Clinical Research Planning and Execution: What Every Researcher Should Know to Avoid Pitfalls and Maximize Success

Beth Bailey, PhD
Professor and Clinical Research Director
Department of Obstetrics and Gynecology
University of Colorado

OVERVIEW

- Clinical research design issues
- Obtaining participants and data
- Power analysis
- Basic statistics
- Forming research teams
- Funding
- Working with statisticians and epidemiologists

CLINICAL RESEARCH VS BASIC SCIENCE RESEARCH

- Basic science research – How does this work?
  - Lab setting
  - “Participants” are typically cells, tissues, animals
  - Easier to control all conditions to look at mechanisms
  - Application not always immediately evident, but lays the foundation
- Clinical research – Is this actually useful?
  - Real world setting
  - Participants are people
  - Messier to do
  - Findings can have direct and immediate applicability to patients
- Basic science research – informs clinical research – which leads to additional basic science research

CLINICAL RESEARCH QUESTIONS

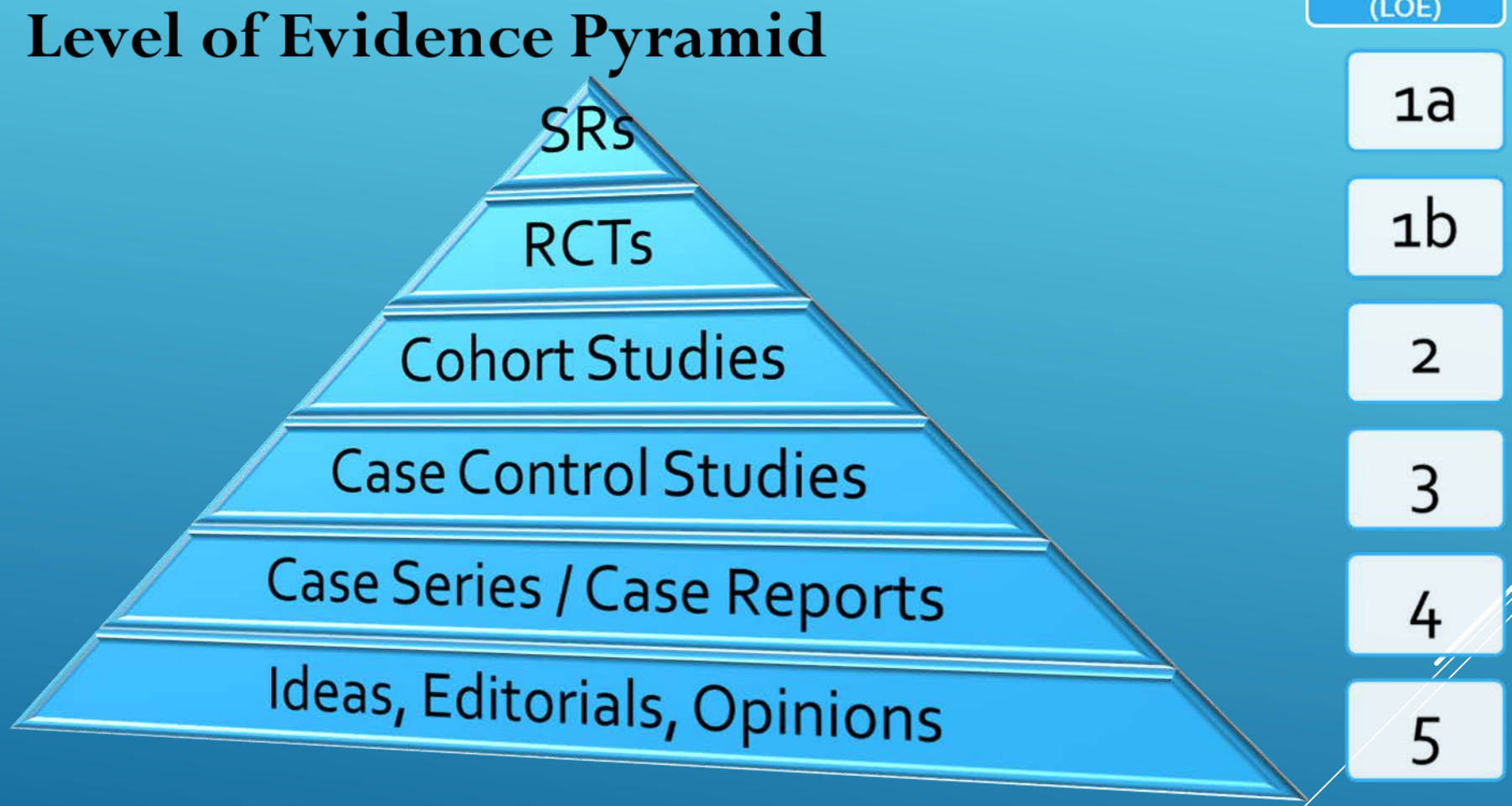
- Picking a topic
  - Interest; Overlap with current work
  - What is already known
- Designing a testable question
  - Operationalize all variables
  - Specific to population, clinical conditions, etc
- Do you need a hypothesis?
  - Can you make a prediction about the answer to the question?
- What information do you ultimately want?

