spurn all systematic, non-random methods of allocation. Trial participants should be assigned to comparison groups based on a random process. Simple (unrestricted) randomisation, analogous to repeated fair coin-tossing, is the most basic of sequence generation approaches. Furthermore, no other approach, irrespective of its complexity and sophistication, surpasses simple randomisation for prevention of bias. Investigators should, therefore, use this method more often than they do, and readers should expect and accept disparities in group sizes. Several other complicated restricted randomisation procedures limit the likelihood of undesirable sample size imbalances in the intervention groups. The most frequently used restricted sequence generation procedure is blocked randomisation. If this method is used, investigators should randomly vary the block sizes and use larger block sizes, particularly in an unblinded trial. Other restricted procedures, such as urn randomisation, combine beneficial attributes of simple and restricted randomisation by preserving most of the unpredictability while achieving some balance. The effectiveness of stratified randomisation depends on use of a restricted randomisation approach to balance the allocation sequences for each stratum. Generation of a proper randomisation sequence takes little time and effort but affords big rewards in scientific accuracy and credibility. Investigators should devote appropriate resources to the generation of properly randomised trials and reporting their methods clearly.

EPIDEMIOLOGY SERIES

Epidemiology series

Allocation concealment in randomised trials: defending against deciphering

Kenneth F Schulz, David A Grimes

Proper randomisation rests on adequate allocation concealment. An allocation concealment process keeps clinicians and participants unaware of upcoming assignments. Without it, even properly developed random allocation sequences can be subverted. Within this concealment process, the crucial unbiased nature of randomised controlled trials collides with their most vexing implementation problems. Proper allocation concealment frequently frustrates clinical inclinations, which annoys those who do the trials. Randomised controlled trials are anathema to clinicians. Many involved with trials will be tempted to decipher assignments, which subverts randomisation. For some implementing a trial, deciphering the allocation scheme might frequently become too great an intellectual challenge to resist. Whether their motives indicate innocent or pernicious intents, such tampering undermines the validity of a trial. Indeed, inadequate allocation concealment leads to exaggerated estimates of treatment effect, on average, but with scope for bias in either direction. Trial investigators will be crafty in any potential efforts to decipher the allocation sequence, so trial designers must be just as clever in their design efforts to prevent deciphering. Investigators must effectively immunise trials against selection and confounding biases with proper allocation concealment. Furthermore, investigators should report baseline comparisons on important prognostic variables. Hypothesis tests of baseline characteristics, however, are superfluous and could be harmful if they lead investigators to suppress reporting any baseline imbalances.

Generation of allocation sequence

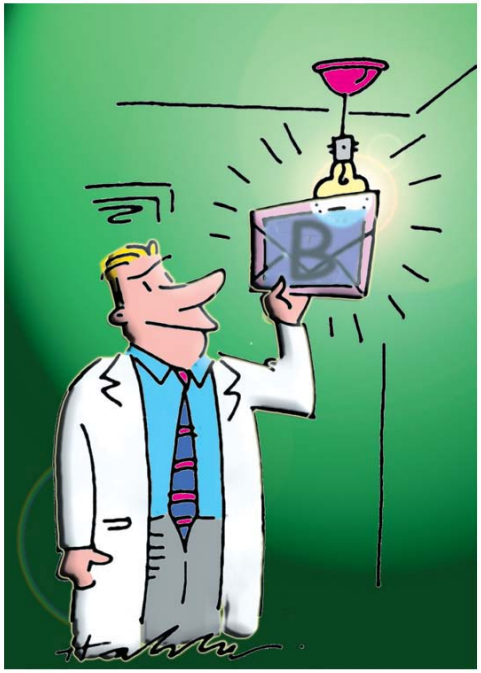
- Simple randomization
  - Analogous to a repeated fair coin tossing
- Restricted randomization
  - Blocking
    - Done to ensure equal balance of arms throughout all portions of the study
    - For example, blocks of six would have 3 active/3 control
    - Block size itself can/should vary
- Stratified randomization
  - Individuals are identified based on important covariates (sex, age, etc.) and then randomization occurs within the strata
- Dynamic or adaptive methods (not common)

Courtesy: J Colford

Concealment of allocation

- If those making the decision about patient eligibility are aware of the arm of the study to which the patient will be allocated --if randomization is unconcealed-- they may systematically enroll sicker-- or less sick-- patients to either treatment or control groups.
- This will defeat the purpose of randomization and the study will yield a biased result.

- Example: RCT of open vs laparoscopic appendectomy (example from Users' Guides):
  - trial ran smoothly during the day
  - at night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one; and the limited operating room availability made the longer laparoscopic procedure an annoyance.
  - reluctant to call in a consultant, and particularly reluctant with specific senior colleagues, the residents sometimes adopted a practical solution.
  - when an eligible patient appeared, the residents checked the attending staff and the lineup for the operating room and, depending on the personality of the attending surgeon and the length of the lineup, held the translucent envelopes containing orders up to the light.
  - as soon as they found one that dictated an open procedure, they opened that envelope. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy group according to the passed-over envelope
  - If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.



Deciphering the allocation concealment scheme

Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002 Feb 16;359(9306):614-8

Panel 2: **Minimum and expanded criteria for adequate allocation concealment schemes**

Minimum description of adequate allocation concealment scheme	**Additional descriptive elements that provide greater assurance of allocation concealment**
Sequentially numbered, opaque, sealed envelopes (SNOSE)	Envelopes are opened sequentially only after participant details are written on the envelope. Pressure-sensitive or carbon paper inside the envelope transfers that information to the assignment card (creates an audit trail). Cardboard or aluminum foil inside the envelope renders the envelope impermeable to intense light.
Sequentially numbered containers	All of the containers were tamper-proof, equal in weight, and similar in appearance.
Pharmacy controlled	Indications that the researchers developed, or at least validated, a proper randomisation scheme for the pharmacy. Indications that the researchers instructed the pharmacy in proper allocation concealment.
Central randomisation	The mechanism for contact—eg, telephone, fax, or e-mail—the stringent procedures to ensure enrolment before randomisation, and the thorough training for those individuals staffing the central randomisation office.

Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002 Feb 16;359(9306):614-8

Allocation concealment

- **Allocation concealed:** the authors were deemed to have taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (eg, central randomisation; numbered, opaque, sealed envelopes; sealed envelopes from a closed bag; numbered or coded bottles or containers; drugs prepared by the pharmacy; or other descriptions that contain elements convincing of concealment).
- **Allocation not concealed:** the authors were deemed not to have taken adequate measures to conceal allocation to study group assignments from those responsible for assessing patients for entry in the trial (eg, no concealment procedure, sealed envelopes that were not opaque, or other descriptions that contain elements not convincing of concealment).
- **Unclear allocation concealment:** the authors did not report or provide us with a description of an allocation concealment approach that allowed for classification as concealed or not concealed.

Haynes BR. Incorporating allocation concealment and blinding in randomised controlled trials *Evidence-Based Medicine* 2000; *5*:38

When is it ethical to randomize?

- At least two answers to this question:
  - uncertainty principle
  - clinical equipoise
- Which is the preferred moral basis of the RCT?

The uncertainty principle

- Richard Peto *et al*. (1976): "Physicians who are convinced that one treatment is better than another for a particular patient of theirs cannot ethically choose at random which treatment to give: they must do what they think best for the particular patient. For this reason, physicians who feel they already know the answer cannot enter their patients into a trial."

Clinical equipoise

- Benjamin Freedman (1987):
  - Clinical equipoise exists when there is genuine uncertainty within the professional community as to which of the two treatment arms is superior

Types of RCT's—classification schemes

- Based on the type of interventions being evaluated
- Based on how participants are exposed to interventions
- Based on the number of participants
- Based on whether goal is evaluation of superiority vs. equivalence
- Based on whether investigators and/or participants know which intervention is being studied

Courtesy: J Colford

Types of RCT's—classification schemes

- Based on the aspects of interventions being evaluated
  - Efficacy vs effectiveness trials
  - Superiority vs equivalence trials
  - Phase I, II, III trials

Courtesy: J Colford

Efficacy vs. effectiveness

- Efficacy—does the intervention work in the people who actually receive it?
  - These trials tend to be explanatory
  - Goal here is high compliance
- Effectiveness—how does the intervention work in those offered it
  - Tend to be pragmatic

Courtesy: J Colford

Superiority vs. equivalence trials

- Superiority trials
  - Intended to determine if new treatment is different from (better than) placebo or existing treatment (active control)
    - Null hypothesis is that there is no difference between treatments.
    - Alternative hypothesis is that the new treatment is no different from (two-sided) or better than (one-sided) control.
- Equivalence trials
  - Intended to determine that new treatment is no worse than active control
  - Null hypothesis and alternative hypotheses are reversed.
    - Null hypothesis is that difference between treatments is greater than X.
    - Alternative hypothesis is that difference between treatments is less than X

Courtesy: J Colford

Example of equivalence trial

RESPIRATORY INFECTION

Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial

M Atkinson, M Lakhanpaul, A Smyth, H Vyas, V Weston, J Sithole, V Owen, K Halliday, H Sammons, J Crane, N Guntupalli, L Walton, T Ninan, A Morjaria, T Stephenson

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See end of article for authors' affiliations

Correspondence to: Dr Maria Atkinson, Paediatric Respiratory Unit, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK; maria@doctors.org.uk

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Objective: To ascertain whether therapeutic equivalence exists for the treatment of paediatric community acquired pneumonia by the oral and intravenous (IV) routes.
Methods: A multicentre pragmatic randomised controlled non-blinded equivalence trial was undertaken in eight paediatric centres in England (district general and tertiary hospitals). Equivalence was defined as no more than a 20% difference between treatments of the proportion meeting the primary outcome measure at any time. 246 children who required admission to hospital and had fever, respiratory symptoms or signs and radiologically confirmed pneumonia were included in the study. Exclusion criteria were wheeze, oxygen saturations <85% in air, shock requiring >20 ml/kg fluid resuscitation, immunodeficiency, pleural effusion at presentation requiring drainage, chronic lung condition (excluding asthma), penicillin allergy and age <6 months. The patients were randomised to receive oral amoxicillin for 7 days (n = 126) or IV benzyl penicillin (n = 120). Children in the IV group were changed to oral amoxicillin after a median of six IV doses and received 7 days of antibiotics in total. The predefined primary outcome measure was time for the temperature to be <38°C for 24 continuous hours and oxygen requirement to cease. Secondary outcomes were time in hospital, complications, duration of oxygen requirement and time to resolution of illness.
Results: Oral amoxicillin and IV benzyl penicillin were shown to be equivalent. Median time for temperature to settle was 1.3 days in both groups ($p<0.001$ for equivalence). Three children in the oral group were changed to IV antibiotics and seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was 9 days in both groups.
Conclusion: Oral amoxicillin is effective for most children admitted to hospital with pneumonia (all but those with the most severe disease who were excluded from this study). Prior to this study, the British Thoracic Society guidelines on childhood pneumonia could not draw on evidence to address this issue. This will spare children and their families the trauma and pain of cannulation, and children will spend less time in hospital.

