So you want to do research: we can fix that

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SO YOU WANT TO DO RESEARCH  
WE CAN FIX THAT

WHY ARE WE HERE?
"Sloppy science doesn’t do anyone any good."
- Emperor Mollusk

BIAS IN ALL ITS HIDEOUS FORMS

The first principle is that you must not fool yourself - and you are the easiest person to fool.

Richard Feynman  
Caltech commencement address, 1974
SELECTION BIAS

• Participants don’t reflect the population of interest
  • Inclusion/exclusion criteria must be well-defined
  • Volunteers always bring this bias
  • Psychology research: a plague of WEIRD people

• Allocation to groups is not uniform
  • Nonrandom allocation
  • Charter schools have better test scores!

PERFORMANCE BIAS

Dr. Smith has been practicing for 20 years, and is an expert at two approaches to the same peripheral nerve block.

Dr. Jones is a resident, and still learning one of those approaches.

They collaborate on a study comparing the two approaches for safety and efficacy, and Dr. Jones performs many of the procedures.

DETECTION BIAS

• Screening for complications tends to find them.
  • Problem of subclinical conditions: when did they arise?

• Study comparing inpatient vs. outpatient complications
  • Outpatients call in with any problems; inpatients get 3x daily screening by a trained anesthesiologist!
  • Found ‘em!

ATTRITION BIAS

Systematic differences in withdrawals

A study medication causes nausea in a subset of patients.

Affected patients withdraw.

Conclusion: no nausea!
REPORTING BIAS

• Authors compete to get published, and journals compete for readers/advertisers.
  • Positive results get published
  • Very tiny p-values get published
  • Surprising results get published
  • Neutral or negative results don’t, or they go into non-English journals
  • Whole studies or parts of studies (outcomes)
    • Well, that didn’t work out– let’s switch the primary outcome!

REPORTING BIAS IS...

A problem with the literature overall

A problem with certain studies

FUNNEL PLOTS

Should be symmetrical.

PROTOCOL REGISTRIES

I call shenanigans!
AN ASIDE

Most journals require registration of your protocol on clinicaltrials.gov prior to enrollment of any patients.

Bug your Principal Investigator attending about this. If they resist, refer them to Dr. Gerstein or me.

RECALL BIAS

“So, Mr. Alzheimer’s Patient, we’re doing a study to see whether aluminum exposure increases risk of developing Alzheimer’s. Were you ever exposed to aluminum?”

CONFIRMATION BIAS

IT DOESN’T MEAN WHAT YOU THINK IT MEANS

SIGNIFICANCE
SIGNIFICANCE

STATISTICAL

• $P$ value below a predefined level, usually 0.05

CLINICAL

• The difference between treatments matters in an important and predefined way

http://www.youtube.com/watch?v=ax0tDcFkPic

UMMM... WHAT?

A statistical $p$ value is the answer to this question:

If there really is no difference between groups, and my chosen statistical test is valid in this situation, what is the chance that samples of this size would find a difference as large or larger than the one I found?

NO, REALLY.

If there really isn’t a difference between groups, how often would I find a difference this big or bigger?

A small $p$ value lets you infer that it’s unlikely that the apparent difference between groups is due to random chance.
LET'S PROVE ... SOMETHING

Science does not prove positive statements.

It proceeds by disproving the null hypothesis: usually “no difference.”

“If there really is no difference between populations, I’d expect to see a result this strong or stronger, \( p \% \) of the time. That’s so unlikely that I can provisionally reject the notion, and behave as if there really is a difference.”

WHAT DO I DO NOW?

RESEARCH BASICS

IT'S JOURNAL CLUB IN REVERSE

- What did the authors set out to show?
- What sample did they use?
- Were their methods appropriate?
- Is the analysis valid?
- Problems with randomization? Blinding?
- Can I apply these findings with confidence?

RESEARCH QUESTION OR HYPOTHESIS

- Needs to be concise and specific
- Not just:
  - Which treatment lasts longer?
  - Which treatment better reduces pain?
- But:
  - Which treatment provides longer interval to first request for analgesic medication?
  - Which treatment leads to lowest opioid consumption?
TIPS ON TAILS

ONE-TAILED TESTS
Less common
• Hypothesize a priori that one treatment is better than the other
• \( H_A: \text{mean}_1 > \text{mean}_2 \)
• \( H_0: \text{mean}_1 \leq \text{mean}_2 \)

TWO-TAILED TESTS
Default
• Hypothesize that there is some difference
• \( H_A: \text{mean}_1 \neq \text{mean}_2 \)
• \( H_0: \text{mean}_1 = \text{mean}_2 \)

OUTCOMES
Much confusion here. What do you plan to measure?

• Primary outcome
  • One very specific main comparison

• Secondary outcomes
  • Some (2-5?) related findings that could also be interesting

AN EXAMPLE
Which type of block lasts longer?

• Primary outcome
  • Time to first request for analgesic meds (define start/stop points)

• Secondary outcomes
  • Time to first report of pain
  • Total opioids used
  • Time to first sensation
  • Time to first return of motor function
STUDY DESIGN

- Types of trials
- Superiority vs. equivalence studies
- Intention-to-treat vs. per-protocol analyses

TRIAL TYPES

- Observational studies
  - Case-control
  - Prospective cohort
  - Retrospective cohort
  - Cross-sectional
  - Ecological
  - How often does ___ happen?

TRIAL TYPES

Treatment studies
- Randomized Controlled Trial
  - Double-blind
  - Single-blind
  - Unblinded

BETTER? OR NOT WORSE?

Superiority trials
- Most common by far

Equivalence trials
- Require larger samples
SUPERIORITY TRIALS

So common they’re usually not even named this way.

