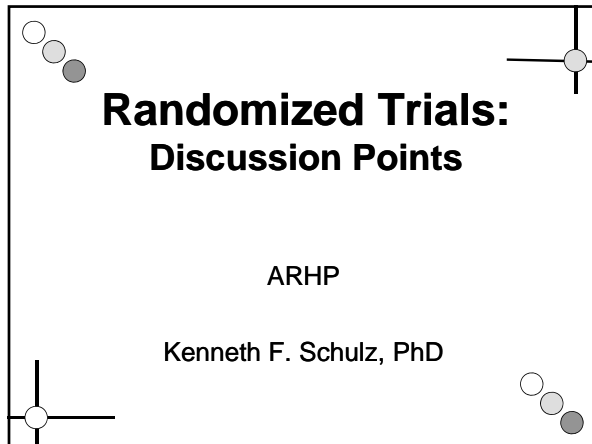


Randomized Trials: Discussion Points

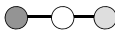
ARHP

Kenneth F. Schulz, PhD



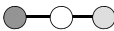
Faculty Disclosure

- Dr. Schulz has no financial affiliations to disclose
- Note: Additional disclosure information is located within the program




Generating a Allocation Sequence

- Quickly conjure up an allocation sequence for a total sample size of 10
- Two groups with 1:1 allocation ratio
-50% chance of A or B
- List such as: BAABABABBA
- Do not flip a coin or the like
- Should take less than 30 seconds



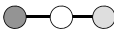
Assures Comparability

- In observational studies, statistical methods allow investigators to control for confounding factors
 - Must be measurable
 - Must be measured



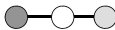

Assures Comparability (Cont.)

- **No** statistical method can achieve comparability on unknown or unmeasured factors in analysis phase
- Random allocation is the **only** known method to assure comparability



Hormone Replacement Therapy (HRT) and Coronary Heart Disease (CHD)

- HRT decrease risk of CHD by 35% to 50%, according to 3 different meta-analysis of numerous observational studies
- Especially strong for secondary prevention in women with CHD



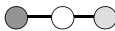
Experimentation Trumps Observation*

- RCT of hormone-therapy for secondary presentation of CHD
- Relative hazard = 0.99; 95% CI 0.80 - 1.22
- No effect of hormone therapy
- Recent Women's Health Initiative RCT in healthy women (JAMA 2002; 288: 321-333)
 - CHD: HR=1.29; 95% CI 1.02-1.63

*Petitti DB. JAMA 1998; 280:650-2

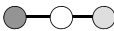
Randomized Trials Require Methodological Rigor

- Improperly conducted RCTs yield biased results
- Researchers must devote assiduous attention to design and conduct of RCTs
- Only properly conducted RCTs will fulfill their promise of minimizing bias



Question

- When someone discusses a high-quality RCT, why is it considered as "high quality"?
- Dispel myths



Double-Blinded Single-Blinded



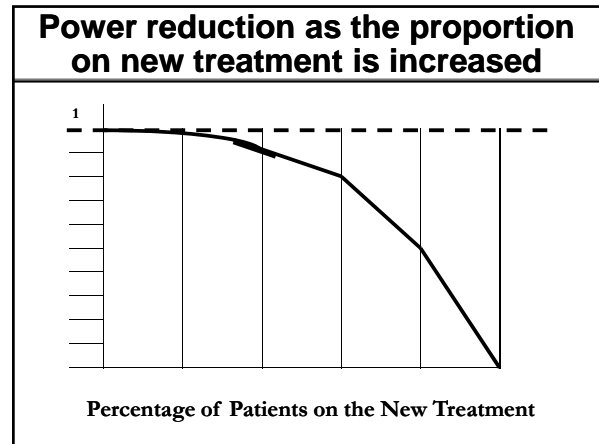
Double-Blinded Triple-Blinded

Inflating the Importance of "Double-Blinding"

- Many over-rate importance of double-blinding
- Indeed, some consider a RCT trial as high quality if "double-blind" . . . the *sine qua non* of an RCT
 - Essential condition or absolute prerequisite
- Scientific life is not that simple
- A randomized trial can be methodologically sound and not be double-blind or, conversely, double-blind and not methodologically sound


