NIH StrokeNet Professional Development Seminar – August 2019

When and How to Consult with a Statistician…etc

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Conflict of Interest / Disclaimer

- I am one of the multiple PIs of the StrokeNet National Data Management Center (NDMC) in Charleston, SC.
- This presentation contains my personal biases and opinions.

StrokeNet NDMC in Charleston, SC

Medical University of South Carolina (MUSC)

↓

College of Medicine (COM)

↓

Department of Public Health Sciences (DPHS)

↓

Data Coordination Unit (DCU)*

* Whence, the database software name, WebDCU™.

DCU Biostatistics Team

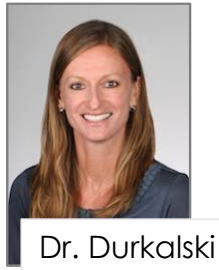

Dr. Yeatts

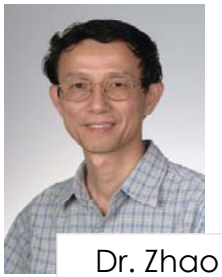

Dr. Palesch


Dr. Martin

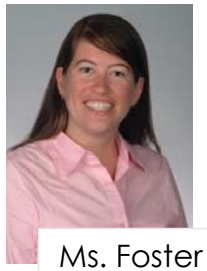

Dr. Meinzer

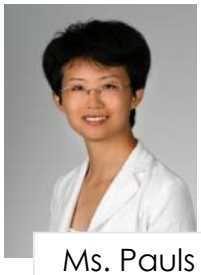

Dr. Elm


Dr. Durkalski


Dr. Zhao


Dr. Cassarly


Ms. Foster

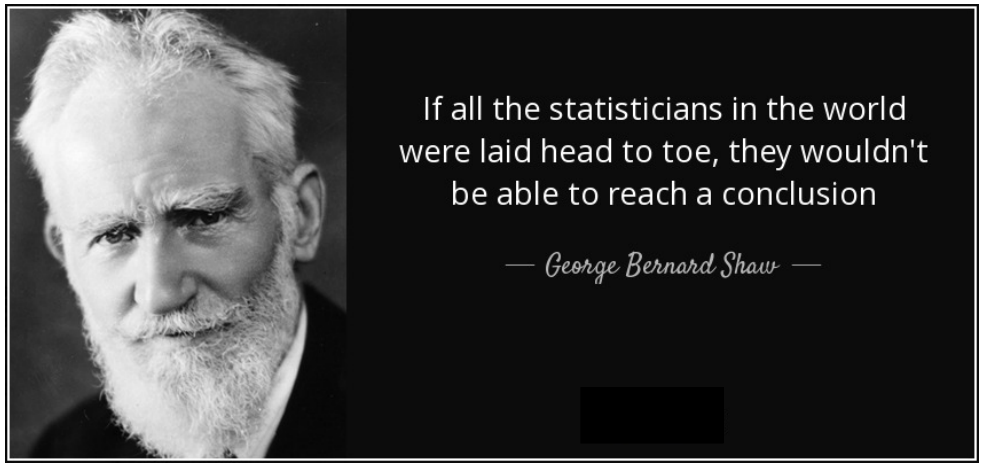

Ms. Pauls


Ms. Underwood


Ms. Gottfried


Ms. Teklehaimanot

World's View of Statisticians



Traditionally (Pre-2015)

Today

THE WALL STREET JOURNAL.

