NIH StrokeNet Professional Development Seminar – November 2024

Statistical Analysis – Collaborating with Data Mgt & Statistical Teams – Experts in Research

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Conflict of Interest / Disclaimer

- Contact PI of the StrokeNet National Data Management Center (NDMC) in Charleston, SC.
- This presentation contains my personal biases and opinions.

StrokeNet NDMC in Charleston, SC

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College of Medicine (COM)

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* Whence, the database software name, WebDCU™.

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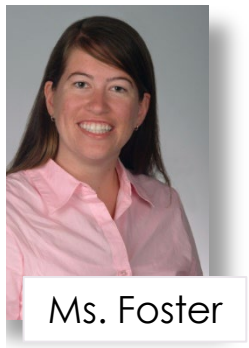
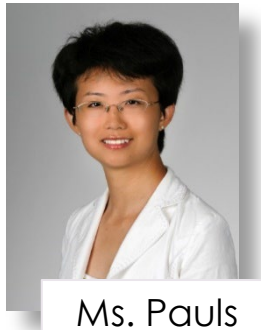


Ms. Foster



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Ms. Teklehaimanot

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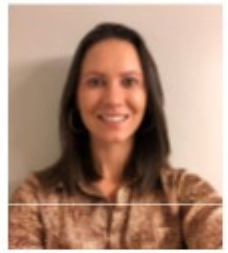

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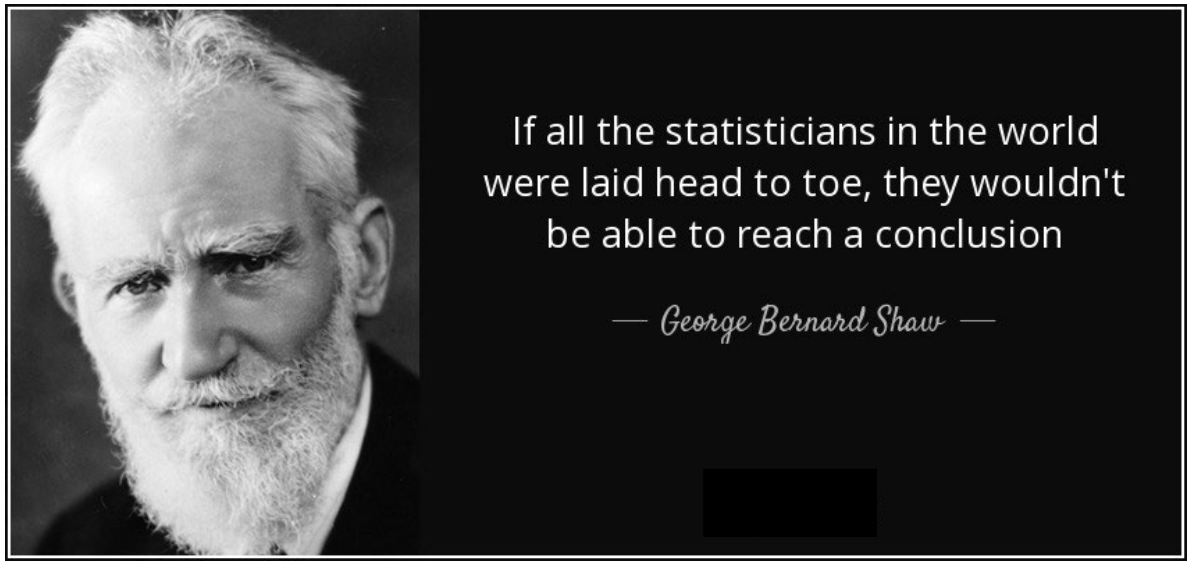
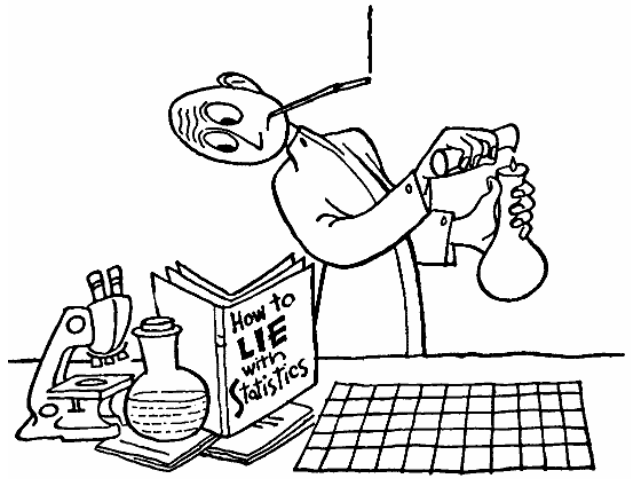
World's View of Statisticians





Traditionally

Past Decade


THE WALL STREET JOURNAL.

