Randomized control trial study

Research methodology

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- Interventional, experimental, prospective study in human.
- The investigators not just observe but assign the association between the outcome and exposure.
- Studied 2 groups randomly allocated to receive or not the experimental intervention.
- Intervention can be drugs, prophylaxis, diagnostic, therapeutic, agents, regimens, procedures.

- Randomization of 2 types:

- **Randomized clinical trial** (participants are individuals), it classical type.
- **Community trials** (all unit taken like school, worksite).

- Randomized trials should be consider when:
- There is continuous uncertainty as to the effect of an exposure or treatment.
- The exposure can be modified in a trial setting.

Explanatory RCT have setting in highly selected participants and under highly controlled conditions.

Pragmatic RCT have setting in everyday practice with relatively unselected participants and under flexible conditions.

General consideration and features of RCT

Selection of participants according to selection or inclusion criteria.

Random allocation of participants into two groups:

(1) Treated group (interventional, experimental group)

(2) Comparator group either:

- Placebo controlled (no treatment)
- Active controlled (old treatment use)

<u>Randomization can achieved by:</u>

- Flic a coin
- Roll a dice
- Random number table
- Computerized (even or odd numbers)

Randomization either:

- **Simple randomization** of 2 groups
- **Stratified randomization** that initially stratified the participants before grouping to reduce external risk factors.

Blinding: essential feature in RCT and may include:

- Single blind: Participants unaware.
- Double blind: Participants and investigators are unaware
- Triple blind: Participants, investigators and independent statistician are unaware

Follow up: should be the same for both group and for appropriate time according to the aim of the study. Cross over between participants in two groups may occur.

Ethical issue: approved by independent scientific reviewers and ethical committee, in addition the participants should be informed and agree to consent.

Analysis: different outcomes measures are found in RCT depend on the study objectives, like:

- **Measurement of risk, relative risk, risk difference, risk ratio** which mention in cohort study design.
- **Efficacy**
- **NNT**
- **Mean difference:** like evaluation of new drug in management of hypertension and found the difference in the means of blood pressure of old and new drugs.

Efficacy: introduce the intervention into one group and measure the outcome of both groups. It reflects the extent of the reduction of disease due to intervention.

$$\frac{\text{Disease Rate in control} - \text{Disease Rate in Intervention}}{\text{Disease Rate in Control}} \text{ X } 100$$

	Disease present	Disease absent	
Intervention present	87	411	498
Not intervention	149	328	477
	236	739	975

Event Rate in control =149/477 = 0.312

Event Rate in intervention = 87/498 =0.174

Efficacy = 0.312-0.174/0.312 x 100 = 55.1 %

NNT: Number Needed to Treat

- Estimate the number needed to be treated to prevent one case of outcome, it is the reciprocal of Efficacy
- NNT = 1 / risk difference

$$\frac{1}{\text{Disease Rate in Control} - \text{Disease Rate in Intervention}}$$

NNT = 1/0.138 = 7

Risk Reduction

Use to assess how much death can be reduced by the intervention.
If mortality is 8% in the placebo arm, and 6% in the intervention arm, then the reduction in mortality is:

8%-6%= 2% reduction

Percent reduction
8% - 6% / 8% = 25% reduction

Advantages

- Most efficient for causality evaluate.
- Confounding factors of limited effect.
- Look for effects of combinations of treatments, interaction between treatments and personal characteristics.
- Only study design proper for a new treatment (medicine, other procedures etc.).

Disadvantages

- Disadvantages of cohort study
- Ethical issue
- It may not suitable for some study aims
- Not suitable for some participants like very young, elderly, pregnant and lactating women

Phases of drug developments

Protocol Animal and or lab studies.

Phase I Small amount of patients, 15-30 patients, lasting several months. Evaluate **safety (how well the drug is tolerated).**

Phase II < 100 patients, lasting near 2 yrs

Evaluate **efficacy**

Phase III 100-1000 patients, lasting 1-4 yrs

Evaluate **safety, efficacy and dosing.**

FDA approval

Phase IV After approval

Evaluate **long term effectiveness, safety** and **cost.**

Phases I and II not RCT while III and IV they are.

Randomized control trials

Critical Appraisal Skills Programme

Are the results of the trial valid? (Section A)
What are the results? (Section B)
Will the results help locally? (Section C)

Screening Questions

1. Did the trial address a clearly focused issue?

❒Yes ❒Can't tell ❒No

HINT: An issue can be 'focused' In terms of

- The population studied
- The intervention given
- The comparator given
- The outcomes considered

2. Was the assignment of patients to treatments randomized?

❒Yes ❒Can't tell ❒No

HINT: Consider

- How was this carried out?
- Was the allocation sequence concealed from researchers and patients?

3. Were all of the patients who entered the trial properly accounted for at its conclusion?

❒Yes ❒Can't tell ❒ No

HINT: Consider

- Was the trial stopped early?
- Were patients analyzed in the groups to which they were randomized?

Is it worth continuing?

Detailed questions

4. Were patients, health workers and study personnel 'blind' to treatment? ❒Yes ❒Can't tell ❒No

HINT: Think about

- Patients?
- Health workers?
- Study personnel?

5. Were the groups similar at the start of the trial?

❒Yes ❒Can't tell ❒No

HINT: Look at

Other factors that might affect the outcome such as age, sex, social class

6. Aside from the experimental intervention, were the groups treated equally? ❒Yes ❒Can't tell ❒No

7. How large was the treatment effect?

HINT: Consider

- What outcomes were measured?
- Is the primary outcome clearly specified?
- What results were found for each outcome?

8. How precise was the estimate of the treatment effect?

HINT: Consider

- What are the confidence limits?

9. Can the results be applied in your context? (or to the local population?) ❒**Yes** ❒**Can't tell** ❒**No**

HINT: Consider whether

- Do you think that the patients covered by the trial are similar enough to the patients to whom you will apply this?, if not how to they differ?

10. Were all clinically important outcomes considered?

❒**Yes** ❒**Can't tell** ❒**No**

HINT: Consider

- Is there other information you would like to have seen?
- If not, does this affect the decision?

11. Are the benefits worth the harms and costs?

❒Yes ❒Can't tell ❒No

HINT: Consider

Even if this is not addressed by the trial, what do you think?

Good Luck