# UCDAVIS HEALTH

# Get funded or published — Writing statistical sections for grants and papers

Applied Statistics for Translational Researchers Seminar Series

## **SCHOOL OF MEDICINE**

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# Learning Objectives

- Understand what needs to be included in grant proposals with respect to statistical analysis plans and sample size justification and how to craft these sections
- Learn what constitutes an adequate statistical analysis section for a scientific paper
- Know what information from statistical analyses to report and how to present it in a scientific paper





### **Context and Preliminaries**

Proposals and manuscripts are produced in distinct phases of a project, but they are linked in important ways and projects are themselves embedded in larger research programs

You must sell others on the qualities and potential impacts of your work



# Operational phases of translational research



Sources: Figure 1.1. from "Institute of Medicine. 2013. The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research. Washington, DC: The National Academies Press. <u>https://doi.org/10.17226/18323</u>", itself a permitted adaptation from "Blumberg RS, Dittel B, Hafler D, von Herrath M, Nestle FO. Unraveling the autoimmune translational research process layer by layer. Nat Med. 2012 Jan 6;18(1):35-41. doi: 10.1038/nm.2632. PubMed PMID: 22227670"



## Integrated model of clinical and translational research



Sources: Figure 1.2. from "Institute of Medicine. 2013. The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research. Washington, DC: The National Academies Press. <u>https://doi.org/10.17226/18323</u>", itself an adaptation from

"Austin, C. P. 2013. *National Center for Advancing Translational Sciences: Catalyzing translational innovation*. PowerPoint presented at Meeting 3: IOM Committee to Review the CTSA Program at NCATS, Washington, DC, January 24.

http://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Research/CTSAReview/2013-JAN-24/Chris%20Austin.pdf (accessed November 6, 2019)"

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"Research data lifecycle" (<u>https://rdmtoolkit.jisc.ac.uk/research</u> <u>-data-lifecycle/</u>) by JISC.AC.UK is licensed under <u>CC BY-</u> <u>ND 4.0 licence</u> (attribution is required and derivative work cannot be shared publicly)

# Research Lifecycle at University of Central FL

Version 2.0



Impact evaluation Proposals, protocols, statistical analysis plans, are meta-data and anticipatory Papers include meta-data but also data summaries Interim analyses Reproducibility & replicability

library.ucf.edu/ScholarlyCommunication

When designing a study, investigators must...

- Choose a study type
- Specify objective(s) (superiority, noninferiority, etc.) & research question
- Account for study resources (time, money, available participants, investigators, facilities, etc)
- Choose units of observation and what/how to measure
- Account for potential sources of variation and bias
- Specify randomization/sampling strategy
- Specify (in a broad sense) the planned analysis

Source: Cox & Donnelly's "Principles of Applied Statistics" Cambridge (2011)



# Elements of a research question

Explicit specification of PICO (PECO), when applicable

- Population, including settings/locations
- Intervention(s) / Exposure,
- Comparison (if relevant)
- Outcome(s), including timing & how measured (Also see: <u>http://guides.mclibrary.duke.edu/ebm/pico</u>)



#### A recently proposed new evidence-based medicine pyramid.



Critical appraisal skills are particularly important, nowadays, because significance of proposed work depends on identified evidence gaps and impact of published work depends on internal and external validity of findings

M Hassan Murad et al. Evid Based Med doi:10.1136/ebmed-2016-110401



"Classical Triple Constraint" (aka Project Management Triangle") & Baratta's proposed "Value Triple Constraint"



Baratta, A. (2006). The triple constraint: a triple illusion. Paper presented at PMI<sup>®</sup> Global Congress 2006—North America, Seattle, WA. Newtown Square, PA: Project Management Institute. <u>https://www.pmi.org/learning/library/triple-constraint-erroneous-useless-value-8024</u>





# Grant proposals



# By the way, submitting/resubmitting the grant proposal is itself a project

- Make as much time available as possible for you and colleagues to prepare grant, including time for allies to read and critique preliminary drafts
- Some tasks, like power and sample size justifications and publishing preliminary study data, pertain not to the proposed study, but also to whether or not to pursue the upcoming grant proposal deadline
- Be mindful that resubmission may be needed
- Be mindful that resubmission may not be wise!



# Scoring of NIH research grant proposals

**Overall Impact.** Reviewers' assessment of the *likelihood* for the project to exert a *sustained, powerful influence* on the research field(s) involved...