EDUCATION

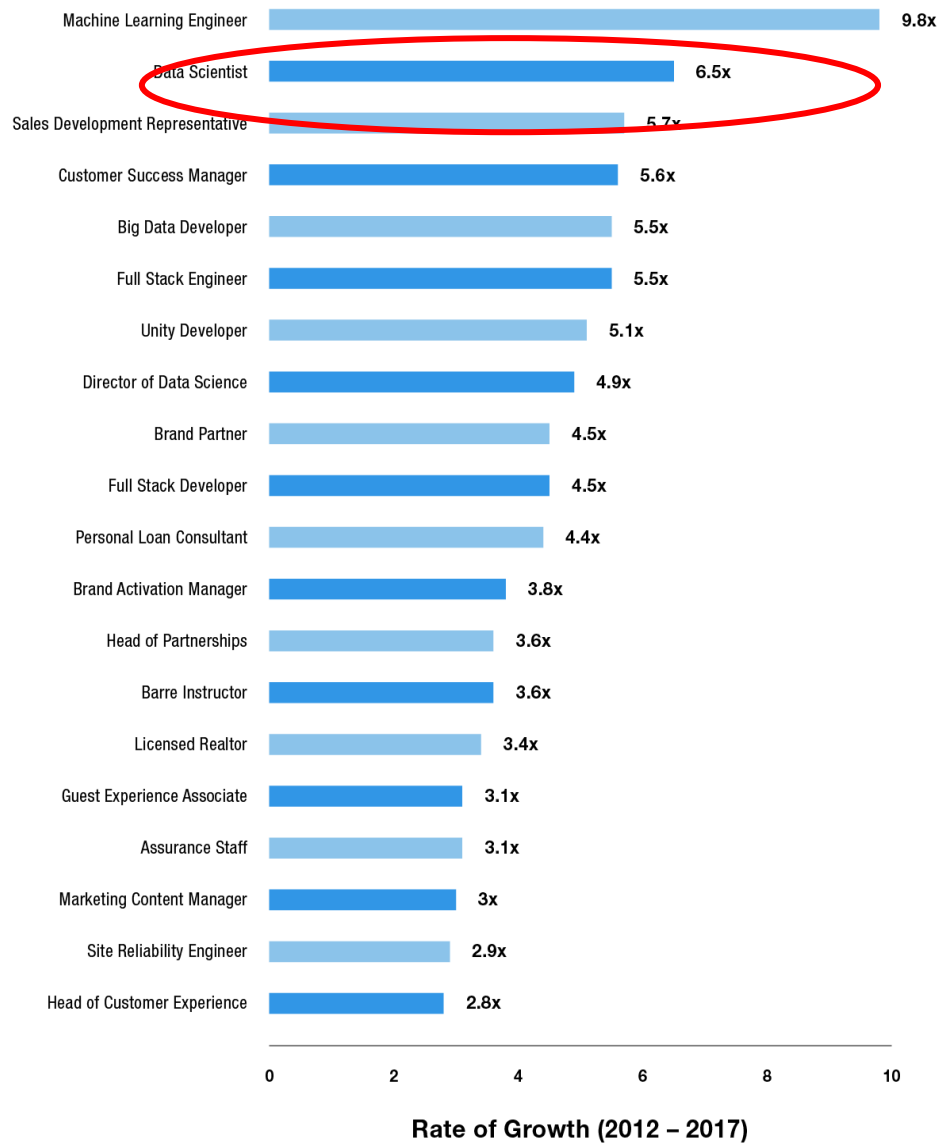
UC Berkeley's Fastest-Growing Class Is Data Science 101

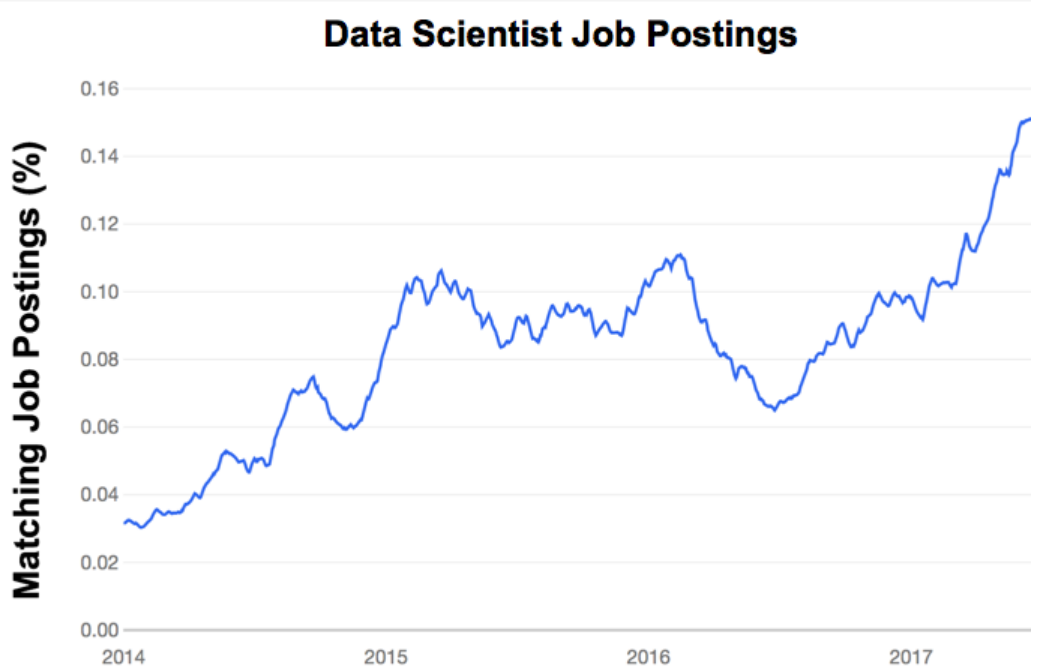
The university has created a division to study the science of mining the tidal wave of digital information that floods our lives. More than 300 universities offer some type of data major at a time when companies like Google can't hire enough specialists