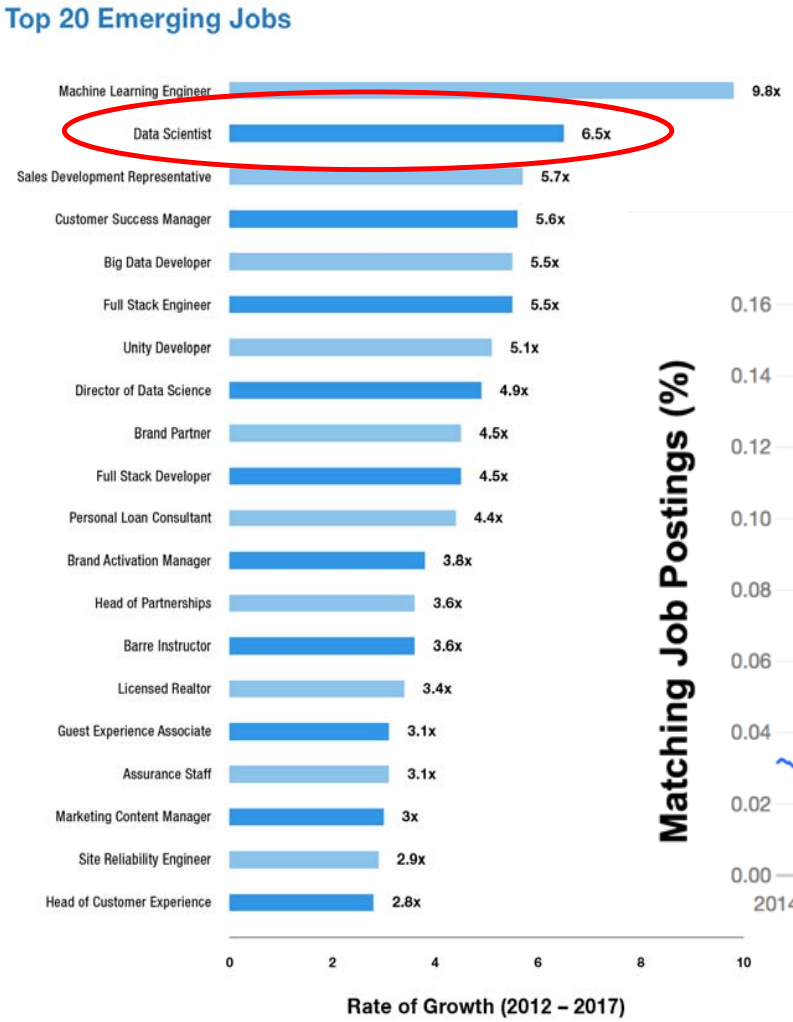
EDUCATION

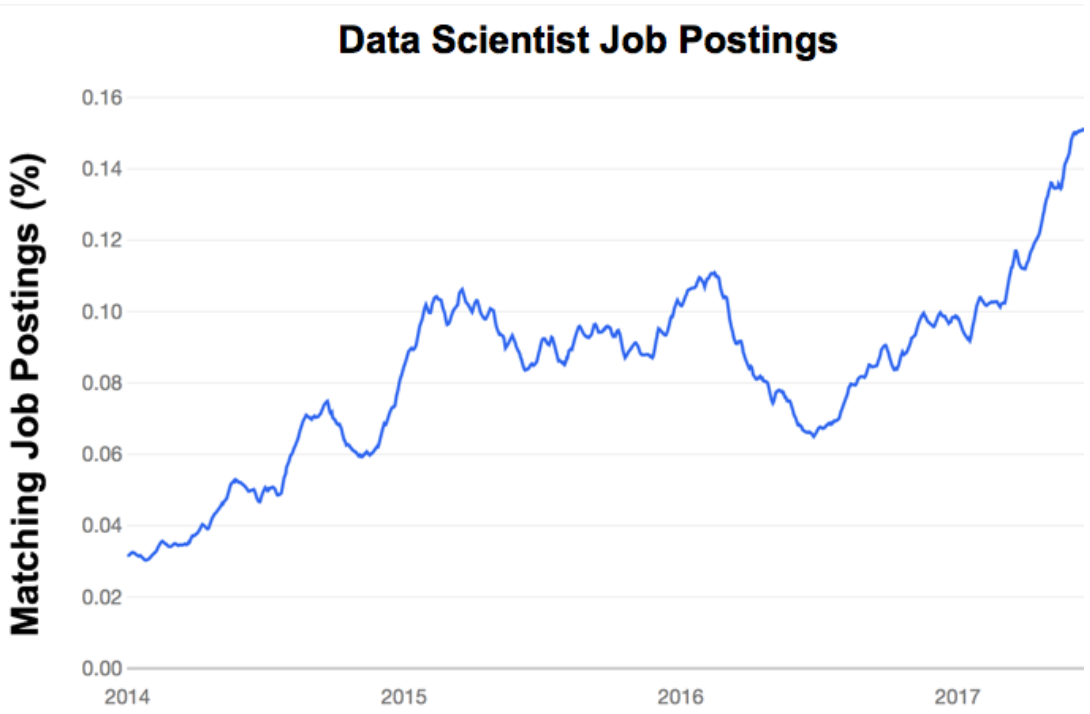
UC Berkeley's Fastest-Growing Class Is Data Science 101