Goal (usually):

• Difference between interventions is not equal to 0.

Remember: statistical ≠ clinical significance!

Failure to reject the null is not evidence that it is true.

EQUIVALENCE TRIALS

Goal:

• For some minimal clinically-significant difference between interventions $d_{C}$, the observed $d_{O}$ fits in: $-d_{C} < d_{O} < d_{C}$.

• English: the difference is too small to care about.

• Huge samples are required.

APPROACHES

Intention-to-treat

• Count everybody, regardless of whether they were compliant, finished the protocol, or were lost to followup

Per-protocol

• Count only those on whom you have good, “clean” data

SAMPLE

How many patients do I need?

• Power analysis: expected size of effect and variation

Who do I include?

• Inclusion criteria

Who do I not want?

• Exclusion criteria
RANDOMIZATION
Almost never gets enough attention
Common errors:
• Alternating assignments
• Tossing a coin
• Unconcealed randomization
• Blocked randomization with obvious treatment differences

DOIN’ IT RIGHT
Always conceal allocation until right now.
Use a series of allocation tickets in envelopes, or have a colleague maintain them
Use computerized randomization resources like random.org

BLINDING
Can be extremely tricky
If possible, blind patient, provider, and outcome assessor
Maybe statistician too… at least for a while!

STATISTICS
Not without help.
THE PROTOCOL

WHATCHA GONNA DO?

FIRST, I’M GONNA...

The protocol is the cookbook.
- Study question/hypothesis?
- Outcomes?
- Which patients?
- What procedures?
- How randomized?
- Analysis?

WHO CARES?

IRB
Protocol registry
You

SOME ARE MORE EQUAL THAN OTHERS

INSTITUTIONAL REVIEW BOARD
### WHY? WHY? WHY?

Some scientists were shockingly awful
- Stanford prison experiment
- Milgram electroshock experiments
- Guatemala syphilis experiments
- Etc.

IRBs review proposals to enforce ethical principles:
- Informed consent
- Risk is minimal and appropriate for benefit
- Respect for persons, Beneficence, Justice

### WHAT IT IS

Committee of scientists and non-scientist community members
Review proposals for:
- Ethics
- Scientific validity

Without scientific validity, it's unethical to even *inconvenience* participants - much less expose them to any risk at all

### HOW IT WORKS

Submit protocol and proposed consent form

Then it's reviewed:
- Exempt
- “Expedited”
- Full Committee

### WHAT THEY DO

- Often, they suggest modifications to a planned study
- Can shut down entire schools
- Can effectively end careers
THE IRB IS ALWAYS RIGHT

Sure, their decisions can be appealed...

- Once
- To them

IRB DOCUMENTS

Application form with ancillary forms (investigator list, etc)
Protocol
Consent form
HIPAA authorization (can be merged with consent)
Conflict of interest disclosures
CONSENT FORM

CONSENT / HIPAA

Separate from consent for procedure

Essentially always needed
  • Waivers are possible, but not common

REQUIRED TRAINING

On Learning Central:
  • HSC 104-002 “HSC Financial Conflicts of Interest Training”

On an external website:
  • CITI human-subjects training: Biomedical Course

WHAT DO WE DO?

OUR PROJECTS
35+ ACTIVE STUDIES

• Neuroimmune reactions to chronic pain
• How often do NPO kids still have gastric contents?
• Does an adjuvant prolong PNB effectiveness?
• Reducing pain post mastectomy
• Making hand surgery patients happier
• Why don’t we do more labor epidurals?
• Does patient race affect pain management?
• Does early anesthetic exposure affect cognitive development?
• Etc.

THEY'RE OUT THERE

• Many (most?) faculty have ideas for projects
  • Some have ideas faster than they can act on them
• They just need a resident to help move it along
• Be that resident
  • There are always areas that are unclear or controversial
  • Look for them, and ask about pursuing them

THEY AIM TO SERVE

HSC RESOURCES

CTSC

• Clinical Data Warehouse
• Biostatisticians
• Cindy Wootton
• Other stuff
PRE-AWARD

Grant awards are contracts.
Neither you nor your PI can sign a contract on behalf of the Regents of the University of New Mexico.
If a grant application is involved, Pre-Award wants a draft application at least 5 days before it's due.
Lots of paperwork.

DIVERSITY & INCLUSION

- 43% of US adults have basic or below-basic reading skills
- 55% basic or below-basic math skills
- Yet they’re supposed to read, understand, and use complex information
- This is a patient-rights issue
- DI staff can help make patient materials more comprehensible

ANIMAL FACILITY + LAB

Drs. Milligan (Neurosciences), Lam, and Reyes
Neuroimmune factors in chronic pain, and treatments thereof

Our department just acquired a new lab in addition to Dr. Milligan’s.

Oooo- shiny!

IN-HOUSE

Wojciech Ornatowski
- PhD research scientist: Milligan’s lab

Me
- Study design, IRB, stats, editing, ....
RECOMMENDED READING

THIS IS THE END

NEVER FORGET

Why Most Published Research Findings Are False

Summary

In the wake of the lead events around the world, there has been a consistent trend of over-reporting, over-interpretation, and over-publication of research findings. This has led to a situation where the majority of published research findings are false. In this article, we present a framework for distinguishing true research findings from false ones.

In the first part of the article, we provide a framework for distinguishing true research findings from false ones. We also discuss the implications of this framework for researchers and policy makers. In the second part, we present a case study of a recent study that illustrates the application of the framework.

In conclusion, we argue that the current system of research publication is broken and that urgent action is needed to address this problem. We conclude with a call to action for researchers, policy makers, and the public to work together to create a new system of research publication that is based on truth and transparency.