11/19/2018

"Sexiest Job of the 21st Century"

Top 20 Emerging Jobs





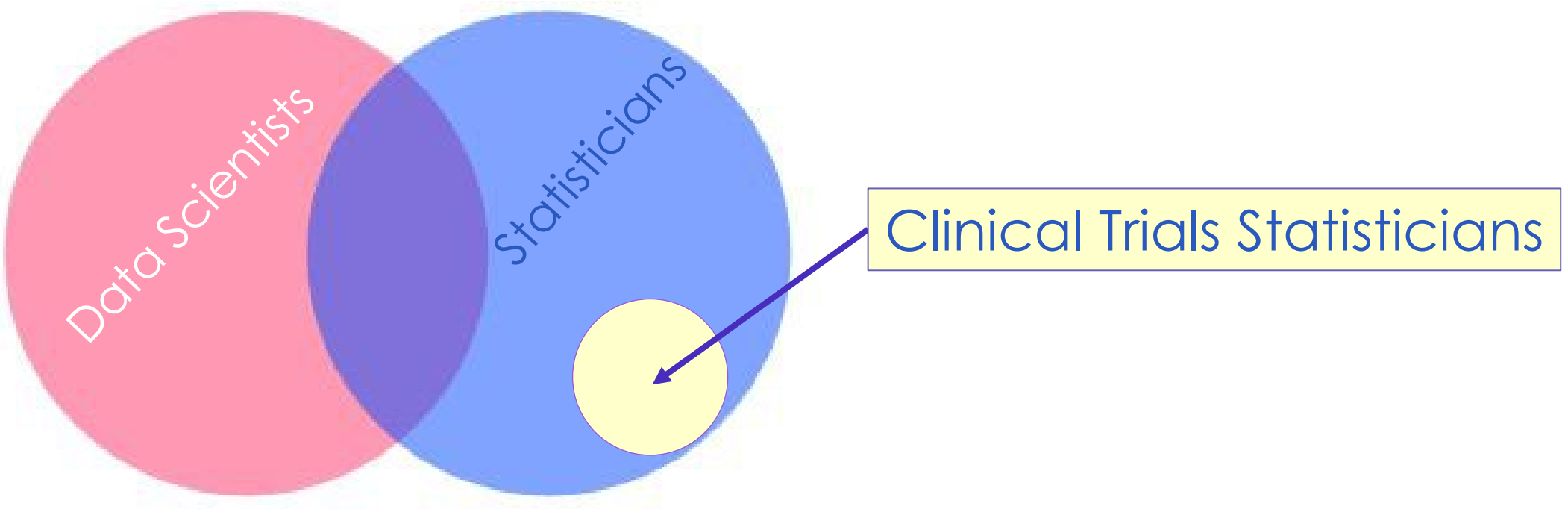
People also ask

What jobs will be in demand in 2024?

What is the hottest job in 2024?

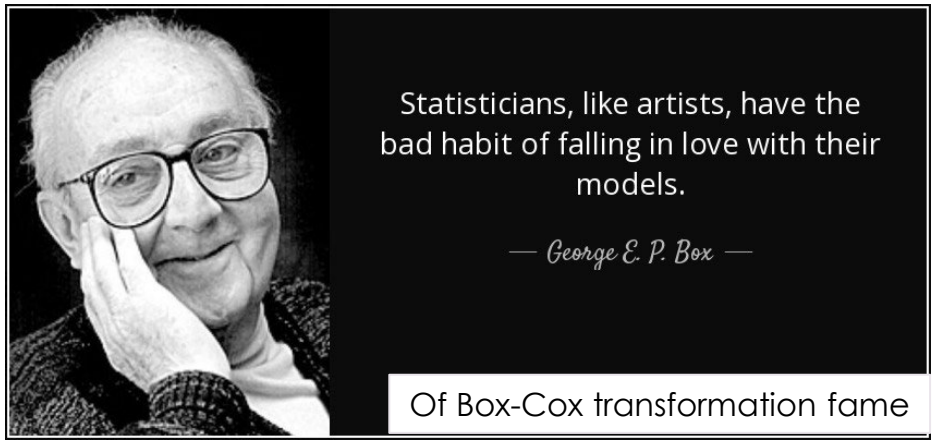
The best jobs for 2024 include positions such as Data Scientist, AI and ML Engineer, Healthcare Professional, Digital Marketer, Cyber Security Analyst, Human Resources Manager, Full-Stack Developer, Cloud Developer, Project Manager, and Digital Content Creator. Jan 30, 2024

