

2017 NINDS Clinical Trials Methodology Course
Eric D. Foster
Department of Biostatistics
University of Iowa

Overview of Randomized Clinical Trials

CLINICAL TRIALS

- Almost daily, the popular media report new research findings related to human health.
- From www.cnn.com (07/13/2017):
- Such results are often the result of clinical trials implemented by teams of researchers.

'Astounding' second-chance cancer drug heading for FDA approval

By Michael Nedelman, CNN

Updated 5:17 PM ET, Thu July 13, 2017



Cancer: The facts 01:00

Story highlights

The treatment genetically modifies the patient's cells so they can attack cancer cells

It was based on research in patients aged 3

(CNN) — A new gene therapy drug, the first in its class, was recommended for approval to the US Food and Drug Administration by an advisory committee on Wednesday. If approved by the FDA, the agency would consider it the

OUTLINE

- Historical Perspective
- Terminology
- Phase of an RCT
- Key Elements

HISTORICAL PERSPECTIVE

1537 – AMBROISE PARÈ Unintended Clinical Trial

- **Population:** Soldiers with wounds sustained in battle to capture the castle of Villaine
- **Standard Treatment:** Boiling oil – supply ran out
- **Test Treatment:** combination of egg yolks, oil of roses, and turpentine
- **Summary:** Soldiers treated with test treatment slept through the night and felt little pain. Those treated with boiling oil were feverish, with pain and swelling around their wounds.

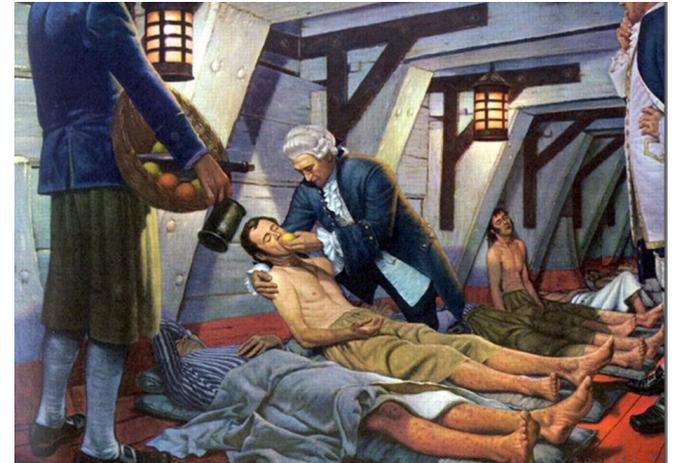


“...I determined never again to burn thus so cruelly the poor wounded by arquebuses” ~ Ambrose Parè

HISTORICAL PERSPECTIVE

1753 – LIND'S SCURVY STUDY First Controlled Clinical Trial

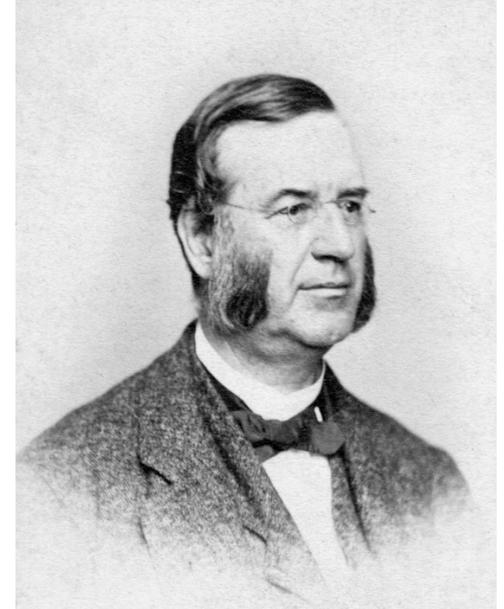
- **Population:** Study of several suggested 'cures' for scurvy in 12 British navy soldiers
- **Control Treatment:** Sea-water, ½ pint/day
- **Test Treatments:**
 - Cider, 1 quart/day
 - Elixir vitriol, 25 gutts, 3 times/day
 - vinegar, 2 tsp, 3 times/day
 - Nutmeg 3 times/day
 - Oranges (2) and Lemons (1)/day
- **Summary:** Two men on citrus treatment were back on their feet and fit for duty after only six days.
- But, British navy did not supply citrus to ships until 1795 - eventually switching to limes due to cost.



