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Critical Appraisal: Randomized Clinical Trials (RCT)

Definition: A defined population with a defined problem is randomly allocated to 2+ treatment conditions for a defined period. Outcomes are then compared between the groups.

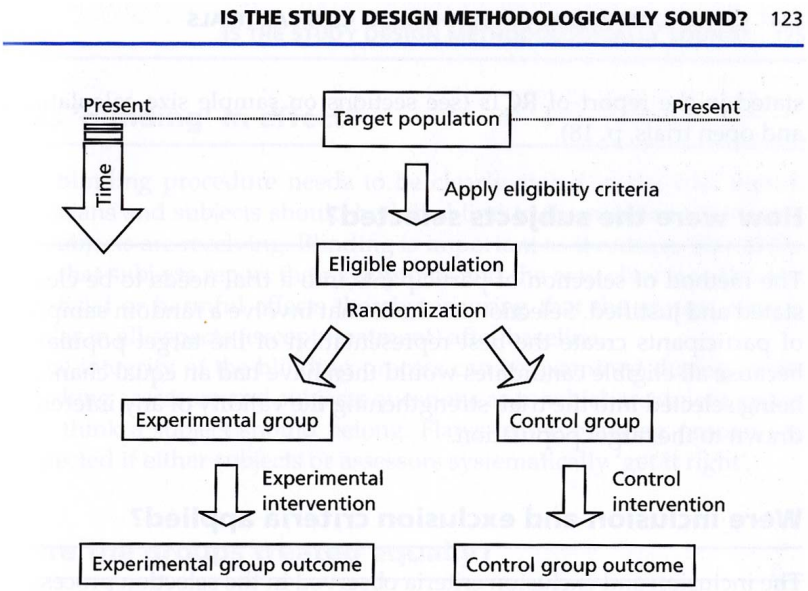

Figure 7.1 Randomized clinical trial (RCT) methodology flowchart.

Advantages:

1. Strength of evidence produced
2. Low recall bias
3. Low observer bias if blinding adopted

Disadvantages:

1. Expensive
2. Complex to setup
3. Subject to ethical committee approval

Appraisal of RCT:

D - Is survey Design methodologically sound?

R - What do Results show?

E - How do the results Effect patient care?

D = Design:

1. Was a sample size calculation performed?
   $ Minimum number needed for required power of trial

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2. How were the subjects selected?
   $ Random sampling = Equal opportunities

3. Were inclusion and exclusion criteria applied?
   $ Set prior to commencement of trial to minimize potential selection bias
   * Exclusion criteria too stringent = exclusion bias

4. Is the randomization procedure described?
   $ Ensures confounding factors distributed equally among groups

5. Were the compared groups similar?
   $ Similar demographics to reduce selection bias

6. Was blinding in effect?
   $ Ideally double blinding to reduce observer bias
   $ Integrity of process can be examined for flaws

7. Were the groups treated equally?
   $ Except for experimental vs. control treatments, all other aspects of management must be identical --> minimizes performance bias

8. Were the treatment interventions clearly described?
   $ Dosages, standardized methods of administration

9. Were the chosen outcome measures appropriate?
   $ Should reflect the outcome of interest, and be justified
   * Multiple outcome measures = increased risk of Type 1 error (false rejection of null)

10. Was there adequate follow-up?
    $ End-point determined before the start of a trial, clearly stated
    $ Duration based on clinical reasoning

11. Was an intention-to-treat analysis performed?
    $ Data on patients entering into trial should be analysed with respect to the groups they were initially randomized, regardless of whether they received or completed the treatment to which they were allocated.
    * Some trials (i.e. purely physiological data) are more appropriately based on actual treatments received

12. Do the numbers add up?
    $ All subjects should be clearly accounted for at end of trial
    $ Attrition rate stated

13. Were the statistical tests used appropriate?

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Attrition Rate: Proportion of patients who drop out for any reason.
i.e. withdrawal from trial, death, migration, loss to follow-up
Data can still be incorporated into overall results via:-
Worst case scenario or Last data carried forward

Worst Case Scenario: Assumes poor outcome for drop-outs for whichever group fared better, and assumes good outcome for drop-outs for whichever group fared worse.
Minimizes difference between groups and is hence prone to type 2 error (false acceptance of null).