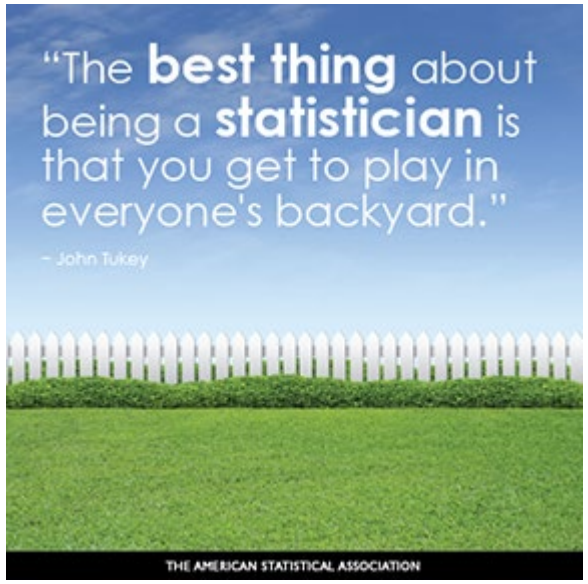
Data Scientists multidisciplinary field which includes statistics



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 know everything 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

(Less ideal) Consultant:

- statistician at the beginning (to give you the necessary sample size) and at the end (to do the analyses).
- Curbside advice
- In name only.
- Not integrated into the team

(Ideal) Collaborator:

- 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 on CRF, 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.
  - Data-Blesser: curb-side advice.
  - Archaeologist: analysis only, no design set-up

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, webDCU)

2016

NIH policy to enhance reproducibility of research through Rigor & Transparency

Reviewers required to pay attention.

Clinical Trial

- To determine if a treatment causes a response

Methods

Group comparisons may be affected by:

1. Sampling variation or chance
2. Inherent differences between the groups regarding *confounding variables*
3. Differences in the handling and evaluation of the groups during the course of the study
4. The intervention under study

Methods

Good experimental design will reduce, if not virtually eliminate, the effects of 1-3 above

1. Randomization
2. Blinding; use of objective outcomes; complete outcome ascertainment
3. Sample size (power)

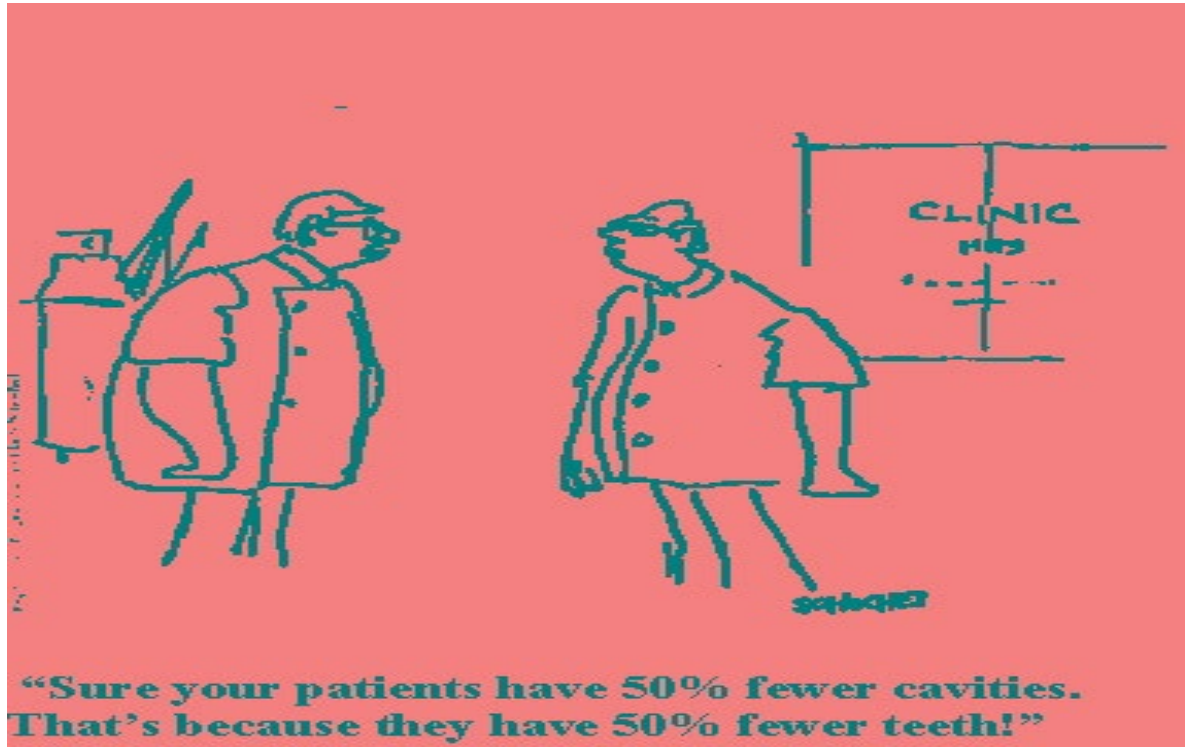
Was Treatment Assignment Randomized?