Why do an equivalence trial?

- Existing effective treatment
- Placebo-controlled trial unethical
  - Life-threatening illness.
- New treatment not substantially better than existing treatment.
  - May have fewer side effects, greater convenience, lower cost, higher quality of life, or provide an alternative or second line therapy.

Courtesy: J Colford

Phase I, II, III, IV trials

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Study Phase

Most clinical trials are designated as phase I, II, or III, based on the type of questions that study is seeking to answer:

- In Phase I clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- In Phase III studies, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- In Phase IV studies, the post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

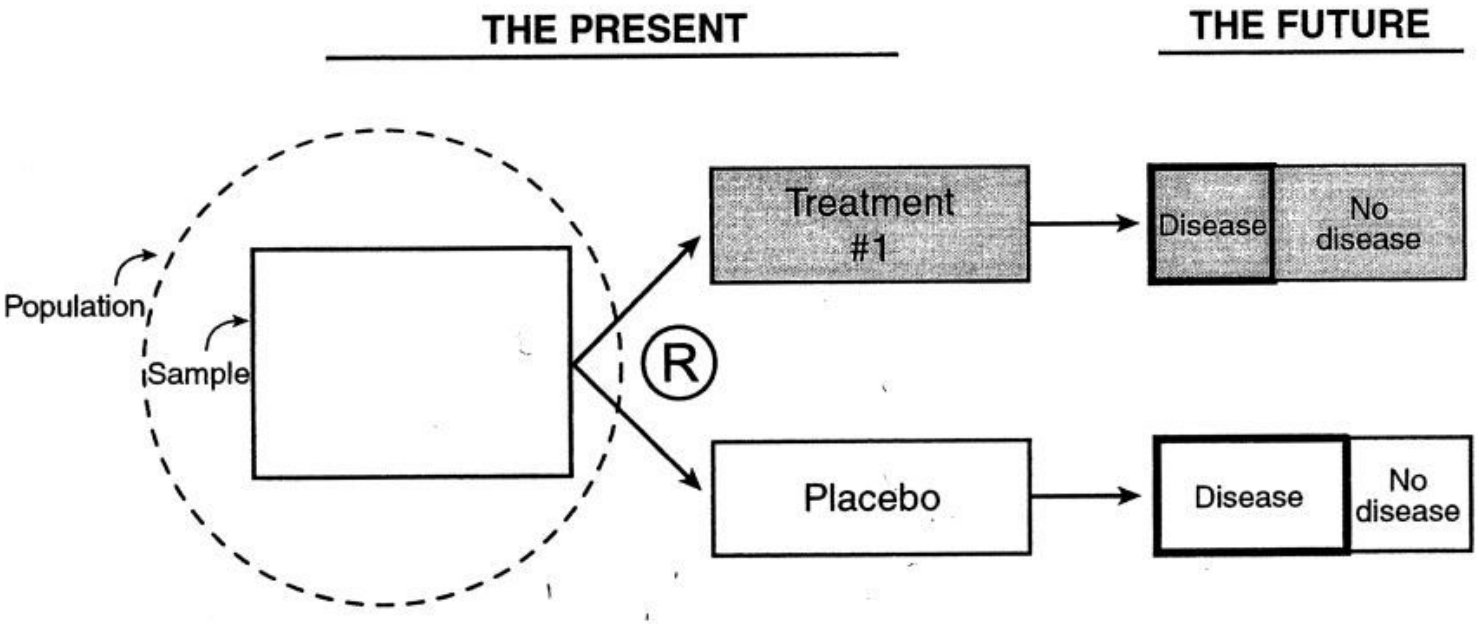
These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

Types of RCT's—classification schemes

- Based on how the participants are exposed to the intervention
  - Parallel trials
  - Crossover trials
  - Trials with factorial design

Courtesy: J Colford

Simple, two-arm (parallel) RCT

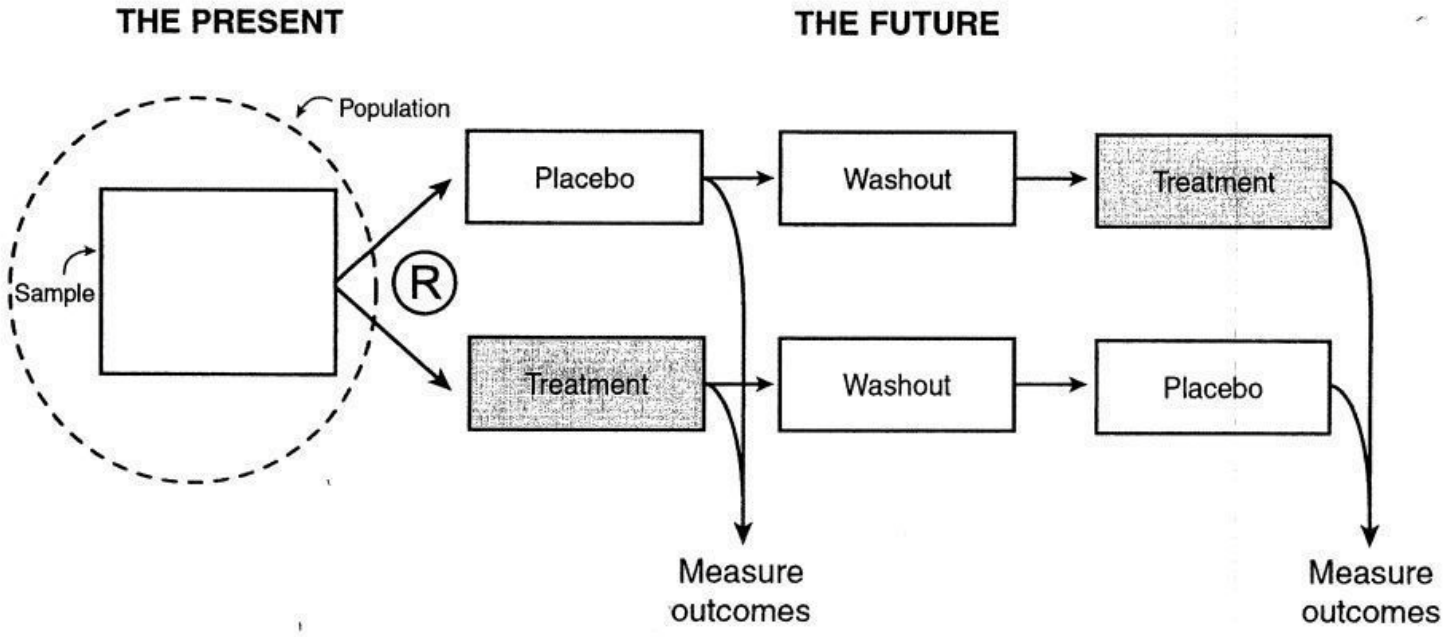


■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Cross-over RCT design



■ **FIGURE 11.4**

In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Example: Crossover trial

Kangaroo Care Is Effective in Diminishing Pain Response in Preterm Neonates

C. Celeste Johnston, DEd, RN; Bonnie Stevens, PhD, RN; Janet Pinelli, DNS, RN; Sharyn Gibbins, PhD, RN; Francoise Filion, MS, RN; Anne Jack, MS, RN; Susan Steele, RN; Kristina Boyer, MSc(A), RN; Annie Veilleux, MD

Objective: To test the efficacy of maternal skin-to-skin contact, or kangaroo care (KC), on diminishing the pain response of preterm neonates to heel lancing.

Design: A crossover design was used, in which the neonates served as their own controls.

Subjects: Preterm neonates (n=74), between 32 and 36 weeks' postmenstrual age and within 10 days of birth, who were breathing without assistance and who were not receiving sedatives or analgesics in 3 level II to III neonatal intensive care units in Canada.

Interventions: In the experimental condition, the neonate was held in KC for 30 minutes before the heel-lancing procedure and remained in KC for the duration of the procedure. In the control condition, the neonate was in the prone position in the isolette. The ordering of conditions was random.

