

Critical Elements of Randomized Controlled Trials (RCTs)

DMID/ICSSC

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Critical Methodological Elements in RCTs

- **Randomization**
- **Avoiding and handling exclusions after trial entry**
- **Blinding**

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

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.

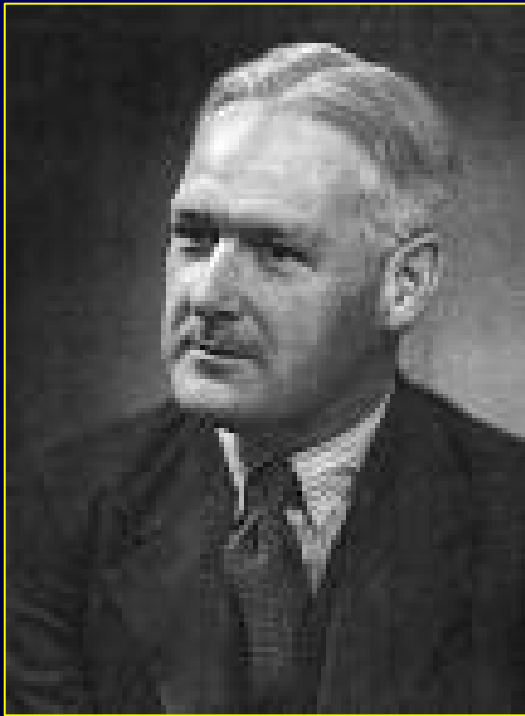
Early Glimpses at the Importance of Quality in RCTs

“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



Sir A. Bradford Hill

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

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**

Randomization

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

“Randomization” or “Random Allocation”

- **Success depends upon two interrelated processes**
 - ◆ **Sequence generation**
 - ◆ **Allocation concealment**

“Randomization”

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

- **Whim**
- **Judgement**
- **Chance**
- **The Quasi- Simulated
“Randomized” Approach**

Allocation Methods

- **Alternate assignment**
- **Chart number**
- **Date of birth**

Random?

Two Problems

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

Sequence Generation

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

Random Sequences ?

AABABBBABAB	5-5
ABBABAABAB	5-5
AABBAAABBAB	5-5
BAABBAAABAB	5-5
ABBAAABABBA	5-5
ABABABABBA	5-5
ABBABBAAABA	5-5
ABBAAABABAB	5-5
ABBAAABBAB	5-5
ABBAAABBAAAB	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
BAABBAAABAB	5-5
ABBAABABBA	5-5
ABABABABBA	5-5
ABBABBAAABA	5-5
ABBAABABAB	5-5
ABBAAABBAB	5-5
ABBAABBBAAB	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
AAABBABB BB	4-6
AABABABBAA	6-4
ABBBBBBBBAB	2-8
ABBAAAAABB	6-4

Sequence Generation

- Table of random numbers?
Preferable & Recommended
 - ◆ Random
 - ◆ Reproducible - can be checked – audit trail
 - ◆ Easier (not widely recognized)
- Same can be said for most random number generations

Types of Sequence Generation

- Simple randomization
- Blocked (*random permuted blocks*) randomization
 - ◆ Small or large block sizes
 - ◆ Randomly varied block sizes
 - ◆ Restricted shuffled randomization
- Stratified randomization

Allocation Concealment

- Crucially, allocation concealment shields those who admit participants to a trial from knowing upcoming assignments.
 - ◆ Accept or reject decisions and informed consent obtained without foreknowledge.

Traditionally, Many Medical Researchers Mistakenly Consider Simply the Sequence Generation as “Randomization”

- **Frequently slight allocation concealment while stressing sequence generation**
- **Without adequate allocation concealment, however, even random unpredictable sequences can be subverted**

e.g. Investigator Adequately Generates a Sequence, Then Posts on a Bulletin Board

- **Basically, equates to no allocation concealment (perhaps a little concealment if the bulletin board is up 5 flights of stairs)**
- **Those responsible for admitting participants could detect the upcoming allocations and then channel them based on prognosis**
- **Bias easily introduced**

Minimal Standards: Common Allocation Concealment Approaches

- Sequentially numbered, opaque, sealed envelopes (SNOSE)
- Pharmacy control
- Numbered or coded containers
- Central randomization

Realistically, these standards should be exceeded

Allocation Concealment Envelopes

- **More susceptible to manipulation through human ingenuity**
- **Less than ideal method of allocation concealment**
- **If used, investigators must diligently develop and monitor the process**

Envelopes (Cont'd)

- **SNOSE**
- **Ensure that the envelopes are opened sequentially, and only after the P's name and other details are written on the appropriate envelope**

Envelopes (Cont'd)

- **Pressure-sensitive or carbon paper inside**
 - ◆ **creates valuable audit trail**
- **Cardboard or aluminum foil inside envelope**

Do Not Confuse Allocation Concealment with Blinding

Allocation concealment seeks to prevent selection bias, protects assignment sequence before and until allocation, and can always be successfully implemented

Do Not Confuse Allocation Concealment with Blinding (*Cont'd*)

