Clinical Research: Straight Talk about When Expectations Meet Reality

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ACCELERATING RESEARCH. IMPROVING HEALTH.

Agenda

Fundamentals

- The scientific method
- Phases of trials
- Basic evolution of trial structure
- History: Errors, Corrections and Successes

Critical skills

Identifying pressures

The business of clinical research vs. the goals and outcomes

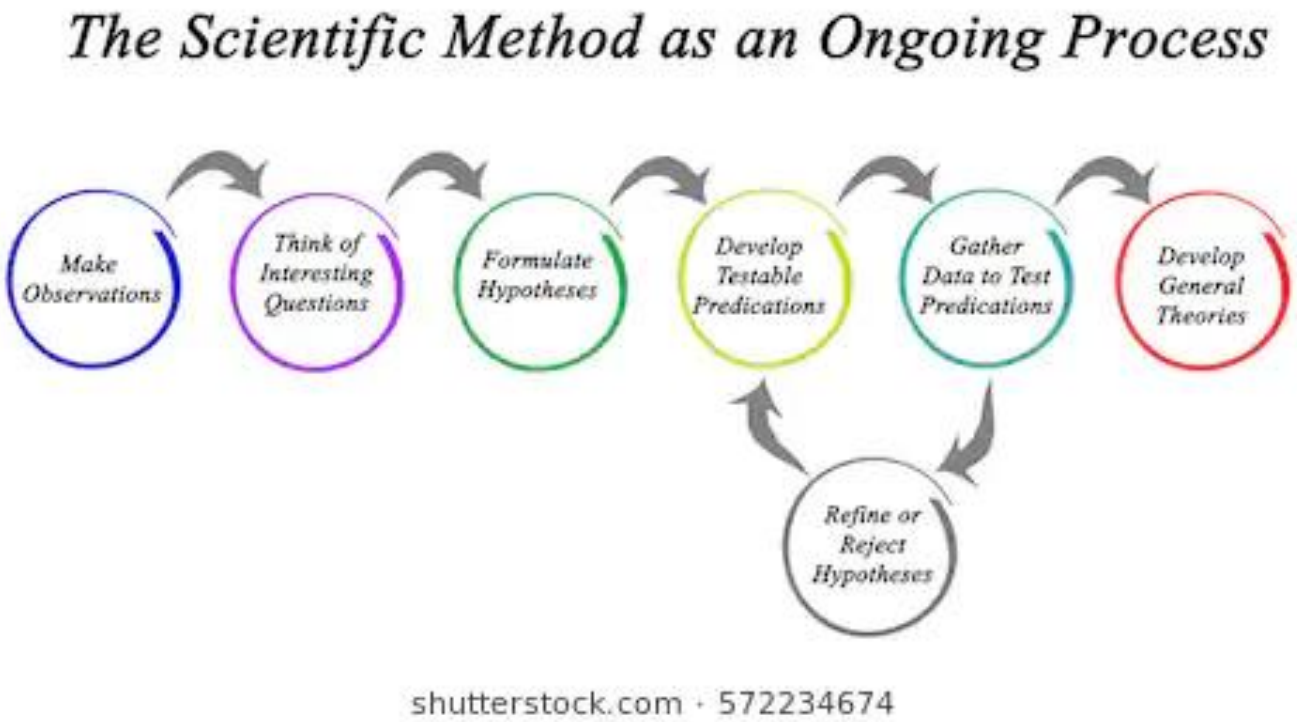
Permission or forgiveness: how do you decide?