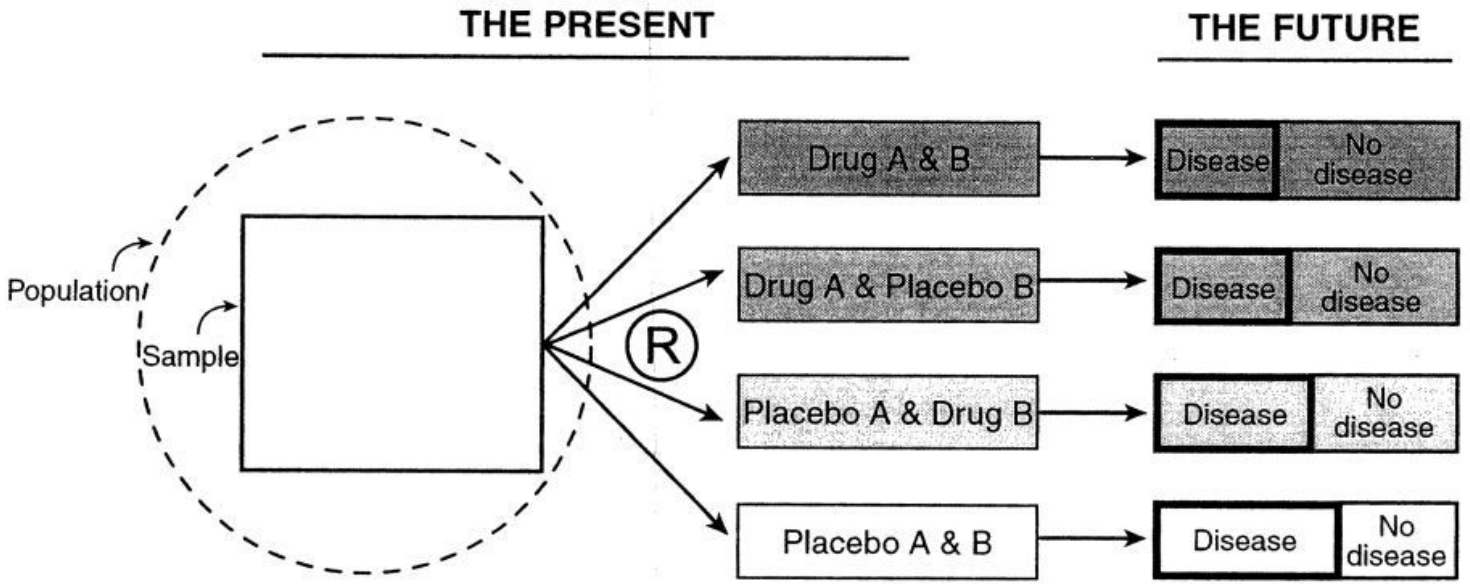
Main Outcome Measures: The primary outcome was the Premature Infant Pain Profile, which is composed of 3 facial actions, maximum heart rate, and minimum oxygen saturation changes from baseline in 30-second blocks. Videotapes, taken with the camera positioned on the neonate's face so that an observer could not tell whether the neonate was being held or was in the isolette, were coded by research assistants who were naïve to the purpose of the study. Heart rate and oxygen levels were continuously monitored into a computer for later analysis. A repeated-measures analysis of covariance was used, with order of condition and site as factors and severity of illness as a covariate.

Results: Premature Infant Pain Profile scores across the first 90 seconds from the heel-lancing procedure were significantly ($.002<P<.04$) lower by 2 points in the KC condition.

Conclusions: For preterm neonates who are 32 weeks' postmenstrual age or older, KC seems to effectively decrease pain from heel lancing. Further study is needed to determine if younger neonates or those requiring assistance in breathing, or older infants or toddlers, would benefit from KC, or if it would remain effective over several procedures. Given its effectiveness, and that parents of neonates in critical care units want to participate more in comforting their children, KC is a potentially beneficial strategy for promoting family health.

Arch Pediatr Adolesc Med. 2003;157:1084-1088

Factorial RCT design



■ **FIGURE 11.2**

In a factorial randomized trial, the investigator (a) selects a sample from the population; (b) measures baseline variables; (c) randomly assigns two active interventions and their controls to four groups, as shown; (d) applies interventions; (e) follows up the cohorts; (f) measures outcome variables.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins, 2001

Example: factorial design

The effects of nicotine gum and counseling among African American light smokers: a 2 × 2 factorial design

Jasjit S. Ahluwalia[1,4], Kolawole Okuyemi[2,4], Nicole Nollen[5], Won S. Choi[5], Harsohena Kaur[3], Kim Pulvers[5] & Matthew S. Mayo[5]

Department of Internal Medicine,[1] Department of Family Medicine,[2] Department of Pediatrics,[3] University of Minnesota Cancer Center,[4] University of Minnesota Academic Health Center, Minneapolis, MN, USA and Department of Preventive Medicine,[5] University of Kansas Medical Center, Kansas City, KS, USA

ABSTRACT

Aim Approximately 50% of African American smokers are light smokers (smoke ≤ 10 cigarettes a day). The prevalence of light smoking in the United States is increasing, yet there has not been a single smoking cessation clinical trial targeting light smokers. The purpose of this 2 × 2 factorial, randomized clinical trial was to evaluate the efficacy of nicotine gum (2 mg versus placebo) and counseling (motivational interviewing versus health education) for African American light smokers. **Design** Participants were assigned randomly to one of four study arms: 2 mg nicotine gum plus health education (HE); 2 mg nicotine gum plus motivational interviewing (MI); placebo gum plus HE; and placebo gum plus MI. **Participants and setting** A total of 755 African American light smokers (66% female, mean age = 45) were enrolled at a community health center over a 16-month period. **Intervention and measurements** Participants received an 8-week supply of nicotine gum and six counseling sessions during the course of the 26-week study. Biochemical measures included expired carbon monoxide (CO) and serum and salivary cotinine. **Findings** Seven-day quit rates for nicotine gum were no better than for the placebo group (14.2% versus 11.1%, $P = 0.232$) at 6 months. However, a counseling effect emerged, with HE performing significantly better than MI (16.7% versus 8.5%, $P < 0.001$). These results were consistent across outcome time-points (weeks 1, 8, and 26). **Conclusions** Results highlight the potential positive impact of directive information and advice-oriented counseling on smoking cessation. Studies are needed to assess other interventions that may further improve quit rates among African American light smokers who are motivated to quit.

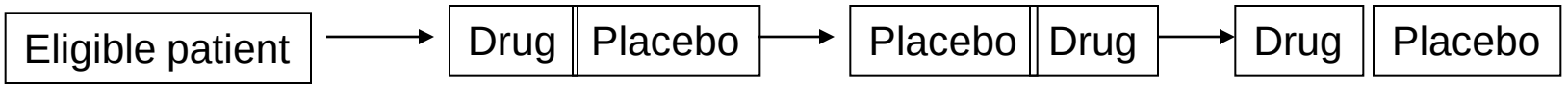
Types of RCT's—classification schemes

- Based on the number of participants
  - N-of-1 trials to mega-trials
  - Fixed size
  - Sequential trials

Courtesy: J Colford

N-of-1 trial

- These can be thought of as a form of crossover trial
- Each participant receives the experimental arm for a period of time and then the control/comparison arm during a different period of time
- There can be many such periods of time in these studies
  - XCCCXXCCXX
- The participant does not know which intervention is occurring during each period



Courtesy: J Colford

Example: N-of-1 trial

Rheumatology 2007;46:135–140
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Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials

M. J. Yelland[1], C. J. Nikles[2], N. McNairn[3], C. B. Del Mar[4], P. J. Schluter[5] and R. M. Brown[6]

Objective. To assess the use of n-of-1 trials for short-term choice of drugs for osteoarthritis, with particular reference to comparing the efficacy of sustained-release [SR] paracetamol with celecoxib in individual patients.
Methods. Evaluation of community-based patients undergoing n-of-1 trials which consisted of double-blind, crossover comparisons of celecoxib 200 or 400 mg/day with sustained-release paracetamol 1330 mg three times a day in three pairs of 2 week treatment periods per drug with random order of the drugs within pairs. Outcomes evaluated were pain and stiffness in sites nominated by the patient, functional limitation scores, preferred medication, side effects and changes in drug use after an n-of-1 trial. Participants were 59 patients with osteoarthritis in multiple sites (hip 6, knee 24, hand 6, shoulder/neck 8, back 14, foot 5), with pain for ≥1 month severe enough to warrant consideration of long-term use of celecoxib but for whom there was doubt about its efficacy. Forty-one n-of-1 trials were completed.
Results. Although on average, celecoxib showed better scores than SR paracetamol [0.2 (0.1) for pain, 0.3 (0.1) for stiffness and 0.3 (0.1) for functional limitation], 33 of the 41 individual patients (80%) failed to identify the differences between SR paracetamol and celecoxib in terms of overall symptom relief. Of the eight patients who were able to identify the differences, seven had better relief with celecoxib and one with SR paracetamol. In 25 out of 41 [61%] patients, subsequent management was consistent with their trial results.
Conclusions. N-of-1 trials may provide a rational and effective method to best choose drugs for individuals with osteoarthritis. SR paracetamol is more useful than celecoxib for most patients of whom management is uncertain.

Mega-trials ("Large simple trials")

- These studies are meant to be HUGE but to collect only a limited amount of data (to make them affordable and practical)
- Are usually multi-center
- Can pick up small effects

Pergamon

0895-4356(94)00150-2

J Clin Epidemiol Vol. 48, No. 1, pp. 23–40, 1995
Elsevier Science Ltd. Printed in Great Britain

LARGE-SCALE RANDOMIZED EVIDENCE: LARGE, SIMPLE TRIALS AND OVERVIEWS OF TRIALS*

RICHARD PETO,† RORY COLLINS and RICHARD GRAY
ICRF/MRC/BHF Clinical Trial Service Unit, University of Oxford, Oxford, U.K.

Courtesy: J Colford

Example: Mega-trial

CAST: randomised placebo-controlled trial of early aspirin use in 20 000 patients with acute ischaemic stroke

*CAST (Chinese Acute Stroke Trial) Collaborative Group**

Summary

Background Aspirin is effective in the treatment of acute myocardial infarction and in the long-term prevention of serious vascular events in survivors of stroke and myocardial infarction. There is, however, no reliable evidence on the effectiveness of early aspirin use in acute ischaemic stroke.

Methods The Chinese Acute Stroke Trial (CAST) was a large randomised, placebo-controlled trial of the effects in hospital of aspirin treatment (160 mg/day) started within 48 h of the onset of suspected acute ischaemic stroke and continued in hospital for up to 4 weeks. The primary endpoints were death from any cause during the 4-week treatment period and death or dependence at discharge, and the analyses were by intention to treat. 21 106 patients with acute ischaemic stroke were enrolled in 413 Chinese hospitals at a mean of 25 h after the onset of symptoms (10 554 aspirin, 10 552 placebo). 87% had a CT scan before randomisation. It was prospectively planned that the results would be analysed in parallel with those of the concurrent International Stroke Trial (IST) of 20 000 patients with acute stroke from other countries.

Findings There was a significant 14% (SD 7) proportional reduction in mortality during the scheduled treatment period (343 [3·3%] deaths among aspirin-allocated patients *vs* 398 [3·9%] deaths among placebo-allocated patients; 2p=0·04). There were significantly fewer recurrent ischaemic strokes in the aspirin-allocated than in the placebo-allocated group (167 [1·6%] *vs* 215 [2·1%]; 2p=0·01) but slightly more haemorrhagic strokes (115 [1·1%] *vs* 93 [0·9%]; 2p>0·1). For the combined in-hospital endpoint of death or non-fatal stroke at 4 weeks, there was a 12% (6) proportional risk reduction with aspirin (545 [5·3%] *vs* 614 [5·9%]; 2p=0·03), an absolute difference of 6·8 (3·2) fewer cases per 1000. At discharge, 3153 (30·5%) aspirin-allocated patients and 3266 (31·6%) placebo-allocated patients were dead or dependent, corresponding to 11·4 (6·4) fewer per 1000 in favour of aspirin (2p=0·08).

