Clinical Research in the 21st Century: Evolving Paradigms for Clinical Trials

Janet E. Dancey

NCIC CTG NEW INVESTIGATOR CLINICAL TRIALS COURSE

August 9-12, 2011 Donald Gordon Centre, Queen's University, Kingston, Ontario

Educational Objectives

- Session Name: Clinical Research in the 21st Century: Evolving Paradigms for Clinical Trials

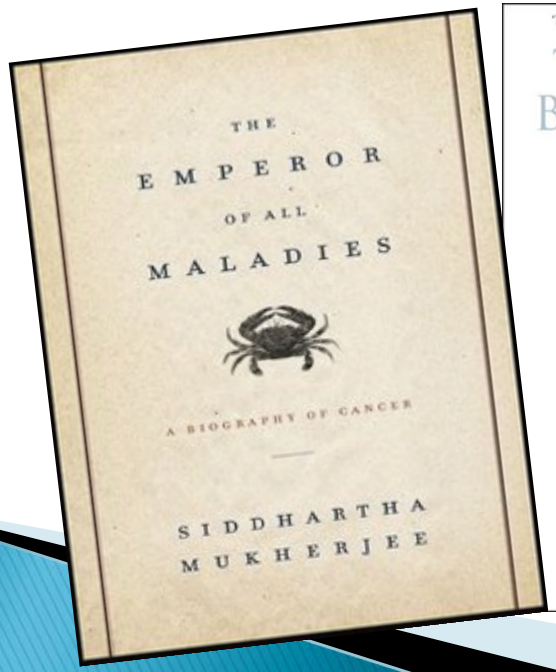
Educational Objectives:

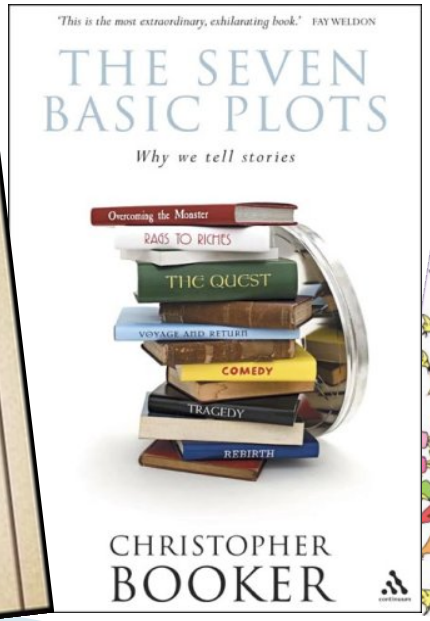
- At the end of the lecture the participant should be able to:

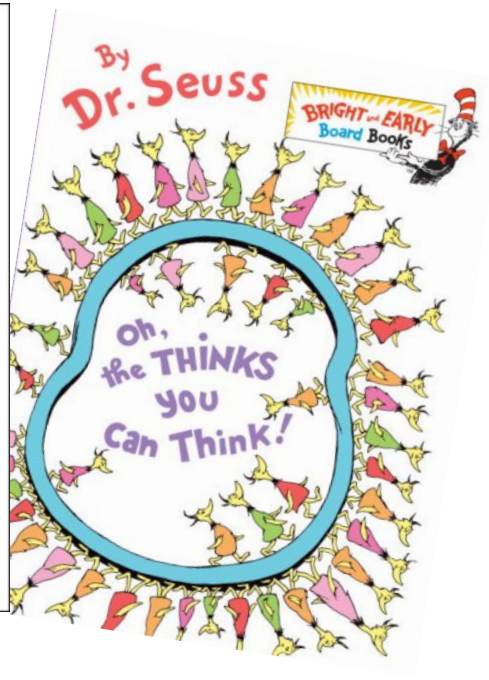
1. Define clinical trial
2. Provide examples of clinical trial designs
3. Understand and list the design elements for clinical trial design and conduct

Keynote

- An opening address that outlines the vision, issues and topics to be considered, the underlying themes
- Sources of inspiration







Introduction: What is a Clinical Trial?

- A clinical trial is a research study to answer specific questions about the effects of an intervention.
- Apply scientific method to test hypothesis/es and rigorously monitor and assess outcomes to understanding human (or animal) biology.
- May be required before the national regulatory authority approves marketing of the drug or device, or a new dose of the drug, for use on patients.

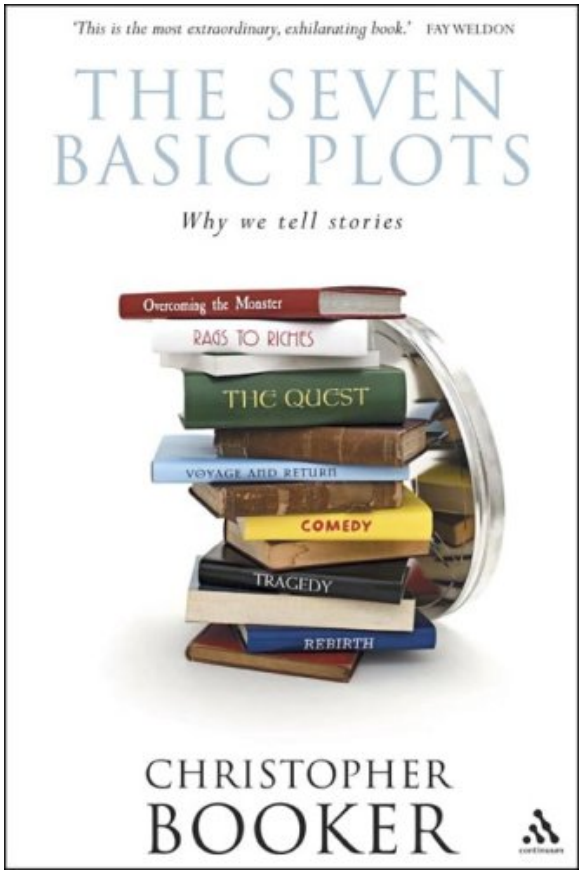
The Building Blocks

- Question
- Design/Method
- Execution
- Analysis
- Result/Outcome
- Ethical Standards
- Regulatory Compliance
- Economics

The Question?