Errors: embracing the chaos to find the opportunities

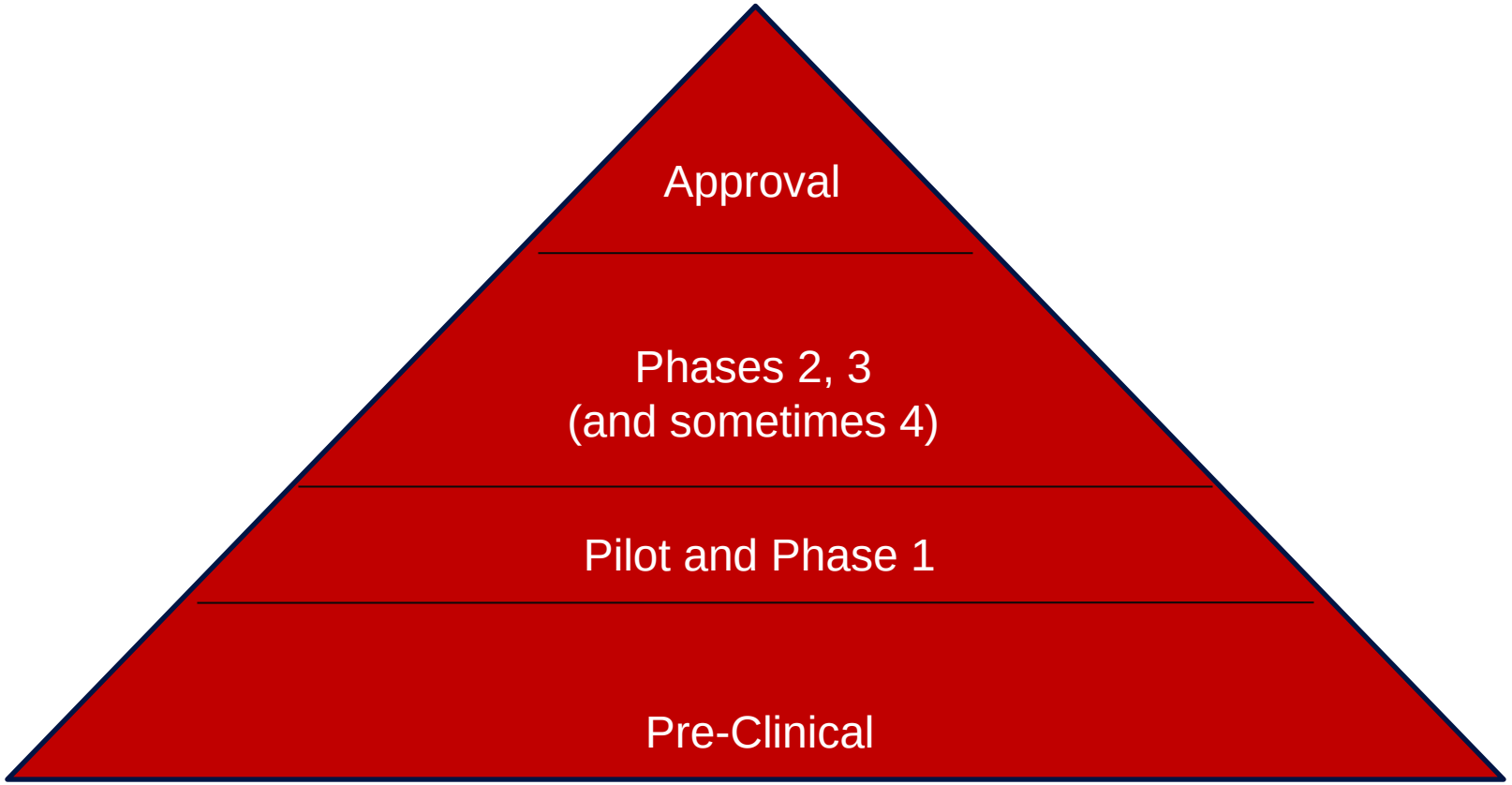
Public perception

The far-reaching effects of research outcomes

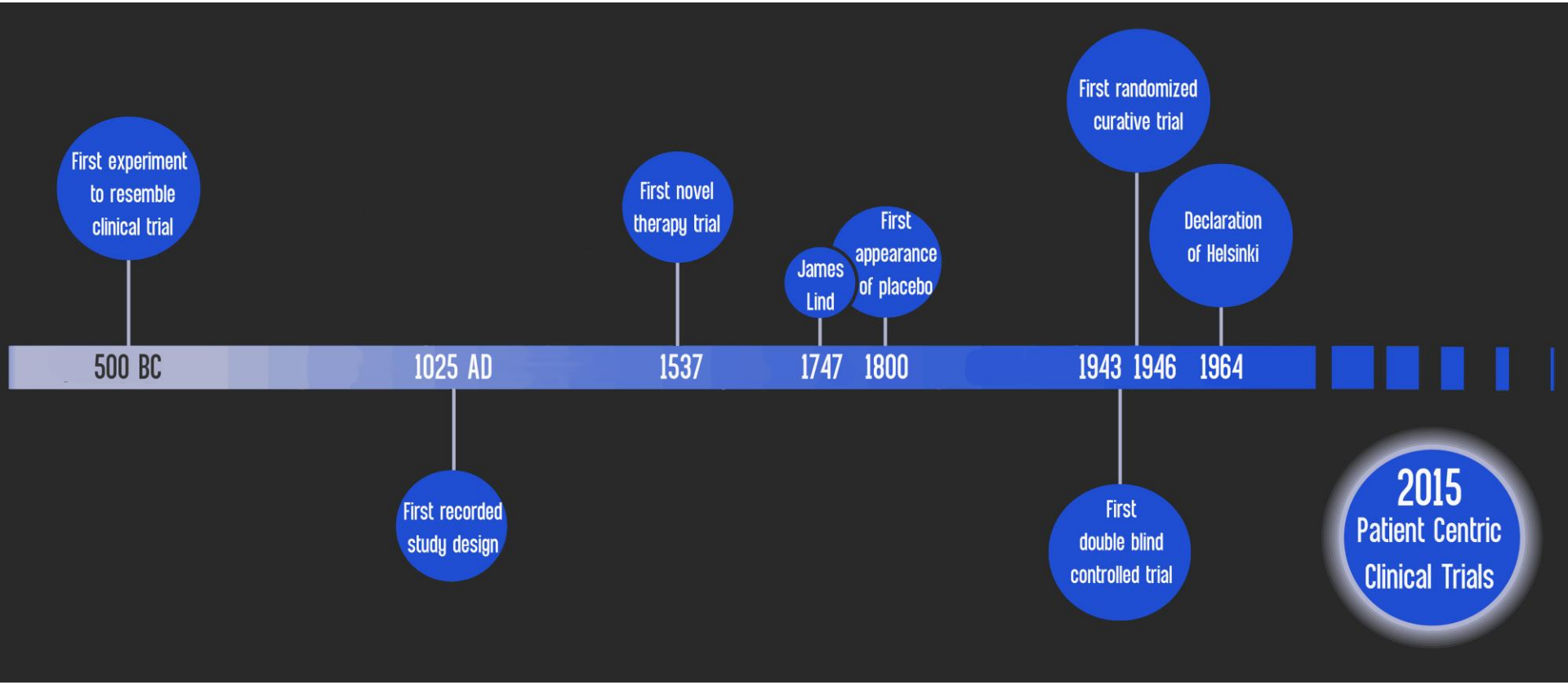
Fundamentals – The Scientific Method



Fundamentals – The Phases of Trials



Fundamentals – A History Lesson



Fundamentals - Historical Errors

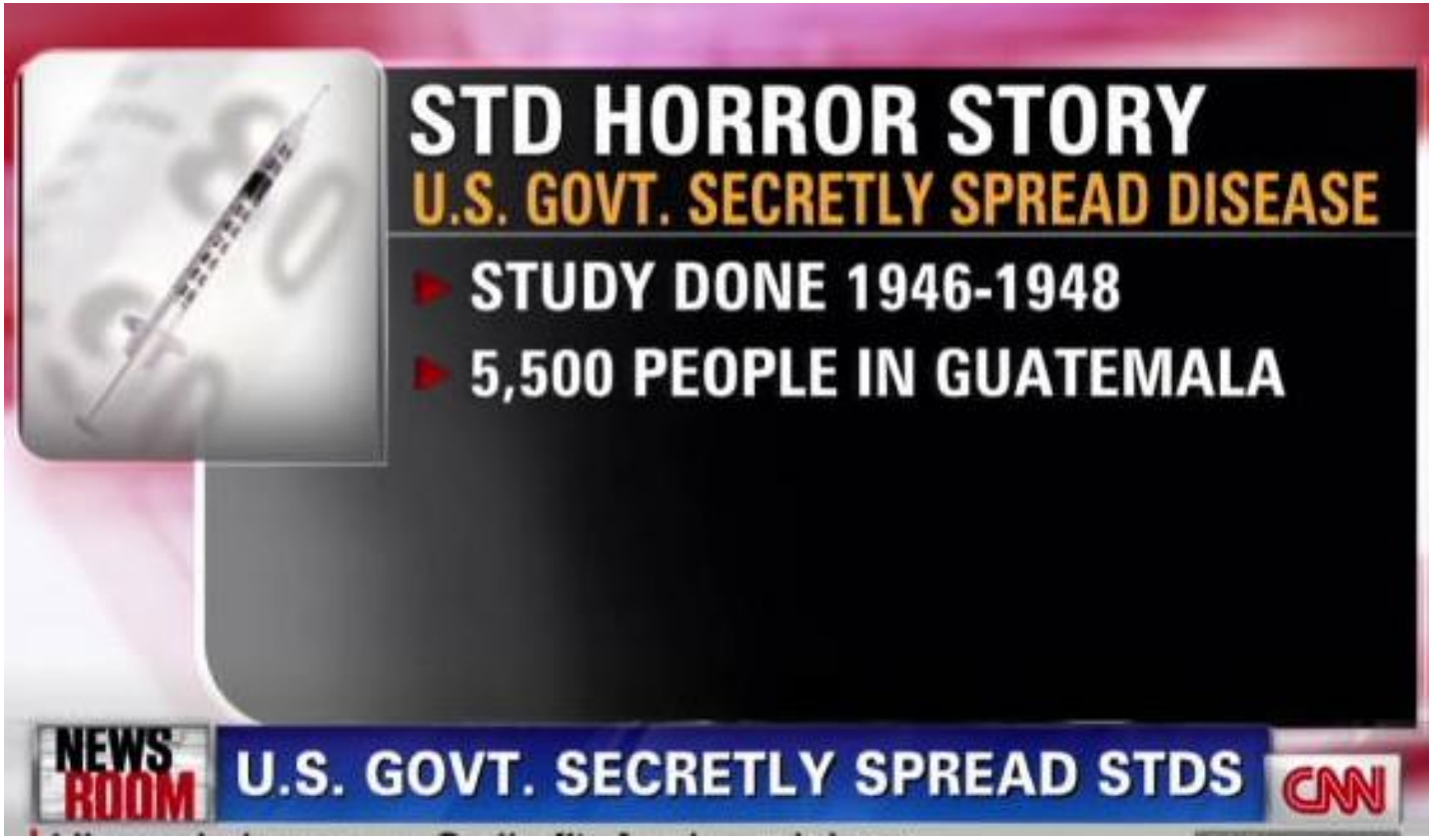
Ojanuga, D. (1993). The medical ethics of the'father of gynaecology', Dr J Marion Sims. *Journal of medical ethics*, *19*(1), 28-31.

Fundamentals – Historical Errors

Tuskegee Syphilis Experiment by US Public Health Service was a study conducted from 1932 to 1972 on 399 black African-American men. They were not given penicillin treatment deliberately to see how the disease propagated naturally in black men.

Brandt, A. M. (1978). Racism and research: the case of the Tuskegee Syphilis Study. *Hastings center report*, *8*(6), 21-29.