Introduction

During the current decade in China there will be about 15 million deaths from stroke, plus much disability.[1] Although the proportion of haemorrhagic strokes is somewhat higher than in western populations, ischaemic stroke still accounts for the majority of new cases and deaths in China.[2,3] If a simple and widely practicable treatment for acute ischaemic stroke could be shown reliably to produce even a moderate improvement in outcome, the population benefit could be substantial. Aspirin is effective in the treatment of acute myocardial infarction,[4] and a systemic overview in 1994 of all previous trials of long-term antiplatelet therapy among patients with a history of previous myocardial infarction, stroke, or transient ischaemic attack showed that about 40 serious vascular events (myocardial infarction, stroke, or vascular death) are avoided per 1000 patients treated for a few years with aspirin.[5] As a result, many patients admitted to hospital with strokes are now being discharged on long-term low-dose aspirin (or other antiplatelet agents), not only in western countries,[6] but also in China[7] and elsewhere.

There is, however, little evidence on the balance of benefits and risks of antiplatelet therapy started during the initial acute phase of ischaemic stroke.[8,9] Consequently, there is much variation in routine clinical practice.[6,7,10,11] The large, randomised, placebo-controlled Chinese Acute Stroke Trial (CAST), and the parallel International Stroke Trial (IST)[12] conducted in other countries, were designed to provide reliable evidence about the effects on early mortality and major morbidity of early aspirin treatment in a wide range of patients presenting with definite or suspected ischaemic stroke. Both trials planned to enrol 20 000 patients, thereby yielding a total of 40 000.

Methods

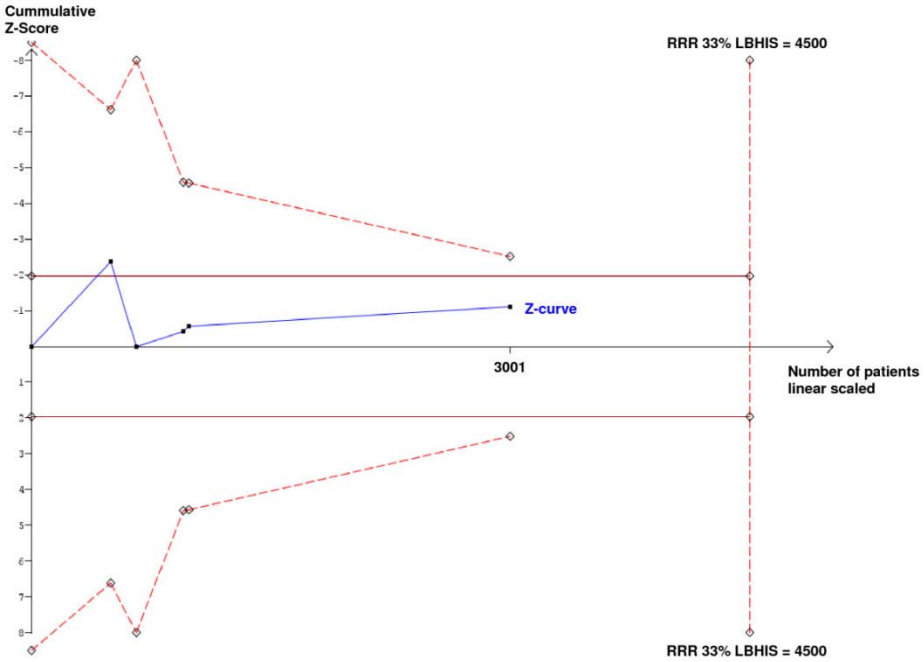
Eligibility

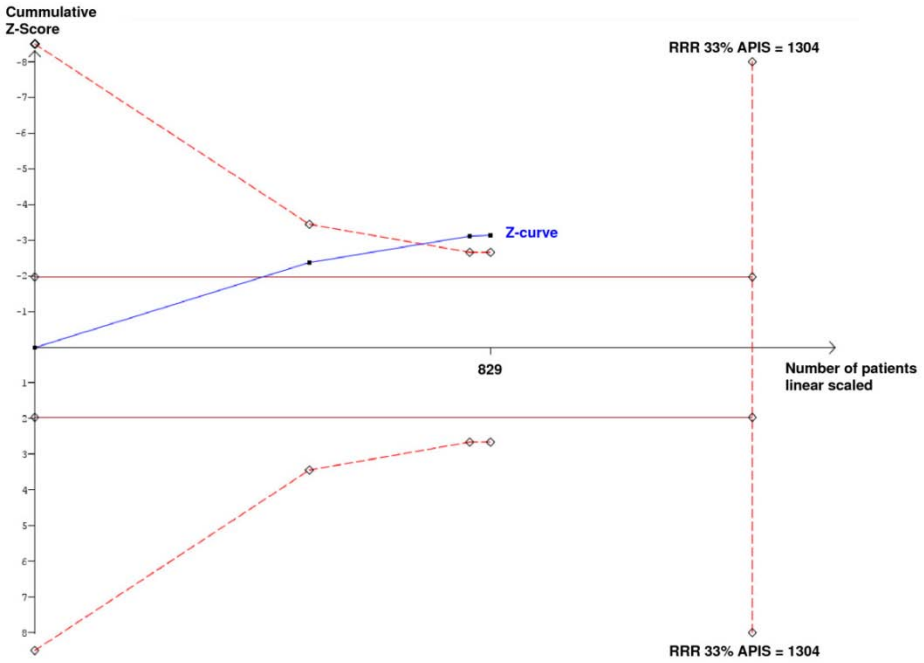
Patients admitted to the 413 participating hospitals in China were eligible for CAST if they were judged to be within 48 h of the onset of symptoms of suspected acute ischaemic stroke, and had no clear indications for, or contraindications to, aspirin. Contraindications were specified not by the protocol but by the

Sequential trial

- Contrast is with the more traditional fixed size trial in which the number of participants is determined based on *a priori* sample size calculations
- Has a parallel design
- Number of participants is NOT specified before the trial begins
- Participants are recruited until the question is answered (or it becomes clear that there is no possibility to detect a difference between the arms)
- Usually the principal outcome occurs (or not) shortly after the study begins

Courtesy: J Colford





Meyhoff *et al. Trials* 2008 **9**:58

Types of RCT's—classification schemes

- Based on who knows what (about the intervention that is being assessed)
  - Open trials
  - Single blind trials
  - Double blind trials
  - Triple and quadruple-blind trials

Courtesy: J Colford

Blinding

- Relevant groups who may/may not have knowledge of treatment assignments
  - Participants
  - Investigators/clinicians administering intervention
  - Investigators assessing outcomes
  - Data analyst(s)
- Open trials
  - All participants and investigators know who is getting which intervention
    - E.g. medical vs. surgical treatments

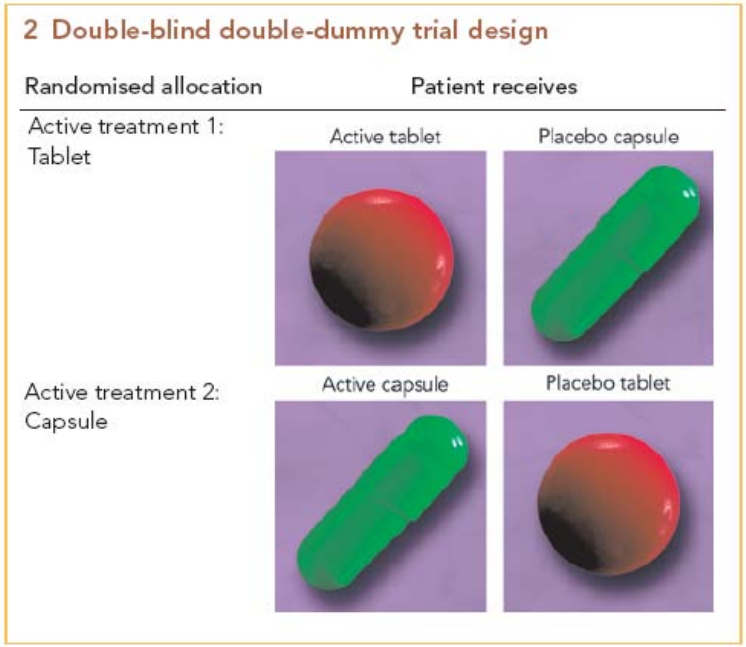
Figure 1: **The authors: double blinded versus single blinded**

Schulz & Grimes. Lancet 2002

Courtesy: J Colford

Single, double, triple, and beyond

- Single-blind
  - The participants (usually) or the investigators assessing outcome (alternately) do not the assignments
- Double-blind
  - Two groups do not know—usually it is the participants and the outcome assessors/investigators
- Triple or quadruple blinding
  - Three or four of the relevant groups (prior slide) are not aware of the treatment assignment



Forder, MJA, 2005

Courtesy: J Colford

Blinding

- Aspirin Myocardial Infarction Study (AMIS), 1982
- Aspirin/Placebo ⟶ survival for 3-4 years after myocardial infarction
- 95 / 285 (33%) deliberately tested the capsule
  - Taste, smell, acid test or professional analysis
- 67% of testers guessed right (47% of non-testers)

Howard, J *et al.* 1982 Clin Pharmacol Ther 32(5), 543-53

Courtesy: J Colford

Please read B-File #5: will be discussed by Dr Stan Shapiro on Monday, 2nd Nov

Bias File 5. How blind are the blind? The story of Vitamin C for common cold

Blinding

Panel 1: **Potential benefits accruing dependent on those individuals successfully blinded**

Individuals blinded	Potential benefits
Participants	Less likely to have biased psychological or physical responses to intervention More likely to comply with trial regimens Less likely to seek additional adjunct interventions Less likely to leave trial without providing outcome data, leading to lost to follow-up
Trial investigators	Less likely to transfer their inclinations or attitudes to participants Less likely to differentially administer co-interventions Less likely to differentially adjust dose Less likely to differentially withdraw participants Less likely to differentially encourage or discourage participants to continue trial
Assessors	Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. Lancet. 2002 Feb 23;359(9307):696-700

Blinding

- **Blinded:** any or all of the clinicians, patients or participants, outcome assessors, or statisticians were unaware of who received which study intervention. If "initially" is indicated (eg, blinded [patients and outcome assessor initially]), the code was broken during the trial, for instance, because of adverse effects.
- **Blinded (unclear):** the authors did not report or provide us with an indication of who, if anyone, was unaware of who received which study intervention.
- **Unblinded:** all participants in the trial (clinicians, patients or participants, outcome assessors, and statisticians) were aware of who received which study intervention.

