Statistics•Collaborative

*design and analysis for biomedical research*

# Learning from Extroverts, or Assuming Statistical Leadership

Janet Turk Wittes

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# Topics

- Who we are
- What are our strengths
- What are our weaknesses
- With whom to we work
- What we do
- And how do we get to sit at the table

# Who we are

# How people see us

- As a field we are not viewed positively
  - (Although Nate Silver may have fixed that)
- People see us as
  - Negative – "Statisticians are the terrorists of clinical trials"[1]
  - Rigid[2]
  - Not fit to socialize with - Auden[3]
  - Boring and humdrum[4]

- 1. Bernie Fisher (I have been told)
- 2. Any number of jokes
- 3. Auden
- 4. Manderville (as quoted by Kendall and Stuart, vol 2)

# Not fit to socialize with: The Hermetic decalogue (Auden 1946)

1. Thou shalt not do as the dean pleases
2. Thou shalt not write thy doctor's thesis on education
3. Thou shalt not worship projects
4. Nor Shalt thou or thine bow down before Administration.
5. Thou shalt not answer questionnaires or quizzes upon World-Affairs
6. Nor with compliance take any test.
7. Thou shalt not sit with statisticians nor commit a social science.
8. Thou shalt not be on friendly terms with guys in advertising firms, nor speak with such as read the Bible for its prose nor, above all, make love to those who wash too much
9. Thou shalt not live within thy means nor on plain water and raw greens.
10. If thou must choose between the chances, choose the odd, read *The New Yorker,* trust in God; And take short views.

# Manderville, The Undoing of Lamia Gurdleneck

"You haven't told me yet, said Lady Nuttal, "what it is your fiance does for a living,"

"He's a statistician," replied Lamia, with an annoying sense of being on the defensive.

Lady Nuttal was obviously taken aback. It had not occurred to her that statisticians entered into normal social relations….

# Humdrum

"But Aunt Sara, it's a very interesting profession," said Lamia warmly.

"I don't doubt it," said her aunt, who obviously doubted it very much….To express anything important in mere figures is so plainly impossible that there most be endless scope for well-paid advice on how to do it.

But don't you think life with a statistician would be rather, shall we say, humdrum?"

# But one (of the many) good side of us:

Lamia…felt reluctant to discuss the surprising depth of emotional possibility with which she had discovered below Edward's emotional veneer.

"It's not the figure themselves," she said finally, "it's what you do with them that matters."

# We statisticians are good at generalizing

- Not being specialists – we are intellectually promiscuous
  - "Consisting of a heterogeneous mixture of persons or things"
- We see similarities in what others see as very different

# Our unique strength – translation of problems to another space

- Jerry and Ruth Cornfield 1969

- ASA Presidential Address 1974
- The first thing I do…

# “The first thing I do…”

| | Adriakinase | Lovamycin | Fentacide |
|---|---|---|---|
| N | 103 | 98 | 102 |
| % success | 43.6 | 22.7 | 35.7 |
| Mean ± SE | 18.7 ±2.3 | 16.2 ±3.8 | 21.7 ±2.9 |
| … | | | |

# "…is replace the nouns with A, B, C…"

| | A | B | C |
|---|---|---|---|
| N | 103 | 98 | 102 |
| % success | 43.6 | 22.7 | 35.7 |
| Mean ± SE | 18.7 ±2.3 | 16.2 ±3.8 | 21.7 ±2.9 |
| … | | | |

# Dual spaces and back translation

## STAT JOURNAL ARTICLE

1. Start: abstract statistical question
2. Solve it
3. Give seemingly unrelated examples
4. Thread that binds: abstract question

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## ACTUAL PROCESS

1. Start: applied question
2. Dual space: make it abstract
3. Solve it
4. Back translate: Answer the original question)
5. Generalize to other applications

# Our strengths and weaknesses

# What we statisticians are good at…

- Presented with a problem
- Abstracting it (Jerry's "I replace the nouns")
- Solve in the abstract space without nouns
- Back translate to the problem posed
  - (Lamia's "it's what you do with them)
- Generalize to other seemingly unrelated problems

# Some of our weaknesses

- I see disconnect between sophisticated methods & simple principles
- We often don't show we care about numbers
  - Why do we let p-values be reported like this: "p=0.4756"?
  - Why use min & max? We know they are sample size dependent.
- Why do we act as if we don't believe in the CLT?
- Why do we ignore regression to the mean?
- Etc. etc. etc….