Research Questions, Hypotheses, and Clinical Questions – Chapter by Judith Haber
https://medicine.utah.edu/ccts/sdbc/files/Research_Question.pdf

CLINICAL RESEARCH DESIGN

- Experimental vs Observational Designs
  - Experimental (RCT)– Cause and effects conclusions
  - Observational (i.e. correlational) – Works in more situations
  - Impacts Level of Evidence
- Choice depends on
  - Topic/Research question
  - Current state of knowledge
  - Resources
- Quality improvement efforts can be research too
  - In and of themselves
  - As a spring board for further clinical research

CLINICAL RESEARCH DESIGN

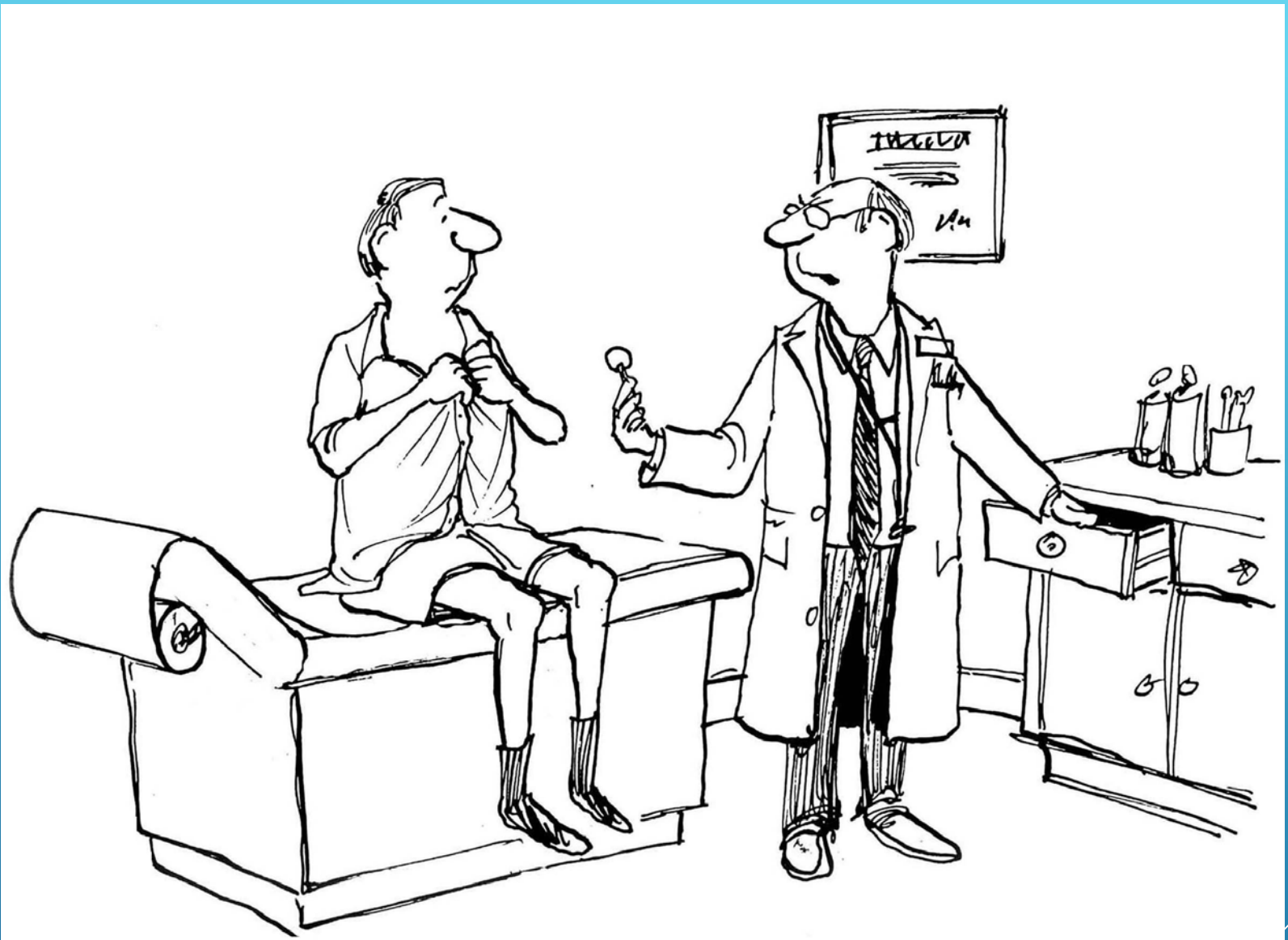


Levels of Evidence (LOE)
1a
1b
2
3
4
5

Hartung DM, Touchette D. Overview of clinical research design. Am J Health Syst Pharm. 2009;66(4):398-408.

DESIGNING/IMPLEMENTING A CLINICAL STUDY

- Control vs real world applicability
  - Will findings apply to typical patients
  - Will findings apply to typical situations
- What's possible and what's not
  - RCT
  - Correlational design – Cohort study, Case control
- Prospective vs Retrospective
- Cross-sectional vs Longitudinal
- In the end – the research question and resources will dictate!



This drug has proven effective in testing of
500 women with your condition.