Fundamentals – Historical Errors



Spector-Bagdady, K., & Lombardo, P. A. (2013). "Something of an adventure": postwar NIH research ethos and the Guatemala STD experiments. *The Journal of Law, Medicine & Ethics*, *41*(3), 697-710.

Fundamentals – Historical Errors

Williams, P., & Wallace, D. (1989). *Unit 731: Japan's secret biological warfare in World War II* (pp. 178-179). New York: Free Press.

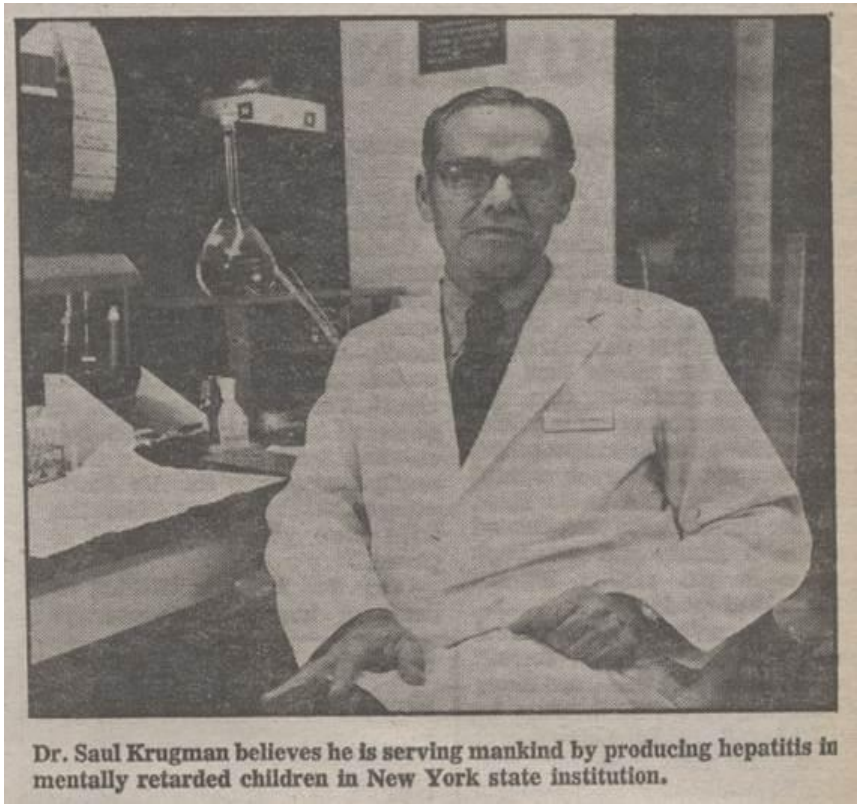
Fundamentals – Historical Errors

Annas, G. J., & Grodin, M. A. (1992). The Nazi doctors and the Nuremberg Code Human rights in human experimentation.

Fundamentals – Historical Errors

Marks, J. (1979). *The search for the" Manchurian candidate": The CIA and mind control* (pp. 127-130). New York: Times Books.
Thomas, G. (1989). Journey into madness: The true story of secret CIA mind control and medical abuse.
Rappoport, J. (1995). CIA Experiments with Mind Control on Children. *Perceptions Magazine*, 56.