# Our most important weakness: back-translation

- Jerry spoke in the noun world, even if he thought "A, B, C"
- "You don't sound like a statistician": an indictment of our field
- David Bartholomew: "what does this have to do with butterflies?"
- Gene Passamani : "if you don't speak in public, it's not useful to me"
- What we need to teach ourselves and others
  - Talk in THEIR language, not ours
  - Don't be afraid of saying something stupid (others do!)

# With whom do we work

# Tribes in clinical trials- Seamus Thompson

- Clinicians, sponsors, patients: want better therapy
  - Clinicians and sponsors: Want new therapy quickly
  - Patients: Want the "right" answer for
    - Self
    - Other's who suffer
    - Grandchildren (WHI)
- Statisticians: we want elegant study with clear design
- Data managers: want reliable data, fast

# Why did you join your tribe?

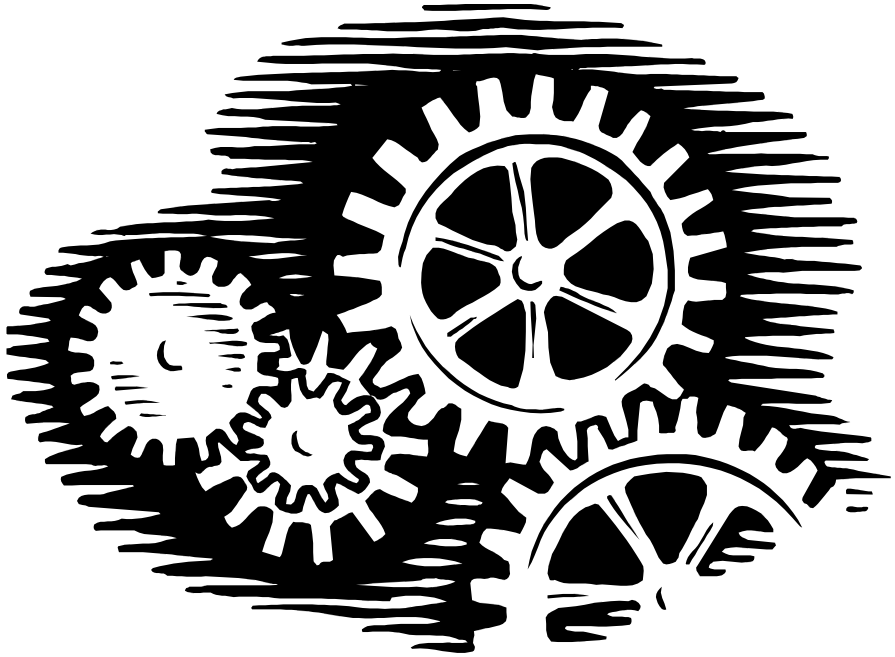
- Clinicians et al.
  - I want to help people.
  - I am a people person.
- Data managers, programmers
  - I like to solve puzzles.
  - I like efficiency.
- Statisticians
  - I liked math but I wanted to do something applied.
  - I don't care about results. I like knowing how we know.

# What do we do?

# Models of organizations

## ASSEMBLY LINE

## GEARS



# How do we get to the table?

# Often there is little evidence of a statistician's involvement

Frequently we have to ask project team to have statisticians join us on calls

# Getting to the table…

- Are statisticians really not at clinical trial tables?
- Why not?
- Why are we useful?
- Who else should be there?
- What should statisticians do to get there?
- What should study leaders do to invite us?

# But: are there tables statisticians should avoid?

The table used during the inquisition in Goa was very elaborate.

It had demonic figures and animals carefully carved out on the legs.

# Example of a Phase 3 analysis

- Analysis plan: incomplete – methods missing
  - We will look at many subgroups
- Report without words
  - Pages and pages of output
  - No structure
- "We always have our statisticians do analysis; we do the reports."