Literature's Seven Basic Plots

- **Overcoming the 'monster'.**
  - Star Wars, James Bond, Dracula.
- **The Quest.**
  - Watership Down, Raiders of the Lost Ark
- **Journey and Return.**
  - The Wizard of Oz, Alice in Wonderland,
- **Comedy.**
  - Bridget Jones Diary, Pride and Prejudice
- **Tragedy.**
  - Devil's Advocate, Hamlet, Doctor Faustus
- **Rebirth.**
  - Snow White, A Christmas Carol.
- **Rags to Riches.**
  - Cinderella, David Copperfield.



Continuum International Publishing Group 2006

There are a limited number of basic themes or plots, but the weaving and shaping of these tales itself make them different.

The Question

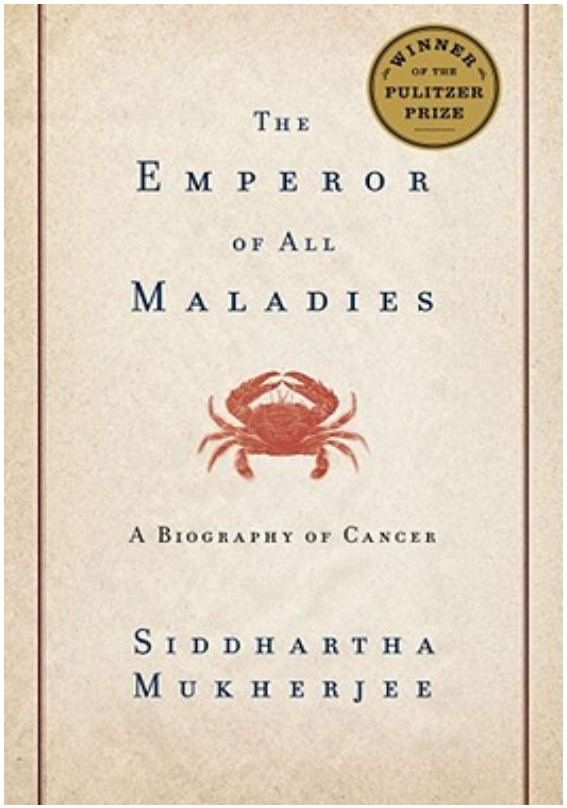
- Science and clinical need provide hypothesis and rationale

- Prevention: Prevent disease with medicines, vitamins, vaccines or lifestyle changes.
- Screening: Detection of diseases or health conditions.
- Diagnostic: Tests or procedures for diagnosing a disease or condition.
- Treatment: Experimental drugs, devices, surgeries, therapies, combinations.
- Quality of life: Improve comfort and the quality of life for individuals (Supportive Care trials).
- (Compassionate use trials or expanded access)

National Institutes of Health Glossary of Clinical Trial Terms, Clinicaltrials.gov

4 Basic Cancer Trial Questions

- New is better
- More is better
- Less is better
- It's equal



4 Basic Cancer Trial Questions

Question	Example
New is better	Radiation therapy for Hodgkin's Lymphoma Cisplatin for testicular cancer Tamoxifen for breast cancer Imatinib for chronic myelogenous leukemia
More is better	Combination therapy in ALL, Lymphoma Adjuvant therapy in breast cancer (More drugs, intensification, density, sequence)
Less is better	Radical mastectomy versus lumpectomy+radiation Minimal chemotherapy, radiation for Hodgkin's disease, testicular cancer
It's equal	Docetaxel versus Pemetrexed in Lung Cancer

There are a limited number of basic themes, but endless variation based on state of knowledge, technology, methods and interest.

Designs, Methods, Endpoints

History of clinical trials methods

- Daniel and Nebuchadnezzar Babylon circa 560 BCE
  - The first diet intervention trial Daniel 1: v12-15
- Avicenna and The Canon of Medicine circa 1025 CE,
  - Guide for practical experimentation for proving the effectiveness of medical drugs and substances
- James Lind, HMS Salisbury, 1747
  - Comparison the effects of acidic substances on groups of sailors
  - group given oranges and lemons recovered from scurvy in 6 days.
- Austin Flint 1863, United States
  - First treatment versus placebo (herbal remedy) in arthritis
  - “an epithet given to any medicine more to please than benefit the patient.” Hooper's Medical Dictionary of 1811
- Austin Bradford Hill, British MRC, 1948
  - streptomycin for treating pulmonary tuberculosis (BMJ 1948;2:769-82).
  - Minimization of bias - blinding and randomization

Key elements: defining intervention and group, comparison to control, minimization of bias, confidence in the result

Collier R CMAJ 2009;180:23-24

Clinical Trial Methods

Standardization and definitions

- Patient population under evaluation
- Interventions
- Endpoints and assessments
- Statistical certainty & power
- Minimization of bias (randomization, blinding, central review)

- Trials pass through phases for the progressive acquisition of information on safety and activity that supports a large multicentre trial and ultimately clinical practice.