Last Data Carried Fwd: Last available data carried forward, tends to worsen the overall results of the control group and indirectly increased magnitude of benefits seen with experimental treatment.
Maximises difference between groups and is hence prone to type 1 error (false rejection of null).

RCT Design Issues:

Surrogate end-points: Event regarded as being highly correlated or predictive of a clinically meaningful outcome.
* Unproven = information bias
* Poor correlation = information bias

Hawthorne effect: Clinical improvements which occur purely due to participation in trial - similar to placebo effect, due to more clinical contact.
$ Counteracted by adding a third "silent" group with no further contact after the recruitment phase.

Randomization:
Fixed = Simple randomization (toss a coin)
Randomized permuted blocks
Stratified randomization (via prognostic factor)
Randomized consent (to assess effect of informed consent)

Adaptive = Play the winner (as previous subject if treatment success, alternative if failure)
Minimization (applying weighting to prognostic factors and allocating thereafter to balance overall distribution)

Interim analyses: Analysis of trial results that are performed at pre-determined time points before conclusion of the clinical trial.
$ Serves to avoid further disadvantage to those subjects allocated to the inferior treatment.
$ Allows for researchers to correct flaws in the trial process

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* Chances of type 1 error with repeated checking; must be guarded against with stricter p values for interim analyses until end of trial (i.e. $p<0.01$ for 1st, $p<0.025$ for 2nd, $p<0.05$ for final)

Factorial designs: 2+ treatment factors are being compared simultaneously; (i.e. Through + No, Through + Yes, Away + No, Away + Yes)
* Only relative comparisons can be made

Cross-over designs: Treatments being received in the groups of a study are switched over after a specified period. Paired data for each subject are then compared at the end of the trial.
$ Subject acts as his own control = best control
* Treatment effects carried over from one period to another

Cluster randomization designs: Centres are randomized, not individual subjects.
All subjects within a given centre receive identical Tx.
$ Practicalities; treatments available at a given centre

n-of-1 trials: Competing treatments are randomized and administered sequentially over allocated time periods to each subject. Blinded.
$ Allows subject to identify best period
$ Good for chronic symptoms, subjective measures
* Only appropriate for conditions with stable symptomatologies
* Treatments should not alter disease process itself, would confound results as symptom severity would be altered
* Initial Hawthorne effect
* Treatment effects carried over from one period to another

Open trials: Required sample size not specified at the start.
Significance level, power + effect size determined prior to start.
Acculumated data inspected periodically until end-point conditions are met.

Non-randomized trials with concurrent control subjects: Arbitrary allocation
$ Cheap + easy
* Introduces bias

NRCT - Historical control subjects:
$ Cheap
$ Access to large pool of data
$ Data on treatments no longer ethical or practical
* Differences may be due to bygone era
* Unilateral Hawthorne effect
* Inclusion/exclusion bias if past criteria vague
* High potential for observer bias

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NNT: Number needed to treat.
The number of patients required to be treated with a therapeutic factor for the stated treatment duration in order to achieve the desired outcome in one patient.

NNT = reciprocal of ARR = 1 / ARR (rounded up)
= 1 / 0.4 = 2.5 rounded up = 3

NNH: Number needed to harm.
The number of patients required to be exposed to a therapeutic factor for the stated treatment duration in order to achieve a harmful outcome in one patient.

NNH = reciprocal of ARI = 1 / ARI (rounded down)
= 1 / 0.03 = 33.3 rounded down = 30

Risk-benefit analysis: RBA = ARR / ARI or (1/NNT) / (1-NNH)
= 0.4 / 0.03 = 13.3
Hence RBA is 13:1 in favour of treatment

E = Effect:

1. Ensure subjects are similar to own patients
2. Implications for practice if RCT directly relevant
3. Would the treatment confer any added benefit or harm to patients?
4. What does your patient think about the said treatment in light of their beliefs, culture etc.
5. Are they comfortable with the RBA as it applies to them?
6. Is treatment accessible and affordable?