HISTORICAL PERSPECTIVE

1863 – FLINT’S RHEUMATISM STUDY First Placebo Controlled Clinical Trial

- **Population:** 13 hospital inmates with rheumatic fever
- **Treatments:** Mint Water
- **Summary:** Same positive results found that were observed in other studies that previously described effects of active treatments.
- Suggested too much importance was being attached to use of medicines, while ignoring natural tendency to get better with “no treatment”.



HISTORICAL PERSPECTIVE

1943 – MRC PATULIN TRIAL First Double Blind Controlled Trial

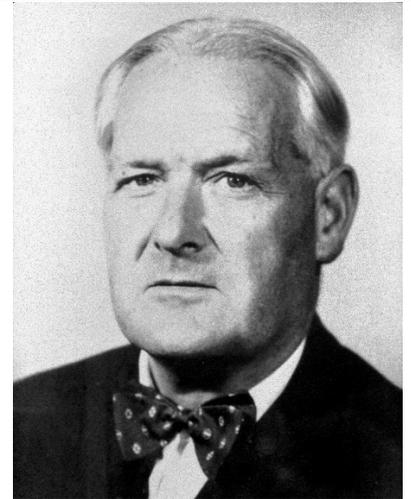
- **Population:** British office and factory workers suffering from colds
- **Treatments:** Patulin vs. Placebo
- **Allocation:** Alternation Procedure
- **Summary:** Study did not show any protective effect of patulin



HISTORICAL PERSPECTIVE

1946 – MRC STREPTOMYCIN TRIAL First Randomized Controlled Trial

- **Population:** Patients with Pulmonary Tuberculosis
- **Treatments:** Streptomycin & Bed Rest vs. Bed Rest Alone (Placebo)
- **Allocation:** Randomization procedure using random sampling numbers and sealed envelopes
- **Summary:** Demonstrated streptomycin was beneficial in treating tuberculosis
- But, patients developed resistance to the drug over time



HISTORICAL PERSPECTIVE

1906 – FOOD & DRUG ACT

- Response to deaths of several children due to contaminated smallpox vaccines
- Provided legal definitions for terms ‘adulterated’ and ‘misbranded’, and prescribed legal penalties for each offense
- No drug review part of law
 - Only required drug to meet standards of strength and purity
 - No requirement for submitting any information to FDA before marketing

HISTORICAL PERSPECTIVE

1911 – US vs. JOHNSON

- Government seized large quantity of product called “Dr. Johnson’s Mild Combination Treatment for Cancer”
- Case went all the way to the Supreme Court – ruled that new law did not prohibit false claims, only ‘false and misleading claims regarding ingredients or identity of drug’
- Led to the Sherley Amendment, which prohibited labeling medicines with false therapeutic claims
- But, government had to prove intent to defraud

CANCER CAN BE CURED

I WANT TO SEND TO ALL SUFFERERS FROM CANCER, THESE TWO BIG BOOKS ABSOLUTELY FREE

and these statements prove it

Back of Every Statement I make Is the Word of Living Hundreds Who Have Used My Mild Combination Treatment.

Ten years of successful practice—in the Exclusive Treatment of Cancer—backed by the scores of testimonials I am able to furnish—from those who have used my Mild Combination Treatment—and are now well—should give me the right to say—Cancer Can Be Cured!

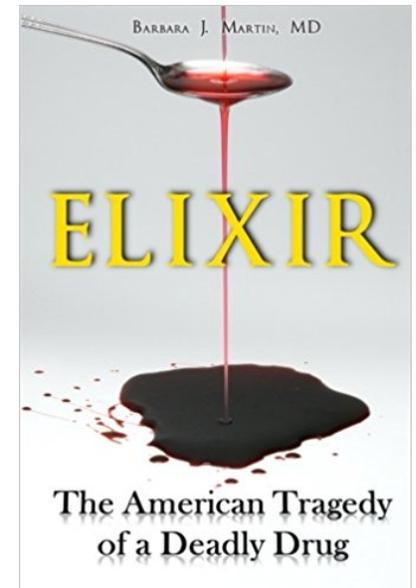
I have no stronger evidence to offer than the actual living proof of those who have suffered and are now well. Read their statements and if you want more proof write for the two large books

DR. JOHNSON REMEDY CO., INC. Kansas City, Mo.