Clinical Trial Phases

- **Phase 0**
  - FDA 2006 Guidance on Exploratory IND Studies.
  - "Window" studies
- **Phase I – Safety**
  - 1A – single agent, FIH
  - 1B – combination or expansion cohort
- **Phase II – Activity**
  - IIA single agent activity or dosing/scheduling.
  - IIB combination activity or activity against comparator.
- **Phase III – Efficacy**
  - Comparison with current 'gold standard'
- **Phase IV/V** – safety surveillance, comparative effectiveness & community-based research
  - integration into widespread public health practice

Trials pass through phases for the progressive acquisition of information on safety and activity that supports a large multicentre trial and ultimately clinical practice.
Design and endpoints are chosen to get to the next phase

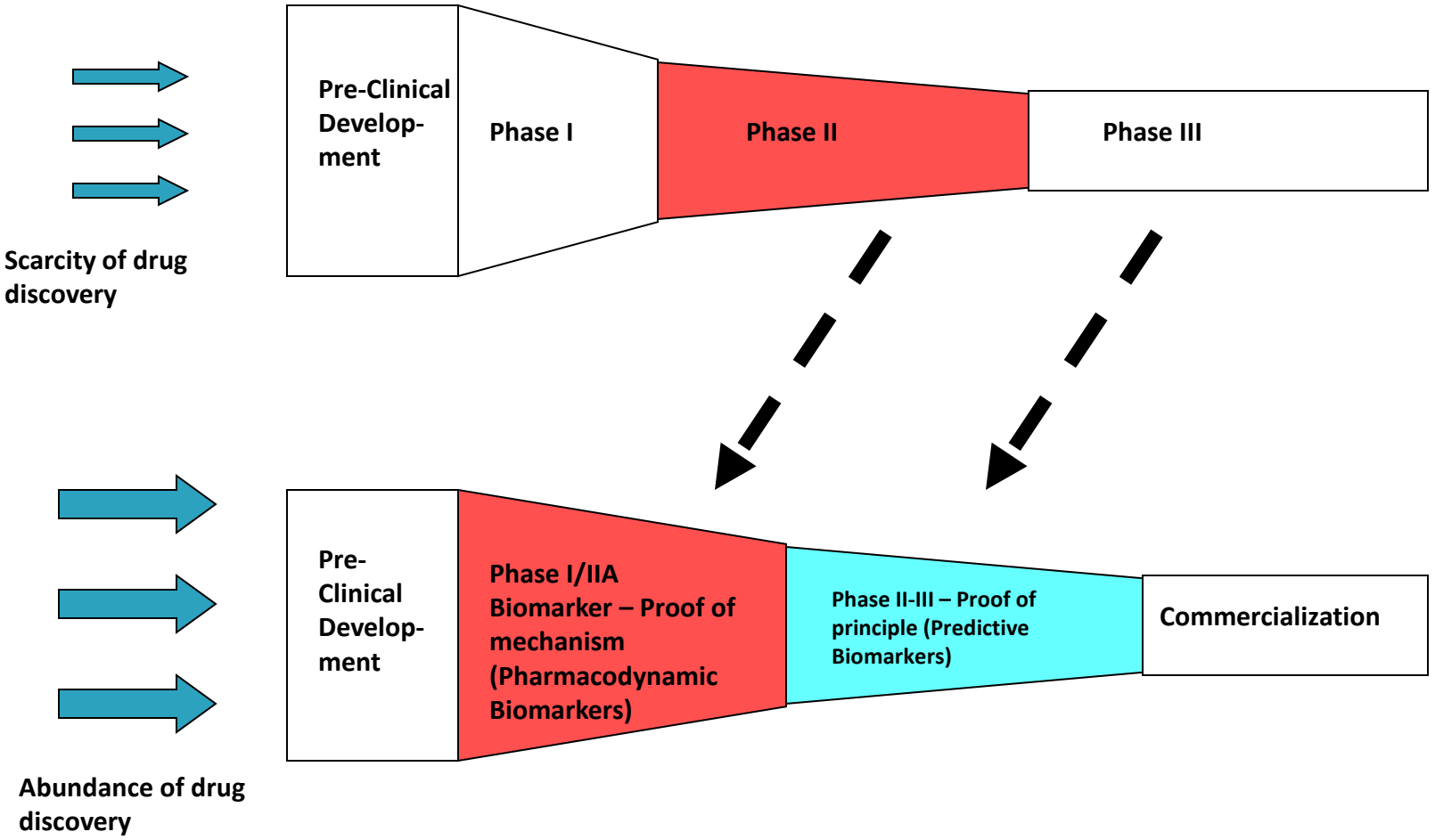
Robey, R. R. (2004). Journal of Communication Disorders, 37, 401-411.

Trial Designs and Endpoints

Trial Phase	Purpose	Endpoints	Modifications
0	Define dose/target Select agents	Target modulation PK	Normal Volunteers Pre-surgical/window
I	Safe dose/schedule	Toxicity Target Modulation PK Activity	Expanded cohorts to evaluate target, toxicity or screen activity
II	Activity	Response, progression Predictive markers	Randomization, markers
III	Efficacy/Clinical benefit	Survival, QoL, Predictive markers, Economics	Adaptive designs, PFS/DFS endpoints
IV/V	Effectiveness Clinical benefit	Safety, Survival, QoL, Economics	Real world testing

FDA 2006 Guidance on Exploratory IND Studies.
Robey, R. R. (2004). Journal of Communication Disorders, 37, 401-411.

