Design and interpretation of clinical trials

Johns Hopkins @ Coursera

(2) Randomization

- **Rationale for randomization**
  - Avoids selection bias
  - Tends to produce comparable treatment groups
  - Assures statistical test will have valid significance levels
  - Defined time-point for trail entry

- **Types of randomization schemes**
  - Simple randomization

    A complete randomization, e.g., coin toss.

    Advantages:

    - Each assignment is completely unpredictable
    - In the long run, number of patients assigned to each group should be about eaqul

    Disadvantages:

    - Imbalances

      + No. of patients assigned/treatment group

      + confounding factor by treatment group

      + both can lower statistical power

    - May diminish credibility or results

- Inversely associated with number of participants

- Restricted randomization

  Scheme with constrains to produce expected assignment ratio according to time and/or specified covariates: blocking and stratification.

  - Blocking

    A block is a list of treatment assignments that achieve the treatment allocation ratio, e.g., A:B=1:1.

    Size of the smallest possible block is the sum of the integers defined in treatment allocation ratio: 2 for 1:1, 3 for 1:2…

    All possible block sequences are randomly permuted.

    Ensure balance of treatments over time.

    Sometimes, we can use more than one block size. (it is especially important in unmasked trial.)

    Advantages:

    1. overall balance, especially in smaller trials: more likely to get equal number in both groups

    2. protects against time-related changes

    3. if trial is stopped early, have balanced groups

    4. analyses are more powerful

    Disadvantages:

    1. can facilitate prediction of future assignments

    2. more problematic for unmasked trials or poorly masked tirals

  - Stratification

    Ensure the balance in treatment groups across groups that can be specified before randomization.(clinic, gender, risk level. For example, at each gender, we are going to meet the allocation ratio.)

    Subgroup should be strongly related to outcome.

Requires a separate set of treatment assignments schedules for each category of each stratum. For example, if you have three clinics, you will need three different treatment assignment lists.

Example of stratification and blocking:

- Breast cancer treatment
- 1:1 treatment allocation
  - A or B
- Stratification
  - Center
    - X or Y
  - Postmenopausal status
    - Post or pre
- Block size 4

Center	X		Y	
Status	Post	Pre	Post	Pre
Blk#	Tx Assignments			
1	B	B	A	B
1	A	B	A	A
1	B	A	B	A
1	A	A	B	B
2	A	A	A	A
2	B	A	A	B
2	A	B	B	B
2	B	B	B	A
	⋮	⋮	⋮	⋮

Note: If stratify without blocking, there is no point of stratification.

Some practical aspects of stratification:

1. limit to a few (1-2) variables(highly related to outcome, logistical). Too many strata may lead to imbalances in overall treatment group allocation.

2. typical ones (clinic in a multicenter trial, surgeon, stage of desease, demographic characteristics(gender, age))

- Adaptive randomization

A process in which the probability of assignment to the treatments does not remain constant, but is determined by the current balance and/or composition of the groups.

➢ Minimization

The treatment assignment that yields the smallest imbalance is chosen.

Balance on a number of characteristics or prognostic factors and ensure that you have balance as the trial goes on.

The allocation scheme cannot be determined in advance.

- Play the winner design

  Change treatment allocation ratio to favor the better treatment based on the primary outcome.

  The patients are more possible to be assigned to the better treatment.

◆ Masking

Treatment assignment is not known after randomization. Single, double, triple, quadruple…

- Rationale

  Reduce bias related to prior knowledge or beliefs about treatment effects on the performance of the trial and on the reporting of outcomes.

- Levels of masking

  Single: participant is masked

  Double: participant and clinical investigator are masked

  Triple: participant and clinical investigator and "others" are masked. Others include outcome evaluators, data analysts, data monitoring committees, sponsors…

- Advantages:

  Protects against performance/reporting bias

  - Data collection and follow-up
  - Outcome assessment and reporting
  - Other care received during the trial
  - Interpretation of results

- Disadvantages:

  - May be logistically or ethically impossible

- May not reflect clinical care practices
- Increases logistical complexity
- Increased cost

- How to decide

Ethical or not?

Possible or not?

Trial design features:

- Types of outcomes, more important for subjective ones
- Will outcome evaluation be masked regardless?
- What are the comparison groups? (no treatment, active control)

Feasible or not?

- Two types
  - Planned

    When you want to reveal the assignment to patients after it is done.

    Strategy depends on closeout design.

    Collect data on participant and clinic guess as to treatment assignment before you reveal it.

    Important to document.

  - Unplanned

    Discouraged: usually not required to treat patient. (stop drug for adverse events)

    Extenuating circumstances.