The Role of CMC Statisticians: Co-Practitioners of the Scientific Method

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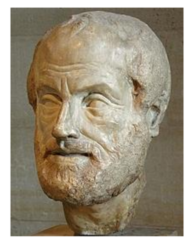
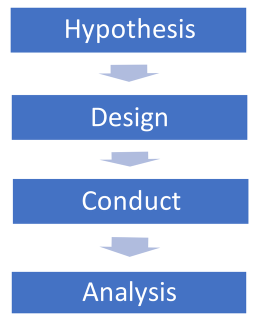
The scientific method

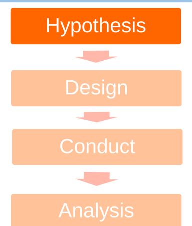


- One needs to understand the evolution of ***the scientific method*** to appreciate its strength, and to avoid reversion to less appropriate forms of scientific reasoning
  - The roots of the scientific method stem from Greece and ***Aristotle's inductive-deductive reasoning*** (400 BC)
    - ***Induction from observations*** to infer general principles (observational studies)
    - Successful in discovering universals by generalization, but ***did not succeed in identifying causes***
  - 11th century Muslim philosophers introduced ***experimentation and quantification***
  - Roger Bacon (13th century) described a ***repeating cycle of observation, hypothesis, and experimentation***
  - Francis Bacon (16th century) ***eliminated induction*** as a basis of the scientific method, emphasizing ***deductive reasoning*** and opening the door to the discoveries of René Descartes, Galileo Galilei, and Isaac Newton
  - Many improved on this, culminating in the work of Karl Popper (20th century) who advocated "***empirical falsifiability***" as the criterion for distinguishing scientific work from non-science

- The four steps of the scientific method
  - ***The study objective*** – the objective of a study which can be framed in the form of a statistical hypothesis
  - ***The study design*** – the ***structure*** (e.g., blocks) and ***replication strategy*** (sample sizes) which ensures representative consideration of the study objective, and manages risk
    - ***Representativeness*** – strategic sampling across the population of interest
    - ***Risk management*** – reduction of the uncertainty of the study result
  - ***Study conduct*** – care in preventing the introduction of biases and mistakes
    - Adherence to ***protocol*** and effective use of ***randomization***
    - Collecting data with ***sufficient digits***, and rounding only at the end of the analysis
  - ***Study analysis***, including conclusion – mathematical treatment of the study data to a form which objectively addresses the study objective
    - Assessment of ***data structure*** including transformation (should have been done at design) and outliers
    - Use of ***confidence intervals*** rather than p-values
    - Consideration of ***Bayesian methods*** to properly address the parameter of interest



"It's the question stupid"



– The alternative H_a represents the "***research hypothesis***" (the study objective)
  – Consider comparing two means (method transfer, method bridging, standard qualification)

A: Are the two means ***different***?	**B**: Are the two means ***equal***?
$H_0: \mu_A = \mu_B$ $\boldsymbol{H_a: \mu_A \neq \mu_B}$	$H_0: \mu_A \neq \mu_B$ $\boldsymbol{H_a: \mu_A = \mu_B}$

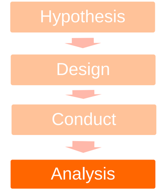
– You can't address ***equality*** with a t-test (***A***) – the conclusion, there's insufficient evidence to conclude $\mu_A \neq \mu_B$ may be due to poor design or excess variability
  – Must use an ***equivalence test*** (***B***) to be able to conclude the two means are equivalent, $\boldsymbol{\mu_A = \mu_B}$
  – "***Equivalent***" = the difference is within a margin (Δ) representing ***minimal impact*** due to the difference

B: Are the two means *equal*?

$$H_0: |\mu_A - \mu_B| > \Delta$$
$$\boldsymbol{H_a: |\mu_A - \mu_B| \leq \Delta}$$

– Hidden equivalence hypotheses – the "plague" of absolutes
  – The product is ***stable*** – The method is ***valid*** – The process is ***robust***

"I can get my computer to do my statistics"

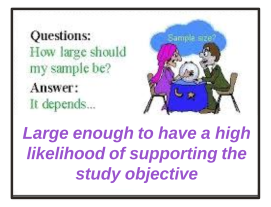


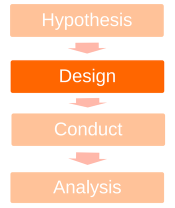
- Instrument software and EXCEL provide simple statistical tools to analyze data
  - Limited to applications such as simple linear regression and one way fixed effects analysis
  - No access to data and assumption screening tools – or robust analysis tools such as nonparametric methods
  - Limited understanding of how to use these for performing equivalence testing
- More comprehensive programs and languages such as R, SAS, Statistica, JMP, Minitab and Design Expert provide greater versatility and guidance, but still require an adequate level of statistical skill to use them effectively
- Some of these provide scripting to develop routine applications
  - Facilitates throughput within the nonclinical statistics community
  - Can be shared with the non-statistical community with appropriate supervision
    - Would you let a statistician perform an experiment without supervision????

