Clinical Trials – Study population

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Overview

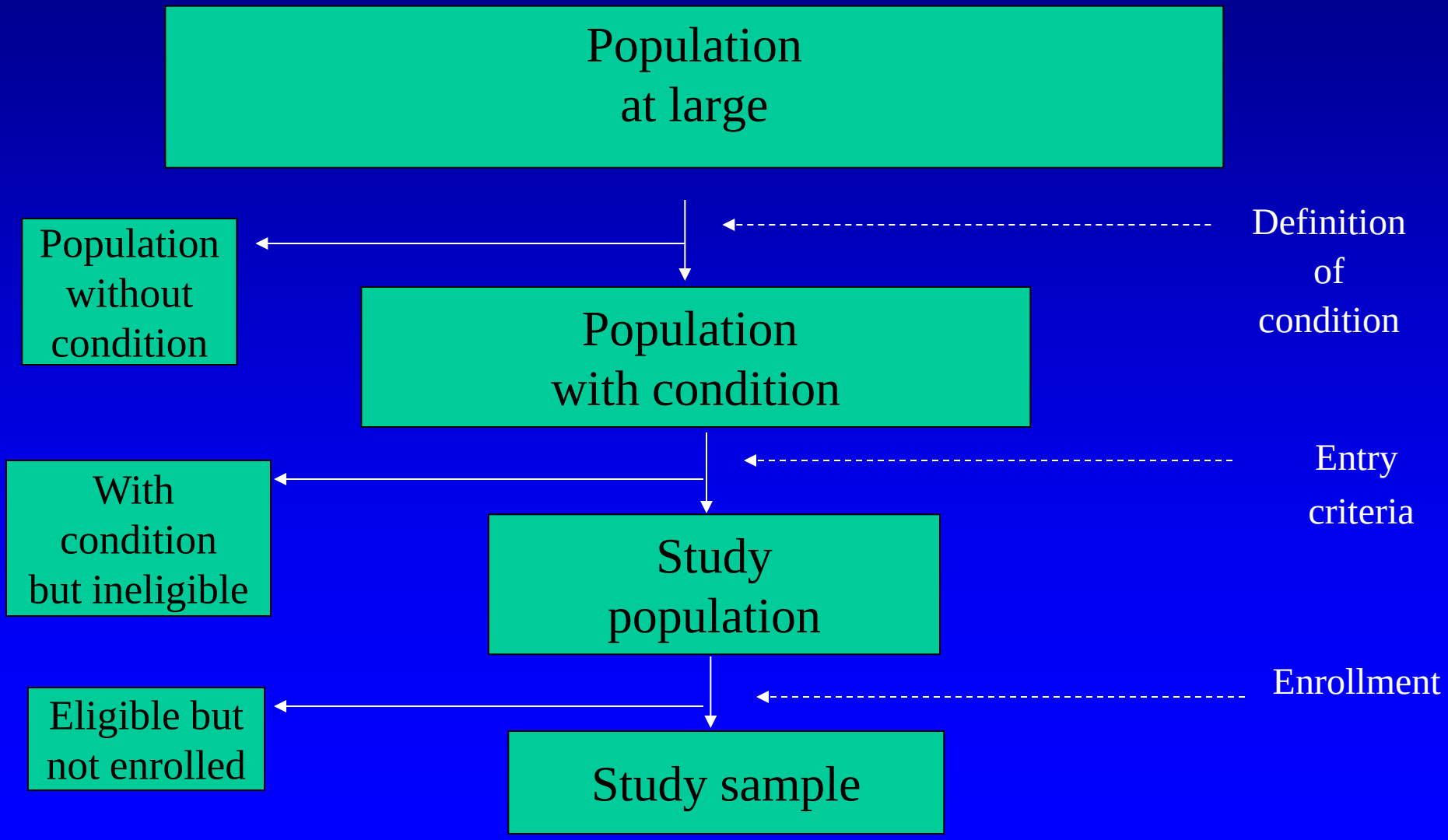
- Study population –
  - Eligibility
  - Generalizability and recruitment
  - Sample size calculations
    - Power and clinically meaningful differences
- Randomization
- Ways to avoid bias
  - Blinded vs unblinded studies
    - Single/double/triple blinding
  - Minimizing LTFU (Withdrawal and drop-outs)
  - Data collection

Study population

Fundamental point

- The study population should be defined in advance, using unambiguous inclusion (eligibility) criteria. The impact that these criteria will have on ability to generalize, and participant recruitment must be considered.

