Clinical Research: Straight Talk about When Expectations Meet Reality

Reina Hibbert, CCRC
Regulatory Manager
Phase 1 & RCC/Melanoma Clinical Trials
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

The Scientific Method as an Ongoing Process

1. Make Observations
2. Think of Interesting Questions
3. Formulate Hypotheses
4. Develop Testable Predications
5. Gather Data to Test Predications
6. Develop General Theories
7. Refine or Reject Hypotheses
Fundamentals – The Phases of Trials

- Pre-Clinical
- Pilot and Phase 1
- Phases 2, 3 (and sometimes 4)
- Approval
Fundamentals – A History Lesson

- First experiment to resemble clinical trial
- First recorded study design
- 500 BC
- 1025 AD
- 1537
- First novel therapy trial
- James Lind
- First appearance of placebo
- 1747
- 1800
- First randomized curative trial
- Declaration of Helsinki
- 1943
- 1946
- 1964
- First double blind controlled trial
- 2015
- Patient Centric Clinical Trials
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.
Fundamentals – Historical Errors

UNIT 731

Fundamentals – Historical Errors


Fundamentals – Historical Errors


Fundamentals – Historical Errors

The Stanford Prison Experiment
1971

Philip G. Zimbardo, Incorporated.


Fundamentals – Historical Errors

Fundamentals – Correcting Our Past

Nuremberg Code

1. Voluntary human consent is essential
2. Experimental results should result 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

Fundamentals – Correcting our Past

The Declaration of Helsinki

- “The well-being of the human subject should take precedence over the interests of science and society”
- Consent should be in writing
- Use caution if participant is in dependent relationship with researcher
- Limit use of placebo
- Participants benefit from research
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.

Fundamentals – Correcting our Past

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
  - **Beneficence**: minimizing potential harms and maximizing benefits of participation
  - **Justice**: distributing benefits/risks fairly
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
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

THIS IS FINE.
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
Constant Tension
Indefinite vs. Detail

Research =

Big Picture

Details
Constant Tension
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
• 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!