Clinical Trials Changes: Compression of Phases



Adapted from Eli Lilly and Company, Lillian Siu

Endpoints

- Clinical Endpoint – a characteristic or variable that reflects how a patient feels or functions or how long a patient survives

Outcome	Failure	Trial Phase
Response	Progression (or stable disease)	II Metastatic
TTP	Progression	II/III Metastatic
TTF	Progression, Toxicity, Death	II/III Metastatic
PFS	Progression, Death	II/III Metastatic
DFS	Recurrence, Death	III Adjuvant
OS	Death	III
DSS	Death Due to Disease	III Adjuvant

VOLUME 25 · NUMBER 15 · MAY 20 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System

Clifford A. Hudis, William E. Barlow, Joseph P. Costantino, Robert J. Gray, Kathleen I. Pritchard, Judith-Anne W. Chapman, Joseph A. Sparano, Sally Hunsberger, Rebecca A. Enos, Richard D. Gelber, and Jo Anne Zujewski

Table 2. Proposed Standardized Definitions for Breast Cancer Clinical Trial End Points in the Adjuvant Setting

End Point	Invasive Ipsilateral Breast Tumor Recurrence	Local/Regional Invasive Recurrence	Distant Recurrence*	Death From Breast Cancer	Death From Nonbreast Cancer Cause	Death From Unknown Cause	Invasive Contralateral Breast Cancer†	Ipsilateral DCIS	Contralateral DCIS	Second Primary Invasive Cancer (nonbreast)‡
OS				X	X	X				
DFS-DCIS	X	X	X	X	X	X	X	X	X	X
IDFS	X	X	X	X	X	X	X			X
DDFS			X	X	X	X				X
DRFS			X	X	X	X				
RFS	X	X	X	X	X	X				
Recurrence-free interval§	X	X	X	X						
Breast cancer-free interval	X	X	X	X			X	X	X	
Distant recurrence-free interval			X	X						

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

General Criteria eg Solid Tumours

VOLUME 25 · NUMBER 13 · MAY 1 2007
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

We Should Desist Using RECIST, at Least in GIST

Robert S. Benjamin, Haesun Choi, Homer A. Macapinlac, Michael A. Burgess, Shreyaskumar R. Patel, Lei L. Chen, Donald A. Podoloff, and Chuslip Charnsangavej

Disease Specific

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

Richard L. Wahl[1,2], **Heather Jacene**[1], **Yvette Kasamon**[2], and **Martin A. Lodge**[1]

J Nucl Med. 2009 May ; 50(Suppl 1): 122S–150S.

Imaging Specific

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

Clin Cancer Res 2009;15(23):7412–20

Treatment Specific

Endpoints

- Surrogate Endpoint – A biomarker intended to substitute for a clinical endpoint.
  - Decrease duration and sample size for trial
  - Often easily & uniformly measured
  - Challenging to evaluate and validate
    - Relationship between surrogate, and clinical benefit is maintained despite intervention
    - FDG-PET in lymphoma
    - CTC in prostate cancer

Read: Sargent DJ, et al. Validation of novel imaging methodologies for use as cancer clinical trial end-points. Eur J Cancer. 2009 45:290-9.
Fleming TR. Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood). 2005 24:67-78.

Execution

It's Not the Idea. It's the Execution.

Ryan P. Allis, Zero to One Million

Efficiency and Excellence

- Rapid accrual
- Unimpeachable data
- Robust analysis
- Hightest ethical standard
- Regulatory compliance

- Teams, cores, tools for trials

Execution – Teams, Cores, Tools

- **Clinical Trial Protocol**
  Describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial.
  Other Documents: Investigator Brochure, Laboratory manual
- **Study Monitoring**
  - Auditing site(s) performing the trial
  - Quality Assurance
  - Data and safety monitoring
- **Trial/Data Management**
  - Case Report Forms
  - Databases
  - Central laboratory, biorepository
- **Regulatory Compliance**
  - Federal, provincial, and local requirements
- **Economics**
  - Is the trial affordable? Is the trial worth it?