CLINICAL STUDY PARTICIPANTS AND SETTING

- Identifying potential participants
  - Inclusion and exclusion criteria
  - Where to find them
  - Enrolling them; retaining them

  https://www.nimh.nih.gov/funding/grant-writing-and-application-process/recruitment-points-to-consider-6-1-05_34848.pdf
- Can you use existing data?
  - Using EHR data
  - Leveraging existing data sets
- Multi-site efforts

BIG DATA SETS

- Using EHR data

Milinovich A, Kattan MW. Extracting and utilizing electronic health data from Epic for research. Ann Transl Med. 2018;6(2):42.

https://aspe.hhs.gov/report/feasibility-using-electronic-health-data-research-small-populations/technical-conditions-required-research-using-ehr-and-other-electronic-health-data

https://epidemiologyinpolicy.org/documents/hhs14.pdf

- Using other big data sets

https://link.springer.com/content/pdf/10.1186/2047-2501-2-3.pdf

https://healthitanalytics.com/news/identifying-big-data-sources-for-population-health-management

https://www.datasciencecentral.com/profiles/blogs/10-great-healthcare-data-sets

http://guides.lib.berkeley.edu/publichealth/healthstatistics/rawdata

https://guides.lib.unc.edu/c.php?g=8742&p=44486

Also – vital statistics data…

HOW MANY PARTICIPANTS ARE NEEDED?