- **Significance.** Does the project address an important problem...? Is there a strong scientific premise for the project? ...
- **Innovation.** (novel theoretical concepts, approaches or methodologies, instrumentation, or interventions)
- Approach. Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? ...Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?...
- **Investigator(s).** Are [they] well suited to the project?...
- **Environment.** Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? ...

https://grants.nih.gov/grants/how-to-apply-application-guide/format-and-write/write-your-application.htm



# Biosketch, budget justification, & facilities and resources

Use key components of grant to convince reviewers of your strengths and to address potential weaknesses...

I am a medical statistician on the faculty in the Department of Pediatrics at the University of California, Davis. I have over two decades experience in developing, applying and teaching methods to address significant statistical design, measurement, analysis and reporting challenges that arise in clinical trials, complex surveys, health services research, observational epidemiological studies and in biomedical laboratory sciences. I am heavily invested in multi-disciplinary research and am highly sought after for the independent statistical leadership that I contribute to team science. My research is represented by a significant body of peer reviewed publications, with more than 225 journal articles published from the time of my faculty appointment in 2007. Before joining the faculty, I had acquired over a decade of research experience as the senior statistical and database programmer for research teams at UC Davis and Rush University engaged in health services research and in population- and clinic-based studies of aging. In addition, I acquired significant expertise in optimal design and analysis for comparative experiments as a graduate student and dissertation advisee of UIC Distinguished Professor Samad Hedayat, which I have further developed in my own professional practice. I direct two research support cores at UC Davis providing statistical support to NIH-sponsored preclinical and clinical research programs in pharmacology and toxicology. The combination of intensive experience as the lead statistical programmer and rigorous training and experience as a doctoral-level mathematical statistician enables me to develop practical, robust and efficient analysis strategies for complex research projects. I bring to Dr. Havel's team specific expertise on efficient design and analytic approaches for ensuring valid and reliable assessment of exposure/outcome associations using imaging, histopathological, behavioral and clinical measures. I have particular expertise in the design and analysis of longitudinal biomedical studies, including animal studies to understand the mechanisms and outcomes of diabetes. Although my collaboration with Dr. Havel is newly forged, I have longstanding and successful collaborations with our mutual colleagues through my involvement as the Director of the Statistics and Data Management Core for the UC Davis NIH CounterACT Center of Excellence and as a past or current co-investigator of several studies in diabetes and in autism. Based on these skills and experiences, I am confident that I will be able to provide statistical leadership on this grant, ensuring that randomization and analysis plans are appropriately and rigorously defined and implemented.

Justify why multiple statisticians ("quants") are needed

If impressive computational resources are required, document them!



# Some recent NIH Policies of particular relevance for statisticians

#### Enhancing Reproducibility through Rigor and Transparency.

"Scientific rigor is the strict application of the scientific method to ensure unbiased and well-controlled experimental design, methodology, analysis, interpretation and reporting of results" <u>https://grants.nih.gov/policy/reproducibility/index.htm</u>

#### Sex as a Biological Variable

"Women now account for roughly half of all participants in NIH-supported clinical research, which is subject to <u>NIH's Policy on the Inclusion of Women in Clinical Research</u>. However, more often than not, basic and preclinical biomedical research has focused on male animals and cells. An over-reliance on male animals and cells may obscure understanding of key sex influences on health processes and outcomes." <u>https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable</u>

### **Clinical Trial Requirements for Grants and Contracts**

"NIH is launching a series of initiatives that are rolling out in 2017-2018 to enhance the accountability and transparency of clinical research. These initiatives target key points along the whole clinical trial lifecycle from concept to results reporting. Learn more about these changes and how they will affect your research." <u>https://grants.nih.gov/policy/clinical-trials.htm</u>



# Reproducibility, replicability, generalizability

- Reproducibility (means) "computational reproducibility—obtaining consistent computational results using the same input data, computational steps, methods, code, and conditions of analysis"
- *Replicability* (means) "obtaining consistent results across studies aimed at answering the same scientific question, each of which has obtained its own data"
   NB: Some sources of non-replicability are helpful to science; others are not
- Generalizability... refers to the extent that results of a study apply in other contexts
  or populations that differ from the original one

"Researchers should take care to estimate and explain the uncertainty inherent in their results, make proper use of statistical methods, and describe their methods and data in a clear, accurate, and complete way."