Importance of Blinding

- **Double-blinding reflects a strong design**
 - but *not* the primary indicator of overall quality
- **Moreover, many trials cannot be double-blinded**
 - must be judged on overall merit *rather* than an inapplicable standard based on double-blinding
- **Blinding is important**
 - Intuitively, blinding should reduce bias
 - Methodological investigations tend to show that double-blinding prevents bias but . . . less important, on average, than allocation concealment



Randomization

- **Principal bias reducing technique**
- **Success depends upon successful implementation**
- **Chance rather than choice eliminates selection bias**



Randomization Depends Upon Two Interrelated Processes

- **Sequence generation**
 - An unpredictable allocation sequence must be generated based on a random procedure
- **Allocation concealment**
 - Strict implementation of that schedule must be secured through an assignment mechanism that prevents foreknowledge of treatment assignment

Sequence Generation

- **Flipping a coin?**
- **Rolling dice?**
- **Shuffling cards?**
- **Random but tempt investigators toward non-randomness (independent events—Jack B)**
 - Adequate methods but not optimal

Random Sequences ?

➤ AABABBABAB	5-5
➤ ABBABAABAB	5-5
➤ AABBAABBAB	5-5
➤ BAABBAABAB	5-5
➤ ABBAABABBA	5-5
➤ ABABABABBA	5-5
➤ ABBABBAABA	5-5
➤ ABBAABABAB	5-5
➤ ABBAAABBAB	5-5
➤ ABBAABBAAB	5-5

Human Notions (20 of 22 had 5-5) (18 of 21 w/o more than 2 As or Bs in a row)	
➤ AABABBABAB	5-5
➤ ABBABAABAB	5-5
➤ AABBAABBAB	5-5
➤ BAABBAABAB	5-5
➤ ABBAABABBA	5-5
➤ ABABABABBA	5-5
➤ ABBABBAABA	5-5
➤ ABBAABABAB	5-5
➤ ABBAABBAB	5-5
➤ ABBAABBAAB	5-5
➤ 24.6% chance of an exact 5-5 split	

Random Sequences ?	
➤ AAABAABABA	7-3
➤ BBBABBBBBB	1-9
➤ ABAABABBAB	5-5
➤ BAAABBBBAB	4-6
➤ ABABAAAAAA	8-2
➤ BABABBBAAA	5-5
➤ AAABBABBBB	4-6
➤ AABABABBAA	6-4
➤ ABBBBBBBAB	2-8
➤ ABBAAAAABB	6-4

Sequence Generation (Cont.)
<ul style="list-style-type: none"> ➤ Table of random numbers? preferable & recommended <ul style="list-style-type: none"> - Random - Creates an audit trail - Easier (not widely recognized) ➤ Same can be said for most computer random number generators

“Randomization” (Cont.)
<ul style="list-style-type: none"> ➤ Crucially, <u>allocation concealment</u> shields those who admit participants to a trial from knowing upcoming assignments <ul style="list-style-type: none"> - Accept or reject decisions and informed consent obtained without foreknowledge

Minimal Standards: Common Allocation Concealment Approaches
<ul style="list-style-type: none"> ➤ Sequentially numbered, opaque, sealed envelopes (SNOSE) ➤ Pharmacy control ➤ Numbered or coded containers ➤ Central randomization ➤ Realistically, these standards should be <u>exceeded</u>

<p>Vol. 334 No. 15 EFFECT OF BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY 939</p> <p>EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY</p> <p>Abstract Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.</p> <p>Methods. In a three-year trial involving 583 patients with renal insufficiency caused by various</p> <p>The patients in each group were then randomly assigned to receive 10 mg of benazepril or placebo once daily.</p> <p>Randomization was balanced for disease severity at each center.</p> <p>NEJM 1996;334:939-41</p>
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THE LANCET

Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris

Clinical trials have demonstrated a prophylactic role for aspirin in myocardial infarction and in unstable angina pectoris. The Swedish Angina Pectoris Aspirin Project (SAPAP) is a randomised, double-blind, placebo-controlled study of aspirin in stable angina pectoris.

"After showing good tolerance of sotalol for at least three weeks the patients were randomised double blind to aspirin 75 mg daily (n=1009) or placebo (n=1026)."

