Study Designs II
Cohort studies and RCTs

F. Farrokhyar, MPhil, PhD, PDoc
Department of Surgery
Department of Clinical Epidemiology and Biostatistics
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Dr. Thoma stated that the research question is the most important part of the project.

Dr. Farrokhyar states that research question doesn't matter in the research project development.

Cohort study

- Defined patient population
- New treatment
- Control treatment
- Outcome
- No outcome
- Time

Cohort studies

- Prospective (concurrent) cohort studies – we recruit patients to new treatment or control treatment at present time and follow them up for certain time period to observe who develops the outcome.

- Retrospective (non-concurrent) cohort studies: we assemble the groups to new treatment or control treatment and go back in time to find out who have developed the outcome and when.

Cohort studies

- Defined patient population
- New treatment
- Control treatment
- Outcome
- No outcome
- Time

Advantages:
- Prospective
- Estimate incidence
- Feasible when randomization is not ethical or practical
- Can assess the relationship between new treatment with many outcomes

Disadvantages:
- Not feasible for rare diseases
- Not feasible when it takes a long time for outcome to develop.
- Expensive
- Selection bias

To minimize bias in cohort studies?

- At the stage of study design
  - Restriction
  - Matching

- At the stage of data analysis
  - Propensity score analysis
  - Multivariable analysis
  - Stratified analysis
What does randomization do?

- The process of randomization controls for the known and unknown confounding factors.
- It provides comparable groups so that the differences in the outcome at the end of the trial can be attributed to the new treatment.

In a well-designed RCT:

- Inclusion and exclusion criteria are pre-described.
- All patients have equal chance of receiving either treatment.
- Known and unknown confounders are similar between the treatment groups. Any differences would be by chance.
- Treatments are concurrent, avoiding temporal trends.
- Data collection is prospective.
- Assumptions underlying the statistical tests are met.
- Potential sources of bias are controlled.
Potential biases in RCTs

- Selection bias – systematic differences in prognostic factors between study groups.
- Performance bias – systematic differences in care provided to study groups.
- Detection bias – systematic differences in outcome assessment between study groups.
- Attrition bias – systematic differences in withdrawal from the study or loss to follow-up between study groups.

Methods to minimize systematic error (i.e. biases)

- Randomization
- Concealment of allocation
- Blinding
- Complete follow-up
- Application of intention-to-treat principle
- Methods to minimize random error
- Sample size calculation (power analysis)

Randomization

- Proper method of randomization
  ⇒ Computer generated randomization sequence
- Poor method of randomization
  ⇒ Date of admission, date of birth or flipping a coin
- Ensure equal number of patients in each groups
  ⇒ Block randomization, random block randomization

Concealment of allocation

- Optimal method – to have the randomization process independently administered:
  a 24-hour telephone randomization line, a web-based randomization service, a hospital pharmacy or a central office.
- Convenient method – the use of envelope is highly susceptible to corruption and should be avoided.
  If envelopes are used, they should be:
  - Opaque, sealed, serially numbered.
  - Opened sequentially and only after the participant’s name and other details are written on the envelope.
  - Kept in locked and secure place.

Blinding

- Blinding relates to what happens after randomizing patients into the study and minimizes performance bias and detection bias.
- Bias occurs when individuals are aware of which intervention participants have received and treat them differently.
- Every effort should be made to blind as many involved individuals as possible in RCT’s.
Blinding in surgical trials

- It is often not possible to blind surgeon.
- Participants, care providers and data collectors can often be blinded (avoids performance bias).
- Data analyst can always be blinded.
- Blinding outcome assessors protects a trial against the differential assessment of the outcomes (avoids detection bias).

Karanicolas et al. (2008) systematically reviewed trials in orthopaedic trauma and concluded that less than 10% of trials blinded outcome assessors.

Authors suggested three techniques of blinding could have been applied into these trials:
- Using one or two independent assessors unaware of the treatment of allocation to assess the outcome
- Concealing incisions or scars
- Digitally altering radiographs to mask the type of implant

Another method of blinding is placebo surgery or sham surgery. Debate among ethicists and not yet justified.