Fundamentals – Historical Errors

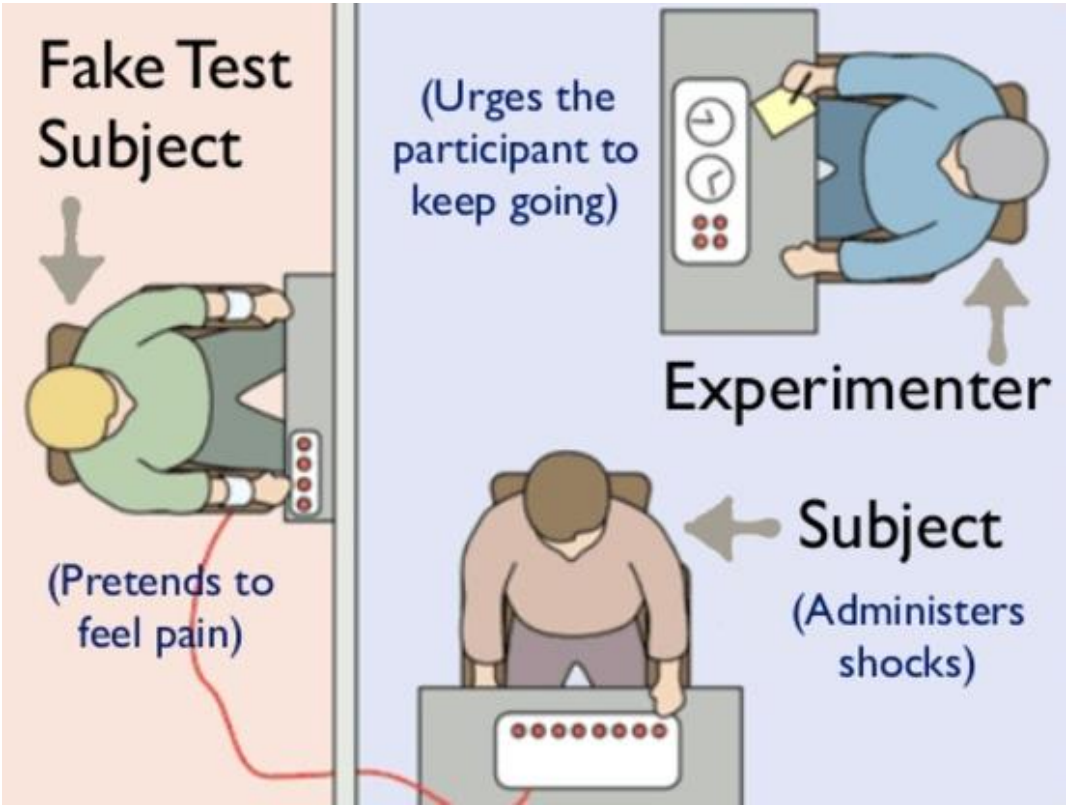


Dr. Saul Krugman believes he is serving mankind by producing hepatitis in mentally retarded children in New York state institution.

Krugman, S., Ward, R., Giles, J. P., Bodansky, O., & Jacobs, A. M. (1959). Infectious hepatitis: detection of virus during the incubation period and in clinically inapparent infection. *New England Journal of Medicine*, *261*(15), 729-734.

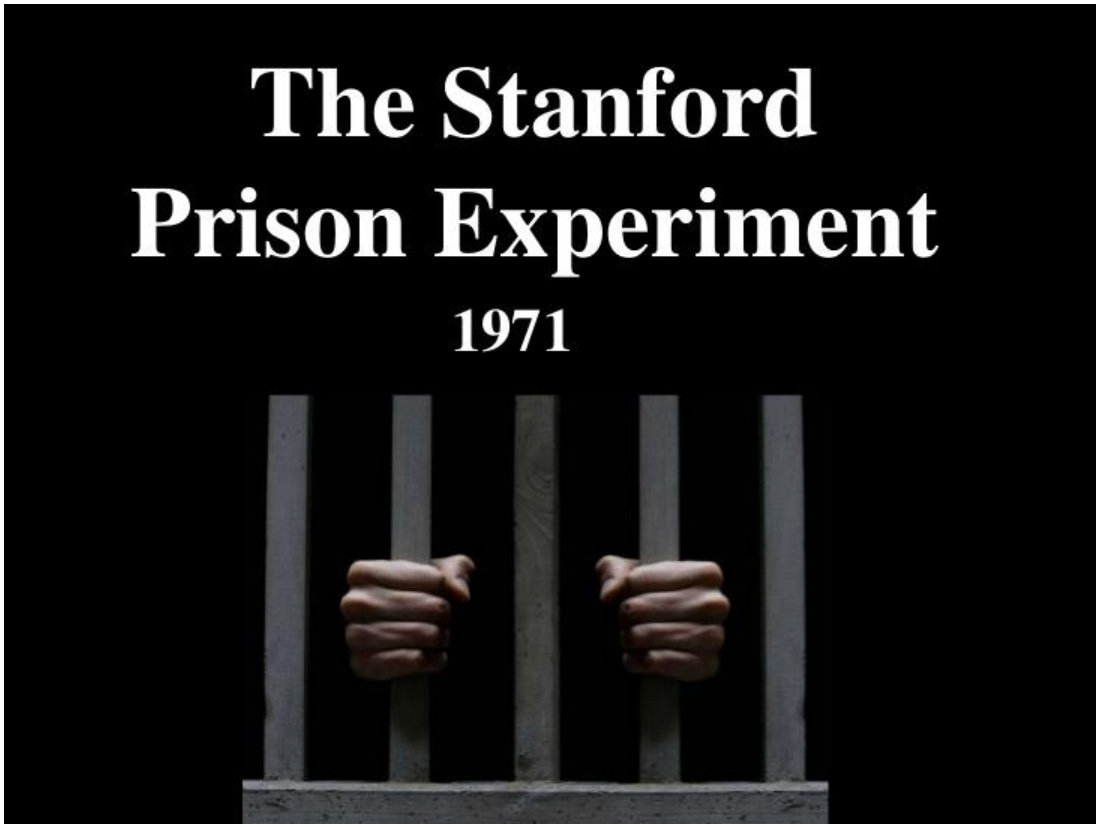
Krugman, S. (1986). The Willowbrook hepatitis studies revisited: ethical aspects. *Reviews of infectious diseases*, *8*(1), 157-162.

Fundamentals – Historical Errors



Milgram, S. (1963). Behavioral study of obedience. *The Journal of abnormal and social psychology*, *67*(4), 371.
Blass, T. (1991). Understanding behavior in the Milgram obedience experiment: The role of personality, situations, and their interactions. *Journal of personality and social psychology*, *60*(3), 398.