Study population



Aims of Eligibility criteria

Minimize risk / enhance participant safety

Select subjects most likely to benefit from the intervention.

Ineligible patients

- Any trial requires precise definition of eligibility criteria
- Ineligible patients have to be reported
- If the proportion of ineligible patients is too large
  - may reflect poor study organization;
  - or, eligibility criteria were too restrictive.
- **Ineligible patients do not affect internal validity.**
  - **BUT, affect <u>generalizability</u> of results**

Internal vs External validity

- Internal validity
  - **Judged by whether effect estimated in the trial could differ from the true effect because of systematic (non-random) error**
    - **selection bias, information bias, confounding**
    - **Random error is permitted**
- External validity or “generalizability”
  - **Judged by whether results are valid for patients with the condition that are not in the study population, but treated in similar settings**

Dekkers OM et al. *Int J Epidemiology* 2010.

Generalizability (to all patients with the condition)

- Study subjects are NOT randomly chosen from the study population, because of the restrictions imposed by the eligibility criteria.
- This creates the risk that the findings may not be generalizable.

Generalizability – impact of refusals

Participants must agree to enroll in a study:

Why do some agree to participate while others do not ?

How does that affect generalizability? If proportion is low? Or high?

Study population: 6 vs 9 months of TB treatment in PLWH

"Objectives: To compare the efficacy of an intermittent 6-month regimen versus a 9-month regimen in HIV/TB" – Swamintham et al *AJRCCM 2010.*

–Population with condition: PLWH and active TB

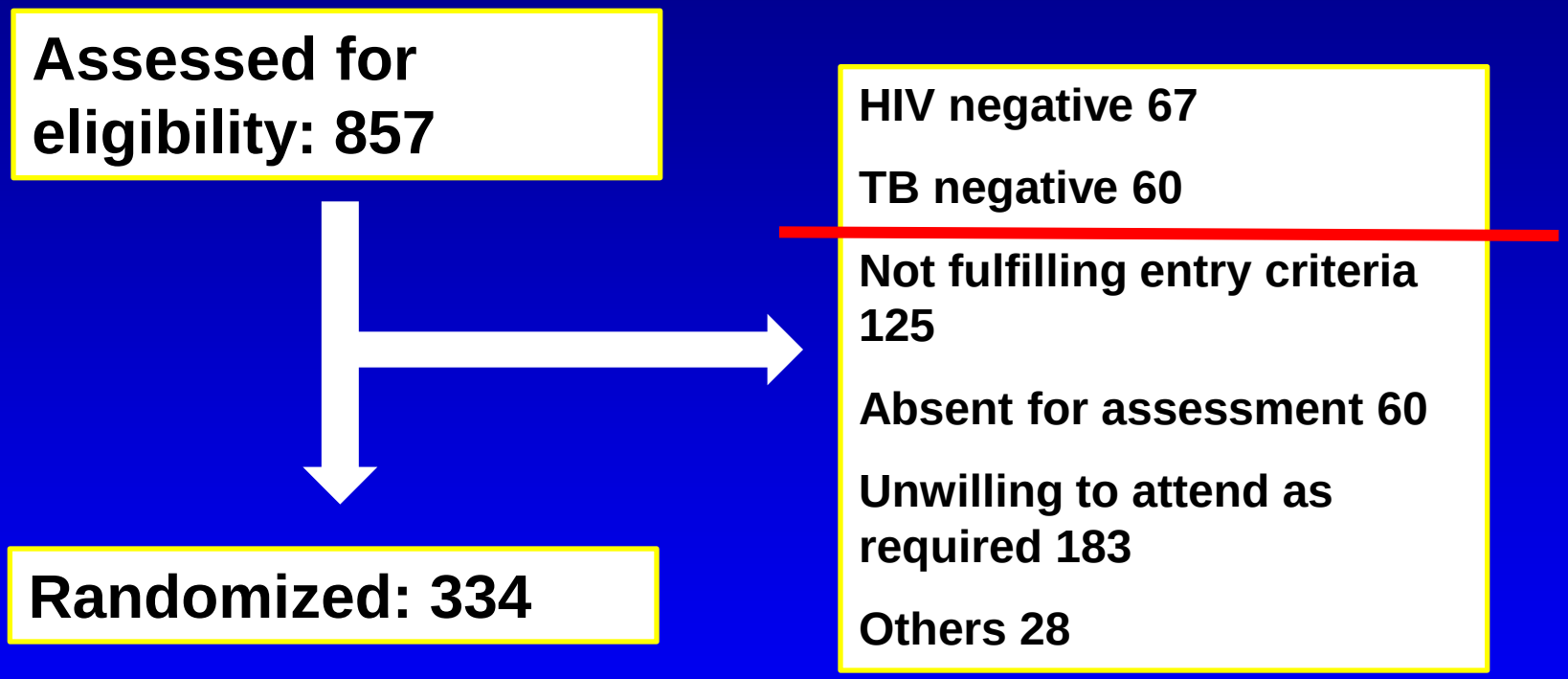
– Assessed for eligibility: HIV-infected patients with symptoms and signs suggestive of TB receiving care at TRC clinics in Chennai and Madurai, aged 15 years or above, not moribund and not pregnant

