NIH StrokeNet Professional Development Seminar – Dec 7, 2017

When and How to Consult with a Statistician… (and a bit more)

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Conflict of Interest / Disclaimer

- I have been an applied biostatistician for almost 30 years, with majority of time spent in clinical trials for stroke with funding from the NIH.
- This presentation contains my personal biases and opinions.
- I am a Co-PI of the StrokeNet National Data Management Center (NDMC).

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

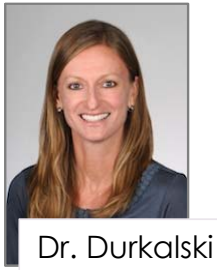

Dr. Yeatts


Dr. Palesch

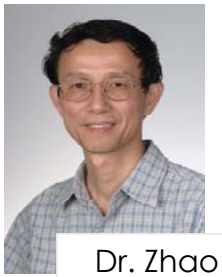

Dr. Martin


Dr. Meinzer

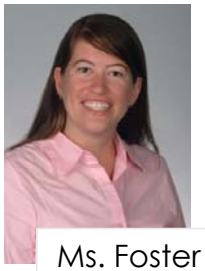

Dr. Elm

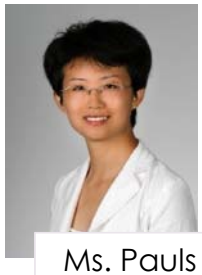

Dr. Durkalski


Dr. Ramakrishnan


Dr. Zhao


Ms. Arora


Ms. Foster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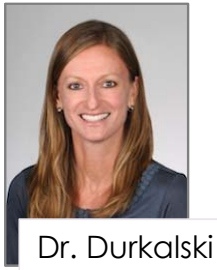
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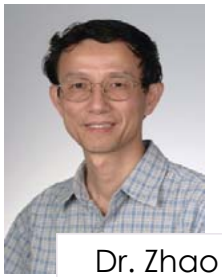
Dr. Zhao


Dr. ??


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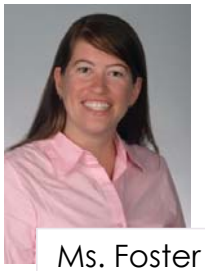
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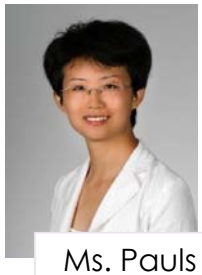
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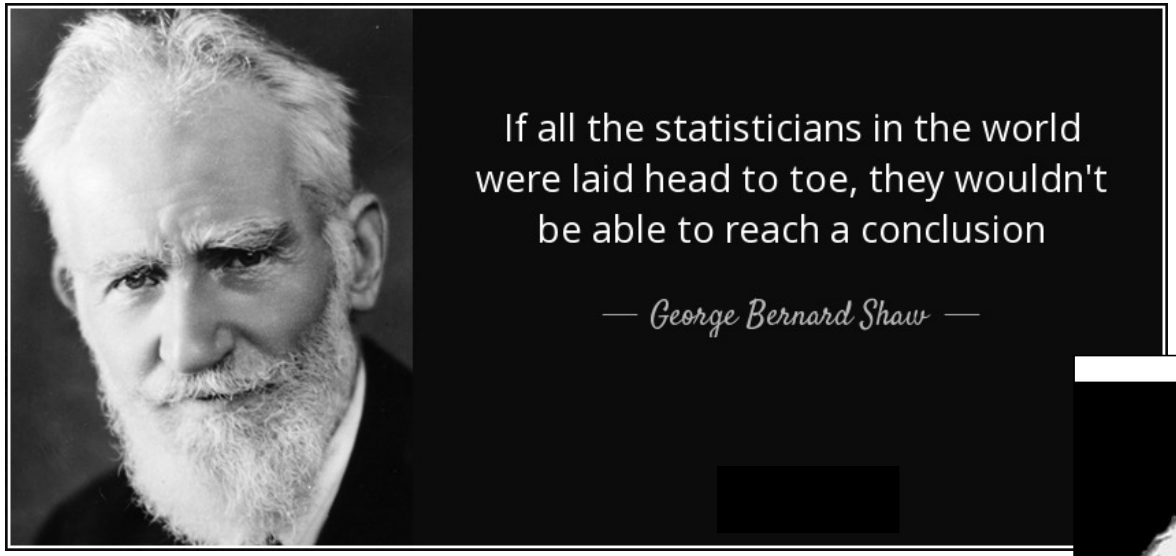
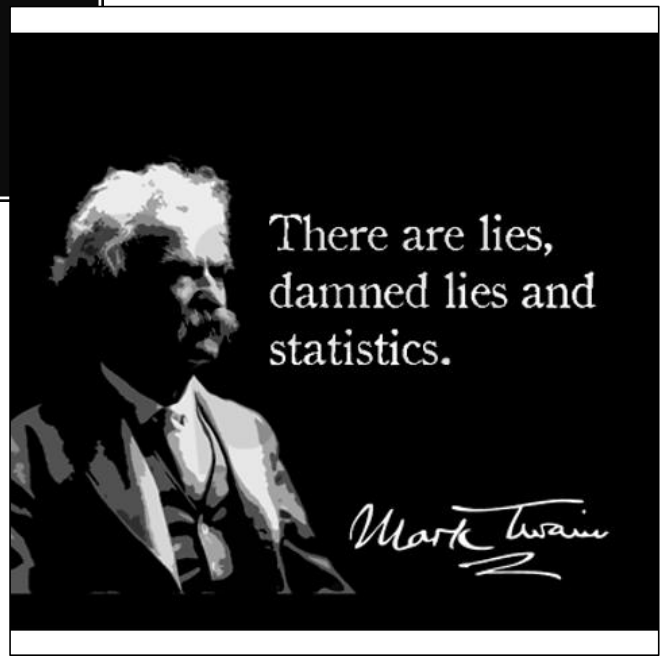