HISTORICAL PERSPECTIVE

1937 – ELIXIR SULFANILAMIDE DISASTER

- Sulfanilamide was one of the first ‘wonder drugs’, used to treat streptococcal infections (i.e., strep throat)
- Responding to consumer demands, the drug company developed a liquid form
- Solvent used was diethyl glycol, a poison (chemically related to antifreeze)
- Product not tested in animals or humans before marketing
- Led to the deaths of more than 100 in U.S.



HISTORICAL PERSPECTIVE

1938 – FOOD, DRUG, AND COSMETICS ACT

- Set of laws giving authority to FDA to oversee the **safety** of food, drugs, and cosmetics
- Prohibited false therapeutic claims & required drug sponsors to submit safety data (clinical and pre-clinical) to FDA officials prior to marketing
- Allowed FDA to block or delay marketing of new drugs, but no true requirement for ‘approval’
 - Default position was approval
 - If no regulatory response was received after 60 days, company could proceed with marketing new drug

HISTORICAL PERSPECTIVE

1961 – THALIDOMIDE

- Thalidomide, a popular sleeping drug in Europe, was discovered to cause severe birth defects in babies whose mothers took the drug during pregnancy
- The drug was never approved for sale in the U.S.
- But, the drug sponsor sent drug samples to thousands of U.S. doctors who gave samples to patients without telling them the drug was experimental
- This unauthorized 'sample program' led to more than a dozen thalidomide babies in the U.S.



HISTORICAL PERSPECTIVE

1962 – KEFAUVER-HARRIS AMENDMENT

- Introduced a ‘proof of efficacy’ requirement, based on ‘adequate and well controlled’ studies
- 60 day approval ‘default’ was removed
- Prohibited testing a drug in humans until preclinical studies predict drug can be given safely
- Required drug advertising to disclose accurate information about side effects and efficacy of treatments
- First U.S. law requiring informed consent

HISTORICAL PERSPECTIVE

1962 – KEFAUVER-HARRIS AMENDMENT

- Sponsors required to file a notice for exemption for use of an investigational new drug (IND)
- Technically, an IND is an exemption from normal pre-marketing requirements for new drug (NDA)
 - Alerts regulators of sponsor's intent to begin clinical studies in the U.S.
 - Provides preliminary animal toxicity data
 - Provides information about manufacturing process
 - Describes initial clinical study being proposed
 - Provides assurance that an institutional review board (IRB) will approve study protocol before it begins

HISTORICAL PERSPECTIVE

Other key dates in the history of clinical trials:

- 1958 Food additives amendment (repealed in 1976)
- 1964 Declaration of Helsinki
- 1979 Belmont Report
- 1983 Orphan Drug Act ('rare' < 200,000 cases in the U.S.)
- 1991 The Common Rule published in U.S.
- 1993 FDA launched MedWatch
- 1996 International Conference on Harmonization (ICH) publishes "Good Clinical Practice"
- 2000 NIH releases clinicaltrials.gov website
- 2006 Clinical & Translational Science Awards (CTSA) program initiated

TERMINOLOGY

- **Clinical Trial:**

- An experiment testing medical treatments or prevention strategies on human subjects
 - Experiment: A series of observations made under conditions controlled by the scientist
 - Prospective
 - Comparative

TERMINOLOGY

- **Randomized Clinical Trial (RCT):**
 - A clinical trial with *at least* one control treatment and one test treatment
 - Some key elements to consider:
 - Blinding (Masking)
 - Type of Treatment
 - Type of Control

TERMINOLOGY

- **Blinding (Masking):**
 - Concealment of the identity of the intervention
 - Single Blind: to the patient
 - Double Blind: to the patient and investigator
 - The more subjective the intervention, the more important the blinding
 - In some cases, an unblinded trial may be the only option (e.g., behavioral interventions)
 - If blinding is not possible, blinded outcome assessment should be considered