Fundamentals – Historical Errors

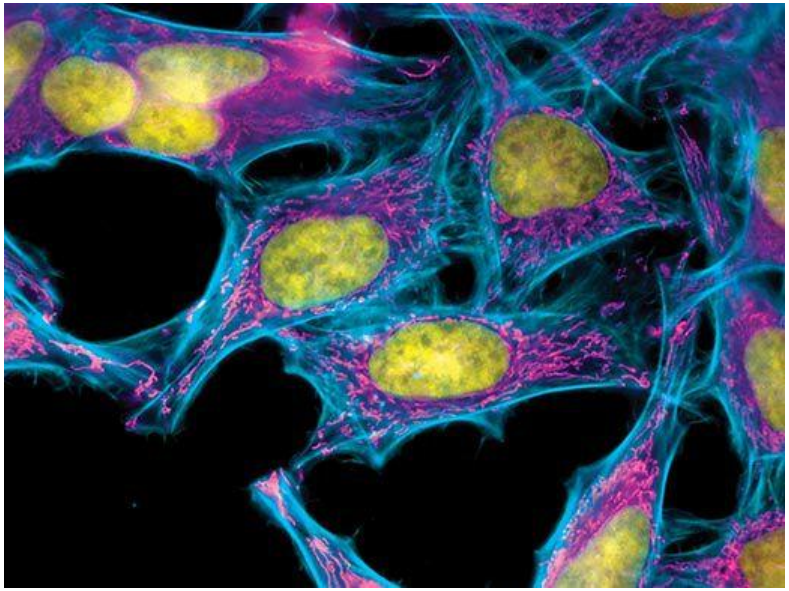


Zimbardo, P. G., Haney, C., Banks, W. C., & Jaffe, D. (1972). *Stanford prison experiment: A simulation study of the psychology of imprisonment*. Philip G. Zimbardo, Incorporated.
Zimbardo, P. G. (1973). On the ethics of intervention in human psychological research: With special reference to the Stanford prison experiment. *Cognition*

Fundamentals – Historical Errors

Culliton, B. J. (1974). The Sloan-Kettering affair: A story without a hero.

Fundamentals – Historical Errors



Skloot, R. (2017). *The immortal life of Henrietta Lacks*. Broadway Books.
Masters, J. R. (2002). HeLa cells 50 years on: the good, the bad and the ugly. *Nature Reviews Cancer*, *2*(4), 315.

Fundamentals – Correcting Our Past

Nuremberg Code

1. Voluntary human consent is essential
2. Experimental results should results in good for society
3. Anticipated results should justify the experiment
4. Avoid all unnecessary physical and mental suffering
5. No experiment if there is a chance of death/disability
6. Minimize risk of subjects
7. Proper preparations and facilities to protect subjects
8. Experiments conducted only by qualified persons
9. Subjects can withdraw at anytime
10. Terminate experiment if results are known or with best judgement

Macrae, D. J. (2007). The Council for International Organizations and Medical Sciences (CIOMS) guidelines on ethics of clinical trials. *Proceedings of the American thoracic society*, *4*(2), 176-179.

Fundamentals – Correcting our Past

World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama*, *310*(20), 2191.

Fundamentals – Correcting our Past

National Research Act (1974)

- Due to the publicity from the Syphilis Study, the National Research Act of 1974 was passed.
- The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- Commission spoke about the ethical principles that should be the basis for Research in Human subjects (Biomedical Research) & developing guidelines to ensure Research is conducted ethically

Culliton, B. J. (1974). National Research Act: restores training, bans fetal research. *Hastings Center Report*, *4*(4), 12-13.

Fundamentals – Correcting our Past

Regulations

Regulations

US 21CFR

- Part 11 – Electronics Records; Electronics Signatures
- Part 50 – Protection of Human Subjects
- Part 54 – Financial Disclosure by Clinical Investigators
- Part 56 – Institutional Review Boards
- Part 58 – Good Laboratory Practices for NonClinical Laboratory Studies
- Part 312 – Investigational New Drug Application
- Part 314 – Application for FDA Approval to Market a New Drug

US Code of Federal Regulations, Title 21, parts, 11, 50, 54, 56, 58, 312 and 314

Fundamentals – Correcting our Past

Belmont Report

- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research created "Belmont Report":
  - **Respect for persons**: treating people as autonomous agents and protecting those with diminished autonomy
  - **Beneficience**: minimizing potential harms and maximizing benefits of participation
  - **Justice**: distributing benefits/risks fairly

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Bethesda, Md. (1978). *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Superintendent of Documents.

Fundamentals – Correcting our Past

ICH Good Clinical Practices, 1996

- Standards for design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials to provide assurance that data and reported results are credible and accurate.
- Assurance that the rights, safety and welfare of subjects are protected.

Failures - Thalidomide

Failures – Vioxx and Bextra

- Caused significant scrutiny into FDA methods of verification of data
- Controversial “correction” of New England Journal of Medicine publication and allegations of researchers knowing about problems prior to approval
- Increased oversight of Data Safety Monitoring Boards
- Bextra resulted in criminal fines after the Pharmacia & UpJohn Company admitted ‘intent to defraud or mislead’ related to promotion of the product
- Fun Fact: FDA approved the use of Vioxx for children the same day that Merck recalled the product for safety issues
- Both are strong reasons for detailed review of AE data in prospective trials

Failures – Able Laboratories

- Example of the importance of Good Manufacturing Practices
- Distributed generic products that were too potent, not potent enough, misbranded and adulterated.
- FDA utilized authority to disbar quality control executives for 5 years.
- Important standards set for the manufacturing of products as well as the preparation of products in pharmacies and hospitals

Successes - Penicillin

- "Without penicillin, 75% of the people now alive would not be alive because their parents or grandparents would have succumbed to infections. The effects of a drug like this are absolutely mind-boggling." Stone, T. W., & Darlington, G. (2000). *Pills, Potions and Poisons: How Drugs Work*. Oxford University Press.
- Irony: over-use has led to resistant bacteria.

Successes - Insulin

- Grandfather of all hormone therapy, identified in 1921.
- Improved quality and length of life for people with diabetes.
- One of the best examples of collaboration between industry and academic researchers.

