Statistical Considerations in Grant Writing

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Name:	Role in Meeting:
Ruta Brazauskas, PhD	Planning Committee
Haley Montsma, BBA	Planning Committee
Aniko Szabo, PhD	Speaker

Learning Objectives

- Understand statistical issues relevant to grant applications
- Become aware of common mistakes and pitfalls
- Learn best practices and solutions for common problems

Evaluation Forms

Your opinion matters!

Help us plan future meetings, by completing and submitting your evaluation forms.

Thank you.

My grant-related background

- Statistical co-investigator on over a dozen grants
  - Basic science, human studies, clinical trials
- Wrote statistical sections for even more grants
  - and saw drafts, unfunded versions, etc
- Statistical reviewer for NIH study sections
  - Clinical and Integrative Cardiovascular Sciences [*CICS*]
  - Biomedical Methods and Research Design [*BMRD*]
  - NIEHS special panel on nanomaterials

Outline

- Specific aims and hypotheses
- Specifying the study population
- Selecting a study design
- Defining outcome measures
- Sample size calculations
- Data analysis plan

Specific aims and hypotheses

- **The hypotheses drive all the statistical aspects of the grant proposal**
- "Specific" aims can be relatively vague, but hypotheses have to be specific
  - Specific aim
    - Explore the effects of XYZ…
    - Characterize the properties
  - Hypothesis
    - XYZ will increase W, but will not affect U
- Always state the working hypothesis (ie what you would like to show), not the null hypothesis

Study population

- Conceptual target population

- Operationalization
  - Inclusion/exclusion criteria
    - How will their presence/absence validated
  - Source of recruitment
    - Patients presenting in the clinic
    - Female Wistar rats
  - Number of potential subjects available

Controls

- **Ideal: differ from the study group only in the study variable**
- Straightforward situation
  - Randomized prospective study
    - Many basic science experiments fall into this category
- Subject as his/her/its own control
  - Regression to the mean can cause spurious results
  - Cross-over designs can correct for this
    - Carry-over effects
  - Within-subject change can be used as an outcome with another control group

Controls in case-control studies

- Cases are subjects with a certain condition, Controls are subjects without that condition
  - What about associated characteristics?
  - Diagnostic process might be relevant
    - Eg diagnosis of cancer is highly dependent on screening practices
- Cases are subjects who received a treatment, Controls are those who did not
  - *Why* did the controls not receive the treatment?
    - Had more/less advanced disease
    - Need to be able to identify who was eligible

Study design

- Prospective vs retrospective
- Observational vs experimental
- Case-control studies
  - Matched vs unmatched
  - Matching can result in either gain or loss of power
  - Unmatched studies still recruit comparable controls, but there is no individual level matching
- Randomization and blinding
  - Rarely mentioned in basic science studies, though highly relevant

Study design

- Interim analysis
  - Check for statistical significance at preplanned time-points during the study
    - Significance levels have to be adjusted
  - Can be useful if there is substantial uncertainty about the expected effect
  - Rare in basic science studies, but could be useful
- Internal pilot
  - Quantities need for power calculation are estimated based on a small initial sample size
  - Needs to be planned in advance: a small adjustment of significance level might be needed

Defining the outcome measure

- Measureable and well defined
  - Measurement procedures
  - Timing
    - Too many repeated measurements just complicate the result
    - Two points at ends are sufficient to show change
- Separate primary versus secondary outcomes
  - Sample size calculation is guided by the primary outcome
  - Primary outcome should be
    - Most clinically/biologically relevant
    - Likely to show a difference

Sample size calculations

Type of Study	Sample Size	Detectable Difference	Power
Retrospective	Fixed known	Fixed Clinically / biologically important difference	Computed
Retrospective	Fixed known	Computed	Fixed (90, 80)%
Prospective	Computed	Fixed Clinically / biologically important difference	Fixed (90, 80) %
Observational	Computed	Fixed Desired precision of estimate	Not applicable

Sample size calculations

- Need to specify the details:
  - Planned analysis method
  - Significance level and power
  - Effect size
  - Additional assumptions (baseline rate, variance, correlation,…)
- Biological versus technical replicates
  - Spend money/effort on largest source of variability
    - Usually the biological variability
  - More than 3 technical replicates are rarely useful

Sample size calculations

- Needs “nuisance” parameters beyond expected treatment difference
  - Variance of measurement
  - Probability of event in control group
  - Correlation of repeated measures
- Source of estimates
  - Preliminary data!!!
  - Literature review
    - Help others! Report SD of key quantities in publications!
  - Educated guess

Sample size fallback options

- Sample size calculation will be done by XYZ (letter of support attached)
- Plan a small pilot study that will provide the data for the sample size calculation
  - Eg plan to update the calculations based on the results of Aim 1
- Plan an internal pilot
- Refer to Cohen's standard effect size scale

Cohen's standard effect sizes

Definition of effect size

- Continuous data:

$$ES = \frac{\mu_1 - \mu_2}{\sigma}$$

- Binary data:

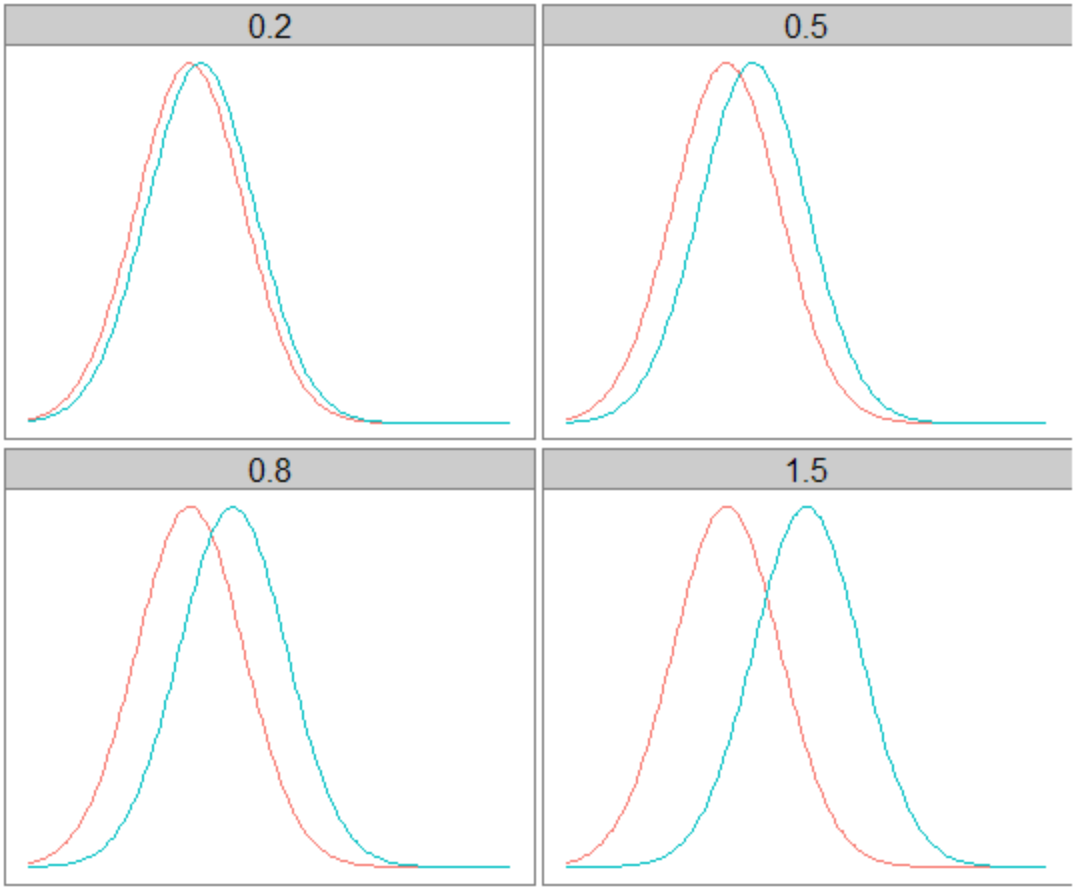
$$ES = 2\left(\sin^{-1}\sqrt{p_1} - \sin^{-1}\sqrt{p_2}\right)$$

Qualitative description	Standard effect size	Group size for a 2-sample test (α=5%,pwr=80%)	Examples	
			Normal data σ=1	Binary data
Small	0.2	394	μ = 3.0 vs 3.2	p = 10% vs 17%
Medium	0.5	64	μ = 3.0 vs 3.5	p = 10% vs 30%
Large	0.8	26	μ = 3.0 vs 3.8	p = 10% vs 44%
Very large*	1.5	8	μ = 3.0 vs 4.5	p = 10% vs 75%

Sample size for 2-sample comparison: $N_{\text{group}} \approx \left(\frac{4}{ES}\right)^2$

(α=5%, power=80%)

Cohen's standard effect sizes



If classification is the goal, small effect sizes are useless

Sample size software

- Online calculators
  - See upcoming talk
- G*Power 3
  - Free Windows/Mac program from the University of Düsseldorf
  - Needs some statistical sophistication
- Consult your friendly neighborhood statistician

Statistical analysis plan

- The goal is to convince the reviewers that you can analyze the data
  - Not all details are necessary
  - Showing awareness of statistical aspects and capability to address issues is important
  - If grant contains many experiments, consider having a separate section with overall analysis approach
- Some details can go outside of main proposal
  - “Protection of Human Subjects” and “Vertebrate Animals” sections have no page limits
  - “Facilities & Other Resources” can describe availability of statistical consulting
  - Data collection forms can be in the Appendix

Common mistakes

- Complicated data with no mention of statistics
- Mistakes/misinterpretations in the analysis of preliminary data
- Statistical methods do not match the study design
  - Statistical methods clearly copied from another grant
  - Matched design vs unmatched analysis
- Incorrect statistical plan
  - Plan to “sample until significance”
  - Superficial plan emphasizing minor details over substantative issues

Thank you!