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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Sample Size</th>
<th>Detectable Difference</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>Fixed known</td>
<td>Fixed Clinically / biologically important difference</td>
<td>Computed</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Fixed known</td>
<td>Computed</td>
<td>Fixed (90, 80)%</td>
</tr>
<tr>
<td>Prospective</td>
<td>Computed</td>
<td>Fixed Clinically / biologically important difference</td>
<td>Fixed (90, 80)%</td>
</tr>
<tr>
<td>Observational</td>
<td>Computed</td>
<td>Fixed Desired precision of estimate</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
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:**
  \[ ES = 2 \left( \sin^{-1} \sqrt{p_1} - \sin^{-1} \sqrt{p_2} \right) \]

<table>
<thead>
<tr>
<th>Qualitative description</th>
<th>Standard effect size</th>
<th>Group size for a 2-sample test ((\alpha=5%, pwr=80%))</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Normal data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\sigma=1)</td>
</tr>
<tr>
<td>Small</td>
<td>0.2</td>
<td>394</td>
<td>(\mu = 3.0) vs 3.2</td>
</tr>
<tr>
<td>Medium</td>
<td>0.5</td>
<td>64</td>
<td>(\mu = 3.0) vs 3.5</td>
</tr>
<tr>
<td>Large</td>
<td>0.8</td>
<td>26</td>
<td>(\mu = 3.0) vs 3.8</td>
</tr>
<tr>
<td>Very large*</td>
<td>1.5</td>
<td>8</td>
<td>(\mu = 3.0) vs 4.5</td>
</tr>
</tbody>
</table>

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

(\(\alpha=5\%,\) 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!