If all the statisticians in the world were laid head to toe, they wouldn't be able to reach a conclusion
— George Bernard Shaw —


"When I grow up, I wanna be a statistician!" said no one ever.
someecards
user card


There are lies, damned lies and statistics.
Mark Twain

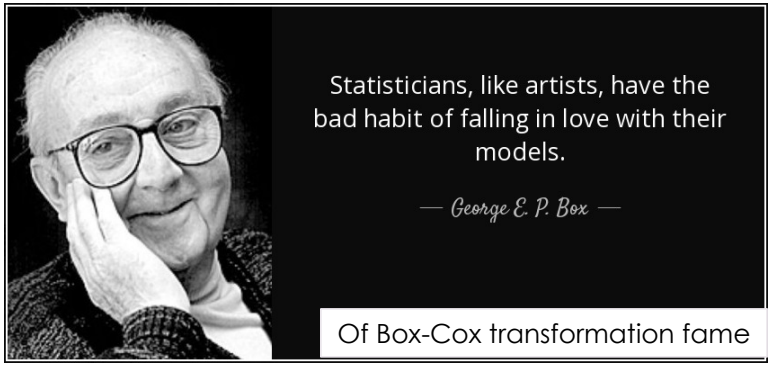
Myths about statisticians in biomedical research

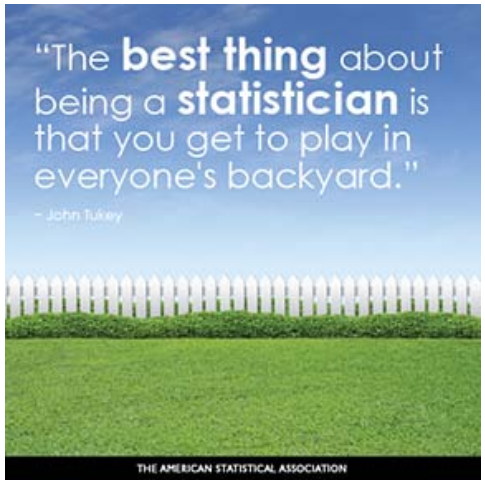
- Anyone with some statistics courses will do.
- Only need a statistician at the beginning (to give you the necessary sample size) and at the end (to do the analyses) of a study.
- A statistician is a service provider.

- You don't need to include them as authors, especially if you pay them.

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.

When and what to look for in a statistician for your clinical trial?

- "Time is Brain" mantra applies to timing of when to solicit statistical help – the sooner, the better.
- Preferably, find a statistician who is familiar with (or at least with interest to learn about) your clinical area –
- Definitely, find a statistician who has clinical trials experiences – not just design and/or analysis but in the actual implementation.*
- Neurologists (some who are closet statisticians) and Statisticians (some who are doctor-wanna-be's), who have **mutual respect** for each other's expertise, make an awesome study team.

*Analogous to finding an architect who has actually "built" a structure.

Where to find a clinical trial statistician?

- Ask your mentors and colleagues at your institution.
- Inquire with Biostatistics department or group (e.g., CTSA) at your institution.
- Browse through published papers of clinical trials designs and/or results.
- Contact someone who has taught you or colleagues a clinical trials course, like instructors at the NINDS-sponsored Clinical Trials Methodology Course.
- Ask NDMC or other DCCs.
- Not always easy to find one…

How to work with a clinical trial statistician?