The university has created a division to study the science of mining the tidal wave of digital information that floods our lives. More than 300 universities offer some type of data major at a time when companies like Google can't hire enough specialists

11/19/2018

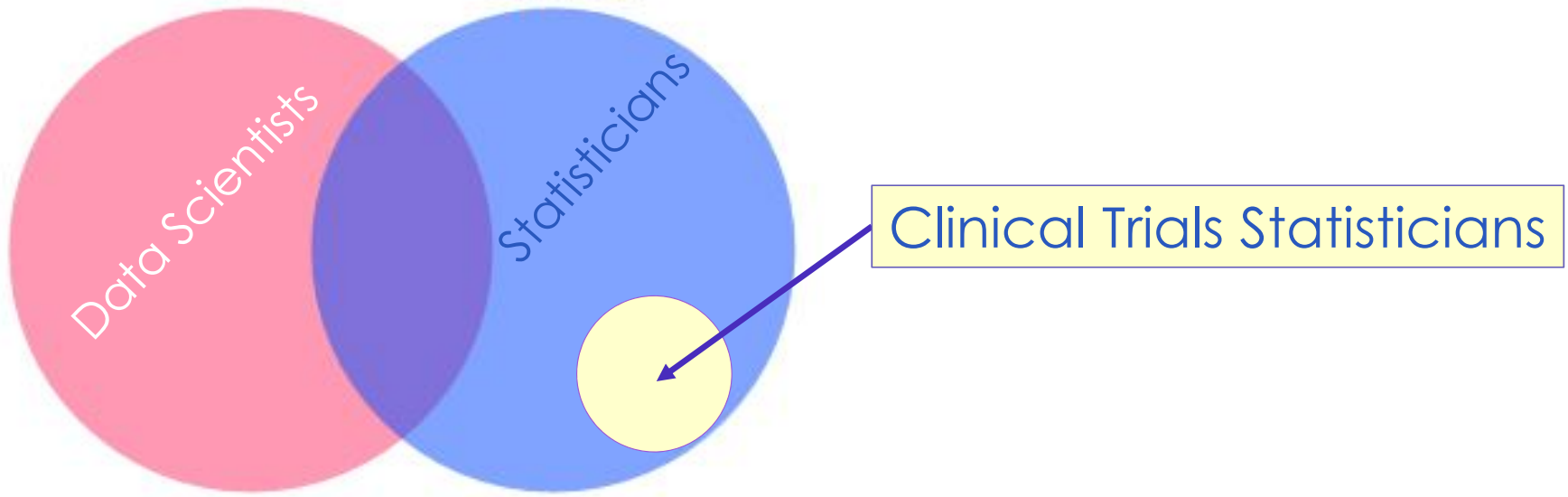
"Sexiest Job of the 21st Century"





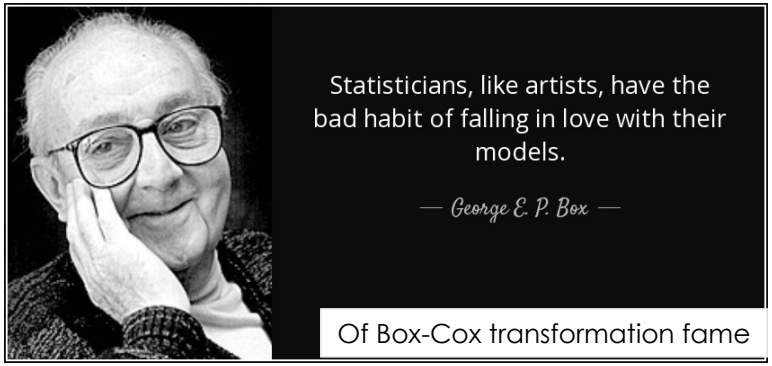
"Big" Data Scientists vs Statisticians

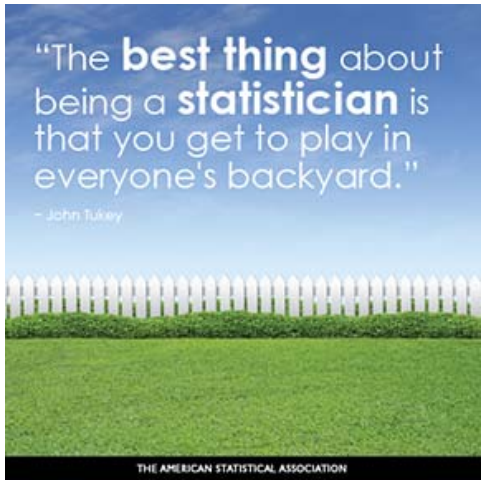
Data Scientist ≠ (clinical trials) Statistician