–Entry criteria: PLWH and active TB (positive smear or abnormal CXR not imporoving with 14d abx), age >14, not moribund, not pregnant, meeting sociological eligibility criteria, Hb>7g/L, WBC >1.1, PLT > 100, ALT<2.5ULN, CR<1.1, gluc<140mg/dL

–Study population: PLWH and active TB meeting the above criteria and receiving care at the clinics where the study was conducted

–Study sample: 334 patients randomized

Study population: 6 vs 9 months of TB treatment in PLWH



730 patients with condition

25.3% (185) ineligible/could not be assessed for eligibility

211/545 (38.7%) of study population eligible but not enrolled

334/545 (61.2%) of study population were enrolled

Study population: 6 vs 9 months of TB treatment in PLWH

730 patients with condition

- 25.3% (185) ineligible/could not be assessed for eligibility
- 211/545 (38.7%) of study population eligible but not enrolled
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Is the study sample representative of the study population?

It would be easier to assess the external validity is we could compare characteristics of eligible-enrolled vs elibigible-not enrolled → this information is rarely provided!

Double-blind RCT: high dose INH vs standard INH vs placebo for MDR-TB

- **"We recruited consecutive, sputum culture-positive, non-HIV infected patients previously diagnosed with pulmonary TB who developed documented MDR-TB and who reported to the study centre during the time of the study."**
- **Excluded: if unwilling to give consent, abnormal renal or hepatic profile, history suggestive of INH hypersensitivity, or were pregnant or lactating were excluded."**
- **134 participants were enrolled.**

Katiyar SK et al. *IJTLD* 2008

Double-blind RCT: high dose INH vs standard INH vs placebo for MDR-TB

- High-dose INH associated with more rapid sputum conversion (HR 2.38, 1.45-3.91), and higher likelihood of being sputum-negative at 6 months (RR 2.37, 1.4-3.84).
- Results internally valid
- No information on number assessed for eligibility, nor number eligible but not enrolled.
- But can they be generalized?

Katiyar SK et al. *IJTLD* 2008

Sample size

Fundamental point

- **Clinical trials should have sufficient statistical power to detect statistically significant meaningful differences between groups.**
- **meaningful = clinically important/relevant**

- **Calculation of sample size is an essential part of planning a trial.**

Steps in Determining Sample Size

1. Define the response with standard therapy.

eg. RCT 6 vs 9 months: assumed rate of unfavourable outcomes with 6 months = 20%

2. Decide on a clinically meaningful difference

- How much is enough to say the new treatment is better (worth it)?

eg. A reduction from 20% to 10%.

