ACTStat Sounding Board on Teaching Investigators How to Interact with Statisticians on Collaborative Grants

James J. Grady UCONN Health Center

Jonathan D. Mahnken The University of Kansas Medical Center

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Jon to introduce…

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ACTStat Sounding Board

- Often asked to give talks to non-statisticians on grant development
  - Frequently students or new/junior investigators (K-scholars, fellows, post-docs)
  - Practical issues usually trump other experimental design factors for new/junior investigators' grants
- Goals of these talks…
  - Prepare for initial project meetings
  - Create realistic expectations for investigators
  - Overall, improve interactions in developing grants

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ACTStat Sounding Board (cont.)

- ACTStat ideal place for broad feedback on this material…
  - Support applications such as BERD SIG workshop for 2016 meeting
  - Relevant to audience presenting similar talks at respective institutions
- Sounding board
  - Is material targeted to the right audience?
  - What did you think of the examples?
  - *Did we cover the right material?*
- We also included practical examples of things we found helpful for statisticians to spur discussion by ACTStat

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Jamie to present…

Different Types of Studies and General Issues

Small clinical studies

Pilot studies

Large confirmatory clinical studies

NIH Studies R01

Proteomics studies

NIH Studies R03
R21

Basic Science & Animal studies

Meta Analyses

Secondary Data Analysis

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General Issues

- We need good science…..but we need to:
  - Finish the study in a timely manner
  - Want to get results into the literature…..move on to next phase of the research
- Practical reasons (like “my fellowship ends in May”)
- Budget: fixed amount of resources
- Human Subjects issues: Don’t want to enroll more subjects than we have to

General Issues (cont.)

- Large studies:
  - Offer more information
  - May be Overpowered
  - Take longer to finish
  - Expose more subjects to potential harm
  - Cost more
  - Takes that much longer for the new knowledge to be disseminated

General Issues (cont.)

- Small studies:
  - Less information
  - May be Underpowered
  - Able to finish
  - Expose less subjects to potential harm
  - Cost less
  - Knowledge is disseminated faster

Blood Pressure Study

Intervention Study: Education about disease

Possible Outcomes: Knowledge, Blood Pressure

Two possible BP-related outcomes were under consideration

Categorical: BP Status control at the end of the Study (controlled vs not controlled)

and

Continuous: Diastolic Blood Pressure

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Blood Pressure Study (cont.)

Mean Difference Treated vs Controls	5	5	5
Standard Deviation	8	10	12
N per group	42	64	92

For a two-group t-test, alpha=0.05, two sided test, 80% power

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Blood Pressure Study (cont.)

Scenario 1	Blood Pressure Status at End of Study		
Group	Under Control	Not Controlled	
Controls	50%	50%	N=?
Treated	60%	40%	N=?

	1	2	3
Controls prop	.50	.50	.50
Treated prop	.60	.65	.70
Odds Ratio	1.5	1.8	2.3
N per group	388	170	93

For a two-group Chi-square test, with two sided significance level of 0.05. 80% power

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Small Clinical Trial

Hello. My name is Bob and I am one of the 2nd year fellows here at UConn. We are planning a study here at UConn and need some help with the sample size, etc. Would you be able to meet with me sometime this week? Thanks.

Small Clinical Trial (cont.)

Two groups: treated vs controls

Outcome: relapse of symptoms for ulcerative colitis

Proposed group differences

50% vs 35%

Small Clinical Trial (cont.)