Ethics and Regulatory Compliance

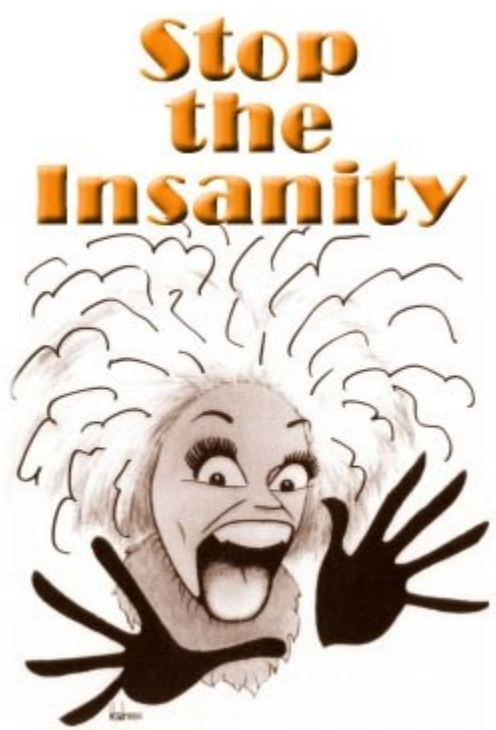
Ethics and Regulatory Compliance

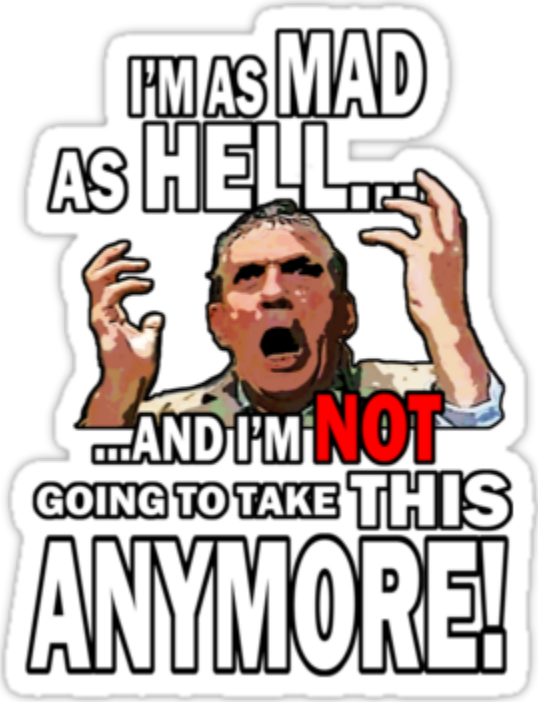
- 1947 Nuremberg Code
- 1964 Declaration of Helsinki revised 1975, 83, 89, 2000, 2008
- 1974 National Research Act
- 1978 Belmont Report
- 1981 DHHS CFR Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards).
- Tri-council policy statement 1998, 2010

- 1902: US Act of 1902 granting the government premarket approval over drugs
- 1906: US Pure Food and Drugs Act
- 1938: US Food, Drugs, and Cosmetic Act
- 1965: First European Directive
- 1976: US Medical Device Amendment
- 1987: EMEA Concertation Procedure established
- 1995: EMEA established
- 1996 ICH Good Clinical Practice (Canada 1997)
- 2001 Clinical Trial Framework added to Canada's Food and Drug Regulations

Interpretation and implementation have significantly increased burden of reporting and documentation without clear evidence of improvement in safety or data quality

Ethics and Regulatory Compliance





Movement toward (more) efficient, sensible activities and oversight to ensure compliance with ethic and regulatory requirements

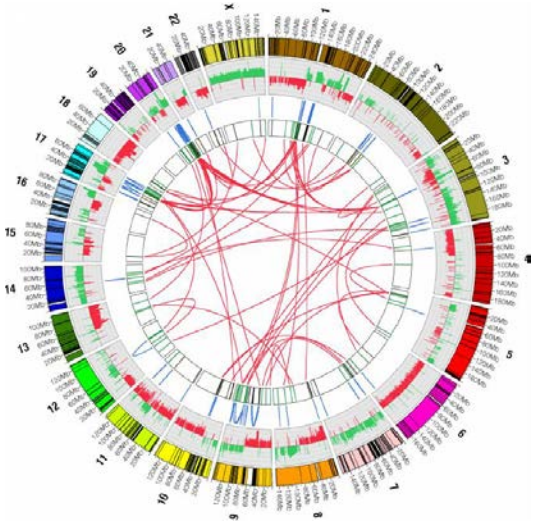
Evolution and Revolution

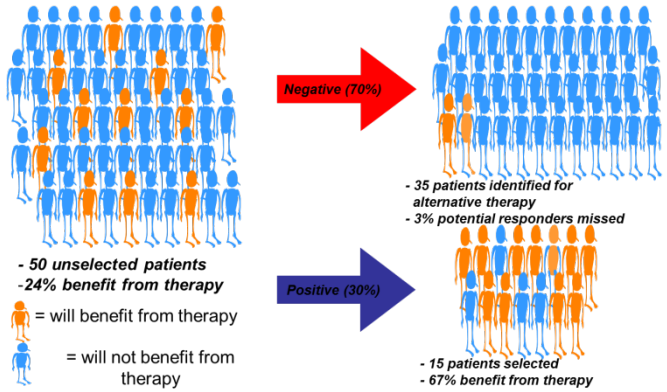
Evolving Questions

- From Erlich's magic bullet for "cancer" to individualized therapy
  - Targeted therapy meets comprehensive diagnostic profiling
  - New treatments
  - Trials of tests
  - Patient report outcomes
  - Economic analysis

Nature, 2000

Genetic heterogeneity, emergence of resistance,





- ?New is better, More is more, Less is more, Sequence,

Evolving Scientific Paradigms

VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Research on Early-Stage Carcinogenesis: Are We Approaching Paradigm Instability?

Stuart G. Baker, *Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, Bethesda, MD*
Antonio Cappuccio, *Bioinformatics and Computational Systems Biology of Cancer, Institut Curie, Paris, France*
John D. Potter, *Fred Hutchinson Cancer Research Center, Seattle, WA*

- **Treasure hunting**
  - The more you dig for treasure marked by Map A …the closer you think you are to finding the treasure at the location on Map A and the more you think the location on Map B is correct.
- **Waiting for the bus**
  - The longer you wait for the bus after the scheduled arrival time, the more you think the bus will arrive at any moment and the more you think the bus will not be coming any time soon…
- **Theories of early-stage carcinogenesis**
  - The more resources expended to try to uncover the exact nature of somatic mutation theory, the more you think that you are nearing a breakthrough in understanding somatic mutation theory and the more you think that a competing theory …is correct.

Design and Methods

- Patients: Rare cancer settings, individual patient as control
- Statistics: Bayesian, Adaptive trial designs
- Complexity: Multiple endpoints, omic and functional imaging data
- Endpoints: Surrogates

Lesson Learned, Not Forgotten

SPECIAL ARTICLE

Analyzing the Same Data in Two Ways: A Demonstration Model to Illustrate the Reporting and Misreporting of Clinical Trials

By Joseph Baar and Ian Tannock

J Clin Oncol 7:969-978, 1989

COLLABORATIVE CLINICAL TRIALS: QUALITY OR QUANTITY?