- There is little risk that a computer will replace a nonclinical statistician in biopharmaceutical development

  . . . or will they?

"If I go to a statistician, I'll have to do more work"

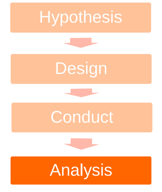




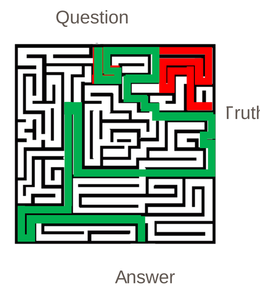
- "Anything worth doing, is worth doing right" (Hunter Thompson)
  - ***The value of n = 3***
    - I don't have to bother partnering with a statistician
    - Most people agree with me
    - If I do n = 4 (33% increase in the amount of work) I'm considered a hero
  - ***The harm of n = 3***
    - I've wasted time and money thinking I've addressed the study objective
    - Sample size does not achieve "representativeness" –also need to think about what changes (more importantly what doesn't change) over 3 or 30 results
- Nonclinical statisticians can be credited with adding value through efficient and effective experimental strategies
  - Use(s) of ***blocking*** to reduce uncertainty in the study result
    - Understand the sources of variability, and ***replicate in the dimension(s) which contribute the most to variance reduction***
    - Treat the study as the ***combination of both process and assay***; coordinate the analytics with the treatments to avoid biases and manage variability
  - Use(s) of sample size to achieve sufficient ***power*** to achieve the study objective, or to ***communicate the risk of study failure*** if the sample size is fixed
  - Use DOE rather than OFAT to address effects (main and interactions) and to reduce overall study burden (note, definitive screening designs - as small as Plackett-Burman but can estimate curvature)

$$VAR = \sqrt{\frac{\sigma_{B1}^2}{k} + \frac{\sigma_{B2(B1)}^2}{nk} + \frac{\sigma_E^2}{mnk}}$$

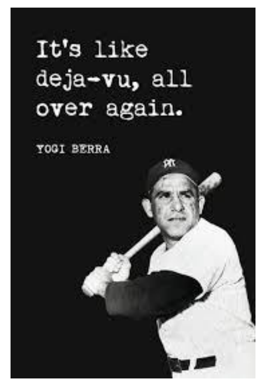
"Liars, damned liars, and statisticians"



– And its corollary:
  – "If you torture the data long enough, it will confess" (Ronald Coase)
– One form of this results from the nonclinical statistician not being being involved in formulating the objective or designing the study
– Bad Bob versus Jo (Simon Raper, *Significance*, 2017)
  – Bob is asked to evaluate the success of TV marketing for a client
    – He doesn't know the goal, what data to use, or how to analyze the data – so he uses an econometric model with many variables
    – He runs some code and up pops a number, but it's low, which he thinks won't please the client
    – So he runs different models until he reaches the conclusion that TV marketing is effective
  – Jo asks why they are evaluating the marketing campaign
    – She finally learns they will cut the TV budget by £120 000 if they don't learn otherwise – this is a "falsifiable claim", the basis of a null hypothesis (recall Popper)
    – She designs an experiment with factors which might impact costs, logs her assumptions, and takes care against the fact that the more questions she asks the greater the risks of a false positive
    – She frames her conclusion, along with assumptions in a way the client can adequately evaluate



Slipping back into induction



- The pathway out of induction was slow (millennia) and painful (rabbit holes, including inaccurate theories and deadly interventions); thus we should be vigilant to the tendencies to slip back into induction
  - Discovering the answer
  - Data snooping and post-hoc analyses
  - Inference from individual measurements
  - Statistical limits as specifications (what you see is what you get)

Some summary remarks

- The history and refinement of the scientific method teaches us the true basis of science, and the pitfalls from slipping back into old practices
- Statistics provides the framework (hypothesis testing) and pathway (variance reduction) for the successful application of the scientific method
- Nonclinical statisticians add value to a biopharmaceutical study, as long as they are engaged in all aspects of the study
- The roles and responsibilities of nonclinical statisticians extend beyond pure statistics, to learning the science, being stewards of the scientific method, and innovating more appropriate approaches for addressing biopharmaceutical study objectives
- Being a nonclinical statistician is fun and rewarding, in partnering with other scientists and regulators, and in bringing life saving medicines to those in need