50% vs 35%

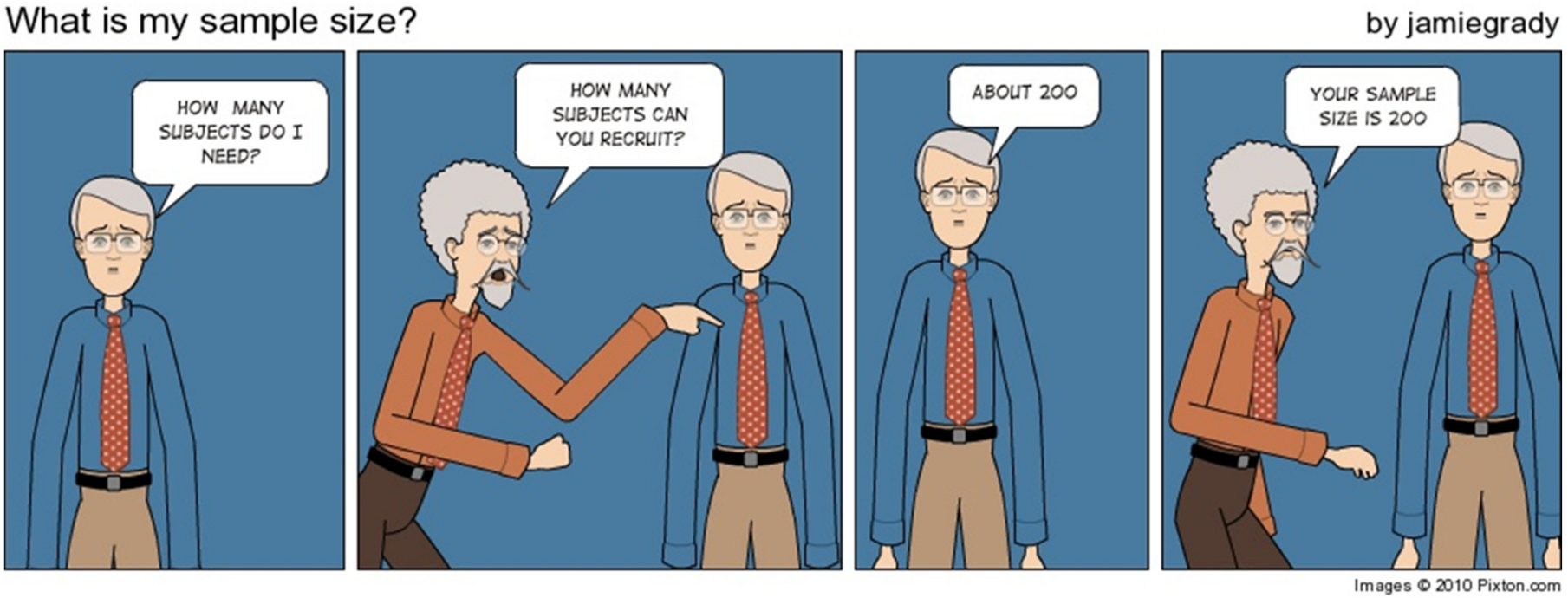
A two group continuity corrected c^2 test with a 0.050 two-sided significance level will have 80% power to detect the difference between a Group 1 proportion, p_1, of 0.500 and a Group 2 proportion, p_2, of 0.350 (odds ratio of 0.538) when the sample sizes are 136 and 272, respectively (a total sample size of 408).

Small Clinical Trial (cont.)

Wow. Can I give you a call later this afternoon or tomorrow? I'm not sure we'll be able to do the study unless there is anything else we can come up with. Thanks.

…from our experiences…

- Start with the practical constraints…



Pilot Studies

Do we need to do a power analysis for a pilot study? Is it even helpful?

Does it make sense to describe power for n=5 or n=10 per group?

Or just offer a general sample size justification?

Pilot Studies (cont.)

Or is it a Human Subjects issue…

How do we justify enrolling subjects into a study that will not advance science? (although it could lead to a study that does…)

What about consent forms for a pilot study. Are some fundamentally misleading when they say things like:

"This study will (help) determine if drug A helps to reduce your disease…"

Pilot Studies (cont.)

Too many pilot studies read like a clinical trial:

We will test the efficacy and safety of…

Why?

Pilot Studies

Why not a general/practical Sample Size justification?

Ten subjects will allow us to do the following:

1) Estimate the SD for parameters A, B and C.
2) Estimate percent who show favorable results
3) Allow us to prove we can measure X, under certain conditions.

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Small Clinical Studies

Typically there is preliminary data

The specific aims read like a clinical trial, more formal hypothesis testing

“We will test the efficacy and safety of ……”

A reasonable power analysis can usually be developed

Small Clinical Studies (cont.)

Small clinical trials usually…

Needs to be finished in a timely manner

May lead to a larger study or R01

…… So the sample size is pretty limited

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Large Confirmatory Clinical Studies

Typically there are “preliminary studies”, phase II studies

Large expensive studies

Statisticians and research group develop a sophisticated power analysis

Now we really can say:

“We will test the efficacy and safety of ……”

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Large Confirmatory Clinical Studies (cont.)

For industry sponsored studies, FDA will be involved and will review/approve the study design before it begins

Animal Studies

These study's sample sizes are usually small

Precedent for small numbers

Expect large effects (If I can't see the effect in 6 rats…)

Cost of animals

Animal IRB (Institutional Animal Care and Use Committee (IACUC))

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…from our experiences…

Why are there always at least N=6 per group?

If you observe a change (eg, from baseline) in all six animals, you reach statistical significance on non-parametric tests (sign, signed rank)

• values: 2,3,1,2,3,2	6/6	P=.0313
• values: 2,3,1,2,3,0	5/6	P=.0625
• values: 2,3,1,2,3,0,2	6/7	P=.0313

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Secondary Data Analysis

Fixed Sample Size

Typically large, or very large

How necessary are power analyses?

Still needed for proposed hypotheses to be tested

Secondary Data Analysis (cont.)

How necessary are power analyses?

- National Institute of Dental & Craniofacial Research (NIDCR)

- Study section still wants to see a well developed power analysis for Secondary Data Analysis

- One reviewer often is chosen for knowledge of data source

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Meta-analysis

Your study condition and study criterion dictate the sample size

From a recent meta-analysis on burn injury:

"We considered all studies conducted after 1980; published in English language journals; that used lactated ringers to resuscitate patients; in either randomized studies or observational cohorts; with major burns, generally at least 40% TBSA; with surface or inhalation burns or both; including adult or pediatric subjects."