McCulloch et al. (2002) used a large dressing covering the entire abdomen to blind outcome assessors in a trial comparing minicholecystectomy to laparoscopic cholecystectomy.

Complete follow-up

- Ideally, every patient should be followed-up to the end to avoid attrition bias.
- Failure to account for all patients at the end of the study presents major threat to internal validity.
- Losses to follow-up is higher when no treatment is required after surgery, especially when a longer follow-up is required.
- The differential loss to follow-ups is higher when cointervention i.e. physiotherapy is required for one arm but not the other.
- Different methods (Schulz 2002, Thoma 2008) are suggested to enhance complete follow-up for all participants.

Intention-to-treat principle

- Intention-to-treat method analyzes participants in the groups to which they were randomized, irrespective of the treatment they have received.
- It maintains the benefits of randomization and provides the least biased assessment of the efficacy of the treatment.
- In surgical trials, some patients are switched from new treatment to control treatment due to practical reasons i.e. surgeon’s limited experience or patient’s condition.
- The complications in these patients are usually higher than others.
- Analyzing data by the treatment patients have received (per protocol analysis) introduces prognostic imbalance between study groups and loses the benefits conferred by randomization.

Learning curve for a new surgical treatment

If we fail to control for learning curve, the estimate may be biased toward the null hypothesis.
To minimize the effect of learning curve

- Pre-specified number of cases in lifetime
- Number of cases in the year preceding the trial
- General training in the area
- Outcomes consistent with good practical practice
- Assessing skills (e.g., videotapes, direct observation, quality scores for specimens) because the number of performed surgery may not guarantee expertise.
- Expertise-based design

Expertise-based trials

- Patients are randomized to different surgeons, some of whom deliver only the control treatment and some only the experimental treatment.
- The advantage of expertise-based design is that it minimizes the effect of learning curve because expert surgeon will perform the treatments.
- The drawback is that it is preferable for large trials:
  - Multiple surgeons are needed with strong viewpoints in favor of different treatment.
  - Each participating centre should have expert surgeons doing each type of operation
  - Add cost and increases complexity of the randomization.

How to arrange our 2x2 table?

<table>
<thead>
<tr>
<th></th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>New treatment</td>
<td>a</td>
</tr>
<tr>
<td>Control treatment</td>
<td>c</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
</tr>
</tbody>
</table>

OR = \( \frac{ad}{bc} \)

EER = \( a / (a+b) \)

CER = \( c / (c+d) \)

RRR = \( \frac{EER}{CER} \)

ARR = EER - CER

NNT = 100 / ARR

Statistics

- Odds Ratio: the ratio of the odds of experiencing the outcome in new treatment group to the odds of experiencing the outcome in control treatment group.
- Relative Risk (RR): the ratio of the event rate in new treatment group to the event rate in control treatment group.
- Relative Risk Reduction (RRR): it is the effect of new treatment that reduces the probability of bad outcome.
- Absolute Risk Reduction (ARR): the proportion of reduction in the outcome that can be attributed to the new treatment.
- Number Needed to Treat (NNT): Number needed to treat to prevent one bad outcome. It is the reciprocal of the ARR.

In surgical research ....

In those situations when conducting a randomized controlled trial is infeasible or unethical, we need to choose alternatives such as prospective cohort study or case-control study that may be less rigorous than the randomized controlled trial but more rigorous than the uncontrolled case-series.

However, the conclusions drawn from these studies should be interpreted with caution.

Assignment ....

1. Is eligibility criteria satisfactory with respect to internal and external validity?
2. Is the randomization process satisfactory?
3. Is the concealment of allocation explained and satisfactory?
4. Is the blinding process explained and satisfactory?
5. Is the primary outcome measure appropriate and well defined?
6. Is it a true expertise-based trial?
7. Is learning curve issue justified?
8. Is follow-up subject to attrition bias?
9. Is intention-to-treat analysis applied?