Haynes BR. Incorporating allocation concealment and blinding in randomised controlled trials *Evidence-Based Medicine* 2000; *5*:38

Concealment of allocation vs. blinding

- Concealment of allocation:
  - Procedure to protect the randomization process **before** the subject enters the trial
    - Failed concealment from the investigator or clinician
    - Failed concealment from the patient
  - Concealment of allocation is ALWAYS feasible
  - If not done, results in selection bias (randomization benefits are lost, and treatment assignment is no longer truly random)
- Blinding:
  - Masking of the treatments **after** randomization (once trial begins)
    - Failed masking of patients, investigators, outcome assessors, etc
  - Blinding is not always feasible
  - If not done, can result in patients biasing their responses because of their knowledge of treatment; can also lead to biased outcome assessment because investigators have knowledge of treatment

Bias in RCTs

- Can occur at all phases:
  - Planning, selection of participants, administration of interventions, measurement of outcomes, analysis of data, interpretation and reporting of results, publication of reports, and even in the reading of the report!
- Selection bias:
  - E.g. due to lack of concealment of allocation
  - Due to attrition and differential losses
- Information bias:
  - Participant response bias (due to lack of blinding)
  - Outcome ascertainment bias (due to lack of blinding)
- Bias due to competing interests
- Reporting biases
  - Publication bias
  - Time lag bias
  - Outcome reporting bias, etc

Courtesy: J Colford

Selection bias

- Definition: Selection bias is when there are systematic differences in the way participants are accepted or rejected for a trial, or in how the intervention is assigned to participants once they have been accepted
- Don't get a false sense of security as a result of randomization, easy to introduce selection bias in a RCT!
- Example: bias due to lack of concealment of allocation

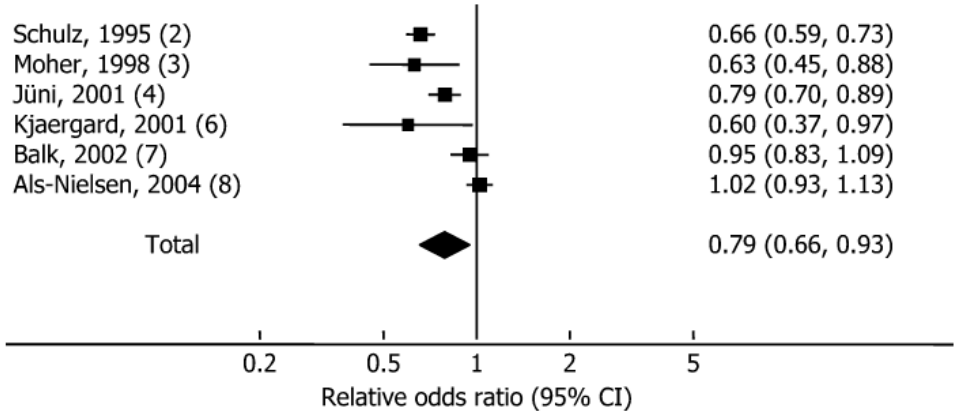


FIGURE 1. Forest plot of a random-effects meta-analysis of methodological studies calculating the relative odds ratio between groups of randomized trials with or without adequate allocation concealment. The squares show the point estimates for individual studies (horizontal bars, 95 percent confidence interval (CI)); the diamond shows the overall relative odds ratio from the meta-analysis.

Gluud, AJE 2006

Information (reporting, ascertainment or detection) bias

- Definition: Ascertainment bias occurs when the results are systematically distorted by knowledge of which intervention each participant is receiving
- Can be introduced by the person administering the intervention, the participants, the investigator, the data analyst, or even the manuscript authors
- Result: Can exaggerate the effect

Courtesy: J Colford

How can ascertainment bias be minimized?

During….

- Randomization → Blind the participant as to which intervention receiving
- Delivery of intervention → Blind the individuals who administer the interventions
- Assessment of outcomes → Blind the individuals who record the outcomes
- Data analysis/manuscript → Blind the statisticians