In contrast, blinding seeks to prevent ascertainment bias, protects sequence after allocation, and cannot always be successfully implemented

RCTs Annoy Humans

- **Investigators**
 - ◆ **Certain Ps to benefit**
 - ◆ **May want the results of study to reveal the “truth”**
- **Some aspects of properly conducted RCTs annoy investigators**
 - ◆ **Trial procedures attempt to impede human inclinations**

RCTs Annoy Humans ⁽²⁾

- The challenge of deciphering may frequently become too great a temptation to resist
 - ◆ Even without intent to bias
 - “The only way to get rid of a temptation is to yield to it”
- Oscar Wilde
- **Whatever** the motivations, such actions **undermine** the validity of the trial

RCTs: Anathema to the Human Spirit

- **Must acknowledge the vagaries of human nature**
- **Must establish methodological safeguards that thwart attempts to contaminate trials with bias**

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. *BMJ* 1998;317:1181-1184.

Reporting of method of randomization

- Review of 122 RCTs of selective serotonin uptake inhibitors in patients with depression (Hotopf et al 1997)
 - **Only 1 trial report included details of the method of randomization**

Hotopf M, Lewis G, Normand C. Putting trials on trial - the costs and consequences of small trials in depression: a systematic review of methodology. *Journal of Epidemiology and Community Health* 1997;51:354-358.

Cross-sectional slice of 519 RCTs from PubMed [Chan & Altman *Lancet* 2005]

- 73% Nothing on sample size calculation
- 55% Did not define primary outcome(s)
- 79% Nothing on the method of random sequence generation
- 82% Did not specify a method of allocation concealment

Method of allocation of treatment in 208 controlled trials in head injury

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

Method of allocation

% (#)

Adequate

11% (22)

Centralised randomisation by telephone

Sequentially numbered identical containers

Randomisation scheme controlled by pharmacy

Sequentially numbered, sealed, opaque envelopes

Not adequate

12% (25)

Alternation

Date of birth

Day of week

Other

Not stated

77% (161)

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 the 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.”

New England Journal of Medicine

March 1991, Vol. 98, pp 260-264

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

"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). "

Br J Obstet Gynaecol

Obstetrics and Gynecology
Vol. 77, No. 3, March 1991

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 (6.25-30 mg sublingually, then 80-120 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.”

Obstet Gynecol

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 wound healing, wound site, pain while walking, sitting, etc.

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

**Effectiveness of antibiotic prophylaxis
in preventing bacteriuria after
multichannel urodynamic
investigations: A blind, randomized
study in 124 female patients**

Am J Obstet Gynecol

On completion of the procedures, the patients were randomly assigned to prophylaxis or nonprophylaxis groups according to hospital number. Both the physician and the nurse technician were blind as to which assignment the patient received. Patients in group A received nitrofurantoin 50 mg four times and phenazopyridine hydrochloride 200 mg three times for 1 day. Patients in group B received phenazopyridine hydrochloride only. The code was broken at the completion of the study.

Table I. Patient demographics

	<i>Group A</i>	<i>Group B</i>	<i>p Value</i>
No. of patients	49	53	
Age (yr)			
Mean	55.29	58.58	NS
Range	27-77	24-81	
Gravidity			
Mean	3.04	3.09	NS
Range	0-10	0-8	
Parity			
Mean	2.43	2.58	NS
Range	0-8	0-7	
Weight (kg)			
Mean	69.89	69.78	NS
Range	49-98	50-106	
Patients with infections on follow-up			
No.	4	10	NS
%	8.2	18.9	

Exclusions Before Randomization

- Whether for valid or whimsical reasons, do not bias the randomized treatment comparison
- If done to extreme, will limit inferential capability (external validity)

Exclusion Criteria

- **Patients may have a condition for which the trial treatment is contraindicated**
- **Patients may be taking confounding medication**
- **They may be unlikely to remain “observable”**
- **Other plausible reasons**

Key Points

- Before randomization
- Criteria should be clear and specific
- Once in, stays in
- Minimize criteria so as not to limit ability to extrapolate - i.e. results will have little meaning from a greatly restricted subset

Exclusions After Randomization

- **Can introduce bias**
- **Should be carefully scrutinized**

Deviations from the Protocol

Some investigators suggest that if a patient deviates substantially from the allocated exposure, then the patient should not be included in that group.

Other suggest otherwise.