Successes – Smallpox & Polio Vaccines

- Made smallpox the first disease to be eradicated
- Important advances in preventative medicine and infectious disease
- Marriage of public health and clinical research

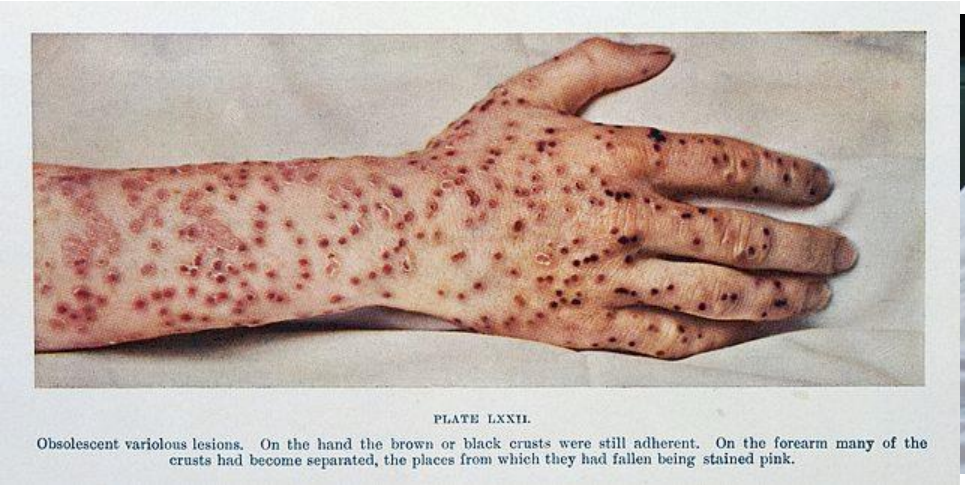
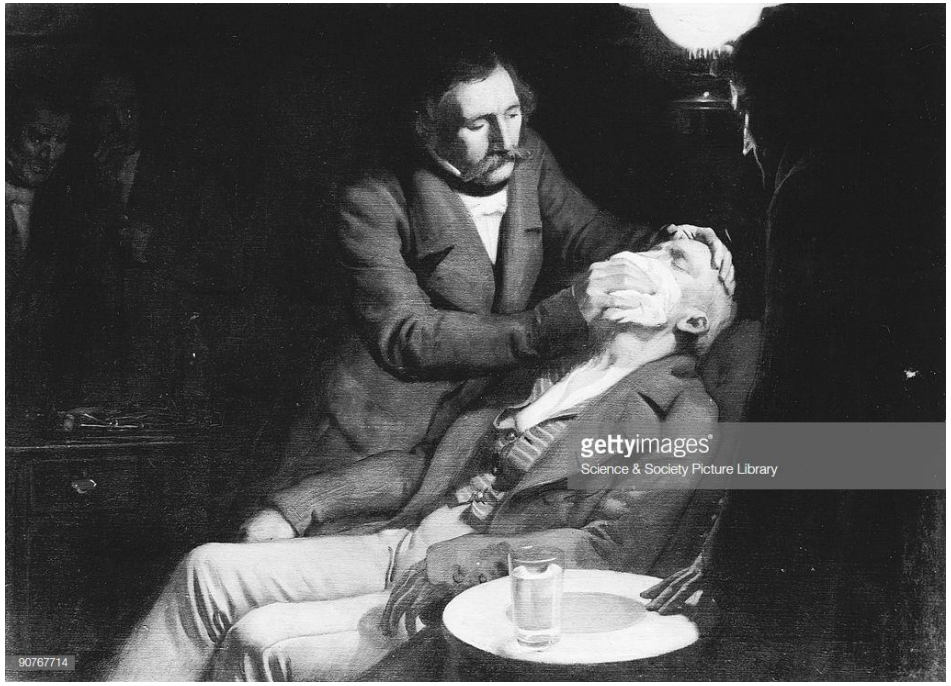


PLATE LXXII.

Obsolescent variolous lesions. On the hand the brown or black crusts were still adherent. On the forearm many of the crusts had become separated, the places from which they had fallen being stained pink.

Successes – Ether (Anesthesia)

- Improved outcomes of surgery and dental interventions



Successes - Others

- Aspirin
  - First drug to allow treatment of simple pain
  - Now at the core of heart disease maintenance
- Oral Contraceptives
  - Provided women with control over their reproductive system
- Psychiatric Medications
  - Allowed improved quality of life for many with mood disorders
  - Led to significant decreases in need for hospitalization

Realistically Working in Clinical Research

Realistically Working in Clinical Research

THE MOST IMPORTANT SKILL….

Communication

Communication

- Strong: consistent message, impactful, thoughtful.
- Effective: anticipates needs, concise, detailed.
- Appropriate: respectful, professional, truthful, helpful.

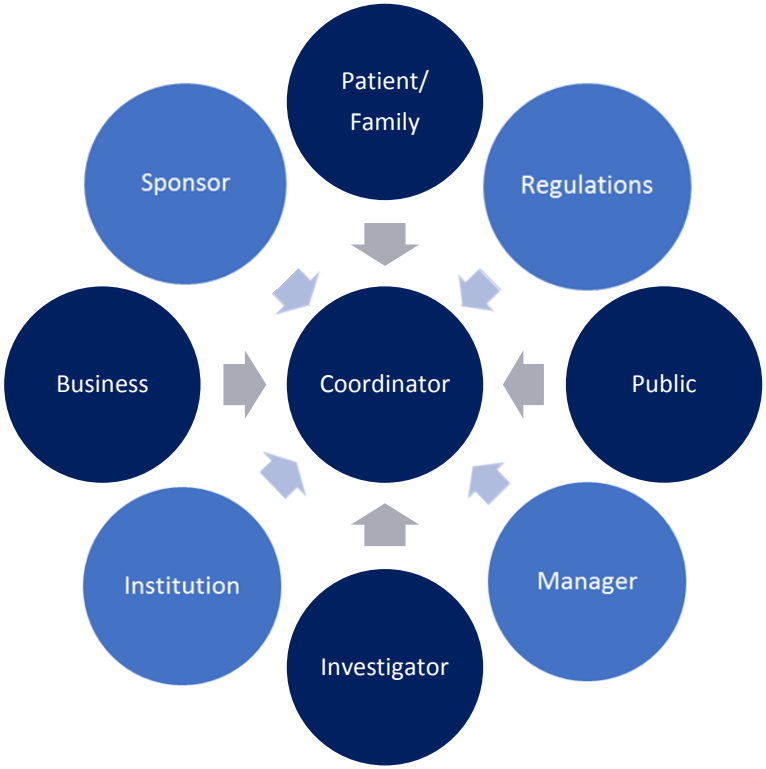
BUT….

It can also mean that you have to say things that are not palatable to your audience.