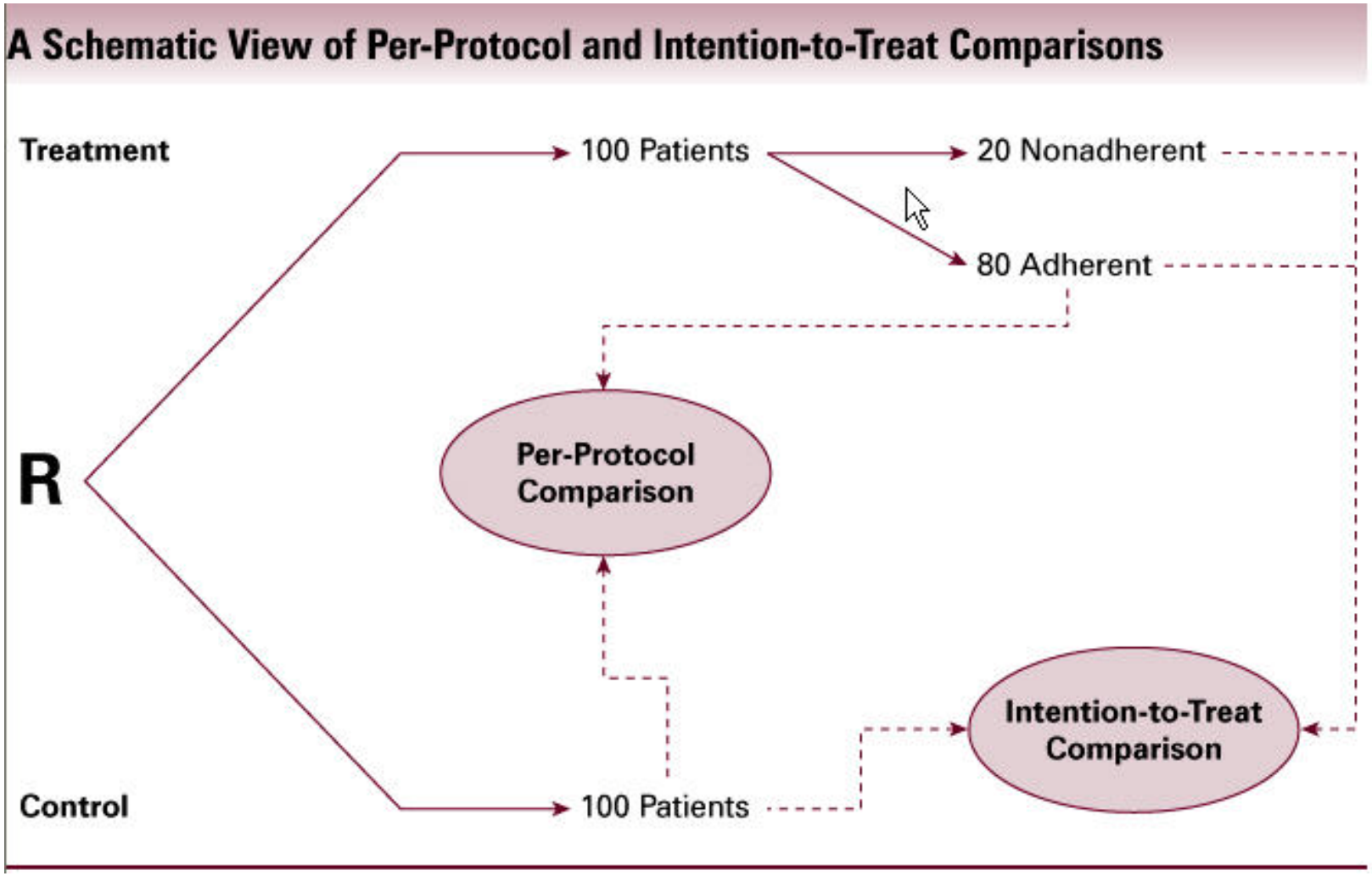
Courtesy: J Colford

Other biases

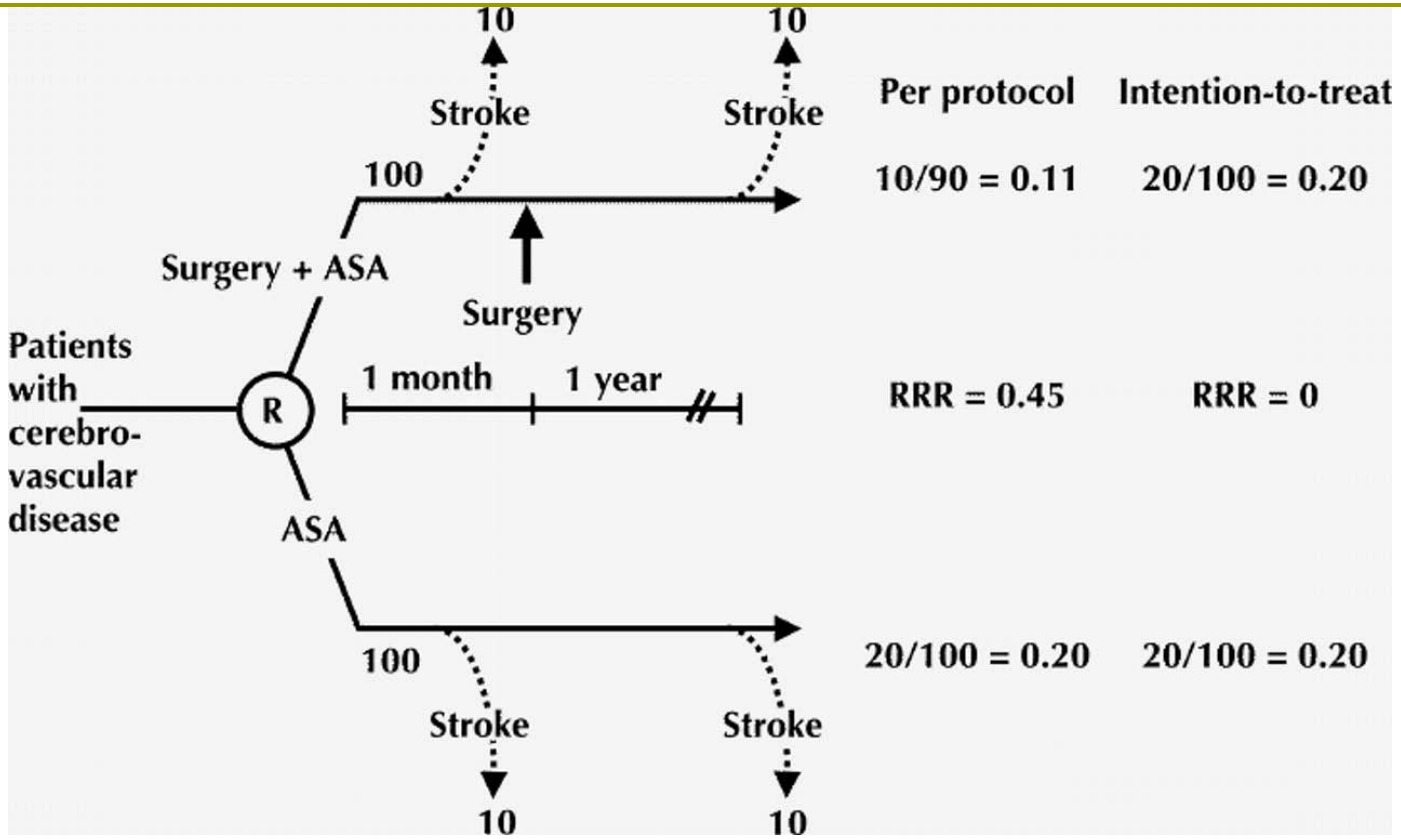
- During the course of a trial - inappropriate handling of withdrawals, drop outs, and protocol violations
  - Intention to treat analysis – all study participants are included in the analyses as part of the groups to which they were randomized regardless of whether they completed the study or not
    - vs. “per protocol” analysis
  - Worst case scenario sensitivity analysis – assign the worst possible outcome to the missing patients or time-points in the group that shows the best results and the best possible outcomes to the missing patients or time-points in the group with the worst results

Courtesy: J Colford

Bias due to not using intention-to-treat analysis



Per protocol analysis introduces bias into the estimate of intervention efficacy



Montori, V. M. et al. CMAJ 2001;165:1339-1341

Loss to follow up and attrition

When Does Loss to Follow-up Seriously Threaten Validity?

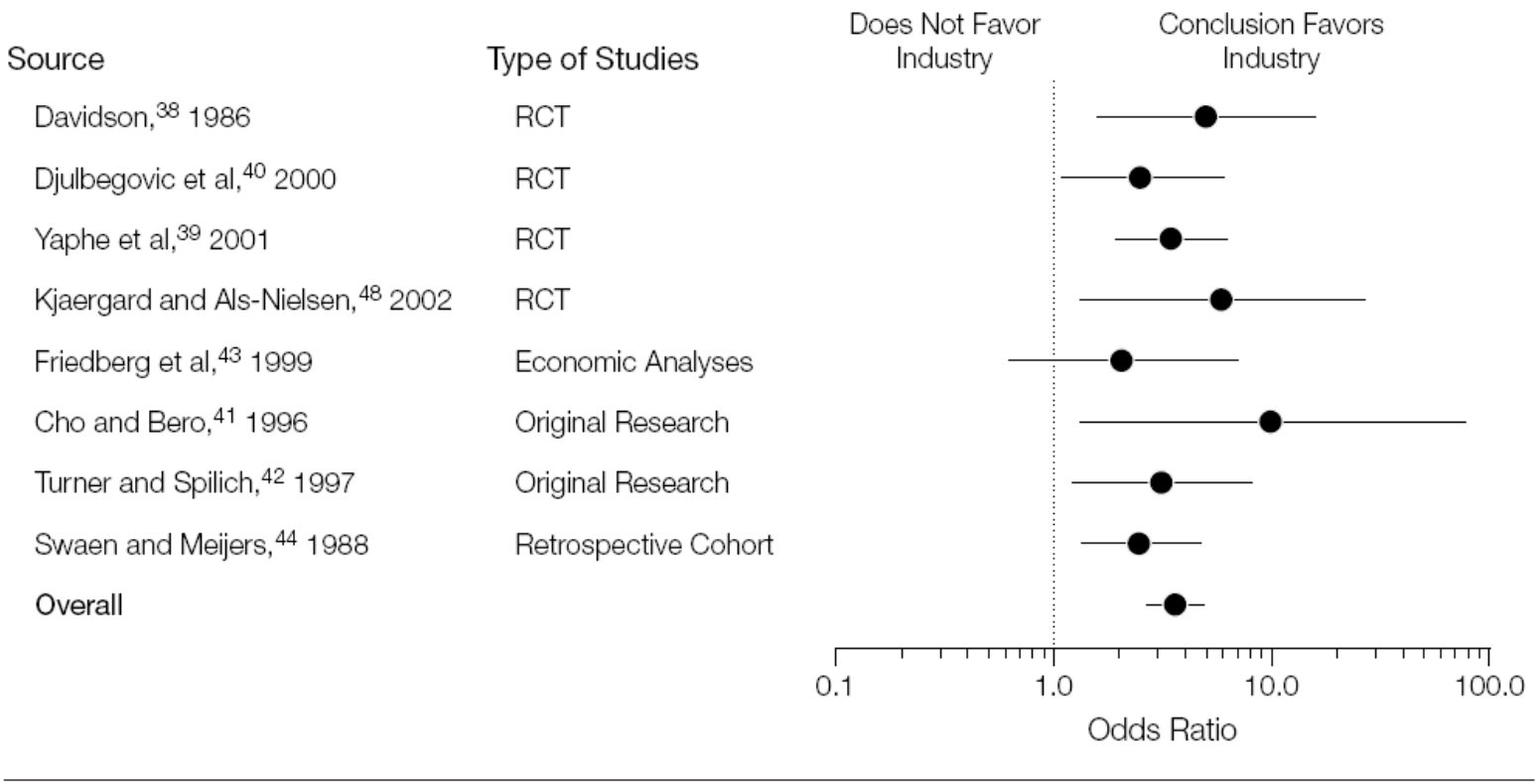
	Trial A		Trial B	
	Treatment	Control	Treatment	Control
Number of patients randomized	1000	1000	1000	1000
Number (%) lost to follow-up	30 (3%)	30 (3%)	30 (3%)	30 (3%)
Number (%) of deaths	200 (20%)	400 (40%)	30 (3%)	60 (6%)
RRR not counting patients lost to follow-up	0.2/0.4 = 0.50		0.03/0.06 = 0.50	
RRR for worst-case scenario*	0.17/0.4 = 0.43		0.00/0.06 = 0	

* The worst-case scenario assumes that all patients allocated to the treatment group and lost to follow-up died and all patients allocated to the control group and lost to follow-up survived.

RRR indicates relative risk reduction.

Bias due to competing interests

Figure. Relation Between Industry Sponsorship and Study Outcome in Original Research Studies



RCT indicates randomized controlled trial. Error bars indicate 95% confidence intervals.

Bekelman, JAMA 2003

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

An-Wen Chan, MD, DPhil
Asbjørn Hróbjartsson, MD, PhD
Mette T. Haahr, BSc
Peter C. Gøtzsche, MD, DrMedSci
Douglas G. Altman, DSc

Context Selective reporting of outcomes within published studies based on the nature or direction of their results has been widely suspected, but direct evidence of such bias is currently limited to case reports.

Objective To study empirically the extent and nature of outcome reporting bias in a cohort of randomized trials.

Design Cohort study using protocols and published reports of randomized trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg, Denmark, in 1994-1995. The number and characteristics of reported and unreported trial outcomes were recorded from protocols, journal articles, and a survey of trialists. An outcome was considered incompletely reported if insufficient data were presented in the published articles for meta-analysis. Odds ratios relating the completeness of outcome reporting to statistical significance were calculated for each trial and then pooled to provide an overall estimate of bias. Protocols and published articles were also compared to identify discrepancies in primary outcomes.

Main Outcome Measures Completeness of reporting of efficacy and harm outcomes and of statistically significant vs nonsignificant outcomes; consistency between primary outcomes defined in the most recent protocols and those defined in published articles.

Results One hundred two trials with 122 published journal articles and 3736 outcomes were identified. Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported. Statistically significant outcomes had a higher odds of being fully reported compared with nonsignificant outcomes for both efficacy (pooled odds ratio, 2.4; 95% confidence interval [CI], 1.4-4.0) and harm (pooled odds ratio, 4.7; 95% CI, 1.8-12.0) data. In comparing published articles with protocols, 62% of trials had at least 1 primary outcome that was changed, introduced, or omitted. Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

Conclusions The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention. To ensure transparency, planned trials should be registered and protocols should be made publicly available prior to trial completion.

SELECTIVE PUBLICATION OF STUDIES with statistically significant results has received widespread recognition.[1] In contrast, selective reporting of favorable outcomes within published studies has not undergone comparable empirical investigation. The existence of outcome reporting bias has been widely suspected for years,[2-12] but direct evidence is limited to case reports that have low generalizability[13-15] and may themselves be subject to publication bias.

Our study had 3 goals: (1) to determine the prevalence of incomplete outcome reporting in published reports of randomized trials; (2) to assess the association between outcome reporting and statistical significance; and (3) to evaluate the consistency between primary outcomes specified in trial protocols and those defined in the published articles.