- Statistical power – ability to conclude there is a significant effect when one does exist
- With low power – may erroneously conclude there is no effect
- Biggest driver of statistical power – sample size
- So – need to make sure you have enough participants to be able to answer your question of interest
- The smaller the effect you expect, the more participants you will need
- Also – distribution of the outcome variable impacts power

HOW MANY PARTICIPANTS ARE NEEDED?

- ClinCalc: http://clincalc.com/stats/samplesize.aspx
- Example - have an intervention to improve birth weight in a population with an average birth weight of 2900gm/30% LBW rate
- How many participants do we need in the treatment and control groups to be able to determine the intervention is effective?
- What assumptions do we make, what sample size do we need?

HOW MANY PARTICIPANTS ARE NEEDED?

Group 1	Group 2	Power	Number of Participants Needed
2900g	3400g (normal wt)	80%	20
2900g	3400g (normal wt)	90%	26
2900g	3190g (inc by 10%)	80%	60
2900g	3190g (inc by 10%)	90%	80

Group 1	Group 2	Power	Number of Participants Needed
30% low birth weight rate	8% (natl avg)	80%	98
30% LBW rate	8% (natl avg)	90%	130
30% LBW rate	24% (dec by 20%)	80%	1716
30% LBW rate	24% (dec by 20%)	90%	2296

BIAS IN CLINICAL RESEARCH

- No study is perfect – many threats to study validity – need to consider effects
- What is validity? A study is considered valid if it uncovers the truth about relationships among variables
  - Internal validity – accuracy of study results in that sample
  - External validity – degree to which study findings generalize to a population
- Threats to validity often referred to as biases – introduction of systematic error into a study that can/does impact study results
- A LOT of identified biases (200+), different terminology and classification schemes:
  - Selection
  - Design
  - Results

BIAS IN CLINICAL RESEARCH

- Pannucci & Wilkins. Identifying and avoiding bias in research. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2917255/
- http://www.equator-network.org/

BIAS IN CLINICAL RESEARCH

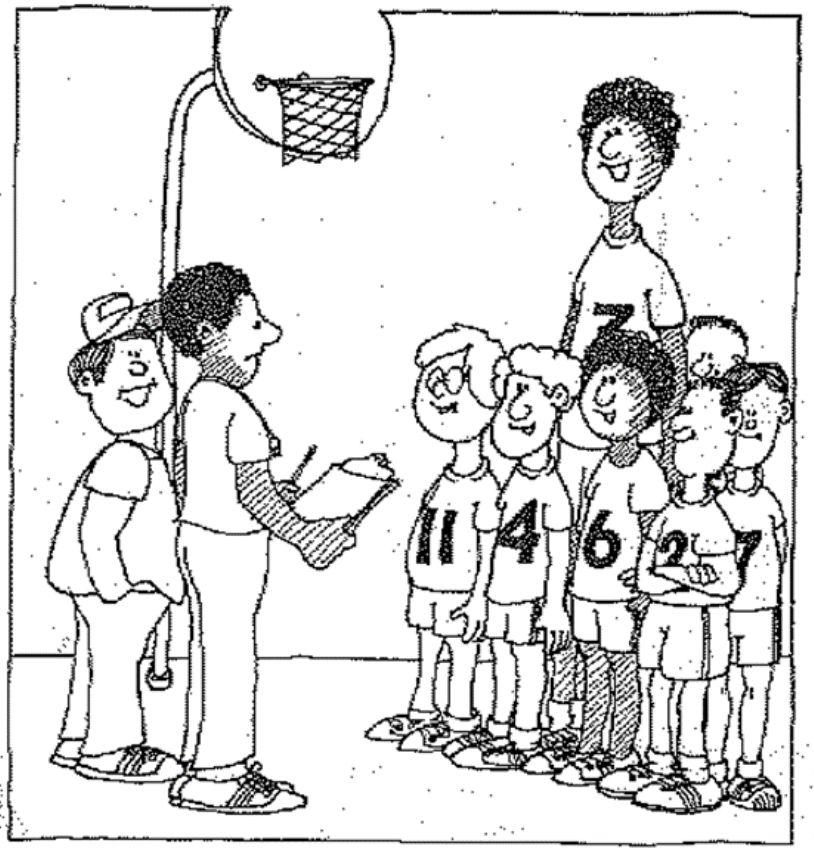
"Excellent health statistics - smokers are less likely to die of age related illness"