National Academies of Sciences, Engineering, and Medicine. (2019). *Reproducibility and Replicability in Science*. Washington, DC: The National Academies Press. <u>https://doi.org/10.17226/25303</u>



Robustness vs. efficiency examples

 For estimating an unknown Gaussian mean, the sample median has 57% more variance than sample mean, but is much more resistant to contamination from outliers.

ARE =  $2 / \pi$ 

• Wilcoxon-Mann-Whitney vs. Student's t-test. ARE =  $3 / \pi$ 

Bias vs. Variance

 $MSE = Variance + Bias^2$ 





# **Robust Statistics**





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- Real-life data don't *really* meet our distributional assumptions.
- Statistical methods that perform well with outliers and other real-life quirks are important and underused.
- These methods can have better power (i.e. lower type-1 error) than standard methods, while offering more accurate control of type-1 error.

Shareable links to UCDavis online access For 3<sup>rd</sup> edition of Rand Wilcox's text: <u>https://ebookcentral.proquest.com/lib/ucdavis/detail.action?docID=858695</u> For 2<sup>nd</sup> edition of Hettmansperger & McKean: <u>https://www.taylorfrancis.com/books/9780429131103</u>

# Central Limit Theorem

Although CLT can ensure sample means become approximately normally distributed as sample sizes increase, the needed sample size to get a good approximation may be unattainable

Similar concerns for other asymptotic approximations used by classical methods

As Lucien Le Cam joked, "If you need to use asymptotic arguments, don't forget to let your number of observations tend to infinity." (www.jstor.org/stable/1403464.)

#### Limit Theorem.



Image from Annenberg Foundation 2017:

https://www.learner.org/courses/mathilluminated/units/7/textbook/06.php



# Even slight contamination of a Normal can have dramatic effects

Normal distribution is ubiquitous, at least in theory!

Impacts of contamination by a different normal can be dramatic

If population is 90% standard N(0,1) (i.e. mean=0, variance=1) and 10% from a N(0,10), then population has a **non-normal** distribution with mean 0 and variance **10.9** 

These fat tails are barely visible in the population histogram, let alone is a sample, but can cause major problems with standard methods

*Example: When Welch t-test has power of about 30%, robust methods could have power of 70+%* 







# Statistical trade-offs (cont.)

Choose a minimally sufficient analysis...

"The enormous variety of modem quantitative methods leaves researchers with the nontrivial task of matching analysis and design to the research question. Although complex designs and state-of-the-art methods are sometimes necessary to address research questions effectively, simpler classical approaches often can provide elegant and sufficient answers to important questions. Do not choose an analytic method to impress your readers or to deflect criticism. If the assumptions and strength of a simpler method are reasonable for your data and research problem, use it. Occam's razor applies to methods as well as to theories."

Source: Wilkinson, L., & Task Force on Statistical Inference, American Psychological Association, Science Directorate. (1999). Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist, 54*(8), 594-604. <u>http://dx.doi.org/10.1037/0003-066X.54.8.594</u>



# Approach

- The planned statistical analysis has to be aligned with the research objectives, study type, study variables and timing of measurement.
  - Common pitfalls: variable type/analysis mismatch; paired data; clustered data; inefficient use of baseline covariates; simultaneous inference (multiplicity)
- Justify why you chose particular approaches
- Account for important assumptions and propose sensitivity analyses to address them



# Example

"A preliminary round of analyses will be used to summarize the distribution of study variables and to identify and apply square-root, logarithmic, or Box-Cox data transformations to skewed distributions and outlying values, when indicated to improve the robustness and validity of statistical inferences (1). Dependent variables include continuous measures, counts and categorical outcomes from histology . To accommodate this variety of response types, generalized linear models—a regression framework that encompasses ANOVA as well as linear, Poisson and logistic regression models--will be used to assess the joint and separate effects on outcomes of the study factors of interest (e.g. maternal serostatus and housing type). For each outcome, models with and without interaction terms for these study factors will be evaluated and compared for goodness of fit, using the Akaike Information Criteria Information(2), to determine whether effects of each factor can be summarized with "main effects" for each or, instead, whether effects of each factor depend on the other factor. **Sex as a biological variable** will be addressed in a similar way. That is, all models will include sex as a covariate, differ by sex. When needed to account for repeated measurements within the same animal and/or experimental batch effects, generalized linear mixed effects models (3-5) will be used. All effect sizes (e.g. means and contrasts of means) will be estimated with 95% confidence intervals. Because a large number of hypotheses are being evaluated simultaneously, the false discovery rate will be controlled by adjusting p-values according to the procedure of Benjamini and Hochberg.(6)"

1. Box GEP, Cox DR. An analysis of transformations. Journal of the Royal Statistical Society, Series B. 1964;26(2):211-52.

