

Randomized controlled trials

Practical and methodological issues

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Definition

A controlled experiment to assess the safety and efficacy of treatments for human diseases and health problems in which, treatments are assigned at random

Randomized Controlled Trial

Unpredictable allocation sequence (random)



EXPT



CTRL



Outcome

Types of interventions

- Pharmacological
- Surgical
- Psychological
- Educational
- Social

RCTs

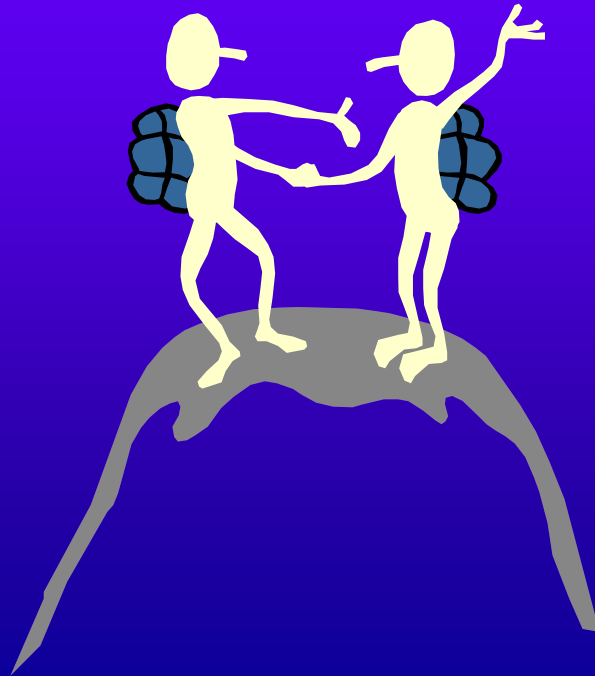
- PHASE I ■ Initial evaluation in human subjects (20-100)
- PHASE II ■ Potential effectiveness, optimal method, route (100-200)
- PHASE III ■ Evaluate the new treatment
- PHASE IV ■ Evaluate long term effects (postmarketing surveillance)

RCT designs

- Parallel
- Successive treatment
 - Replacement therapy
 - Cross-over

When are RCTs appropriate?

- Effectiveness
- Small - moderate effects



Why are RCTs important?

- Results of RCTs provide the most secure basis for valid causal inferences
 - Control for confounders
 - Prevent selection bias

Confounder

- A variable independently associated with the intervention or exposure
- Random allocation enables
 - controlling for known confounders
 - random distribution of unknown confounders in treatment groups

Confounder

- Maternal physical activity and pregnancy outcome (low birth weight)
 - Age
 - Nutritional status
 - Obstetrical history

Bias

- A systematic error or deviation in results or inferences

Types of bias

- Selection bias
- Performance bias
- Attrition bias
- Detection bias

Prevention of selection bias

- Randomization
(Generation of an unpredictable sequence of allocation)
- Allocation concealment



Concealment of allocation

- Centralised
- Coded, identical containers
- On-site computer system
- *Sequentially numbered, sealed, opaque envelopes*



Concealment of allocation

- Inadequate
 - Alternation
 - Day of birth
 - Case record no.
 - when nothing reported
- Not used
 - Open list



Effect size increases with reduced concealment

- Nonrandomized studies yield larger estimates of treatment effects than RCTs
- RCTs using inadequate concealment of allocation yield larger estimates of treatment effects than adequately concealed RCTs

Local sealed envelope randomisation in a multicentre trial: a cautionary tale.

Kennedy A, Grant A.

- Surgical trial
- Sealed envelopes
- Median age of patients allocated to EXPT significantly higher (59 vs 63 y)
- For 3 surgeons (57 vs 72)
- No differences existed after switching to central allocation

Performance bias

- Protection: Blinding
 - Providers
 - Patients
- More important when subjective outcome measures are used

Attrition bias

- Bias due to differences between groups in losses of participants from the study
 - withdrawals
 - dropouts
 - protocol deviations

Detection bias

- Were persons responsible for outcome assessments unaware of the assigned therapy?