- In person meeting is the best.
- Sending a written synopsis of the project, and other relevant references prior to the first meeting would be helpful.
- Agree early on about expectations – role in the grant (e.g., co-PI or co-I), order of authorship in the paper, 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 him/her in the loop on all aspects of the project.
  - Remember, he/she is on your team as a collaborator.

Some random statistical issues in a nutshell

- Adaptive designs
- Sample size calculations
- P-values
- Interpretation pitfalls
- Big data - quality vs quantity
- Grant writing and budgeting

Adaptive Designs

"This really is an innovative approach, but I'm afraid we can't consider it. It's never been done before."

- Still innovative?
- Often useful for phase II trials when there're still many uncertainties about the intervention.
- 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  !!

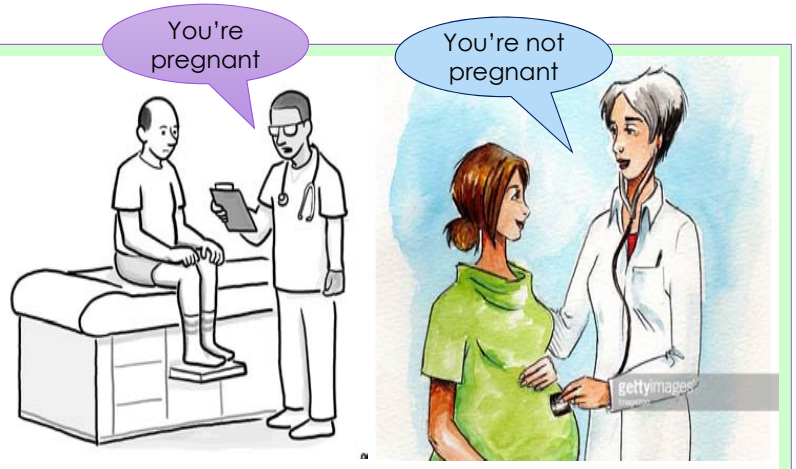
- Consider using it gingerly for phase III trials – don't make it so complicated such that it makes the study results difficult to interpret.
- Try to remember the KISS principle.

Sample Size Calculation - Need to know…

- Primary scientific hypothesis.
- Primary outcome measure and its statistical characteristics under the H_0 (e.g., distribution, mean, sd, etc).
- MCID - minimum clinical effect size you want to see that could lead to changing clinical practice. (This is implied in your H_A.)
- **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.
- Does α have to be 0.05? (NOTE: β can generally range from 0.1 to 0.2.)

Definition: $\alpha = \Pr(\text{reject } H_0 \mid H_0 \text{ true})$
$\beta = \Pr(\text{fail to reject } H_0 \mid H_A \text{ true})$

Superiority: $H_0: \mu_T = \mu_C$ vs $H_A: \mu_T > \mu_C$



False positive (**Type I** error)

False negative (**Type II** error)

P-value (a quick review)

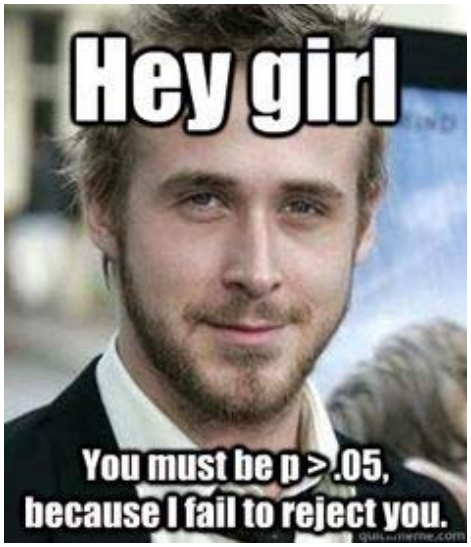
- Definition of ***p***-value: The probability of observing treatment effect (e.g., group difference in mean response) as extreme or more extreme (away from the H_0) if the H_0 is true. Hence, the smaller the ***p***- value, the more extreme or rare the observed data are, given the H_0 to be true. – i.e., **_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.)