Building and Maintaining Relationships

- Both patients and investigators have commented that building and maintaining relationships is critical to the research coordination role.
- Relationships and communication are often cited in patient feedback in medicine
- The complications of taking part in clinical research require nuanced, clear communications and strong relationships

Constant Tension



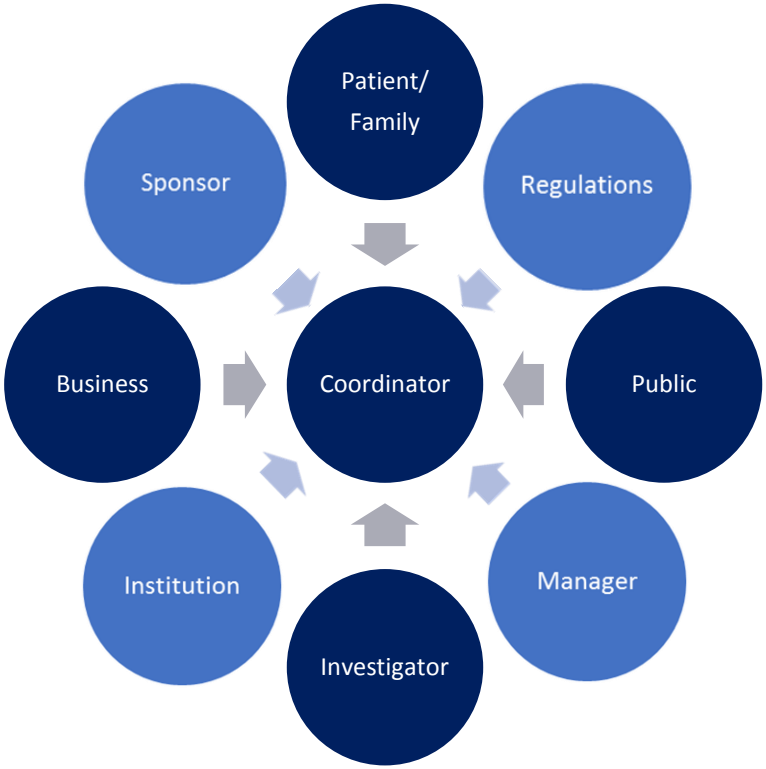
Treating Patients vs. Study Subjects

Highest goals of treating patients = Do no harm

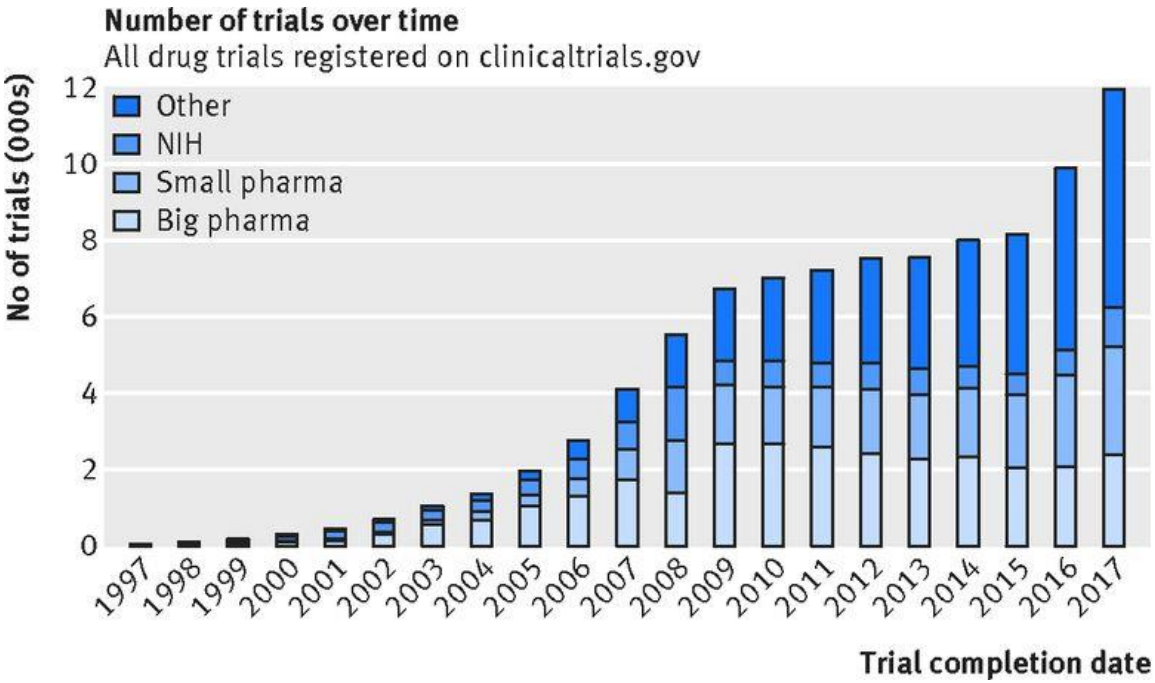
Goals of treating study subjects:

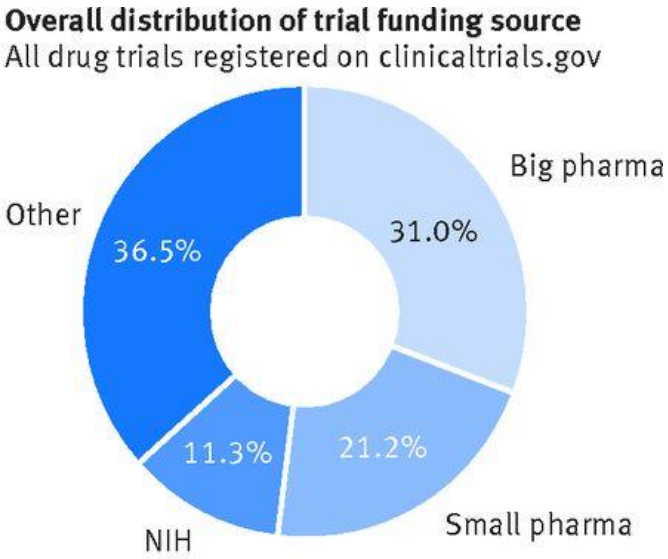
- Protecting subjects from potential abuses
- Minimizing risks, maximizing benefits
- Gathering information/new knowledge