How to conduct RCTs

- Careful planning essential
- Protocol with a systematic review
- Resources needed
 - staff
 - money
 - expert support (statistician, trialist)
- Institutional support

Design of an RCT

- Question/hypothesis
- Methods
 - Randomization process
 - Power calculation/sample size
 - Eligibility (inclusion/exclusion criteria)
 - Outcomes
 - Primary
 - Secondary

Randomization process

- *Generation of allocation sequence*
- *(Concealment of) allocation*

Analysis

- Baseline comparisons
 - descriptive statistics
- Outcomes
 - intention-to-treat
 - measures of effectiveness
 - relative risk
 - odds ratio
 - Number needed to treat

Reporting - Problems

- 49% specified an adequate method of random number generation
- 15% reported both adequate method of random number generation and an adequate allocation concealment
- 45% of double-blind trials described similarity
- 26% of double-blind trials provided information on the allocation schedule
- Exclusions after randomization usually ignored

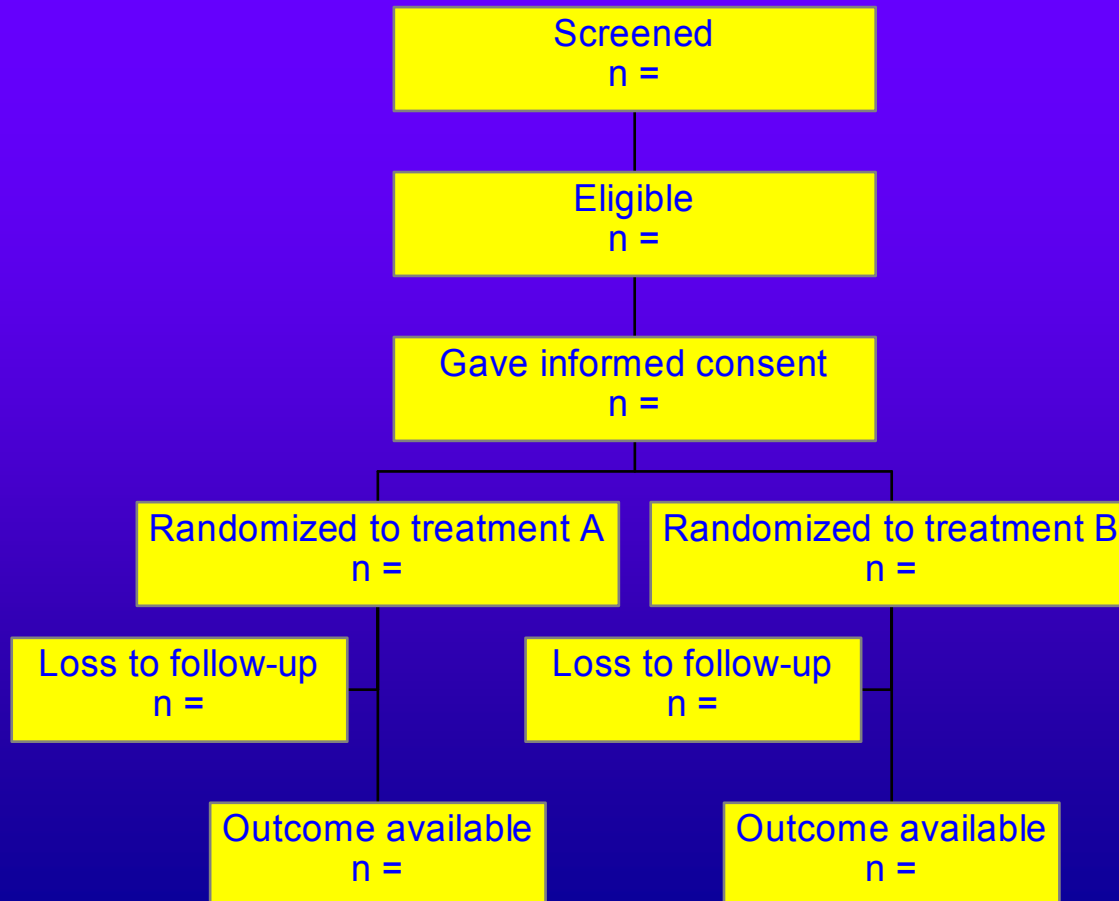
Schulz et al. 1995/96

Reporting

- CONSORT guidelines
 - Identify in the title RCT
 - Structured abstract
 - Methods
 - Participants
 - Interventions
 - Outcomes
 - Planned analyses

CONSORT statement

Trial outline



Small trials

- Freiman 1978 NEJM
- 71 negative trials (no significant effect)
- 67 had < 90% power of detecting a 25 % change
- 50 would have missed a 50 % change with the new treatment

Conclusion

- RCTs need
 - careful planning
 - careful execution
 - comprehensive reporting