Lancet 1992;340:1421-25

TREATMENT OF HIV INFECTION WITH SAQUINAVIR, ZIDOVUDINE, AND ZALCITABINE

Abstract Background. In patients with human immunodeficiency virus (HIV) infection, combined treatment with several agents may increase the effectiveness of antiviral therapy. We studied the safety and efficacy of saquinavir, an HIV-protease inhibitor, given with or without two nucleoside antiretroviral agents compared with the efficacy of a combination of two nucleoside antiretroviral agents.

"The study (AIDS Clinical Trials Group protocol 229) was a randomized, double-blind, phase 2 trial of three treatment regimens"

NEJM 1996;334:1011-17

Obstetrics & Gynecology

Bacterial Vaginosis: Treatment with Topical Intravaginal Clindamycin Phosphate

We tested topical intravaginal clindamycin phosphate at concentrations of 0.1, 1.0, and 2.0% in the treatment of 62 women with symptomatic bacterial vaginosis in a prospective, randomized, double-blind, placebo-controlled trial.

"... prospective, randomized, double-blind, placebo-controlled trial."

Obstetrics & Gynecology

Randomized Controlled Trial of Antenatal Social Support to Prevent Preterm Birth

Abstract

Objective--To test the effect of a programme of additional antenatal social support on the occurrence of preterm birth (a birth from 20 to 36 weeks gestation) in women at risk of preterm birth.

Design--A prospective randomized controlled trial. The design was one of randomization before consent for a new treatment.

Setting--Three public hospital antenatal clinics in Perth and the offices of 67 obstetricians and gynaecologists.

"Design - A prospective randomized, controlled trial."

British Journal of Obstetrics and Gynaecology
October 1991, Vol. 98, pp 1001-1008

Vol. 334 No. 15 EFFECT OF BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY 939

EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

Abstract Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

Methods. In a randomized trial involving 583 patients with renal insufficiency caused by various underlying renal diseases, we compared the effects of benazepril (10 mg twice daily) with those of placebo. The primary end point was the time to a doubling of the serum creatinine level or the need for dialysis.

We conducted a prospective, double-blind, randomized study involving 49 European hospitals.

NEJM 1996;334:939-41

(Patho)physiological Implications of Chronic Dietary Sodium Restriction During Pregnancy; a longitudinal prospective randomized study

Abstract:

Objective--To study the possible pathophysiological implications of long continued dietary sodium restriction in pregnancy

Design--Longitudinal prospective randomized study of the effects of a low sodium diet compared with unrestricted sodium intake in pregnancy.

Setting--Academic Department of Obstetrics and Gynaecology at Sint Elisabeth Hospital, Nijmegen, The Netherlands.

"Design - Longitudinal, prospective randomized ..."

British Journal of Obstetrics and Gynaecology
October 1991, Vol. 98, pp 980-987

The Term Prospective Trial Is a Pleonasm

- > Trial used increasingly in combination with prospective
- > A PubMed search "prospective trial" yielded 507 hits for the period 1999-2001
 - Prospective is a pleonasm (superfluous)
- > "Because all trials are prospective by definition; the only way to do a retrospective trial is for the investigator to travel back in time with a box of pills."

Letter in *The Lancet*, Sept 2002 by Martijn B Katan, Netherlands

Quality of Reports of Randomized Trials

- > Reviewed 2000 randomized trials of all treatments for schizophrenia
 - Only 4% (n=80) of the trials clearly described the methods of allocation

Thornley B, Adams CE. Content and quality of 2000 controlled trials in schizophrenia over 50 years. *British Medical Journal* 1998;317:1181-1184.

Method of Allocation of Treatment in 208 Controlled Trials in Head Injury

Method of allocation	No. of trials
<i>Adequate</i>	
Centralised randomisation by telephone	1
Numbered/coded identical containers administered sequentially	11
Randomisation scheme controlled by pharmacy	8
Sequentially numbered, sealed, opaque envelopes	2
<i>Not adequate</i>	
Other	18
Date of birth	1
Day of week	3
Alternation	3
<i>Not stated</i>	161

Dickinson K, et al., *BMJ* 2000;320:1308-1311.

Allocation Methods (Cont.)