Truths about (most) biostatisticians

- Most PhD statisticians train, on average, 4~6 years post-baccalaureate.
- Some get post-doc training.
- Love seeing our skills and knowledge put to practical use.



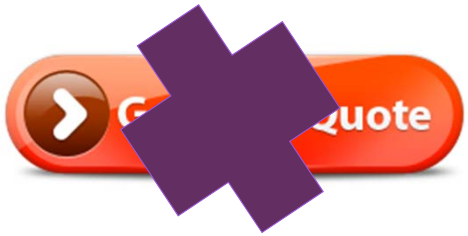


- Don't necessarily know everything and anything about statistics (e.g., not all of us are Bayesians or econometricians) – but very adaptable/flexible in application of the statistical skills and knowledge.
- Do more than just give you the required N and calculate *p*-values for the studies.
- Are your peers / colleagues.

(Clinical Trials) Statistical Collaboration

Do NOT think that:

- Anyone with just some statistics courses will do.
- You only need a statistician at the beginning (to give you the necessary sample size) and at the end (to do the analyses).
- You don't need to include them as authors, especially if you pay them.



Do consider to:

- Find a statistician sooner than later - http://www.youtube.com/watch?v=Hz1fyhVOjr4
- Find a statistician who is familiar with (or at least with interest to learn about) your clinical area.
- Find a statistician who has clinical trials experiences – not just design and/or analysis, but in the actual implementation (like finding an architect who has actually "built" a structure).

Statistical collaborator

- Throughout the life of the project / end-product focused
- Assist PI with hypothesis development/study design
- Consult on database design
- Check that necessary variables are present, etc.
- Check that unnecessary variables are not included
- Statistician can be your advocate – stress importance of data integrity
- Perform Interim analyses (if necessary)
- Perform Final analyses
- Assist in manuscript preparation

Where to Find a Clinical Trials Statistician?

- Ask your mentors and colleagues at your institution.
- Inquire with biostatistics departments or groups (e.g., CTSA) at your institution.
- Browse through published papers of clinical trials designs and/or results.
- Contact someone who has taught you a clinical trials course, like instructors at the NINDS-sponsored Clinical Trials Methodology Course.
- Ask NINDS.
- Ask NDMC or other DCCs.

How to Work with a Clinical Trial Statistician?

- In-person meeting is the best, at least at the beginning.
- Agree early on about expectations – role in the grant (e.g., co-PI or co-I), order of authorship in the papers, funding/financial issues, timeline, etc.
- Keep the ball moving… You ask for input, you get it, and then, not get back in touch for months is problematic (yes, it's a two-way street).
- Communicate regularly!
  - Ask questions until you understand the design/methods.
  - Keep the statistician in the loop on all aspects of the project.
  - Include them in the interpretation of analysis results.
- Remember, he/she is on your team as a collaborator.

Collaborator: involvement throughout the project.

- **Ideal Collaborations**
  - ∗ Hypothesis Development/Grant writing
  - ∗ Database setup
  - ∗ Data Analysis
  - ∗ Manuscript Preparation
  - Teacher (mutual)
- **Non-Ideal Collaborations**
  - Helper: technician; responds to questions. Accountability problems.
  - Leader: lack of substantive expertise.
  - Data-Blesser: curb-side advice.
  - Archaeologist: my other statistician stopped returning my e-mails…

Reimbursement

- You get what you pay for….
  - 1% effort < 30 min per week
  - 5% effort = 2 hours per week (104 hours in a Year)
- Depends on the level of input:
  - Reviewing protocol and CRFs
  - Statistical Analysis Plan
  - oversight of data management
  - Statistical Reports (to NIH/DSMB/PI/IRB)
  - Dealing with missing data (tracking it down)
  - Manipulating and Merging Datasets (Cleaning Up erroneous data/visits)
  - Drafting Results for Manuscript & Presentations
- Don't forget to budget for Data Management Team (RedCAP)