Steps in Determining Sample Size

3. How much power do you want
   - Power equals ability to detect a statistically significant difference, if some difference truly exists.
     - often 80% power is used
   - Low power increases risk of falsely concluding no difference, when there IS a difference. (Type 2 error)
     - often a 20% probability of Type 2 error is considered acceptable
4. Costs and Feasibility
   - How much money do you have?

Sample size
Web calculators

Web pages for sample size calculators

http://statpages.org/

http://www.surveysystem.com/sscalc.htm

http://stat.ubc.ca/~rollin/stats/ssize/b2.html

PS Power – can download and use

http://www.mc.vanderbilt.edu/prevmed/ps/index.htm

contains up to date information about the program PS Power. You can download the latest version from there.

[[Dupont WD and Plummer WD: PS power and sample size program available for free on the Internet. Controlled Clin Trials,1997;18:274]]

Sample size
Web calculators

Inference for Proportions: Comparing Two Independent Samples

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values (as decimal fractions) for p1 (proportion in population 1) and p2 (proportion in population 2) and, if calculating power, a sample size (assumed the same for each sample). You may also modify alpha and the power, if relevant. After making your entries, hit the calculate button at the bottom.

- Calculate Sample Size (for specified Power)
- Calculate Power (for specified Sample Size)

Enter a value for p1:

Enter a value for p2:

- 1 Sided Test
- 2 Sided Test

Enter a value for alpha (default is .05): .05

Enter a value for desired power (default is .80): .80

The sample size (for each sample) is:

Calculate

http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html

Estimated sample size required

(using http://stat.ubc.ca/~rollin/stats/ssize/b2.html)

% Cure expected		Number per group required to detect a difference with power of:		
Tx A	Tx B	60%	80%	90%
65%	90%	28	43	57
70%	90%	39	62	82
75%	90%	63	100	133
65%	85%	46	73	97

Statistical power: additional considerations

Estimated pre-trial	
Control response	60%
Intervention response	80%
Expected difference	20%
Scenario	Total number of subjects
No LTFU & adequ. adh.	182
10% failure to adhere	226
10% loss to follow-up	204
10% LTFU and 10% failure to adhere	250

Jindani A, Nunn A & Enarson D. *Controlled Clinical Trials in Tuberculosis.* IUATLD 2004.

http/www.theunion.org/what-we-do/publications/technical/english/pub_controlled-clinical-trials_eng.pdf

Azinroimodatn

Tonmaioazndri

Adormnztiniao...

Randomization

http://textmechanic.com/Word-Scrambler.html

Randomization in Experimental Studies

Fundamental point

Randomization tends to :

- produce study groups comparable with respect to known and unknown risk factors
- remove investigator bias in the allocation of subjects
- guarantee that statistical tests will have valid significance levels

Randomization: allocation concealment

- **Allocation concealment – "A technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment. Allocation concealment prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group."**

http://www.consort-statement.org/resources/glossary

Randomization: Allocation concealment

- Allocation concealment is necessary to ensure assignment to treatments are *truly* randomized

  -Concealed from whom?

- Goal of the allocation concealment process:

Investigators and clinicians should not be able to predict the group to which the next enrollee will be assigned (TxA vs TxB, control vs intervention)

- not to be confused with: method used to randomize patients, nor with blinding

Allocation bias

- **Selection bias, occurs if the allocation process is predictable **This is what allocation concealment is trying to protect against**
    - eg. investigator knows next enrolee will be assigned to control group (or “suspected” control group). They wait to enrol a patient with worse prognosis.
    - Trials with inadequate concealment “yield up to 40% larger estimates” (Schulz KF & Grimes DA, *The Lancet* 2002)
- **Accidental bias, can arise if the randomization procedure does not achieve balance on risk factors or prognostic covariates**

Allocation bias may be a more important determinant of outcome than the treatment itself

Adequate randomization

Means that allocation bias minimized:

- **Concealed process – so investigators do not know in advance. Which of following will be adequate?**
  - Central randomization
  - Computer generated
  - Random numbers table
  - Draw numbers from a hat
  - Day of the week
  - Toss a coin

Types of randomization

Randomization – participants have the same probability of being assigned to control or intervention arms

Individual randomization

- Simple
- Blocked
- Stratified

Group randomization

Simple randomization

The most elementary form of randomization:

- toss an unbiased coin each time for each consenting subject;
- use a random number producing algorithm (computer generated - more convenient especially for large studies).
- Large trials – should reliably produce groups with equal sizes and distribution of confounders
- Smaller trial – possible to end up with groups of unequal in size or distribution of confounders

Blocked randomization

Randomization occurs within blocks, to ensure that numbers in each group remain as close to equal as possible, at all times (also called permuted block randomization)

Advantages	Disadvantages
• Avoids imbalance in the number of subjects assigned to each group; Particularly if sample size is small, or numbers within strata/centre are small	• If the study is not blinded, the study staff know the assignment for the last person before randomization of that person

Blocked randomization

Example: Block size = 4. Gives 6 possible combinations of group assignments :

AABB, ABAB, BAAB, BABA, BBAA, and ABBA.

If study unmasked (not blind) then investigator will know which intervention every 4th participant will be assigned (sometimes for 3rd and 4th participant)

- can get around this by randomly varying block sizes

Variable block randomization

Each Block is of different size

Ranges from N=2 to N=16 (or 2-8, or 2-6)

Commonly used in multi-centre studies

Prevents anyone from guessing what the next subject will be randomized to

But – adds complexity

Can result in imbalance:

- If study stopped early, or,
- Many sites and fewer patients at these sites

Stratified randomization

Randomize within sub-groups – defined on basis of most important potential confounders

To improve chances that important baseline characteristics will be similar in the 2 groups.

Advantages	Disadvantages
• Reduce variability in group comparison if the stratification is used in the analysis	• Sometime the variables initially thought most important and used for stratified randomization turn out to be unimportant • Other factors identified later are more important

Stratified randomization Example

Age	Sex	Smoking Hx
1. 40-49 yr	1. Male	1. Current smoker
2. 50-59 yr	2. Female	2. Ex-smoker
3. 60-69 yr		3. Never smoker

In this example, there will be 18 strata…

- Blocked randomization is then performed to ensure an equal number of participants are assigned to each intervention within each strata

Stratified randomization
By Centre

This should always be done if multi-centre

Balances differences in population

- Differences in patient population

  Illness severity, comorbidities

- Differences in MD practice - referral

- Differences in study staff – refusal rate

- Differences in recruitment rate

Maintains balance if centres drop out

see article by Doig & Simpson *Journal of Critical Care* 2005 – describes step by step how to do stratified and block randomization using SNOSE (sequentially numbered opaque sealed envelopes)

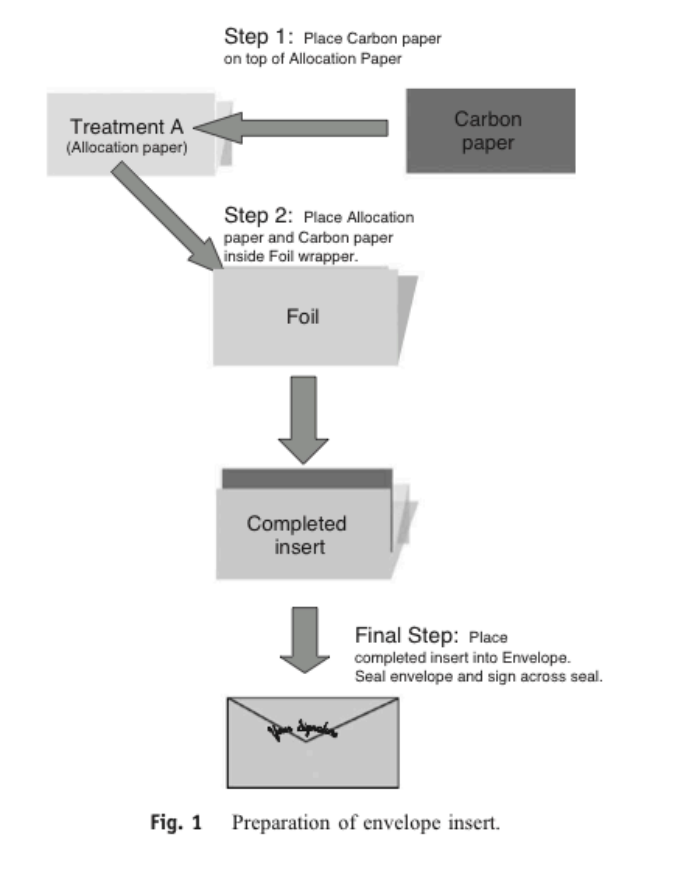

Fig. 1 Preparation of envelope insert.