- > Alternate assignment **ABABABAB...**
- > Chart number **Smith01-1956-M**
- > Date of birth **12_02_1956**

Random?

A Controlled Trial of Povidone-Iodine as Prophylaxis Against Ophthalmia Neonatorum

Abstract Background. Neonatal conjunctivitis (Ophthalmia neonatorum) continues to cause blindness, because the agents used prophylactically to prevent this condition are not completely effective and are not widely available in many parts of the world. Povidone-iodine ophthalmic solution is an effective antibacterial agent with broad spectrum activity against organisms to which no bacteria are known to be resistant.

"Randomization was achieved by rotating the three medications after each was used for a week."

NEJM 1995;332:562-6

Stopping Smoking in Pregnancy: Effect of a Self-help manual in Controlled Trial

Summary. For medical reasons, encouraging women to stop smoking during pregnancy and post partum has high priority. Many smokers want to stop smoking but decline clinical treatment when it is offered. The aim of this study was to find a method which was accepted by a large number of smokers, had a low cost, and was easy to use.

"Women were randomized . . . born on days 1-10 of every month formed the control group (n=231), and those born on days 11-31 formed the treatment group (n=492)."

British Journal of Obstetrics and Gynaecology

Nifedipine in the Treatment of Severe Preeclampsia

We conducted a randomized clinical trial in which patients with severe preeclampsia between 26-36 weeks of gestation receive either nifedipine (10-30 mg sublingually, then 40-120 mg/day orally; N= 24) or hydralazine (6.25-12.5 mg intravenously, then 40-120 mg/day orally; N= 24).

"We conducted a randomized controlled trial. . ."

"Subjects were assigned to the nifedipine or hydralazine group according to the week of the month."

Obstetrics and Gynecology

The use of Histoacryl for Episiotomy Repair


Summary. Histoacryl-tissue adhesive (B. Braun Melsungen AG W. Germany) was used in place of skin sutures (2/0 chromic catgut, Ethicon Ltd, Edinburgh, Scotland) for episiotomy repair in a group of 20 women. This group was compared with two groups of women undergoing first and repeat episiotomy. Variables analysed included pain in the episiotomy site, pain while walking, sitting, sleeping, lying down, breast-feeding, micturating and defaecating. The results are discussed.

"Groups 1 and 3 (first episiotomy repair) were selected randomly, by registration number; group 1 odd and group 3 even numbers."

British Journal of Obstetrics and Gynaecology
ADONIS 0306545910019N

Two Problems

- **Non-random**
- **Difficult to conceal anyone assigning or referring patients know in advance the next assignment**
 - Decide eligibility
 - Time their referral



Eye Canada/014

A. Bradford Hill's Early Attempts at "Randomization"

"The reason . . . the allocation of alternate cases to the treated and untreated groups is often satisfactory, is because no conscious or unconscious bias can enter in, as it may in any selection of cases, and because *in the long run* we can fairly rely upon this random allotment of the patients to equalise in the two groups the distribution of other characteristics that may be important."

A. Bradford Hill. Principles of medical statistics. *Lancet* 1937, pp. 41-43.


Early Glimpses at the Importance of Quality in RCTs

"I suspect that Hill's failure initially to distinguish clearly between alternation and randomization was due partly to an underestimate of the danger of selection bias, and partly to a feeling that alternation would be easier to swallow than randomization."

"The problem is one of 'selection bias'."

Peter Armitage. Bradford Hill and the Randomized Controlled Trial. *Pharmaceutical Medicine* 1992; 6: 23-37.

AB Hill: The First Real Randomized Trial



- **Realization of selection bias problems with alternate allocation**
- **Hill looked for opportunities to employ proper randomization**

Sir A. Bradford Hill

Hill and Doll: The First Real Randomized Trial



Sir Richard Doll

- **Pertussis vaccine trial; pilot in 1944; completed in 1950**
- **Streptomycin for tuberculosis; initiated later; published in the BMJ in 1948**

Critical appraisal of RCTs

- **Non-reporting**
 - Little confidence in the findings
- **If methods reported**
 - Evaluate sequence generation, e.g. did they use a table of random numbers
 - Evaluate allocation concealment, e.g. , SNOSE, not just “envelopes”
 - Must have both
- **Obviously non-random**
 - Interpret as a non-random study

END