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

Ms. Foster
Ms. Pauls
Ms. Underwood
Ms. Gottfried
Ms. Teklehaimanot
Traditionally (Pre-2015)

If all the statisticians in the world were laid head to toe, they wouldn’t be able to reach a conclusion

— George Bernard Shaw —
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.
Top 20 Emerging Jobs

Sexiest Job of the 21st Century

Data Scientist

Rate of Growth (2012 - 2017)

Data Scientist Job Postings

Matching Job Postings (%)
“Big” Data Scientists vs Statisticians

Data Scientist ≠ (clinical trials) Statistician

Clinical Trials Statisticians
Aside: Big Data – Quality vs Quantity

- Be careful about using survey and registry data without understanding how the data were collected and cleaned (or not).
- 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.
- You can show statistical significance if you have large enough N – be cautious of over-powered analysis that has no clinical value.

“Twitter and Facebook can’t predict the election, but they did predict what you’re going to have for lunch: a tuna salad sandwich. You’re having the wrong sandwich.”
(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](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).
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.
Some Random Statistical Issues in a Nutshell

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

My ex-girlfriend thinks I’m mean and my current one thinks I’m average…
Maybe you’ve set your bar too high?
Study Designs

DOUBLE BLIND STUDY...
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.

- Keep publication efforts in mind when designing ADs.
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
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** ($\alpha$) and **Type II** ($\beta$) error probabilities – know their interpretation under your hypothesis setting (e.g., superiority, non-inferiority, futility), and the consequences of committing these errors.
  
  - $\alpha = \Pr \{\text{reject } H_0 \mid H_0 \text{ is true}\}$
  - $\beta = \Pr \{\text{fail to reject } H_0 \mid H_A \text{ is true}\}$

• Smaller the values of $\alpha$ and $\beta$, the larger the sample size.

In a superiority study setting:

$\alpha$ error = **false positive** error

$\beta$ error = **false negative** error
Choice of the Alpha Level

Does $\alpha$ have to be 0.05 (2-sided) or 0.025 (1-sided)? (NOTE: $\beta$ 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 \( \alpha \) value

• The \( p \)-value obtained from the data is judged against the \( \alpha \). (NOTE: Remember that \( p \)-values and \( \alpha \) are not the same thing.)

• If the \( p \)-value < pre-specified \( \alpha \), 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 $\alpha =0.05$, 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.
"That's all folks!"

Thank you for your attention!