Double-blind RCT: high dose INH vs standard INH vs placebo for MDR-TB

- **"We recruited consecutive, sputum culture-positive, non-HIV infected patients previously diagnosed with pulmonary TB who developed documented MDR-TB and who reported to the study centre during the time of the study."**
- **Excluded: patients with exposure to SLD for > 30days and also "patients who were unwilling to give consent, had abnormal renal or hepatic profile, had a history suggestive of INH hypersensitivity or were pregnant or lactating."**
- **"Subjects were randomised to three treatment groups by block randomisation to ensure comparable allocation to the trial arms." www.randomization.com (randomly permuted blocks?)**
- **"Both study investigators and patients were blinded to the INH dose"**

Katiyar SK et al. *IJTLD* 2008

Characteristic	High dose INH	Low dose INH	Placebo	p-value
Age	38	**42**	37	0.017
EMB resistance	52%	55%	**76%**	0.06

Other baseline characteristics similar: sex, smoking, prior anti-TB treatment, SM-resistance, PZA-resistance, INH MIC

- **Differences in age and ethambutol resistance→ chance or inadequate allocation concealment?**
- **Block randomization and double-blinding**

Katiyar SK et al. *IJTLD* 2008

Group randomization

- For some interventions (psychosocial, education, etc) randomization by individuals does not work, because there is interaction among subjects (contamination).
- Groups of subjects, clinics or communities are randomized to intervention vs control; The basic sampling units are groups, not individuals.
- This design is not as efficient as individual randomization. A larger sample size required

Appropriately conducted & effective randomization = groups that differ only in terms of the intervention received

→ strongest study design for causal inference

But bias still possible!

Ways to avoid bias during the trial

Confounding (imbalance of known and unknown variables that can affect outcomes)

- Randomization with allocation concealment

Information bias (most importantly differential misclassification of outcome related to exposure)

- blinding
- quality control of data

Selection bias – can occur during allocation and follow-up (differential loss to follow-up related to assigned intervention)

- Randomization with allocation concealment
- Avoid withdrawals, Minimize losses to follow-up

Blinding (masking)

- **Bias can occur in many ways in a clinical study**
- **Caused by investigators and/or patients.**
- **Caused by conscious factors, subconscious factors, or both**

The general solution to the problem of bias is to keep the subject and the investigator blinded, or masked, to the identity of the assigned intervention

Types of Blinded Studies

Single Blind

- The investigator is aware of the intervention. But the subject is not.

Double Blind

- Neither the subjects nor the investigators responsible for following the subjects know the identity of the intervention assignment.

Triple-Blind

- In addition to subject and investigators, the data analyst, and the committee monitoring the trial, are not told who is getting what.

Importance of Blinding

Example :

Benefits of the vitamin C in the common cold

Lewis et al. Ann NY Acad Sci 1975; 258 : 505-12

Participants: Medical staff

Evaluation: severity and duration of common cold was self-reported by the participants

Importance of Blinding

Blinding: Many participants could tell (taste) whether they were on active or placebo

Results:

Participants who stated they did NOT know

Vitamin C = placebo

BUT, Participants who stated they DID know

Vitamin C > placebo

Data collection: blinding of individuals evaluating outcomes

eg. Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis

- participants randomized to cyclo vs. PE vs. placebo
- double-blind
- 2 neurologists:
  - 1 “ monitoring” unmasked, 1 “evaluating” masked
  - only masked assessment used.
  - Unmasked: more likely to observe improved outcomes in PE group
  - Masked: no differences in groups

Noseworthy JH et al. *Neurology* 1994; Lewis SC & Warlow CP. *J Neurol Neurosurg Psychiatry*. 2003

If Blinding not possible

In many studies intervention cannot be blinded

Surgery, different durations of therapy

Solutions:

Objective outcomes

– Death, days in hospital, lab-confirmed disease (culture/smear/PCR positive)

Blinded independent review of outcomes

– Serious adverse events, complications

– X-ray changes

Data gathering during an RCT: Baseline assessment

• Relevant baseline data should be measured in all study participants before the intervention starts

• Useful for:
- stratification
- analysis of baseline comparability
  – assess if randomization worked
- evaluation of change
- natural history analysis
- subgrouping

Data collection & quality control

Major types of problems:

- missing/incomplete data (one indicator of the quality of the trial)
- erroneous data (error will not necessarily be recognized)
- variability in the observed characteristics (reduce the opportunity to detect the real changes): random, systematic or combination of both
- differential misclassification of outcome – could bias study results.
    - eg. could arise in an open-label trial if placebo group assessed more often/intensely for outcome

Selection bias *during* the trial

- **Investigator-initiated withdrawal**
- **loss-to-follow-up/drop-out of participants related to the outcome and differ by group**

Reasons for investigator-initiated withdrawal

- Ineligibility (error made to enrol them)
  - at times inevitable that participants become ineligible *after* enrolment and allocation to treatment
- Nonadherence or non-compliance
- Poor quality or missing data
  - Especially if drop-out and no idea of outcomes
- Withdrawal of participants after they have been randomized to an intervention group compromises the comparability of the groups provided by randomization

Withdrawal: high risk of bias

- Ineligibility (error made to enrol them)
  - problem arises if discovery of ineligibility is not random
  - even if an equal number of subjects are withdrawn due to ineligibility from control and intervention groups, this can alter the results of the trial if their outcomes differed.
  - exception: if difficult to establish eligibility immediately before randomization. Decision to withdraw can be made later by a blinded person, based on data collected at time of randomization
  - eg. MDR-TB discovered in trial of 6 vs 9 months of treatment for drug-susceptible TB in PLWH
  - eg. Rifapentine+INH vs INH for LTBI: post-allocation ineligibility if source case culture(-), resistant to INH/Rif, or no DST

Withdrawal: high risk of bias

- Non-adherence or non-compliance
  - people who comply with treatment are different than those who do not comply
    - Mortality in trial of lipid-lowering agents:
      Overall: 18% intervention vs 19% placebo
      Comparing compliant vs non-compliant:
      Intervention: 15% vs 25%; placebo: 15% vs 28%
  - non-adherence could be related to intervention or outcome
    - **non-adherence in controls could be due to different reasons than non-adherence in intervention group**
    - **exclusion could create non-comparable groups**

May GS et al. *Circulation* 1981, Schulz & Grimes *Lancet* 2002.

Strategies to improve compliance

Factors that maximize compliance:

- Duration of intervention: Shorter = Better
- Simplicity of intervention: Single dose = Better
- Subject selection: Run-in period used to identify OCD
    - can limit external validity of results by excluding non-compliant persons or those who will have more side-effects
- Fully informed consent: Patient ***really*** understands

Losses to follow-up

- participants who can no longer be followed up: refuse to participate, move and can't be contacted
- Different than participants who were able to complete follow-up
- eg. In TBTC 22, open-label RCT loss to follow-up associated with:
  - birth outside USA/CANADA (aOR 2.07, p<0.01)
  - homelessness (aOR 1.94, p<0.01)
  - enrollment at a health department (aOR 2.71, p<0.01)

- losses to follow-up can bias results – particularly when they are differential between intervention & control arms and associated with the outcome
- differential losses could arise because of differences in side-effects or efficacy

Caldwell et al. *Contemporary Clinical Trials* 2002, Schulz & Grimes *Lancet* 2002.

Minimizing losses to follow-up

- **Employ study personnel responsible for managing & ensuring follow-up**
- **Call or visit participants that miss appointments**
- ***Prior to randomization* exclude those unlikely to return for follow-up (likely to move or unwilling to return)**
- **Obtain lots of contact information**
- **Follow-up visits done in locations convenient for participants**
- **Keep follow-up visits short and sweet**
- **Provide free medical care**
- **Monetary subsidies or incentives**

Schulz & Grimes *Lancet* 2002.

THANKS!