IAN F. TANNOCK, M.D., PH.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 2, pp. 339–343, 2001

BRIEF COMMUNICATION: False-Positive Results in Clinical Trials: Multiple Significance Tests and the Problem of Unreported Comparisons *Ian F. Tannock**

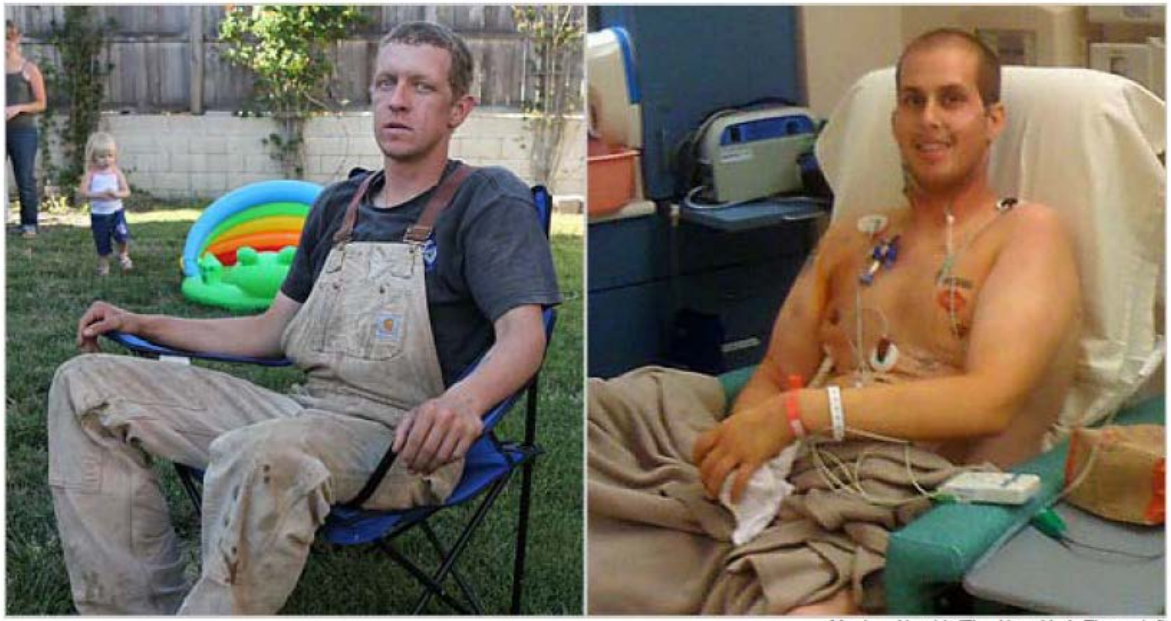
J Natl Cancer Inst Vol. 88, No. 3/4, 1996

The role of phase III trials

- Smith G, Pell JP. Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials. BMJ 2003;327: 1459–61.

TARGET CANCER

New Drugs Stir Debate on Rules of Clinical Trials



Monica Almeida/The New York Times, left

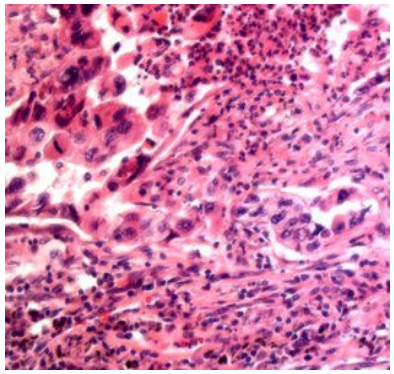
Two Cousins, Two Paths Thomas McLaughlin, left, was given a promising experimental drug to treat his lethal skin cancer in a medical trial; Brandon Ryan had to go without it.

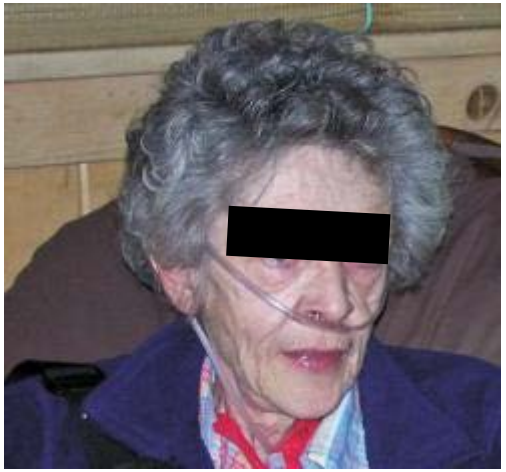
By AMY HARMON
Published: September 18, 2010

