7-1-2013

So you want to do research: we can fix that

Timothy Petersen

SO YOU WANT TO DO RESEARCH

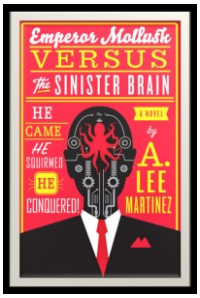
WE CAN FIX THAT

UNM SCHOOL of MEDICINE | *Department of Anesthesiology & Critical Care Medicine*

WHY ARE WE HERE?

"Sloppy science doesn't do anyone any good."

-Emperor Mollusk



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

Richard Feynman

Caltech commencement address, 1974

STOP FOOLING YOURSELF

BIAS IN ALL ITS HIDEOUS FORMS

SELECTION BIAS

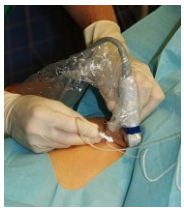
- **Participants don't reflect the population of interest**
  - Inclusion/exclusion criteria must be well-defined
  - Volunteers always bring this bias
  - Psychology research: a plague of WEIRD people
- **Allocation to groups is not uniform**
  - Nonrandom allocation
  - Charter schools have better 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!

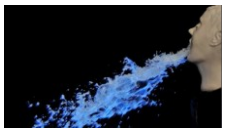
ATTRITION BIAS

Systematic differences in withdrawals

A study medication causes nausea in a subset of patients.

Affected patients withdraw.

Conclusion: no nausea!



Larry, the projectile-vomiting robot

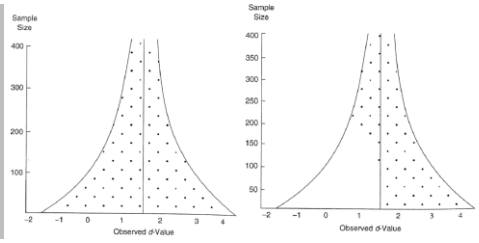
REPORTING BIAS

- **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…

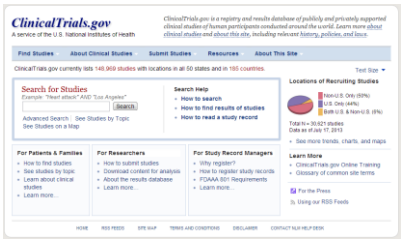
A problem with the literature overall

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

Saturday Morning Breakfast Cereal

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

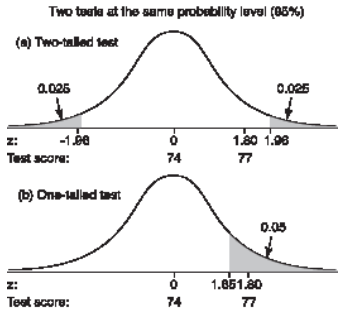
Less common

- Hypothesize *a priori* that one treatment is better than the other
- H_A: $mean_1 > mean_2$
- H_O: $mean_1 \leq mean_2$

TWO-TAILED TESTS

Default

- Hypothesize that there is some difference
- H_A: $mean_1 \neq mean_2$
- H_O: $mean_1 = mean_2$



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?

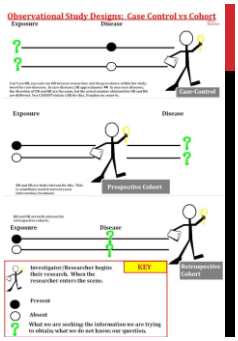
- **Primary outcome**
  - Time to first request for analgesic meds (define start/stop points)
- **Secondary outcomes**
  - Time to first report of pain
  - Total opioids used
  - Time to first sensation
  - Time to first return of motor function

STUDY DESIGN

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

TRIAL TYPES

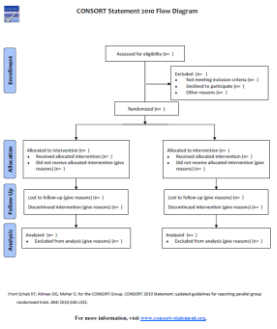
- **Observational studies**
  - Case-control
  - Prospective cohort
  - Retrospective cohort
  - Cross-sectional
  - Ecological
  - How often does __ happen?