- Randomization
  - Participants have a known probability (not necessarily ½) of being allocated to any particular treatment group
  - Allocation is determined by a *random* mechanism (coin flip)
  - Simple randomization may, by chance result in imbalances in risk factors associated with outcome especially if the trial has a small to moderate sample size
  - Many novel adaptive randomization methods

Was Treatment Assignment Randomized?

- Nonrandomized trials tend to be overly optimistic with regard to the potential effectiveness of a treatment
  - Generally result in non-comparable groups
  - Bias in participant selection
  - Bias in treatment assignment
  - Bias in outcome assessment
  - Bias in follow-up, ancillary care/treatment

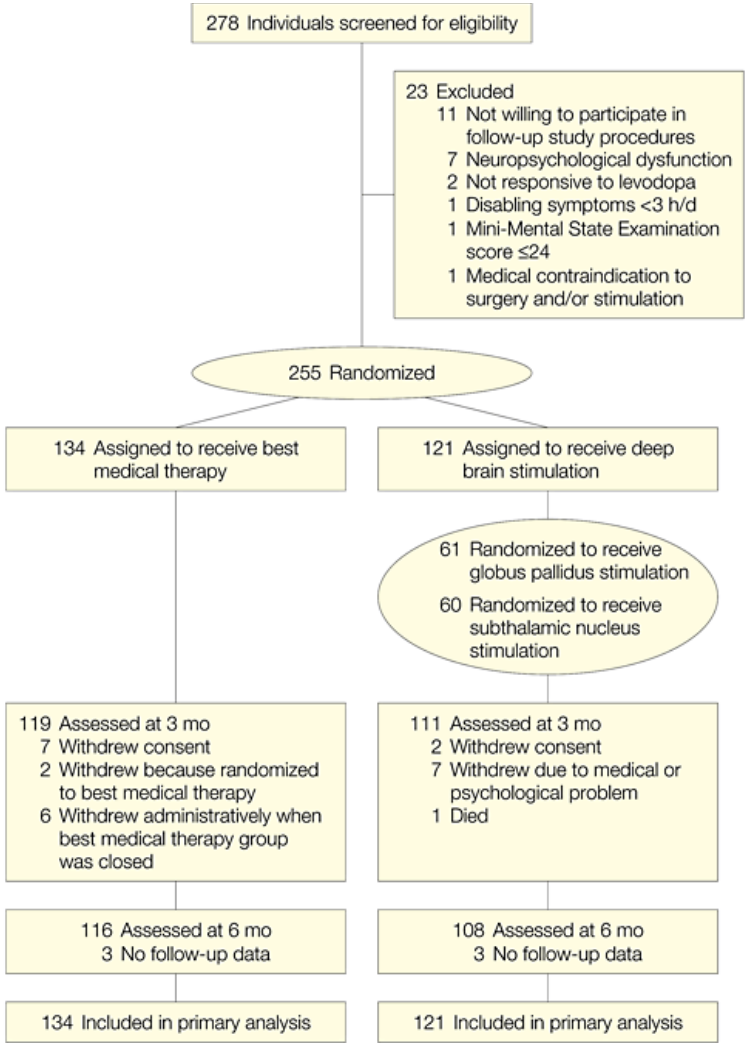
Selection Bias ….



Were All Participants Accounted for at Trial Conclusion?

- What percentage of participants failed to complete follow-up?
- Are reasons for dropout sufficiently documented?
  - Often related to prognosis
- Comparability of dropout rates and reasons among treatment groups

Patient Enrollment and Randomization Assignment



Weaver FM et al. JAMA 2009; 301:63-73

JAMA

Excellent health statistics - smokers are less likely to die of age related illnesses.'

Were all the participants accounted for?

Were All Participants Analyzed in the Groups to Which They Were Randomized?

- Intention-to-treat principle
  - Comparison of treatment policies
    - Issue of protocol/treatment noncompliance
  - Preservation of the benefits of randomization

- Safety Analysis Sample
  - If didn't receive treatment, then can't be harmed by it.

- Per Protocol
  - Sensitivity analysis, early phase efficacy trials

Were All Participants Analyzed in the Groups to Which They Were Randomized?

"Excluding randomized participants or observed outcomes from analysis and subgrouping on the basis of outcome or response variables can lead to biased results of unknown magnitude or direction"

Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials, 3rd Edition. New York: Springer-Verlag, 1998, p. 284.

Were Participants, Clinicians, and Other Study Personnel Kept Blind to Treatment Assignments?

- Need for double-blind
  - Subjectivity of evaluation of the response
  - Comparability of subject care
- Not always possible
  - Studies of surgery
  - Adverse events

Were Participants, Clinicians, and Other Study Personnel Kept Blind to Treatment Assignments?