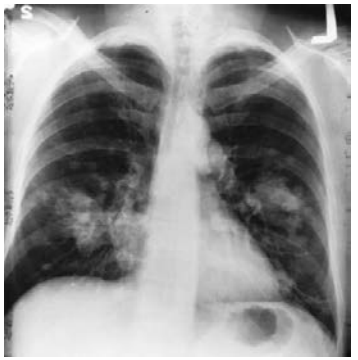
Integration of Information

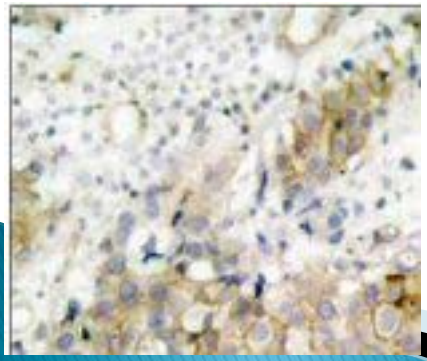
The NEW ENGLAND JOURNAL of MEDICINE

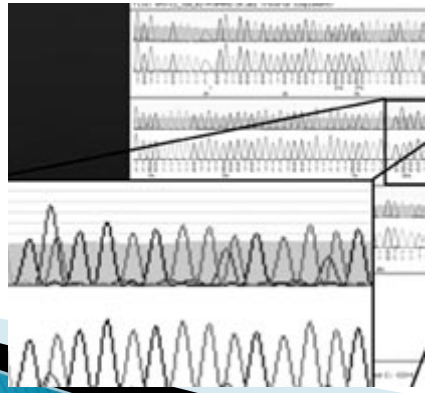
THE JOURNAL of IRREPRODUCIBLE RESULTS

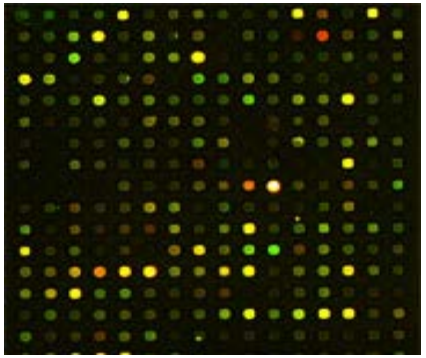


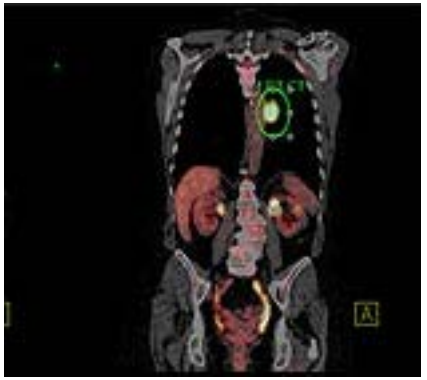








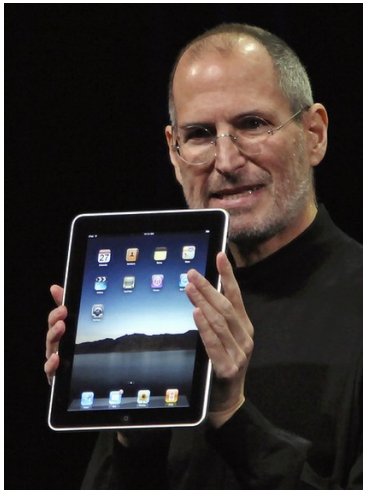




Information Systems and Technologies

http://www.armyofwomen.org/

http://www.patientslikeme.com/



Expanding Collaborations

The Team Science Revolution

By Kate Travis on March 11, 2010 11:35 AM 0 0 Recommend 0

http://community.sciencecareers.org/ctscinet/articles/2010/03/team-science.php

COMMENTARY

TEAM SCIENCE

The Road We Must Take: Multidisciplinary Team Science

Mary L. Disis[1,2*] and John T. Slattery[1]

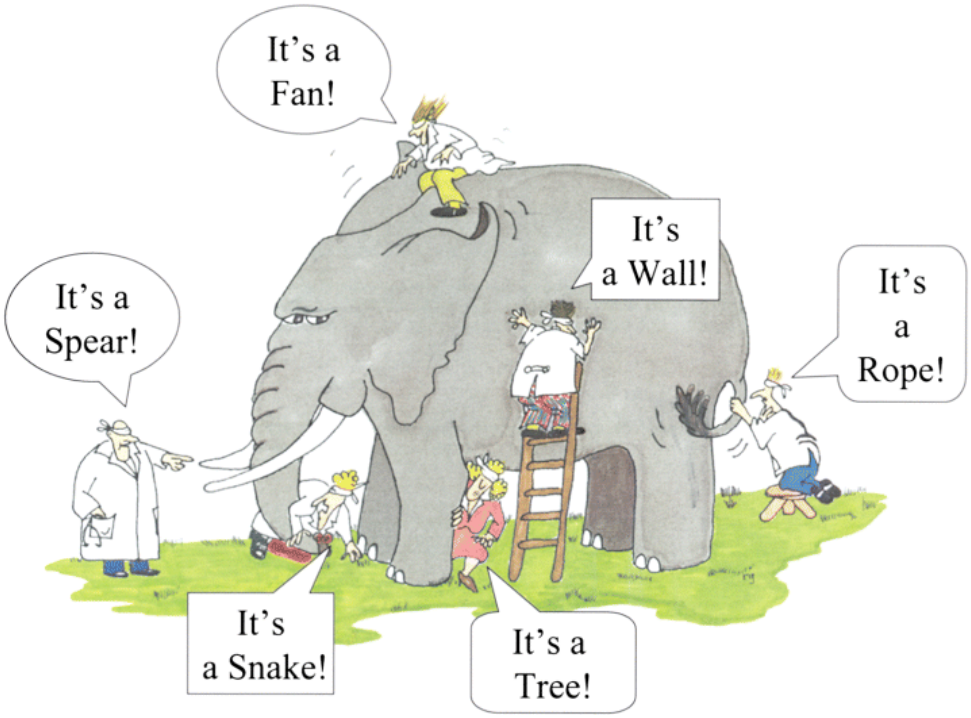
Published 10 March 2010; Volume 2 Issue 22 22cm9

Translational research is acknowledged to be complex and to require a diverse skill set. Many organizations, particularly academic institutions, have invested in educational pro grams, facilities, and enhanced resources to encourage translational research. Critically needed, however, is an emphasis on creating and sustaining multidisciplinary research teams. It is through the power of many and a diverse approach to our health care prob-lems that we will realize lasting solutions.