METHODS

JAMA 2004

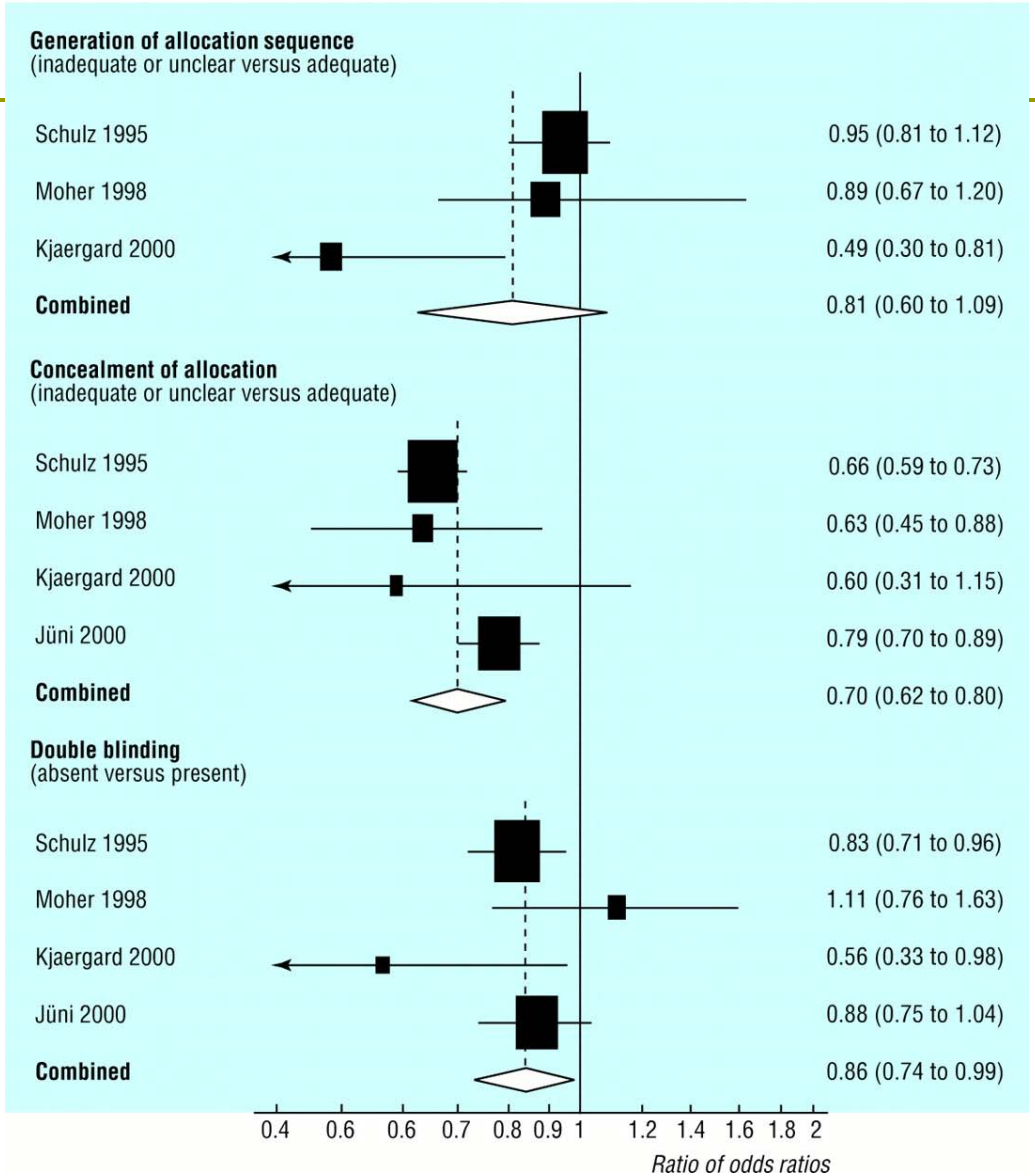
Publication and reporting biases

Table 1. **Steps in the Publishing Process Where Publication Bias May Intrude**

Phases of research publication	Actions contributing to and/or resulting in publication bias
Preliminary and pilot studies	Small studies, more likely to be negative (discarded failed hypotheses), are unpublished—some under "industrial secret."
Trial design, organization, and funding	Proposal selectively cites positive studies.
Institutional/ethics review board approval	No registries are kept of approved trials.
Study completion	Interim analysis shows that study is likely to be negative and project is dropped.
Report completion	Authors decide reporting a negative study is worthless and uninteresting, and no time or effort is assigned.
Report submission	Authors decide to forgo the submission of the negative study.
Journal selection	Authors decide to submit the report to a nonindexed, non–English-language, limited-circulation journal.
Editorial consideration	Editor decides that the negative study is not worth peer review process and rejects manuscript. If editor decides it is worth reviewing, manuscript goes to lower priority list.
Peer review	Reviewers conclude that the negative study does not contribute to the field and recommend rejection of the manuscript.
Author revision and resubmission	Author of rejected manuscript decides to forgo the submission of the negative study or to do it again at a later time to another journal (see "Journal selection").
Report publication	Journal delays publication of the negative study.
Lay press report	The negative study is not considered newsworthy.
Electronic database indexing	Medline, EMBASE, Best Evidence do not scan or index articles in the journal/language of publication of the negative study.
Decision-maker retrieval	Health managers and policymakers do not retrieve the negative study to dictate policy.
Further trial evidence	New trial reports discuss their findings but do not cite the findings of the negative study.
Narrative review	Experts draft a review, but the negative study is never cited.
Systematic review	Reviewer goes to extremes to identify negative reports but misses the negative study. Industry-associated reviewer uses arbitrarily selected unpublished data "on file"; this further discredits incorporation of unpublished reports in systematic reviews.
Systematic review submission	Journal editors reject a meta-analysis because it included unpublished reports not exposed to the rigor of peer review. Review then follows the same path described here for the negative study.
Practice guidelines	Evidence-based guidelines are produced based on a systematic review that missed the negative study.
Funding opportunities	Further funding opportunities are identified without consideration of the negative study.

Montori et al. Mayo Clin Proc 2000

Do design flaws actually affect RCT results?



Juni, P. et al. BMJ 2001;323:42-46

Quality assessment of RCTs

- Various approaches used:
  - Checklist approach
  - Quality scoring system approach
- Quality scores are complicated and tend to vary depending on the instrument used – so, not encouraged

Checklist approach

Users' Guides for an Article About Therapy

Are the results valid?

Did experimental and control groups begin the study with a similar prognosis?

- Were patients randomized?
- Was randomization concealed (blinded or masked)?
- Were patients analyzed in the groups to which they were randomized?
- Were patients in the treatment and control groups similar with respect to known prognostic factors?

Did experimental and control groups retain a similar prognosis after the study started?

- Were patients aware of group allocation?
- Were clinicians aware of group allocation?
- Were outcome assessors aware of group allocation?
- Was follow-up complete?

What are the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

How can I apply the results to patient care?

- Were the study patients similar to my patient?
- Were all clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?

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A Manual for Evidence-Based Clinical Practice

Quality score approach

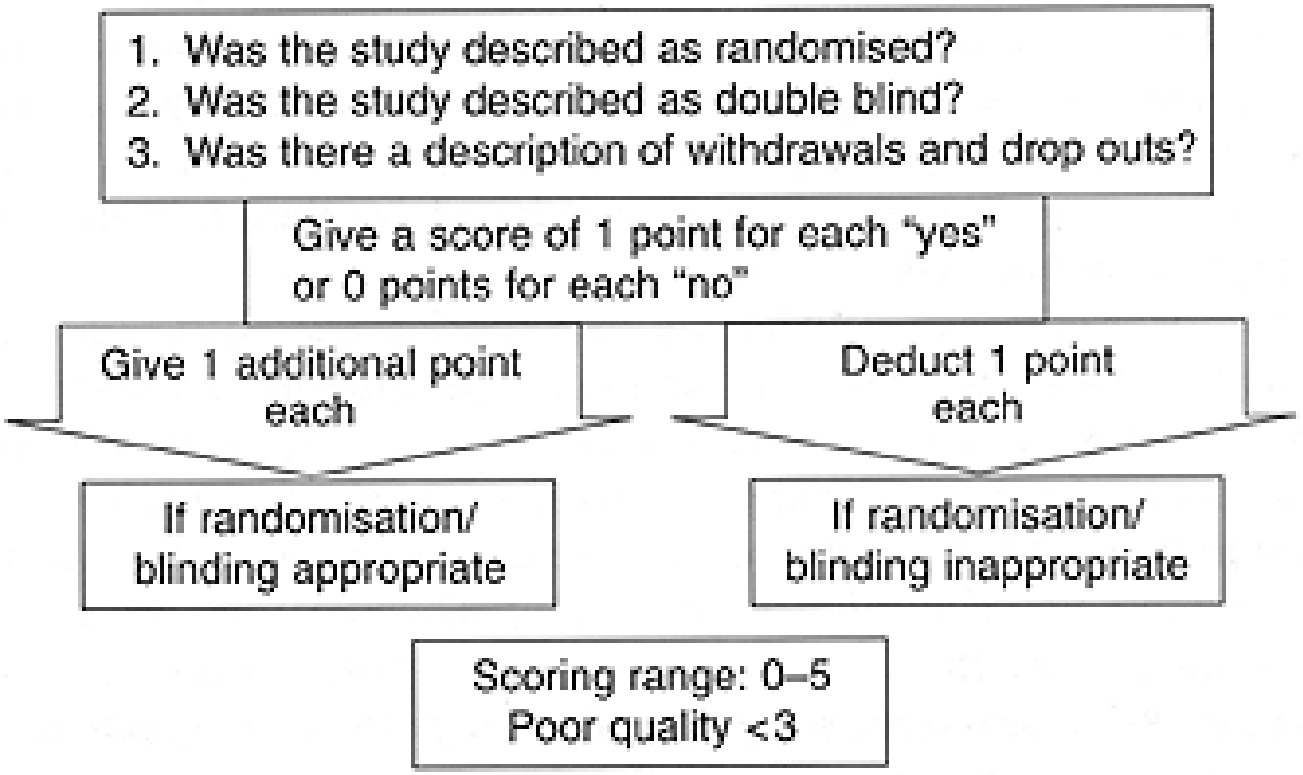


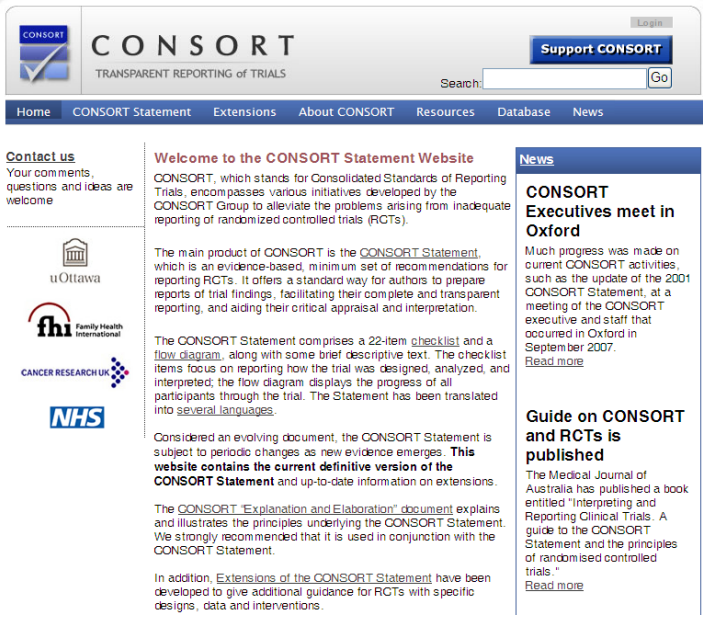
Figure 4.1 Validated quality scale. (From Jadad et al.[1]*)*