- Documentation of efforts to preserve blinding
  - Similarity of interventions
  - Randomization/enrollment process
- Partially blinded trials
  - Blinding of evaluators (Assessor not present at the time of treatment)
  - Independent adjudicators
  - Separate evaluators for efficacy and safety

Were Participant Follow-Up and Ancillary Care Consistent Over Time and Across Treatment Groups?

- Aided greatly by randomization and blinding
- Differences can occur POST randomization
- Adherence to treatment (CRF)
- If possible, the use of co-interventions should be minimized during the study
- Can only determine this for measured characteristics (CRF design)
- Often shown in the first table of the Results section

Results

- Estimated magnitude of the treatment effect
  - Differences between means (averages)
  - Relative risk [p_1 / p_0]
  - Relative risk reduction [$1 - (p_1 / p_0)$]
  - Odds ratio [$\{p_1 / (1 - p_1)\} / \{p_0 / (1 - p_0)\}$]
  - Absolute risk reduction [$p_1 - p_0$]
  - Hazard ratio (similar to relative risk)

- Estimands framework to interpret treatment effect

Estimands & Intercurrent Events

- New terminology to describe old concepts
- Estimands ---”clarifying the exact research question being evaluated in a study, both to avoid misinterpretation and to ensure that study methods are aligned to the overall study objectives.”
- Intercurrent event—something that happens between randomization and outcome which impacts the interpretation of the treatment effect
  - Missing data, LTFU, treatment non-compliance, crossover, rescue therapy

- https://www.bmj.com/content/384/bmj-2023-076316

Study Protocol

- Operational definitions: Standard definitions of key variables used for research
- Standardized Data Measurement/ Collection/Use of Validated Outcomes (Reproducibility)
- Standardize procedures
- Changes to the protocol after the study starts should be minimized/documented.

Pre-specified Statistical Analysis Plan

- Avoid of Statistician Bias
- Sample Size/Power/Study Design should be in agreement.
- State error rates, approach to deal with multiplicity.
- Randomization plan
- Baseline comparisons
- Missing data
- Analysis Samples, ITT/Per Protocol
- Plans for Interim Analyses
- Pre-specify model building approach and baseline covariates/confounders to be adjusted
- Prioritization of outcomes
  - Primary vs. secondary vs. exploratory outcomes (Standard definitions)

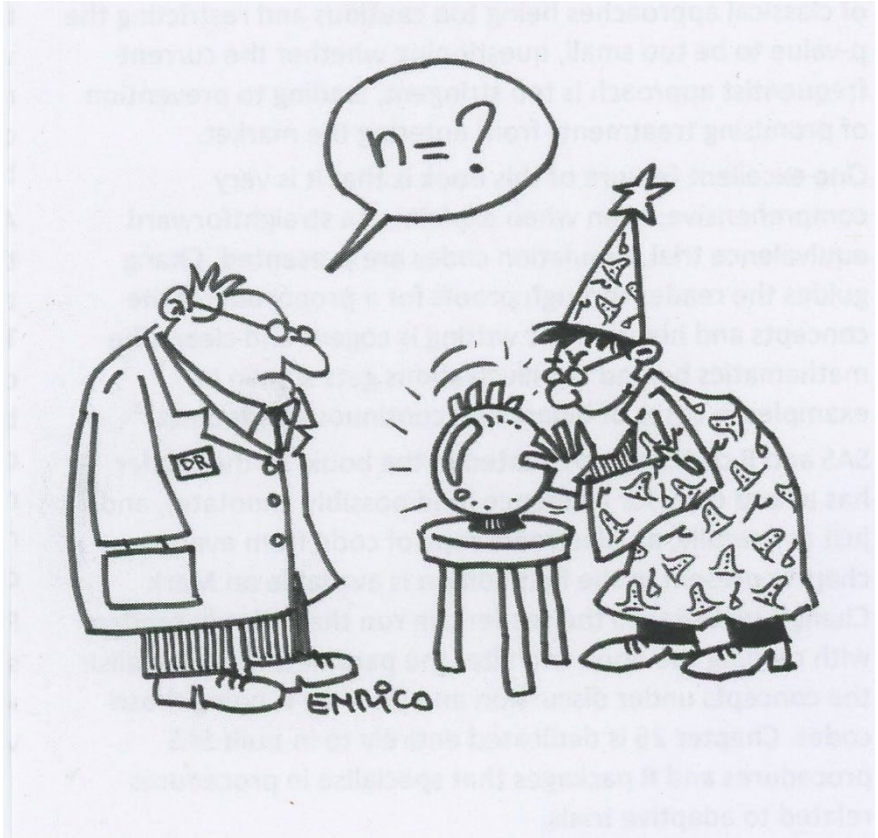
Adaptive Designs

Adaptive clinical trials are designed to be more flexible, efficient, and fast than traditional clinical trials. They **allow for changes to be made to the trial or its statistical procedures after it has started, based on preliminary data analysis**. Some examples of adaptive clinical trial designs include:

- **Sample size re-estimation**: The total sample size can be re-estimated at an interim point in the trial.
- **Allocation ratio changes**: The ratio of participants allocated to different interventions can be changed part way through the study.
- **Dynamic stopping decisions**: The trial can be stopped early based on interim data analysis.