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Jon to present…

Statistical Sections of the Grant

Important Components of a Grant

- Research question aligned with specific aims
- Research hypotheses aligned with research question
- Study measures and definitions
  - *Should be supplied by PI, but statistician should ensure they are included—and defined*

…from our experiences…

- You will be viewed as 100% responsible for all aspects of the data collection and analyses, so you will be blamed if this information is not there…

Important Components… (cont.)

- Study design
  - E.g., randomized, controlled trial; prospective cohort, etc.
  - Specify timing of data capture (*from PI*)
- Statistical tests
  - How will underlying assumptions be verified? …for each test?
  - Propose alternative strategies

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Important Components… (cont.)

- Justification for the sample size
- Personnel
  - Qualifications and experience
  - Effort levels
    - Do not neglect time to write-up findings… often identifies need for further analyses… more effort
  - Data management personnel

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Initial Meeting with Investigator

- Request aims prior to meeting
  - Often change when we meet, but good starting point
- Identify all relevant study measures
  - Type of measure (continuous/nominal/ordinal)
  - Use of measure (response/explanatory/covariate)
  - Timing of collection (baseline/1 month/2 months)
- "Ball-park" n they can afford
  - Again, constraints not always financial

…from our experiences…

- Need to focus the investigator: “If your study could only answer ONE question, what would it be?”
  - *This will be basis for sample size—and justification*

…from our experiences…

- IMMEDIATELY following initial meeting, clean up notes to bullet-points/outline
  - Aims and corresponding research hypotheses, measures (type and use), timing… update/re-phrase/re-write altogether…
  - Analysis plan, e.g.:
    - Kidney volume (time t) = Biomarker A + time function + covariates
      - Linear mixed model (trend analysis)
      - Model assessment: residual histograms, q-q plots, etc.
      - Alternate strategies: transform kidney volume measure
  - This "skeletal" draft will make it much easier to write the prose for the grant later

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…from our experiences…

- Clean up notes… (cont.)
  - Try to block time for this immediately
    - ***Very difficult to "resurrect" discussion when balancing many projects***
    - Send skeletal draft to PI ASAP (same day)
    - Request they confirm your understanding… better to discover misunderstandings here than after spending considerably more time writing in prose for the wrong analysis plan

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Writing the Grant

- Helpful to restate each aim and hypothesis, and for each:
  - Use precise language in describing statistical tests… and be clear about which measures will be used
- Knowing types of measures, when they are collected, and research hypotheses determines analysis
- Make clear what measure is proxy for (*from PI*)
  - E.g., "The CES-D will be used to measure depression. This measure is on a scale from…, with higher levels indicating…"

Good Example

- Research hypothesis: Active drug decreases SBP
- Data analysis section: We will use linear regression to compare whether treatment (active drug vs placebo) decreases SBP, adjusting for age and sex
  - What is response variable?
  - What is explanatory variable?
  - Are there any covariates?
  - What statistical method will be used?
- Is this analysis appropriate?

Bad Example

- Research hypothesis: Active drug decreases SBP
- Data analysis section: We will use regression to analyze our data
  - What is response variable?
  - What is explanatory variable?
  - Are there any covariates?
  - What statistical method will be used?
- Is this analysis appropriate?
  - Even if the reviewer knows how to analyze this, you must convince them that you know how to analyze it

Writing the Grant (cont.)

- Justify each sample collected
  - E.g., if two cohorts will be used justify each
  - Consider justifying multiple measures if they are expensive
- Multiplicity
  - Essential to address, but not always easy…

Opinion: Reasonable to identify one of many measures to be a primary measure (*PI*), and—*so long as* results reported ALWAYS identify the primary and secondary measures as such—no "further" multiplicity adjustment is needed

…this MUST be carried out through publication with this disclosure to be effective

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Writing the Grant (cont.)

- "Rule of thumb" on space for statistical sections
  - If there is not enough room in the application to:
    - State the research hypotheses
    - Describe all study measures
    - Identify statistical tests
    - Describe how assumptions will be assessed
    - State alternative strategies (if assumptions violated)
    - Justify the sample size

  …then there are probably too many aims for that funding mechanism

Space is essential!!!

Find out how much you have early on…

General Comments

- Assume the reviewers are *completely unfamiliar* with the measures

  …in many cases they are, so "connect the dots" for them

- Assume the reviewers are too busy to spend much time reading the application—*particularly the stats section*

  …in many cases they are, so make it easy for them to read

- Use helpful section and paragraph titles to guide your reviewers

…from our experiences…

- Allow for plenty of time
  - Block time immediately following meetings to organize your thoughts
  - Block time around critical dates for last minute changes or additions… not uncommon
- *Proofread carefully*
  - Typos and poor writing provide easy excuse for a reviewer to not understand the proposal…

    …and score it accordingly
    - Read it out loud, or have someone *unfamiliar with the project* read it (I usually just read it out loud)

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BOTH Jamie or Jon to facilitate sounding board…

Sounding Board…

- Is material targeted to the right audience?
- What did you think of the examples?
- *Did we cover the right material?*

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Thank You

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