Constant Tension



Clinical Trials as a Business





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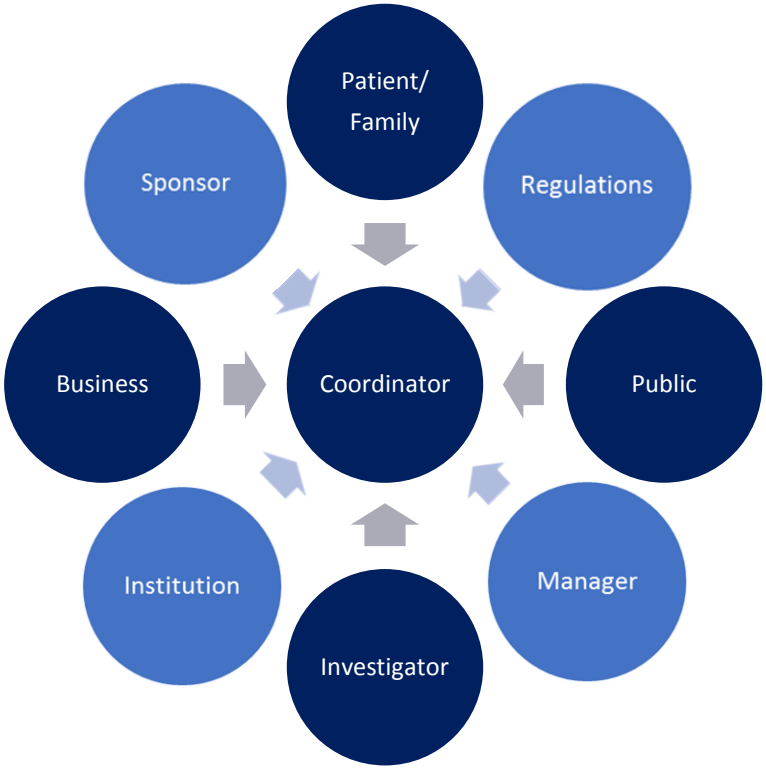
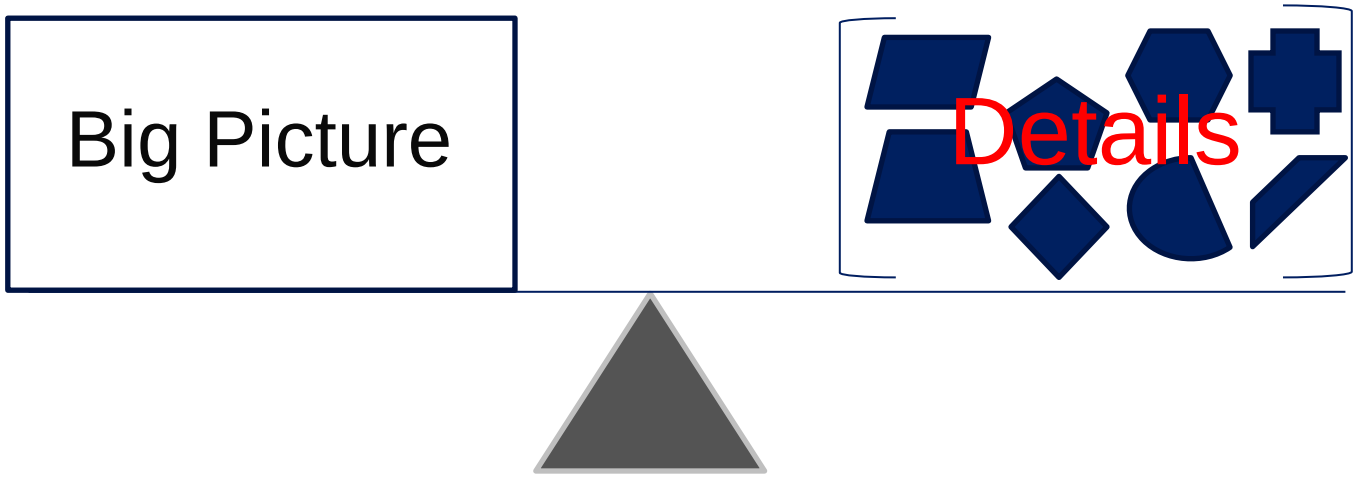
Zwierzyna Magdalena, Davies Mark, HingoraniAroon D, Hunter Jackie. Clinical trial design and dissemination: comprehensive analysis of clinicaltrials.gov and PubMed data since 2005 *BMJ*2018; 361 :k2130

Constant Tension



Indefinite vs. Detail

Research =



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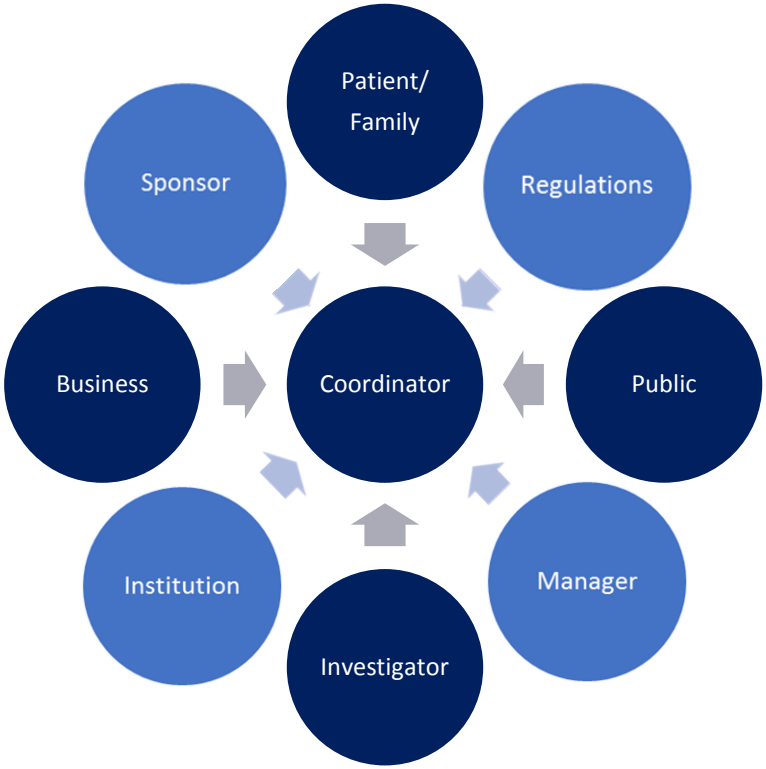

Agenda: Everyone Has One

Your Workload and You

- Learn to ask for help
- Remember there are no “stupid” questions
- Find and know your limits
- Honesty is the best policy, responsibility is how you earn respect
- Know that you are a representative and own it

Permission or Forgiveness?

- Marrying the regulations, expectations of the protocol and policies, procedures and culture of the institution can be the most challenging part of getting the job done.
- What is better:
  - Justifying your best intentions
  - Convincing everyone that you have the best intentions
- What factors matter in making the decision?

Stress, Pressure and Burnout

Saints, Warriors, & Scholars

- Whether you are a multi-talented, can-do coordination master or a fresh-faced idealist with big dreams (and anything in between!), you are ESSENTIAL to the clinical research process.
- Your work will remain relevant long after you have moved onto other parts of your career.
- This is an industry of change. You are an integral part of where we are headed!