Some Random Statistical Issues in a Nutshell

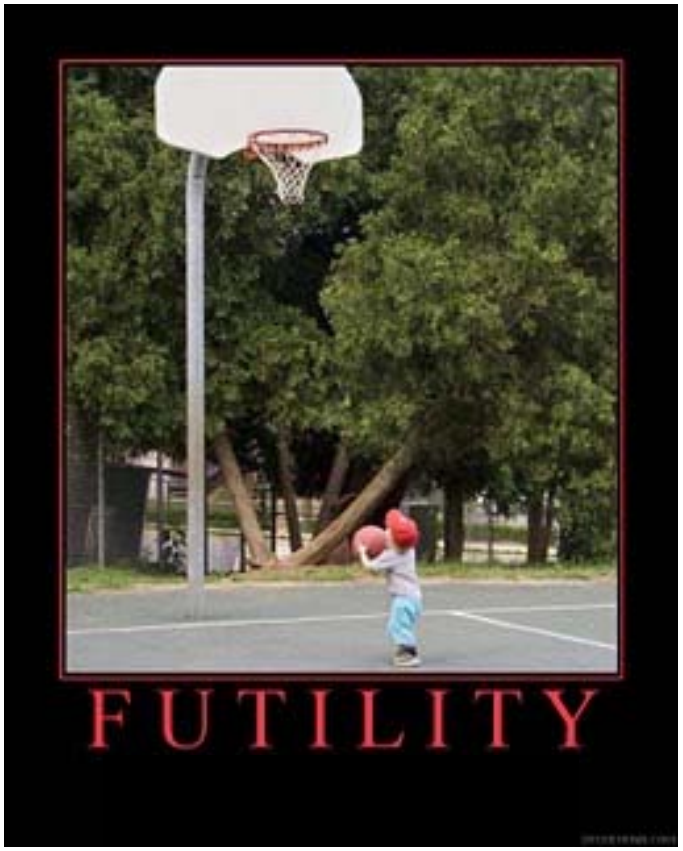
- Study designs
- Sample size calculations
- P-values vs alpha levels
- Grant writing and budgeting

Study Designs

Adaptive Designs (ADs)

- Purpose - often useful for Phase II trials when there're still many uncertainties about the intervention – best for exploratory/phase II studies.
- Adaptive Designs ≠ smaller sample size, nor is it necessarily efficient.
- Frequent looks at the data may be vulnerable to unblinding, biases, etc.
- Implementation can be a real 
- Use gingerly for Phase III trials – don't make it so complicated such that it makes the study results difficult to interpret.

Futility Designs

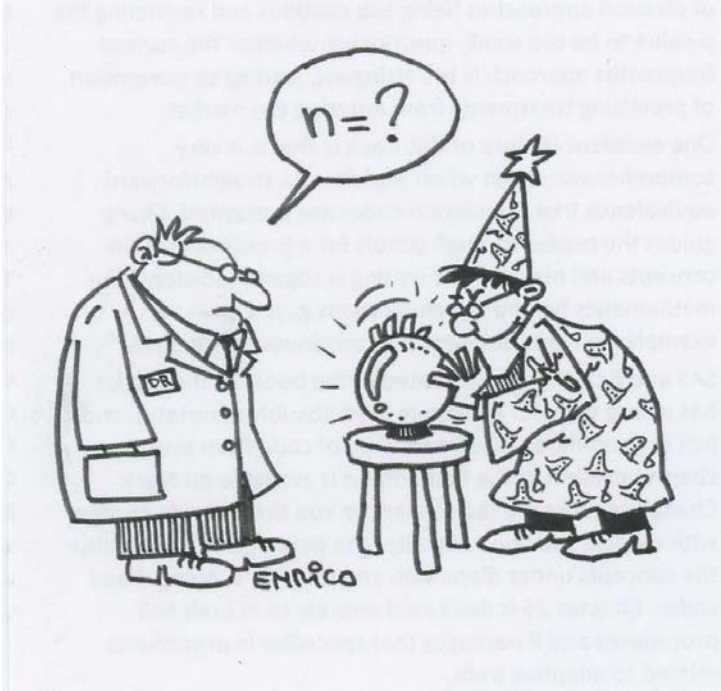


- Purpose – to ascertain whether a treatment is worth moving forward to a Phase III assessment for its effectiveness, i.e., to rule out a complete dud.
- Futility designs should be for an exploratory, Phase II stage of a drug/treatment development.
- Not to be confused with "futility analysis" in a Phase III trial (or even in a Phase II trial).