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 *rightnow*.

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.

WHATCHA GONNA DO?

THE PROTOCOL

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**

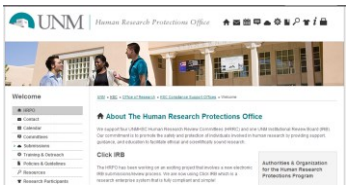
Without scientific validity, it's unethical to even *inconvenience* participants- much less expose them to any risk at all

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

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U.S. Halts Human Research at Duke

By Rick Weiss
Washington Post Staff Writer
Wednesday, May 12, 1999; Page A1

The U.S. government has temporarily shut down federally funded research on humans at Duke University Medical Center, one of the nation's largest and most prestigious medical research facilities, after federal investigators determined that the university could not ensure the safety of participants.

THE SACRAMENTO BEE sacbee.com

This story is taken from Sacbee / -- Root

2 UC Davis neurosurgeons accused of experimental surgery are banned from human research

mlundstrom@sacbee.com

PUBLISHED SUNDAY, JUL. 22, 2012

A prominent UC Davis neurosurgeon was banned from performing medical research on humans after he and an underling were accused of experimenting on dying brain cancer patients without university permission, The Bee has learned.

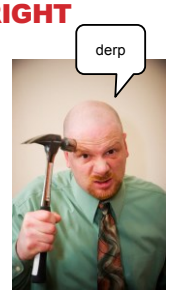
Dr. J. Paul Muizelaar, who earns more than $800,000 a year as [redacted] of [redacted] was ordered last fall to "immediately cease and desist" from any research involving human subjects, according to documents obtained by The Bee.

Also banned was the colleague, Dr. Rudolph J. Schrot, an assistant professor and neurosurgeon who has worked under Muizelaar the past 13 years.

THE IRB IS ALWAYS RIGHT

Sure, their decisions can be appealed…

- **Once**
- **To them**



IRB DOCUMENTS

Application form with ancillary forms (investigator list, etc)

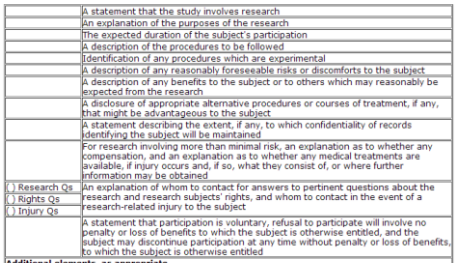
Protocol

Consent form

HIPAA authorization (can be merged with consent)

Conflict of interest disclosures

CONSENT FORM



	A statement that the study involves research
	An explanation of the purposes of the research
	The expected duration of the subject's participation
	A description of the procedures to be followed
	Identification of any procedures which are experimental
	A description of any reasonably foreseeable risks or discomforts to the subject
	A description of any benefits to the subject or to others which may reasonably be expected from the research
	A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject
	A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
	For research involving more than minimal risk, an explanation as to whether any compensation, and an explanation as to whether any medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained
( ) Research Qs	An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject
( ) Rights Qs	
( ) Injury Qs	
	A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits, to which the subject is otherwise entitled

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

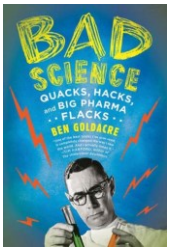
Wojciech Ornatowski

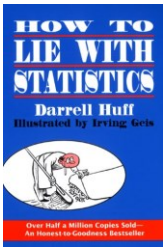
- PhD research scientist: Milligan's lab

Me

- Study design, IRB, stats, editing, ….

RECOMMENDED READING





NEVER FORGET

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a p-value less than 0.05. Research is not most appropriately represented and summarized by p-values, but, unfortunately, there is a widespread notion that medical research articles

It can be proven that most claimed research findings are false.

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2×2 table are given in Table 1. After a research finding has been claimed based on

PLoS Medicine 2005; 2: e124

THIS IS THE END