2. Burnham KP, Anderson DR, Burnham KP. Model selection and multimodel inference : a practical information-theoretic approach. 2nd ed. New York: Springer; 2002. xxvi, 488 p. p.

3. Skrondal A, Rabe-Hesketh S. Generalized Latent Variable Modeling: Multilevel, Longitudinal, and Structural Equation Models. Boca Raton, FL: Chapman & Hall/CRC Press; 2004.

4. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York: Springer; 2000.

5. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. Second ed. Hoboken, NJ: Wiley; 2011.

6. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. J Roy Stat Soc B Met. 1995;57(1):289-300. PubMed PMID: WOS:A1995QE45300017.



# Example

Don't say you'll do impossible things, like test whether data are missing at random!

Instead, explain your assumptions and how you will assess them:

"Based on experience, we anticipate a relatively small amount of missing data, which would arise from failure to complete follow-up surveys or from intermittently missing clinical or survey items. We will characterize nonresponse and missing data patterns between the two arms of the study. We will follow a principled approach to addressing missing data that includes conducting primary analyses using the generalized linear modeling framework under a plausible missingness assumption and supplementing this with sensitivity analyses that make alternative assumptions about the missing data.(1) In trial reports, we will provide a range of intervention estimates, graded according to the plausibility of the missing data assumption. We anticipate that the most plausible assumption will be missing at random, and we will use a multiple imputation framework within our mixed-effects modeling strategy to estimate intervention effects under this assumption.(2) Estimates based on alternative missing data assumptions will also be produced within a multiple imputation framework, by varying the imputation model accordingly."

1. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ. 2011;342:d40. Epub 2011/02/09. PubMed PMID: 21300711; PMCID: 3230114.

2. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken, N.J.: Wiley; 2002. xv, 381 p. p.



# Julious's "7 Key Steps to Cook Up a Sample Size"

- 1. Decide on (primary) study objective
- 2. Decide on the endpoint
- 3. Determine the effect size (or, for either a noninferiority or equiv. study, the tolerance margin)
- 4. Assess population variability
- 5. Specify Type-1 error
- 6. Specify Type-2 error
- 7. Account for other factors (e.g. attrition)

Determining effect sizes; tolerance margins

- Often, applicants will make effect sizes solely on previous results
- This is questionable for at least two reasons:
  - What's a meaningful potential benefit depends also on potential costs and harms (1) discounting for group vs. individual effects (2)
  - Effect sizes from exploratory studies tend to be biased (3)

#### References

- (1) McGlothlin AE, Lewis RJ. Minimal Clinically Important Difference: Defining What Really Matters to Patients. JAMA. 2014;312(13):1342–1343. doi:10.1001/jama.2014.13128
- (2) Beaton DE et al. Looking for important change/differences in studies of responsiveness. OMERACT MCID Working Group. Outcome Measures in Rheumatology. Minimal Clinically Important Difference. The Journal of Rheumatology Feb 2001, 28 (2) 400-405
- (3) Fanelli D & Ioannidis JPA. US studies may overestimate effects. Proceedings of the National Academy of Sciences. Sep 2013, 110 (37) 15031-15036; DOI: 10.1073/pnas.1302997110



# Three practical sample size strategies

### • The effective sample size approach:

- Determine necessary (so-called *effective*)sample size for less complicated setting, using widely available formulas & apps
- To account for variation arising from design, measurement and analysis effects, apply variance inflation factors<sup>1</sup> to the effective sample size to determine a target sample size for actual enrollment

### • Exemplary dataset approach

- Create example data that reflects expected configuration of study data, especially the design matrix (i.e. independent variables) and expected values of response variables
- Fit regression models to this data while specifying values for variance components. Analysis results can then be used to derive estimates of relevant noncentrality parameters, which can then be used to do power and sample size justifications

### Simulated data

Use Monte-Carlo simulation to estimate study power

*Note:* **1.** Hsieh et al. 2003. An overview of variance inflation factors for sample size calculation. *Eval Health Prof* 26:239-57



# Example

"Experiments will yield data from at least 4 biological replicates for each distinct treatment condition (combination of key study factors) and we anticipate that in many cases the effects of binary factors will be summarized with adjusted main effects from regression models, yielding at least 8 animals at each level being compared. A sample size of 8 per level has at least 80% power (under two-sided testing with alpha=5%) to detect a pairwise between-level difference in means of 1.5 sd(7) with 2-sided alpha=5%. To characterize detectable effects under the cautious assumptions that we will control the false discovery rate at 5% and that 3% of tested null hypotheses will be false, we determined that detectable effects would be 2.5 sd.(8)"

7. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G\*Power 3.1: tests for correlation and regression analyses. Behavior research methods. 2009;41(4):1149-60. doi: 10.3758/BRM.41.4.1149. PubMed PMID: 19897823.