Non-Inferiority Designs

- Purpose – to ascertain whether a new treatment is as effective as (or no worse than) the currently available treatment.
- Must have an active control (with or without a placebo control).
- Usually a very large Phase III stage trial.
- Must define and quantify "margin of non-inferiority" – NOT the same as MCID.
- Analyses are often based on confidence intervals.

Sample Size Estimation



Why is "Power/Sample Size" important?

- Provides assurance that the study has a reasonable probability of being conclusive

- Bad strategy to "figure out the analysis later"
  - "Any data" is NOT BETTER than "No Data"!
  - It's Worse if can't detect an association that truly exists

First things first … What your Statistician Will Ask you

- What's the research question?
- Experimental Design
- What are you measuring? Data Type not the Construct
  - "Apoptosis"
  - "Functional Independence" (mRS ranges from 0 to 6),
  - "Parkinson Disease Progression" (UPDRS change)
- When are you measuring? Baseline, week 12, week 52, etc.

- What are you comparing (What is your question)?
  - Mean difference between groups (HOW MANY GROUPS?)
  - % with Rating Scale>3 (Higher after treatment?)
  - Time to Tumor Recurrence (Longer after Exposure?)
- Estimates from other studies (mean, SD, proportion).

Before asking about sample size ….**… be prepared to talk about …

- Level of significance alpha (set)
- Power** (80%-90%)
- Minimum Scientifically Important Difference**
- Expected variability in response
  - based on relevant clinical literature
  - Better yet, a range of plausible values
  - what's the smallest difference which will change practice?
  - If the sample size proves to make the trial not feasible, there's room for compromise.
- Experimental Design
- Controls (Can you make use of historical controls?, Can subjects serve as their own control?
- Are there multiple questions which can be answered in the same design?
- Is a hypothesis test the best way to achieve your goal? Dose-finding, Selection
- Logistics (recruitment, drop-outs)

Statisticians Need to know…

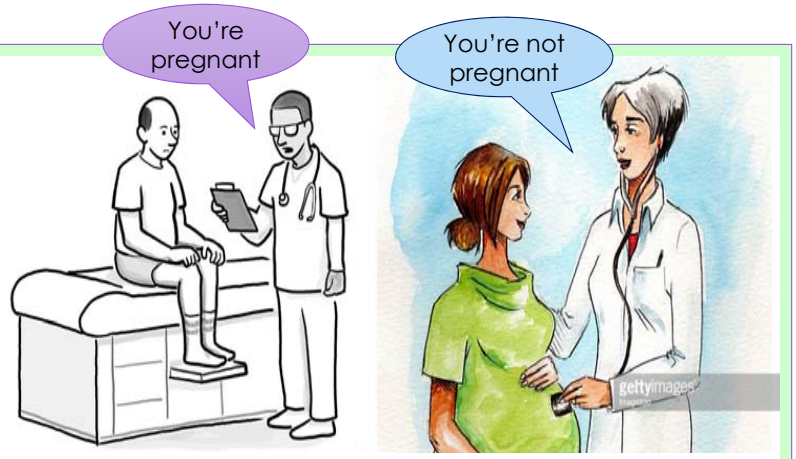
- Primary scientific hypothesis.
- Study design.
- Primary outcome measure and its statistical characteristics under the H_0 (e.g., distribution, mean, sd, etc), aka control group's presumed data.
- MCID - minimum clinical important difference, i.e., ***effect size***, you want to see that could <u>lead to changing clinical practice</u>.

NOTE: effect size is not a statistical issue.

Statisticians Need to know…

- **Type I (α)** and **Type II (β)** error *probabilities* – know their interpretation under your hypothesis setting (e.g., superiority, non-inferiority, futility), and the consequences of committing these errors.
  - α = Pr [reject H_0 | H_0 is true]
  - β = Pr [fail to reject H_0 | H_A is true]
- Smaller the values of α and β, the larger the sample size.