doi: 10.4103/0253-7613.68417

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…

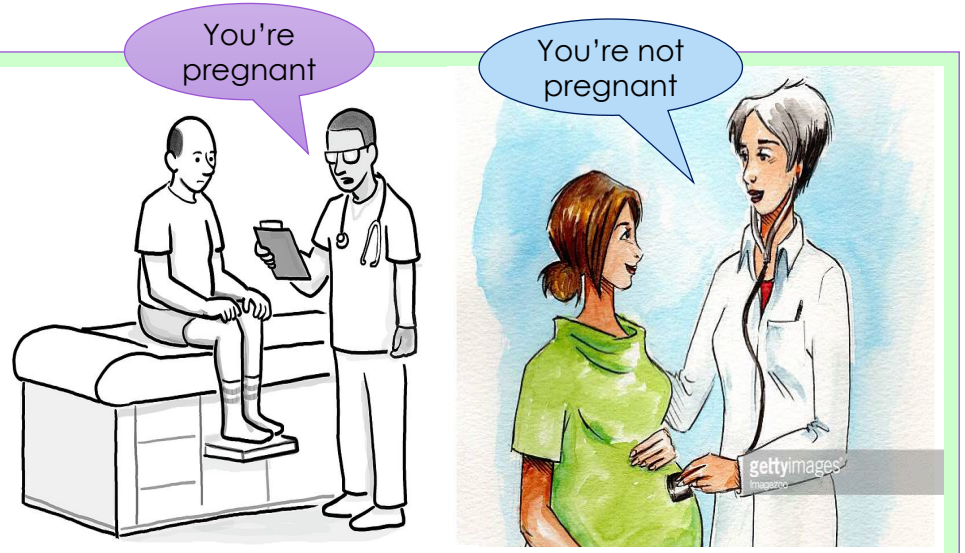
- Primary scientific hypothesis.
- Study design.
- Primary outcome measure and its statistical characteristics under the H_0 (e.g., distribution, mean, sd, etc), aka control group's presumed data.
- MCID - minimum clinical important difference, i.e., *effect size,* you want to see that could lead to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

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:

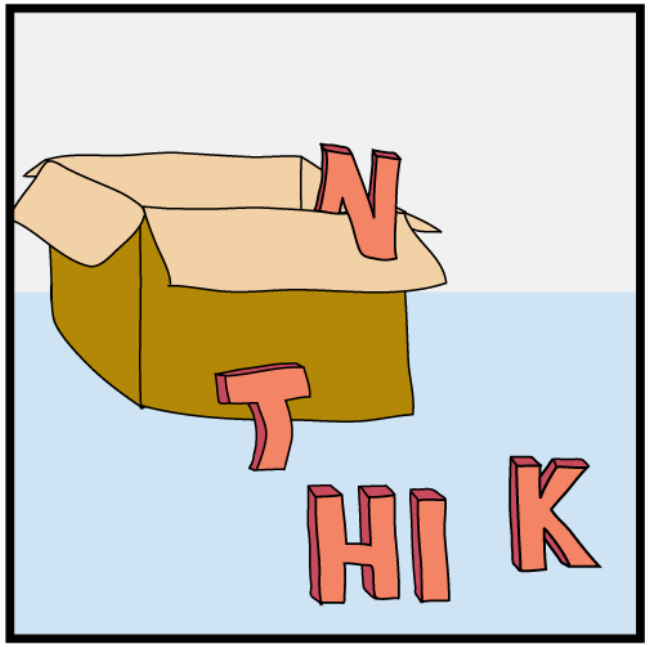


α error = **false positive** error

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

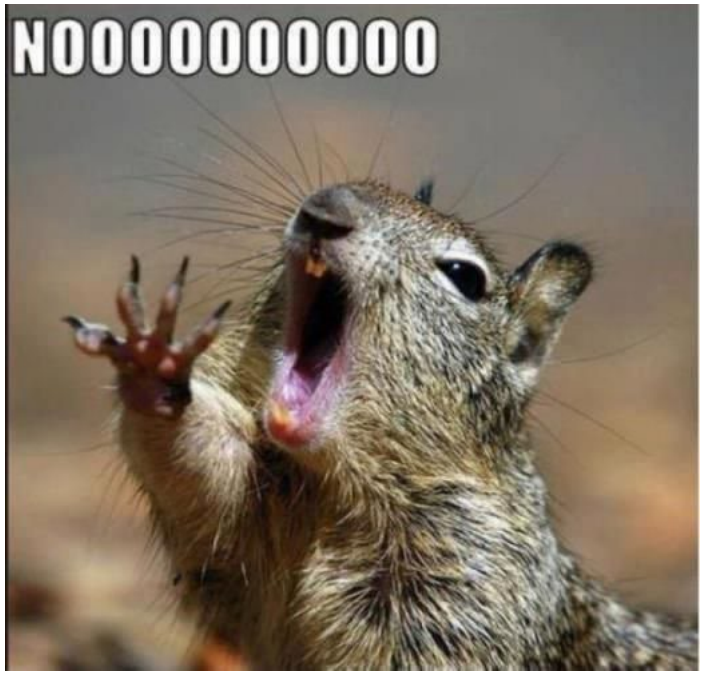

Researchers
and the Holy Grail
P<0.0
5
© 1974 National Film Trustee Company Limited. All Rights Reserved. Python (Monty) Pictures, Ltd.
© 2006 Layout and Design Sony Pictures Home Entertainment Inc. All Rights Reserved.