# Why are we not at the table?- Blame others

- You don't appreciate our worth: the MD syndrome
- You don't know what we do (just "statistical issues")
- Upper management sees us as a service group
- Management want to minimize costs
- You are too busy to get us involved early
- You have impossible deadlines, so you squeeze us
- You find what we say too difficult to understand

# Or, in 2013

- "Let's not talk about the plumbing, the nuts and bolts – that's for plumbers, for statisticians" –
  - Diederik Stapel
  - as quoted by Yudhijib Bhattacharjee,
  - NY Times Magazine, April 28, 2013, page 50

# Who was Stapel?

- Born 19-Oct-1966 in the Netherlands
- Former professor of social psychology
  - Tilburg University
  - University of Groningen
- 2011: Tilburg suspended Stapel for fabricating and manipulating data for his research publications
- This scientific misconduct took place over a number of years and affected at least 55 publications.

Wikipedia

# Why are we not at the table?- our fault

- We are, by nature, asocial
- More comfortable with abstractions than with words
- We think you won't understand anyhow
- We are too busy
- We don't know what you are talking about
- We are too negative (the terrorists of clinical trials-pace B Fisher)
- We like ambiguity

# We are introverts

# USA Today 5/5/09 on Ruth Bader Ginsburg

-Joan Biskupic

**As a young, female lawyer male peers often ignored her voice. "I don't know how many meetings I attended in the '60s and the '70s, where I would say something, and I thought it was a pretty good idea… Then somebody else would say exactly what I said. Then people would become alert to it, respond to it.“**

# AND NOW ON THE COURT

"It can happen even in the conferences in the court. When I will say something — and I don't think I'm a confused speaker — and it isn't until somebody else says it that everyone will focus on the point."

# Factors involved in decisions

- Basic science
- Medical need
- Importance of question (e.g., how many people affected?)
- For pharma, competitive landscape

# Factors involved in decisions

- Basic science
- Medical need
- Size of market
- Niche of product

MY VIEW:

- Assume all tribes are in at all stages.
- Let different tribes opt out.

# Strategic tables – statisticians are often not there

- Choice of disease and targets
- Preclin→Phase 1 →Phase 2 →Phase 3 →beyond
- Medical/financial/marketing landscape
  - New drug for an underserved condition?
  - Me-too drug?
- Phase 2 and 3: what studies do we need?

# Tactical tables

- What population should we choose?
- How to design a Phase 2 or 3 trial?
- How to design *this* study
  - Choice of outcome variables
  - Choice of length of follow-up
- Fill in the blanks in this protocol

# Another set of tables…

- How should statistics be organized?
  - With what other groups?
  - Who is on top?
  - Are you together or in disease groups?

# How do we get to the table?

- First, know ourselves
- Then, change ourselves
- Then, change others

# Know thyself….

- What do you
  - Truly believe
  - Care about, but no line in the sand
  - Don’t care about

# Change yourself

- We are more comfortable with abstractions than with words
- We think they won't understand anyhow
- We are too busy
- We don't know what they are talking about
- We are too negative

# We are, by nature, asocial

- Practice talking to non-statisticians
- Speak up in meetings
  - FDA statisticians often sit at the side of the table
  - What I learned from Gene Passamani
  - Force people to invite you to meetings
    - (and express anger if they don't)

# Why are statisticians useful?

- We understand experimental design
- We are quick learners of new subjects
  - We are good readers
  - We see similarities among diseases
  - We see differences where others don't
- (But we must learn the nouns!!!)
- (And we shouldn't be afraid of asking questions)

# Our main weakness is passivity

- "This is not a statistical question"
- We allow our field to be degraded
  - Why should data management rule us?
    - Example: what is "study drug" or IP of "study med"?
    - Why should templates allow two groups only?
    - Why should MedDRA rule us? – a tool, not a rule
  - Why should medical writing have the upper hand?

# Other main weakness – failure to communicate

- Statisticians don't hear what others are saying
- Others don't hear what we are saying
- We talk in jargon

# Other things we do wrong

- We tolerate (and encourage) false precision
  - Sample sizes to the nearest whole number
    - "Someone else can reproduce it"
  - P-values to lots of significant digits (e.g., p=.9436)
    - "That's what SAS gives"

# Other things we do wrong

- We accede to physicians' demands
  - "I know xx is better statistically, but yy is more meaningful clinically"
  - E.g., % change in nodule count in acne
    - Point out that a change from 1 to 0 is 100%
    - A change from 20 to 5 is 75%