In a superiority study setting:

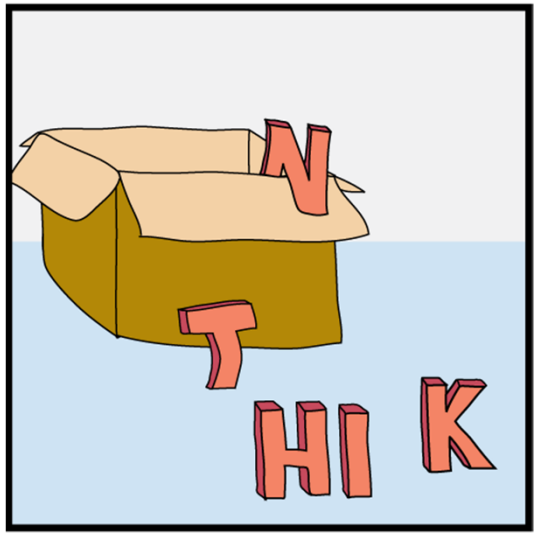


α error = **false positive** error

β error = **false negative** error

Choice of the Alpha Level

Does α have to be 0.05 (2-sided) or 0.025 (1-sided)? (NOTE: β can generally range from 0.1 to 0.2)?



- Treatment that is not expensive with few side effects…
- Treatment for a condition that has no remedy or cure…
- Treatment to be tested in a Phase II stage, using futility design…
- Treatment that is very promising but moderately toxic and expensive…

Note: These same thought process can/should be applied to the choice of MCID.

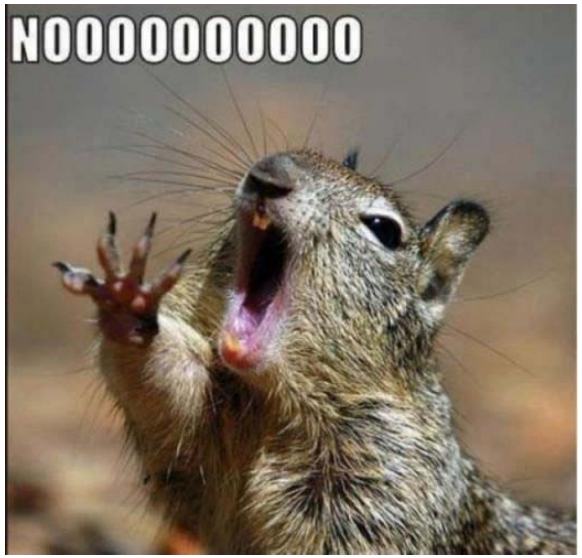
P-values

P-values

- Definition of ***p***-value: The probability of observing treatment effect (e.g., group difference in mean response) as extreme or more extreme (away from the H_0) if the H_0 is true. Hence, the smaller the ***p***-value, the more extreme or rare the observed data are, given the H_0 to be true.
- ***p*-values are premised on the condition specified in the null hypothesis, as is the α value**

