Statistical Considerations for Research Design

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Analytic Goal

Usually, to compare an outcome between groups of research "subjects", where one of the groups has received a treatment, intervention, or exposure.

Sometimes, we may have only a "treated" group and want to examine how the outcome changes over time.

Analytic Process

You will collect data and carry out statistical tests to compare the outcome between groups, or over time.

If there is an effect on outcome, you want to be sure that your statistical test can detect it.

If you do detect an effect, you want to be sure that you can attribute it to your specific treatment, intervention, or exposure, and not to outside factors.
Implications

From the start, you should work with a statistician, epidemiologist, or experienced investigator to turn your general idea into a very specific study design. This will involve identifying:
- Hypothesis
- Study design
- Sample size
- Analysis plan

Hypothesis

What do you want your research to demonstrate?
- What are the primary and secondary outcomes?
- At what time points will they be measured?
- What groups will be compared? How many groups?
- What is the justification for expecting your hypothesis to be true (pilot data?) and what is the expected result?

Study Design

- Cross-sectional or Longitudinal?
- Prospective data collection or Existing Data?
- Comparative trial or Cohort study or Case-Control study?
- Randomized or Natural experiment or Pre-Post comparison?
Sample Size
How many subjects need to be in the study?
This will be determined by:
- **Feasibility:** Time and resources.
- **Statistical Power:** The chance that the study will lead to a significant finding. This will depend on the:
  - Magnitude of the experimental effect
  - Variability of the outcome measure

Outcome Measures
**Issue:** Continuous “physiologic” measures usually offer better statistical power than binary “clinical” measurements.

But, binary “clinical” measures are often preferred for interpretability.

Outcome Measures
**Basic Science:** Almost always continuous

**Translational Science:** Usually continuous, but sometimes binary or time-to-event

**Randomized Trials:** Usually binary or time-to-event, but sometimes continuous

**Observational Studies:** Sometimes binary or time-to-event, but can also be continuous
Variability

**Issue:** Our ability to successfully detect the effect of an exposure or an intervention depends on both the magnitude of the effect and the variability in the outcome measure.

**Basic Science:** Usually, the most direct biological link between the exposure/intervention and the outcome. If the intervention works at all, it will be very obvious.
- Experimental "subjects" are homogeneous.
  → Large effects and low variability.

**Translational Science:** Usually, still a physiologic outcome which responds directly to the intervention.
- But, humans are intrinsically more heterogeneous than laboratory "subjects". In small studies, they can be chosen to be similar to each other.
  → Large effect but more variability

**Randomized Trials:** Usually a "clinical outcome" which reflects the intervention but many other factors as well.
- Human characteristics are balanced between arms by randomization, but still heterogeneous within arms.
  → Smaller effect and even more variability.

**Observational Studies:** Usually a "clinical outcome" which reflects the exposure, but many other factors as well.
- Human characteristics are heterogeneous within groups and some are unbalanced between groups as well.
  → Smaller effect and even more variability.
Sample Size

**Issue:** Even if your hypothesis is correct, the analysis will not lead to a significant conclusion unless there are a sufficient number of subjects in your study.

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Sample Size

**Basic Science:** Usually, a small number of subjects (5?).
- Often justified by historical precedent rather than actual calculations.
- The small sample size may still be reasonable given the anticipated strong effect and low variability.

**Translational Science:** Usually, a moderate number of subjects (20-100).
- Sufficient power for continuous outcomes.
- Low power for binary or time-to-event outcomes. This is okay as long as these are recognized as exploratory.
- Often provide pilot data for subsequent clinical trials.

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Sample Size

**Randomized Trials:** Usually moderate to large sample sizes (100’s or 1000’s of patients).
- Size will depend on the rarity of the clinical outcome and the anticipated magnitude of the intervention effect.
- Almost always based on pilot studies that provide information for formal sample size calculations.

**Observational Studies:**
- Sometimes, very large cohorts (1000’s or 10,000’s) where sheer numbers provide enough power to look at relatively rare outcomes.
- Sometimes, moderate “in-house” clinical cohorts (100’s) where the patients are more homogeneous and outcomes are more common.
Analysis Plan

You must have, in advance, an analysis plan that will produce valid interpretations of the study results. The plan must match:
- the study design (i.e., repeated measures over time)
- the type of outcome data collected
And be able to deal with contingencies like:
- missing data and patient withdrawal

Threats to Validity

Issue: Can we trust the results of the research?

Validity

Basic Science:
- Statistical Perspective: We can trust the results. (Unless the investigator has measured too many outcomes or compared too many groups.)
- Scientific Perspective: The main concern is generalizability to clinical outcomes in humans.
Validity

Translational Science:
- Statistical Perspective: If the results are not significant, especially for clinical outcomes, we should be concerned with lack of power.
  - If the study is uncontrolled, we should be concerned whether the same trends over time might have occurred in a control group (natural temporal trends)
  - If controlled but not randomized, we have limited ability to adjust for factors not balanced between groups.

Scientific Perspective: The main concern is with extrapolation from physiologic measures to clinical outcomes.

Randomized Trials: Assuming a solid design and implementation, there should not be concerns statistically or scientifically.

Observational Studies: From the statistical and scientific perspectives, we should be concerned with confounding (outside factors which differ between the comparison groups).