# Other things we do wrong

- We don't believe in the Central Limit Theorem

# Safety report sample

| Time Point | A [N= 150] | B [N= 148] | Total [N= 298] |
|---|---|---|---|
| SCREENING | 0 | 0 | 0 |
| RANDOM | 0 | 0 | 0 |
| WEEK 2 | 0 | 0 | 0 |
| WEEK 3 | 0 | 0 | 0 |
| WEEK 4 | 0 | 0 | 0 |
| WEEK 5 | 0 | 0 | 0 |
| WEEK 6 | 0 | 0 | 0 |
| WEEK 7 | 0 | 0 | 0 |
| WEEK 8 | 0 | 0 | 0 |

# But wait! You also get:

| Time Point | A [N= 150] | B [N= 148] | Total [N= 298] |
|---|---|---|---|
| SCREENING | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| RANDOM | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 2 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 3 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 4 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 5 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 6 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 7 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 8 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |

# 150 pages of Where's Waldo

| Time Point | A [N= 150] | B [N= 148] | Total [N= 298] |
|---|---|---|---|
| SCREENING | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| RANDOM | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 2 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 3 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 4 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 5 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 6 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 7 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 8 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Early termination | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| Unscheduled | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |

# And 150 pages of where's Waldo

| Time Point | A [N= 150] | B [N= 148] | Total [N= 298] |
|---|---|---|---|
| SCREENING | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| RANDOM | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 2 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 3 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 4 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 5 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 6 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 7 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| WEEK 8 | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| EARLY TERM | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |
| UNSCHEDULED | 0 (0.00 %) | 0 (0.00 %) | 0 (0.00 %) |

# Example: Why we all need to be at table

- Data come from case report forms
  - Operations people and medical people
    - What data should we collect?
  - Data managers
    - How should we collect data?
  - Statisticians
    - How will be analyze data?

# Study had no death form

- Clinical tribe
  - Extra form not necessary
  - Deaths are on SAE form
- Database tribe
  - We've never seen no death form, but…
  - We solve problems so we can program this away
- Statistical tribe
  - There will be confusion!
  - It will slow up the querying and the analysis

# Decision

- Operations –forms about to go to printer
- Data – we can change database easily
- Us – hold the presses

- Decision: form sent to printer

# Upshot

- Study stopped early
- Deaths were on SAE forms
- Dates of death confusing
- Causes of death in comment fields
- Added HUGE expense and time

# Phase 2 to Phase 3

- Typically scientists look at Ph 2 to predict Ph3
- Statisticians: need to incorporate uncertainty
- If statisticians not at table,
  - effect size typically overestimated

  - See Lan, Wittes. **Some thoughts on sample size: A Bayesian-frequentist hybrid approach .**Clinical Trials Oct 2012

# So, who should be there?

- Answer: everyone involved in the development
- Let people and groups opt out

# How should statisticians get there?

- Invite yourselves
- Crash the party
- Complain if you are not there (with examples)
- But, PARTICIPATE

# Where do late stage trials go wrong?

- Surprising harms
- P-value that doesn't quite make it
- Inconsistent data

# What can statisticians do to prevent these events?

- Looking critically at data
  - Animal data
  - Phase 1 and 2
- Thinking hard about outcomes
  - E.g., when MACE, MACE+, all-cause vs CV mort
  - What continuous measure should you use?
- Dealing up front with missing data
- BUT, we need time

# Remember, there are toxic tables

- People who insist on analyses that are incorrect
- People who insist on "foolish consistency"
- People who shade language unfairly
- People who demand small p-values
  - "You're a New Yorker"
- Think hard, then go away
  - There are many more fish in the sea!

# 3 types of toxic tables ($3T^3$)

- Failure to do what's right
- Failure to invite us to the table
- Setting things up so we will fail

# Failure to do what's right

- Make sure your name is not used in vain

# Failure to invite us to the table

- You are the statistician designing a study
- Design is innovative
- Clinical leader sets up a meeting with outside statisticians
  - And doesn't invite you
- What do you do?
  - First time, figure it's a mistake
  - 2nd time? Third time - quit

# Setting things up so others will fail

- My mantra to staff
  - You are responsible for doing things in a way that makes others efficient
  - Consequence: no squeeze play on others
- The squeeze player
  - Find out if it's your problem or the other person's
  - If it's the other person
    - Remember:  people don't get personality transplants

# Conclusion: All tribes should be at the table

- It is valuable for the clinicians and scientists
- It is valuable for statisticians
- We need to see ourselves as
  - Full team members
  - Teachers and students, simultaneously
- Don't let them (or us) separate "statistical" issues from "medical" issues – we are in this together!