Jadad AR, et al. Assessing the quality of reports on randomized clinical trials: Is blinding necessary? *Controlled Clin Trials* 1996;**17**:1-12. URL: http://www.bmjpg.com/rct/chapter4.html

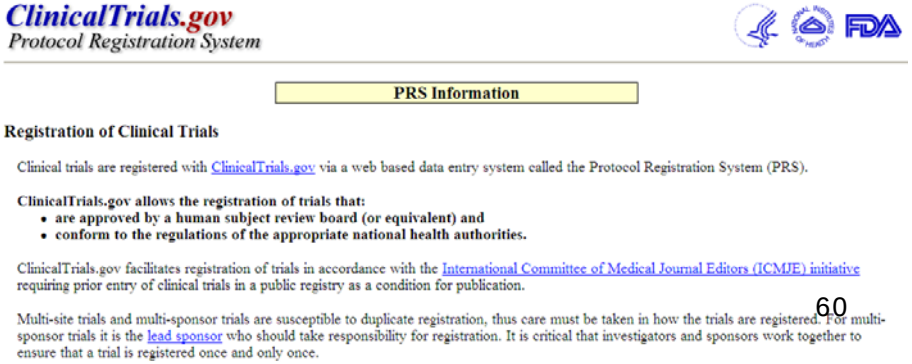
Initiatives to improve quality of reporting of studies

- CONSORT: reporting of RCTs
- STARD: reporting of diagnostic studies
- STROBE: reporting of observational studies
- PRISMA: reporting of meta-analyses of RCTs
- MOOSE: reporting of meta-analyses of observational studies

- Move towards registration of RCTs>>



http://www.consort-statement.org/



The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials

David Moher, MSc
Kenneth F. Schulz, PhD, MBA
Douglas Altman, DSc
for the CONSORT Group

To comprehend the results of a randomized controlled trial (RCT), readers must understand its design, conduct, analysis, and interpretation. That goal can be achieved only through complete transparency from authors. Despite several decades of educational efforts, the reporting of RCTs needs improvement. Investigators and editors developed the original CONSORT (Consolidated Standards of Reporting Trials) statement to help authors improve reporting by using a checklist and flow diagram. The revised CONSORT statement presented in this article incorporates new evidence and addresses some criticisms of the original statement.

The checklist items pertain to the content of the Title, Abstract, Introduction, Methods, Results, and Comment. The revised checklist includes 22 items selected because empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect or because the information is essential to judge the reliability or relevance of the findings. We intended the flow diagram to depict the passage of participants through an RCT. The revised flow diagram depicts information from 4 stages of a trial (enrollment, intervention allocation, follow-up, and analysis). The diagram explicitly includes the number of participants, according to each intervention group, included in the primary data analysis. Inclusion of these numbers allows the reader to judge whether the authors have performed an intention-to-treat analysis.

In sum, the CONSORT statement is intended to improve the reporting of an RCT, enabling readers to understand a trial's conduct and to assess the validity of its results.

A REPORT OF A RANDOMIZED CONtrolled trial (RCT) should convey to the reader, in a transparent manner, why the study was undertaken and how it was conducted and analyzed. For example, a lack of adequately reported randomization has been associated with bias in estimating the effectiveness of interventions.[1,2] To assess the strengths and limitations of an RCT, readers need and deserve to know the quality of its methods. Despite several decades of educational efforts, RCTs still are not being reported adequately.[3-6] For example, a review of 122 recently published RCTs that evaluated the effectiveness of selective serotonin reuptake inhibitors as first-line management strategy for depression found that only 1 (0.8%) article described randomization

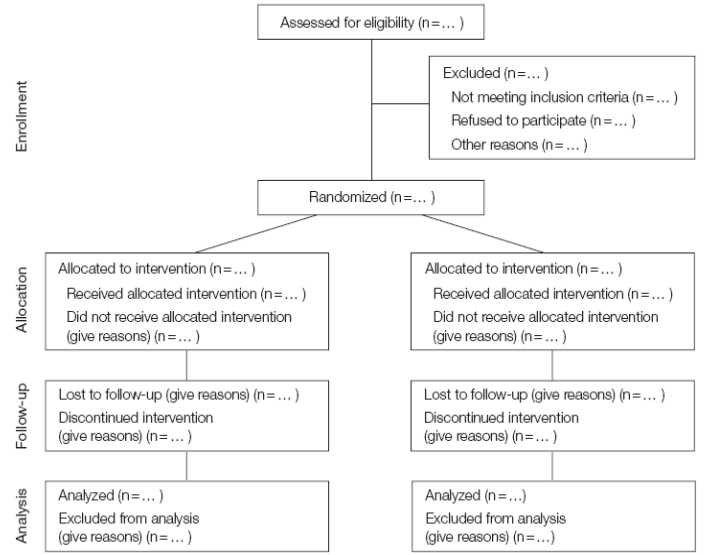
JAMA. 2001;285:1987-1991 www.jama.com

CONSORT: checklist and flow diagram

Table. Checklist of Items to Include When Reporting a Randomized Trial

Section and Topic	Item #	Descriptor	Reported on Page #
Title and Abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat." State the results in absolute numbers when feasible (eg, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (eg, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Comment			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Figure. Flow Diagram of Subject Progress Through the Phases of a Randomized Trial



Bibliography and further reading

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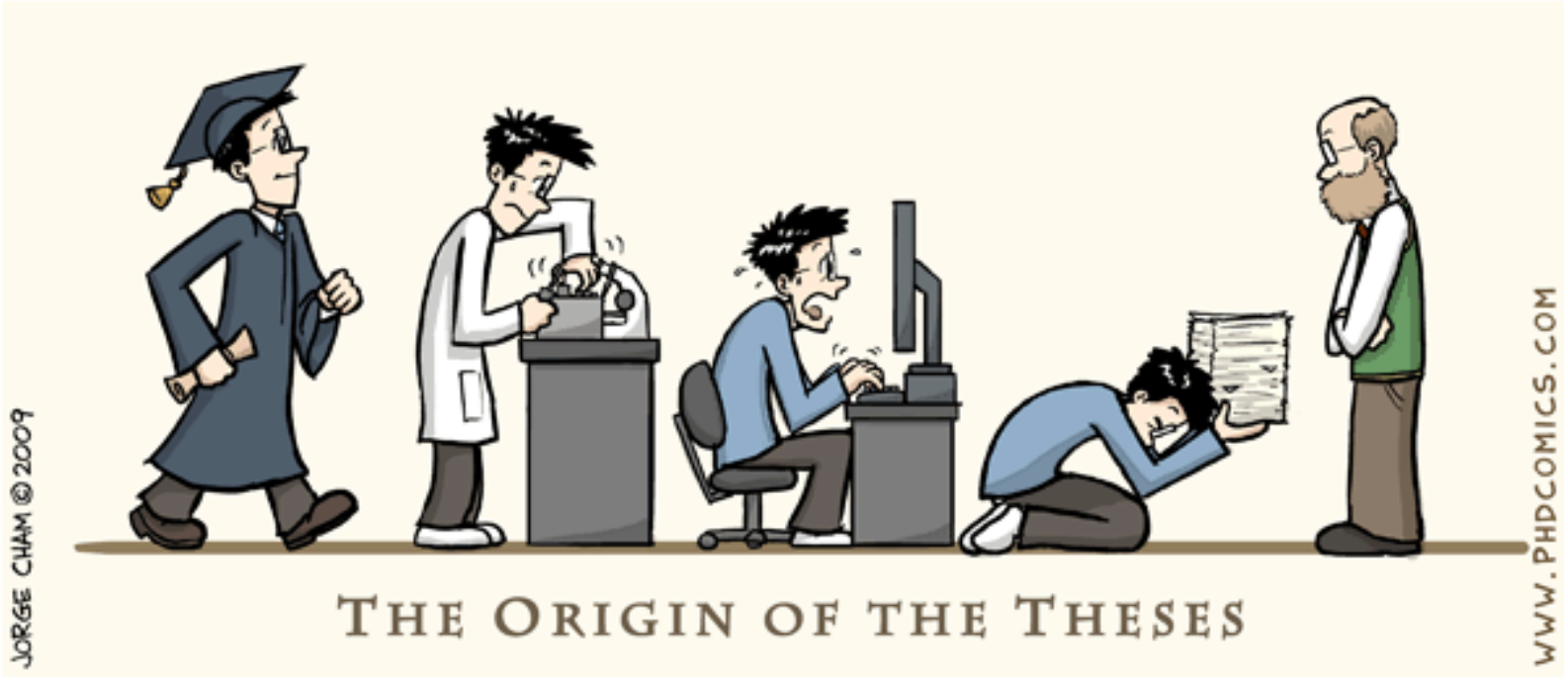
- Users' guide to the medical literature: a manual for evidence-based clinical practice. Gordon Guyatt and Drummond Rennie (editors). Chicago: AMA Press, 2002.

If you are interested in RCTs,
take **EPIB-635 Clinical Trials**
Dr. S. Shapiro

Textbook readings for this lecture

- Gordis text:
  - Chapter 7 and 8



***footnote**:Happy belated birthday, Charles Darwin (thanks to Maciek from UBC for this comic idea)!*