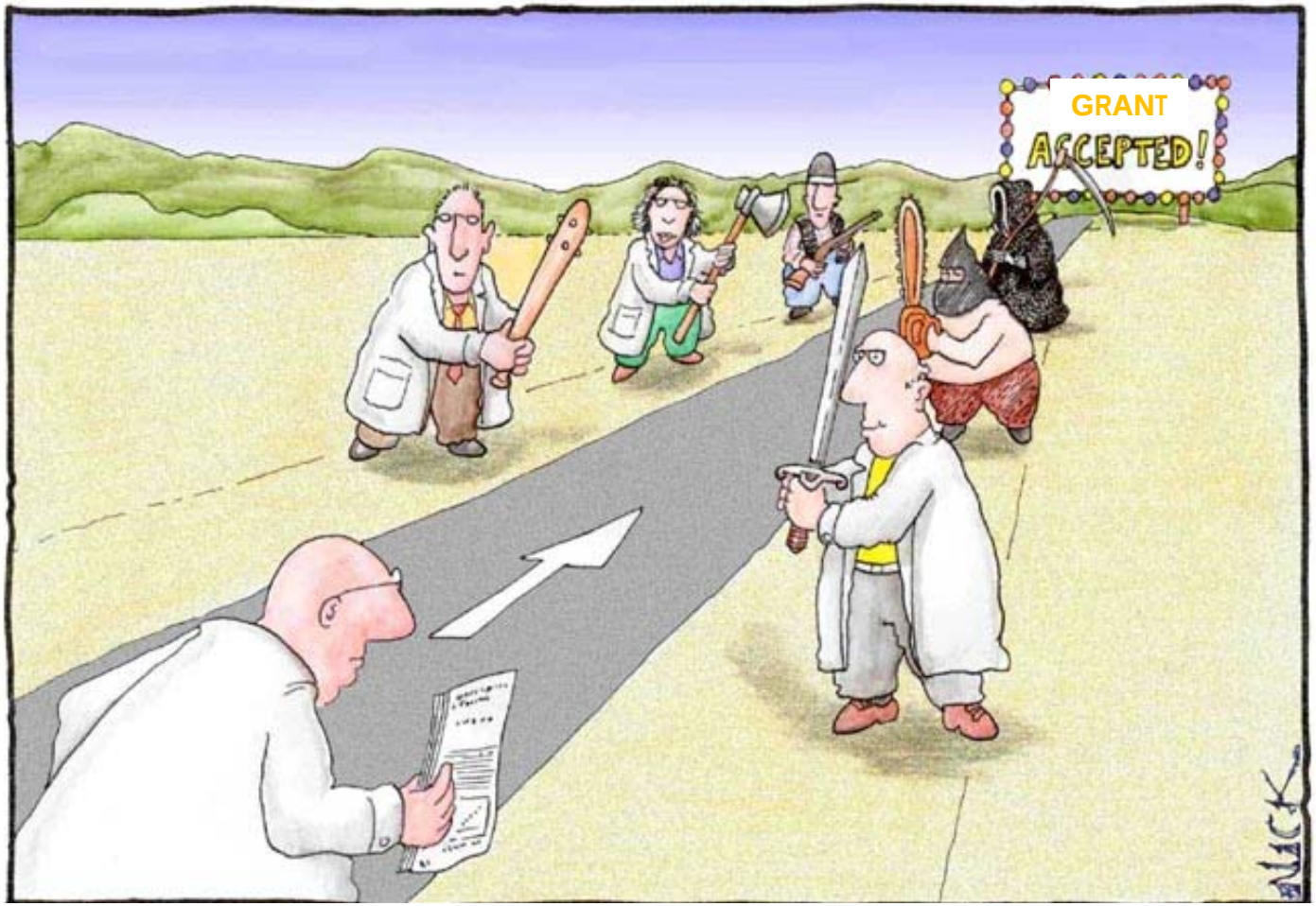
- The ***p***-value obtained from the data is judged against the α. (NOTE: Remember that p-values and α are not the same thing.)
- If the p-value < pre-specified α, then the data suggest that the study result is so rare under the H_0 that lead us to question the veracity of condition specified in the null hypothesis; hence, we reject the H_0.

P-values



- Suppose for a study with a pre-specified α =0.05, the result was p=0.09, i.e., could not reject H_0.
- Note that "failure to reject H_0" does not prove that the treatment groups are equal with respect to the outcome, i.e., you don't "accept H_0".
- Don't say, "There was no difference in the treatment groups…", unless your hypotheses were set up to prove this (e.g., equivalence design).
- Put the research hypothesis that you want to prove in the alternative.

Grant Writing with a Statistician



Grant Writing and Budgeting (for NDMC)

- **DON'T procrastinate!**
- If you are relatively new to grant writing, strongly recommend having an experienced mentor. StrokeNet (NCC, NDMC, WGs) also can help.
- Get the draft of the near-final Specific Aims and Research Strategy sections ASAP to the statistician – tough for statistician to write his/her section in a vacuum.
- FYI - Items included in the NDMC budget for StrokeNet trials include:
  - Personnel Effort (Statisticians, DMs, PMs, Programmers, Neuroimaging Managers);
  - Travel;
  - Supplies; and
  - **On-Site Monitoring costs (a big ticket item).**
- NDMC moving more towards remote monitoring to save on travel costs, and to central monitoring (by DMs and statisticians) to reduce on-site monitoring time.

Thank you for your attention!