BASIC STATISTICS FOR THE CLINICIAN

- Three published papers:
  - Reed JF, Salen P, Bagher P. Methodological and statistical techniques: What do residents really need to know about statistics? Journal of Medical Systems, 2003;27(3):233-238.
  - Narayanan R, Nugent R, Nugent K. An investigation of the variety and complexity of statistical methods used in current internal medicine literature. Southern Medical Journal, 2015;108(10): 629-634.
  - Arnold LD, Braganza M, Salih R, Colditz GA. Statistical trends in the Journal of the American Medical Association and implications for training across the continuum of medical education. PloS ONE, 2013;8(10):e77301.
- Reviewed a randomly selected set of published papers and categorized the statistics used in each
- Identified the basic statistics that if you understand, will allow you to read and interpret 65% to 70% of the studies published in clinical fields

BASIC STATISTICS FOR THE CLINICIAN

- Descriptive statistics
- Concept of a p value
- Understanding what determines statistical test selection
- T-test; F test
- Chi-square/Fisher's Exact Test
- Odds ratios & CIs
- Regression
- Correlations
- Basic epidemiology concepts:
  - Risk statistics
  - Incidence and Prevalence
  - Sensitivity and Specificity

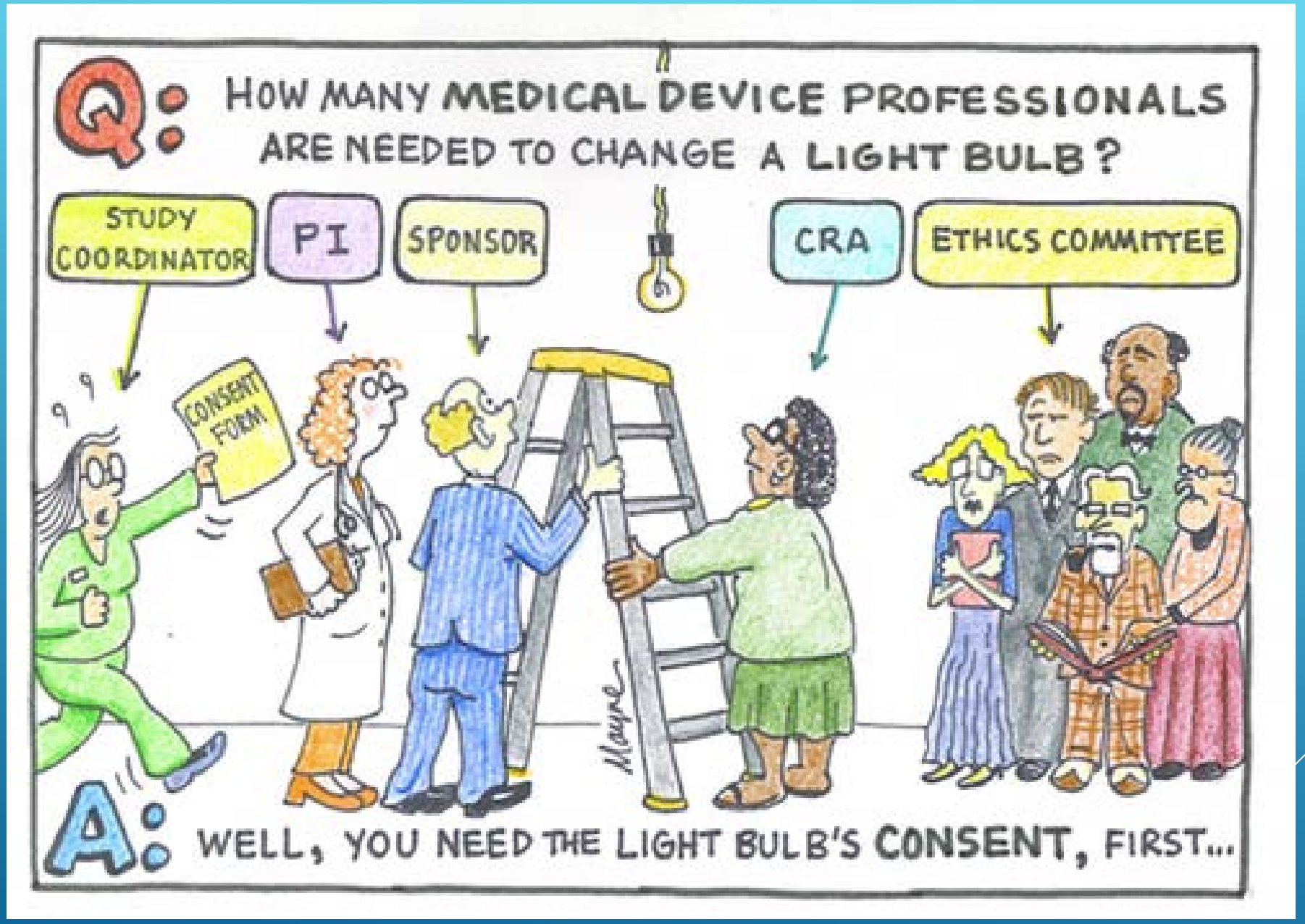


" SHOULD WE SCARE THE OPPOSITION BY ANNOUNCING OUR MEAN HEIGHT OR LULL THEM BY ANNOUNCING OUR MEDIAN HEIGHT ? "

moore

FORMING RESEARCH TEAMS

- Multidisciplinary is key!
- Developing research groups around topics and interests
- Who should be on the team
  - Experts in the science
  - Experts in the methods (including analysis and interpretation)
  - Clinical experts
- Defining roles and responsibilities