An Example

Patients with TB

Randomize

Placebo

New Oral Drug

40% Non-compliance

60% Compliance

25% Non-compliance

75% Compliance

Group representing the policy of no Tx

Group representing the policy of oral treatment

Outcome

Outcome

RCT Compared the Effectiveness of Clofibrate in Preventing Cardiac Deaths in Men Who Had Survived a Myocardial Infarction

	<u>Clofibrate</u>	<u>Placebo</u>
5-year mortality	20.2%	20.9%
	(p = .55)	
Eliminating deviates from clofibrate (80% adherence)	15.0%	20.9%
	(p < .05)	
Eliminating deviates from both groups	15.0%	15.1%

Authors state that **one can justify almost any conclusion, dependent upon the analysis chosen.**

Actual Text Lifted from Protocols Submitted to DMID

- “Subjects may be withdrawn from the study for”
 - ◆ “Protocol violation/deviation (including non-compliance”
 - ◆ “Other”
- “Reasons for drop-out”
 - ◆ “Protocol violation (to be specified)”
 - ◆ “Migration from the study area”
 - ◆ “Other (to be specified)”

Actual Text Lifted from Protocols Submitted to DMID

- **“Intent to Treat Population: all randomized subjects who received at least one dose of study medication (i.e. tafenoquine or chloroquine/primaquine).”**
- **“Subjects may be terminated from”**
 - ◆ **“Failure or inability to comply with the treatment protocol”**

Exclusions After Randomization

- **Can introduce bias and should be carefully scrutinized**
- **All randomized patients should be analyzed, and analyzed as part of the group to which they were initially assigned**
- **ITT (Intention-to-treat)**

Blinding

- Usually reduces differential assessment of outcomes (information bias)
- May improve compliance and retention of trial participants while reducing biased supplemental care or treatment (co-intervention)
- Place greater credence in results when investigators at least blind outcome assessments, except with “hard” outcomes, such as death.
- Confusion with allocation concealment reflects misunderstandings of both



Blinded

vs

Masked



Double-Blinded

Single-Blinded



Double-Blinded

Triple-Blinded

Blinding and Reporting

- Universally accepted definitions of single, double, and triple blinding elude the scientific community.
- Should explicitly state **who** was blinded – and **how**. With proper reporting, readers should be able to determine what benefits accrued.
- For “total-blinding” ensure that the intervention regimens are similar on, for example, **appearance, shape, size, weight, taste, color, and administration**
 - ◆ provide details in the trial report

Inflating the Importance of “Double-Blinding”

- Many over-rate importance of double-blinding
- Indeed, some consider a randomized trial as high quality if “double-blind”
 - ◆ . . . the *sine qua non* of an RCT
- Unfortunately, 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, should reduce bias
 - ◆ Methodological investigations tend to show that double-blinding prevents bias but . . .
 - less important, on average, than allocation concealment

At a minimum, for a RCT, include in the protocol:

- **Entry criteria**
- **Unit of randomization**
- **Method of generating the allocation sequence (including stratification if used)**
- **Method of allocation concealment**
- **Who will generate the allocation sequence and who will enroll and assign participants**

For an RCT, include in protocol

(Cont'd)

- **The blinding procedures, if any, implemented after assignment.**
- **The approaches to handle losses, withdrawals, and deviations.**
- **Procedures to retain participants (later)**

Summary of NIAID R34 Planning Grants for Clinical Trials

Supports R34 grants for complete planning and design of investigator-initiated Phase I, II, III, and IV clinical trials.

- Permits early peer review of the rationale for the proposed clinical trial;**
- Permits assessment of the design/protocol of the proposed trial in an early form;**
- Provides support for the development of a complete study protocol and associated documents including a manual of operations**
- Supports the development of other essential elements of a clinical trial.**

Summary of NIAID R34 Planning Grants for Clinical Trials

- Will provide up to one year of support.
- Applicants may request up to \$75,000 in direct costs for planning and design of a Phase I trial
- May request up to \$150,000 in direct costs for planning and design of a Phase II, III, or IV trial.
- Pre-approval from NIAID is required for submission of an R34 application.
- Completion of the required products of an R34 grant is a prerequisite for submission of a clinical trial implementation (U01) application.

END

Summary of NIAID R34 Planning Grants for Clinical Trials

NIAID will support clinical trials planning (R34) grants for complete planning and design of, and documentation for, investigator-initiated Phase I, II, III, and IV clinical trials. A clinical trial is defined by NIH as “a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.”

The R34 planning grant is designed to: (1) permit early peer review of the rationale for the proposed clinical trial; (2) permit assessment of the design/protocol of the proposed trial in an early form; (3) provide support for the development of a complete study protocol and associated documents including a manual of operations and (4) support the development of other essential elements of a clinical trial. Completion of the required products of an R34 grant is a prerequisite for submission of a clinical trial implementation (U01) application.

- The R34 grant will provide up to one year of support. Applicants may request up to \$75,000 in direct costs for planning and design of a Phase I trial and up to \$150,000 in direct costs for planning and design of a Phase II, III, or IV trial.
- Pre-approval from NIAID is required for submission of an R34 application.
- R34 applications will be peer reviewed by NIAID initial review groups.
- The product of the R34 will be either an application for a clinical trial implementation (U01) cooperative agreement or a document summarizing the work completed and the reasons for not proceeding to an application.
- **Eligible organizations:** For profit organizations; Non-profit organizations; Public or private institutions, such as universities, colleges, hospitals and laboratories; Units of State government; Units of local government; Eligible institutions of the Federal government; Domestic institutions; Foreign institutions
- **Eligible Project Directors/Principal Investigators (PD/PIs):** Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.
- Applicants may submit more than one application, provided each application is scientifically distinct.