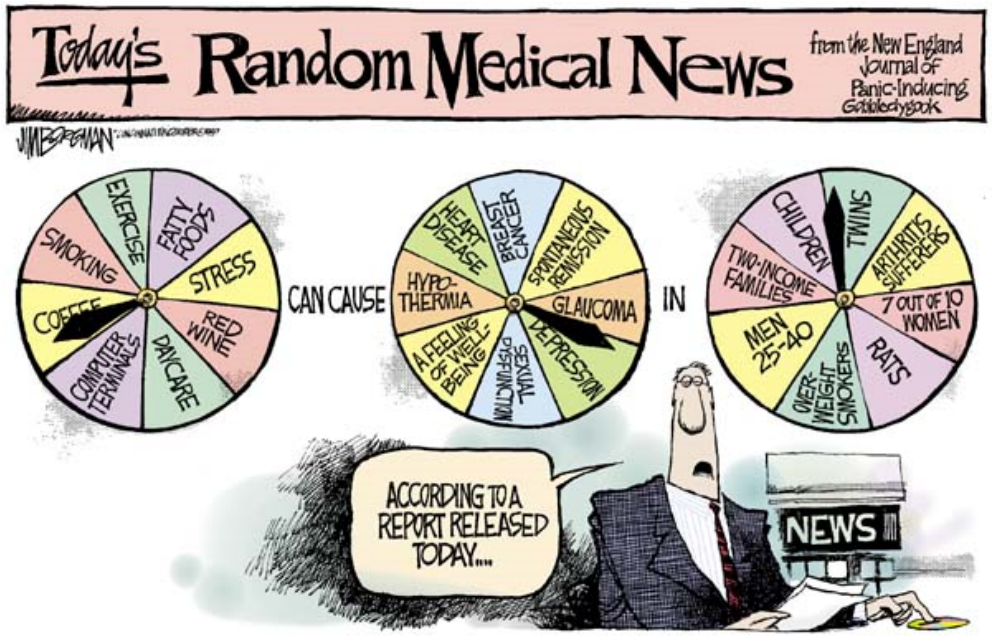
- Thus, if the ***p***-value < pre-specified α, then the data suggest that the study result is so rare under the H_0 that lead us to question the veracity of condition specified in the null hypothesis; hence, we reject the H_0.

P-value (continued)

- For a study with α =0.05 and p>0.05 (i.e., not significant), 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, like an equivalence design.
- Moral of the story: Put the research hypothesis that you want to prove in the alternative.



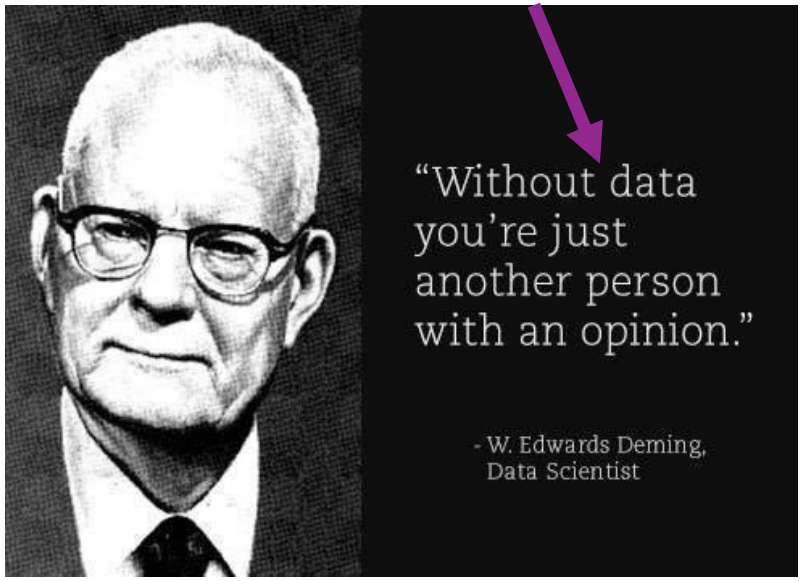
Interpretation Pitfalls



- Gives science (and statistics) a bad rap.
- Effect on subsequent randomized trials….?

Big Data – Quality vs Quantity

good quality



- Be careful about using EMR, survey and registry data without understanding how the data were collected.
- Be careful about "meta-analysis" using patient level data – make sure you are concatenating apples and apples – example of "baseline" NIHSS in IMS 3 vs MR CLEAN in the context of IV-tPA treatment timing.
- Also, you can show statistical significance if you have large enough N – be cautious of over-powered analysis that has no clinical value.

Grant Writing and Budgeting (related to stats)

- **DON'T procrastinate!**
- If you are relatively new to grant writing, strongly recommend having an experienced mentor. StrokeNet (NCC, NDMC, WGs) also can and will 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.**

- 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.

Finally, the biggest myth about statisticians …

Boring

Dull

Nerdy

Humorless

And that's "normal" for him…

Thank you for your attention!