- Authorship, percent effort issues
- For funding – a collaborative track record is important


Q:
HOW MANY MEDICAL DEVICE PROFESSIONALS ARE NEEDED TO CHANGE A LIGHT BULB?
STUDY COORDINATOR
PI
SPONSOR
CRA
ETHICS COMMITTEE
CONSENT FORM
A:
WELL, YOU NEED THE LIGHT BULB'S CONSENT, FIRST...

FINDING FUNDING

- Where to find funding
  - Traditional sources
  - Get creative
- Funders look for
  - A project that logically extends from what is already known
  - A testable question and feasible project
  - Relevance and applicability
  - Qualified team with a proven track record
  - Capacity to do the project
  - Potential for further work
- Prepare early; Plan to be patient!

FINDING FUNDING

https://www.grants.gov/learn-grants/grant-programs.html

https://www.fic.nih.gov/Funding/NonNIH/Pages/default.aspx

https://www.grantwatch.com/cat/14/health-and-medical-grants.html

Dunlop M. Steps for successful funding applications. Injury 2010; 415:S7-S9. https://ac.els-cdn.com/S0020138310002238/1-s2.0-S0020138310002238-main.pdf?_tid=e92abd65-874c-4d7c-b588-9dae47f7c154&acdnat=1548731904_f57b77ee5974a3a8e639da90691c2952

Isaac Newton struggles to write the economic impact section of his 'gravity' proposal.

WHAT IF YOU HAVE NO FUNDING?

- Assess what resources you do have
  - Students, trainees, volunteers
  - Institutional support
  - Existing data
- Work in teams – maximize output with more minimal effort
- Leverage current data to get funding for further work

WORKING WITH STATISTICIANS/EPIDEMIOLOGISTS

- What resources are available?
- Involve them EARLY
- Bring them up to speed on the clinical topic
- Make sure expectations are clear and realistic
- Credit and authorship

QUESTIONS AND DISCUSSION