8. Liu P, Hwang JTG. Quick calculation for sample size while controlling false discovery rate with application to microarray analysis. Bioinformatics. 2007;23(6):739-46. doi: 10.1093/bioinformatics/btl664. PubMed PMID: WOS:000245511800012.



# Example for a "split-plot" design...

The first cluster randomization will be of 30 site (18 from Network 1 and 12 from Network 2) in a 2:1 allocation to FOO Yes vs. No. In the second stage, clinicians at the "FOO Yes" sites will be randomized 1:1 to use BAR versus routine care. Clustered data logistic regression will be used to estimate the adjusted odds-ratios associated with FOO and BAR. Each of 30 sites will contribute ~26 infants, which we translate into variance inflation factors (VIF) of 2.0 for inferences about FOO and 1.3 for inferences about BAR, assuming intracluster correlation of  $\sim 4\%$  (1). To detect (with 80% power, 2-sided alpha=5%) an odds ratio of 0.5 for FOO Yes when the outcome incidence is as high as 70% in the FOO No arm requires 654 infants in our design, which we would achieve with the planned enrollment of 30\*26 = 780 total patients from 30 clusters. For inferences about BAR's effect within FOO Yes sites, our design will perform equivalently to a design with 200 independent patients per group, providing the power to detect such differences as 57% vs. 43%, or 20% vs. 10%.

(1). Hsieh FY, Lavori PW, Cohen HJ, Feussner JR. An overview of variance inflation factors for sample-size calculation. Evaluation & the health professions. 2003;26(3):239-57. PubMed PMID: 12971199.



## **Basic Principles**

- Make sure analyses are well-aligned with research objectives, study type, and variables
- Make sure every quantitative research objective is addressed
- Understand that choices have to be made and justified. A clear and well-reasoned presentation inspires confidence from reviewers
- Report power calculation with sufficient detail to permit replication, if possible





# Reporting



# NAP Recommendation 4-1

"To help ensure the reproducibility of computational results, researchers should convey clear, specific, and complete information about any computational methods and data products that support their published results in order to enable other researchers to repeat the analysis, unless such information is restricted by nonpublic data policies. That information should include the data, study methods, and computational environment:

- the input data used in the study either in extension (e.g., a text file or a binary) or in intension (e.g., a script to generate the data), as well as intermediate results and output data for steps that are nondeterministic and cannot be reproduced in principle;
- a detailed description of the study methods (ideally in executable form) together with its computational steps and associated parameters; and
- information about the computational environment where the study was originally executed, such as operating system, hardware architecture, and library dependencies. "

National Academies of Sciences, Engineering, and Medicine. (2019). *Reproducibility and Replicability in Science*. Washington, DC: The National Academies Press. <u>https://doi.org/10.17226/25303</u>



# NAP Recommendation 6-1

"All researchers should include a clear, specific, and complete description of how the reported result was reached. Different areas of study or types of inquiry may require different kinds of information.

- Reports should include details appropriate for the type of research, including:
- a clear description of all methods, instruments, materials, procedures, measurements, and other variables involved in the study;
- a clear description of the analysis of data and decisions for exclusion of some data and inclusion of other;
- for results that depend on statistical inference, a description of the analytic decisions and when these decisions were made and whether the study is exploratory or confirmatory;
- a discussion of the expected constraints on generality, such as which methodological features the authors think could be varied without affecting the result and which must remain constant;
- reporting of precision or statistical power; and
- a discussion of the uncertainty of the measurements, results, and inferences."

Source: https://doi.org/10.17226/25303









# **Confidence intervals rather than P values: estimation rather than hypothesis testing**

Well known article by Martin Gardner and Doug Altman [Br Med J (Clin Res Ed). 1986 Mar 15;292(6522):746-50] led to recent high-profile recommendations from CONSORT, APA, & ICMJE (http://www.icmje.org/manuscript 1prepare.html ), like

this:

"...When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size..."



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# Questions?

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