"You should look for people who value-add to what you do, rather than people who recapitulate your own opinions. Think immediately about developing your career as a team science career."
- Nora Disis

A successful multidisciplinary research team…requires strong leadership, the appropriate infrastructure, and a learning environment that creates shared experiences that team members can use to build their projects.

Multi-disciplinary Teams "The Blind Men and the Elephant"



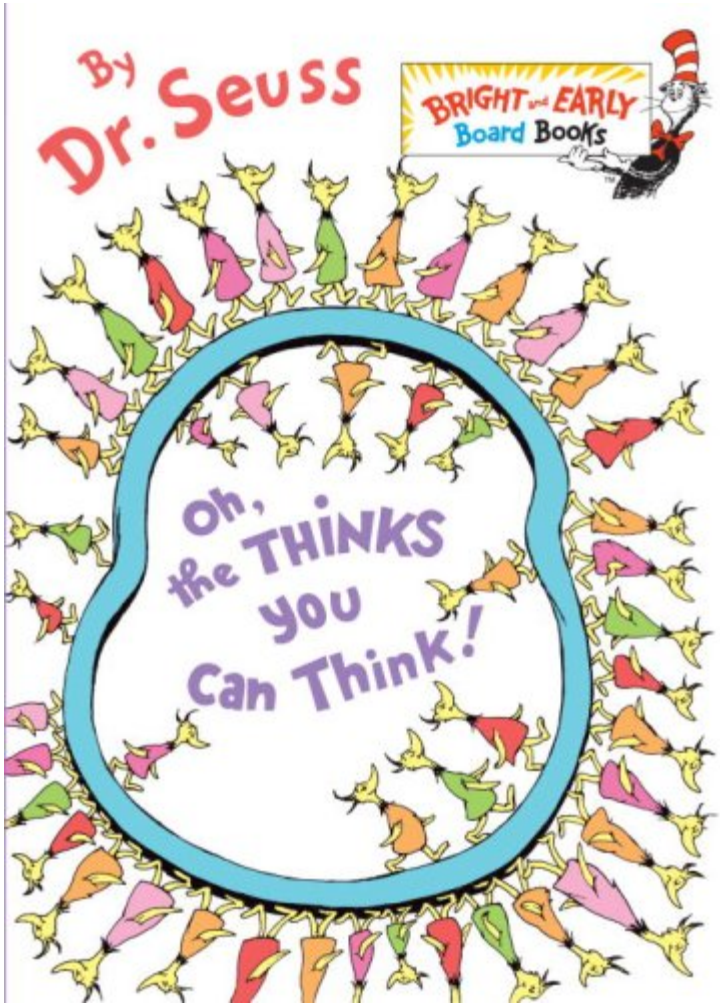
- It was six men of Indostan
- To learning much inclined,
- Who went to see the Elephant
- (Though all of them were blind),
- That each by observation
- Might satisfy his mind

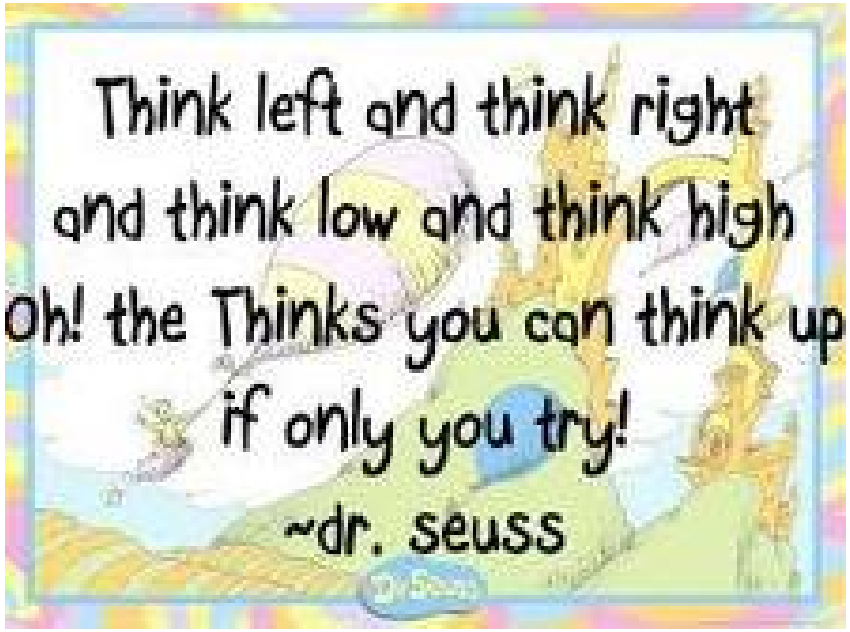
The elephant is like a wall, snake, spear, tree, fan or rope, depending upon where they touch.

They have a heated debate (no physical violence) but the conflict is never resolved.

John Godfrey Saxe (1816-1887)

The first steps for "translational research are literally building understanding of knowledge, culture and language, building trust that allows for honest discussion and disagreement, and finding the time to do these.





- "sagacity" of being able to link together apparently innocuous facts to come to a valuable conclusion

Final Words

- Advances arise when
  - Curiosity meets opportunity and preparation
  - Through discipline, dedication
  - Efficiency, excellence in execution
  - Participation, collaboration, leadership
- You stand on the shoulders of giants
  - Reach higher, see farther, advance science, improve outcomes
- Ask questions, share options and HAVE FUN