TERMINOLOGY

- **Types of 'Treatments':**
 - Drug (or drug regimen)
 - Surgical procedure
 - Medical device
 - Therapeutic modality (radiation, biologic therapy)
 - Diet
 - Behavioral intervention (education)
 - Exercise regimen

TERMINOLOGY

- Types of 'Controls':
 - Placebo
 - Another drug regimen (Active Control)
 - Adding an additional agent to a standard regimen
 - Different doses/intensities of an intervention

PHASES

- Phase I:
 - Mainly focus on safety & toxicity profile of investigational compound
 - First in humans
 - Small, uncontrolled
 - Healthy volunteers / failed conventional therapy
 - Dose-escalation protocols: Maximum Tolerated Dose (MTD)

PHASES

- **Phase II:**

- “Proof of Concept” – Examine whether drug has sufficient biologic activity/effect
 - Strict eligibility criteria
 - With or without comparison group
 - Performed in patients with disease/condition of interest
 - “Go”/”No Go” decisions
 - Nonworking drugs should be “killed” at this stage to avoid investing more resources & effort
 - Determine safety profile – estimate rates of adverse events

PHASES

- **Phase III:**

- Confirmative evaluation of effectiveness (overall benefit to risk assessment)
 - Compare with standard therapy or placebo
 - Large sample size
 - Generally multi-site
 - Superiority / Equality / Equivalence / Non-Inferiority

PHASES

- **Phase IV:**

- Long-term surveillance studies (“post-marketing”) for safety
 - Continue to collect evidence regarding the safety, efficacy, & toxicity of the treatment
 - Look for rare side effects & interactions with other treatments
 - Generally non-randomized
 - Can lead to new warning labels or withdrawal of drug from market

PHASES

- **Comparative Effectiveness Trials:**
 - A type of health care research that compares results of different approaches for managing a disease
 - Usually compares two or more types of treatment for the same disease
 - Designed to inform health care decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options

KEY ELEMENTS

- **Fundamental Point:**

- Every clinical trial must have one or more primary question(s)
- The question should be of interest and should be capable of being answered
- This is the question on which the sample size should be based
- Successful trial vs. positive/negative result
- The primary question should be:
 - Carefully selected
 - Clearly defined
 - Stated in advance

KEY ELEMENTS

- **Study Protocol:**
 - Provides a comprehensive description of key information for conduct of the trial
 - Go-to resource for questions regarding many study issues
 - Should be adhered to as strictly as possible
 - Any protocol deviations should be reported

PROTOCOL: TABLE OF CONTENTS

SYNOPSIS

1. STUDY OBJECTIVES

- Primary Objectives
- Secondary Objectives

2. BACKGROUND

- Rationale
- Supporting Data

3. STUDY DESIGN

PROTOCOL: TABLE OF CONTENTS

4. SELECTION & ENROLLMENT OF SUBJECTS

- Inclusion Criteria
- Exclusion Criteria
- Subject Enrollment Procedures

5. STUDY MEDICATION/DRUG/DEVICE

- Interventions, Administration, and Duration
- Handling of Study Medications/Interventions
- Adherence Assessment

PROTOCOL: TABLE OF CONTENTS

6. CLINICAL AND LABORATORY EVALUATIONS

- Schedule of Evaluations
- Timing of Evaluations
- Special Instructions and Definitions of Evaluations

7. MANAGEMENT OF ADVERSE EXPERIENCES

6. CRITERIA FOR INTERVENTION DISCONTINUATION

PROTOCOL: TABLE OF CONTENTS

9. STATISTICAL CONSIDERATIONS

- General Design Issues
- Outcomes
- Sample Size & Accrual
- Data Monitoring
- Data Analysis

10. DATA COLLECTION, SITE MONITORING, & ADVERSE EXPERIENCE REPORTING

- Records to be Kept
- Role of Data Management
- Quality Assurance
- Adverse Experience Reporting

PROTOCOL: TABLE OF CONTENTS

11. HUMAN SUBJECTS

- Institutional Review Board (IRB) Review & Informed Consent
- Subject Confidentiality
- Study Modification / Discontinuation

12. PUBLICATION OF RESEARCH FINDINGS

13. REFERENCES