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

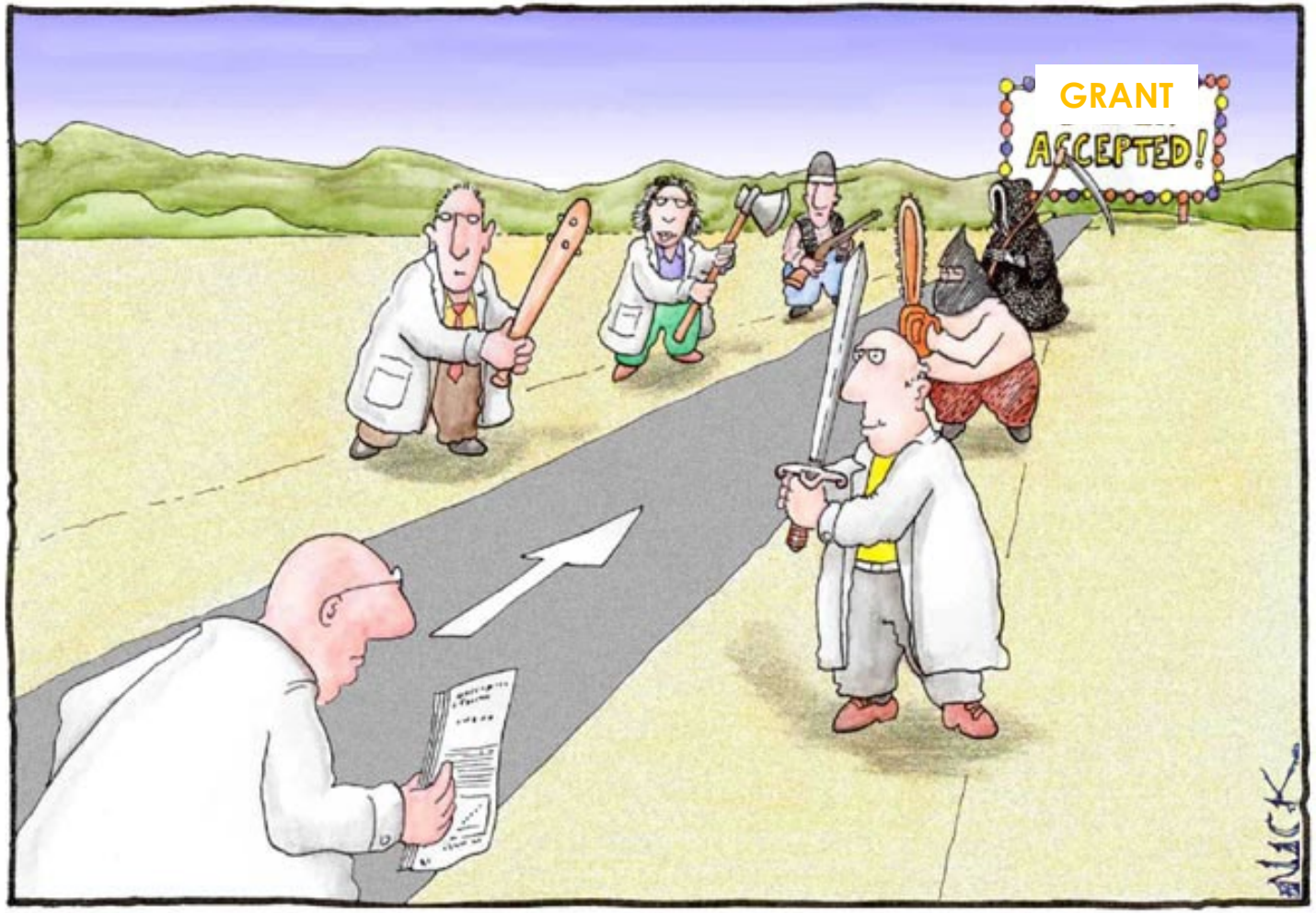


- Suppose for a study with a pre-specified α =0.05, the result was p=0.09, i.e., could not reject H_0.
- Note that "failure to reject H_0" does not prove that the treatment groups are equal with respect to the outcome, i.e., you don't "accept H_0".
- Don't say, "There was no difference in the treatment 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.

Bayesian probabilities

- Old idea/new method
- Bayesian probability is more direct answer for the research question:
  - What is the probability treatment is better than control
  - The "answer" or calculation can require more complex math (computers, computationally intensive)
  - Differences in approach (prior assumptions) and the need to control error rates have led to a lot of statistical bickering/delayed uptake

Grant Writing with a Statistician



Most scientists regarded the new streamlined peer-review process as "quite an improvement."

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.