2019

CLINICAL RESEARCH COURSE

FROM IDEA

TO PUBLICATION

CERID

Center of Excellence for Research in Infectious Diseases

The Center of Excellence for Research in Infectious Diseases is proud to present its annual training course on clinical research. This course has two primary aims:

Aim 1: For participants to acquire the skills necessary to critically evaluate medical literature.

Learning how to perform a critical evaluation of published clinical studies will help physicians, nurses, or other practitioners to use the best clinical evidence when making decisions about patient care.

Aim 2: For participants to acquire the skills necessary to develop and implement clinical studies.

Learning the process of clinical research from generation of a research idea to publication of a study manuscript will help clinical investigators, research associates, or other health care workers interested in a career in the field of clinical research.

Course Directors

Julio Ramirez, MD, FACP
Division Chief and Professor
Division of Infectious Diseases
University of Louisville School of Medicine
Center Director, CERID

Ruth M. Carrico, PhD, DNP
Professor
Division of Infectious Diseases
University of Louisville School of Medicine
Director of Epidemiological Research, CERID

Course Sponsors

UNIVERSITY OF LOUISVILLE | Office of the Executive Vice President for Research & Innovation

IRIS International Respiratory Infections Society

UNIVERSITY OF LOUISVILLE | Division of Infectious Diseases, Department of Medicine

UNIVERSITY OF LOUISVILLE® SCHOOL OF MEDICINE

Course Faculty

Class 1. Clinical Research: An Overview
Objective: To perform a summary of the clinical research process.
Speaker: Julio Ramirez, MD, FACP
Department of Medicine, Division of Infectious Diseases

Class 2. Developing the Research Question: Key Considerations
Objective: To review the characteristics of a good research question.
Speaker: Ruth Carrico, PhD, DNP
Department of Medicine, Division of Infectious Diseases

Class 3. Planning the Study: Observational Studies
Objective: To describe the elements of study design in observational studies.
Speaker: Maxwell Boakye, MD
Department of Neurosurgery, Center for Advanced Neurosurgery

Class 4. Planning the Study: Systematic Reviews and Meta-Analyses
Objective: To describe how to perform a summary of the best available evidence.
Speaker: Rodrigo Cavallazzi, MD
Department of Medicine, Division of Pulmonary, Critical Care & Sleep Disorders Medicine

Class 5. Planning the Study: Ethics & Regulations
Objective: To review important ethical and regulatory considerations.
Speaker: Rebecca Redman, MD
Department of Medicine, Division of Medical Oncology & Hematology

Class 6. Planning the Study: Budget & Funding
Objective: To describe elements of the study budget and sources of research funding.
Speaker: Craig McClain, MD
Department of Medicine, Division of Gastroenterology, Hepatology & Nutrition

Course Faculty

Class 7. Planning the Study: Interventional Studies
Objective: To describe the elements of study design in interventional studies.
Speaker: Janice Sullivan, MD
Department of Pediatrics, Kosair Charities Pediatric Clinical Research Unit

Class 8. Performing the Study: Data Collection and Data Quality
Objective: To review essential principles for data collection and quality.
Speaker: Beatrice Ugiliweneza, PhD
Department of Neurosurgery, Kentucky Spinal Cord Injury Research Center

Class 9. Analyzing Study Results: Statistical Significance
Objective: To review statistical considerations when analyzing your study results.
Speaker: Stephen Furmanek, MPH
Department of Medicine, Division of Infectious Diseases

Class 10. Analyzing Study Results: Clinical Significance
Objective: To review clinical considerations when analyzing your study results.
Speaker: Ozan Akca, MD
Department of Anesthesiology and Perioperative Medicine

Class 11. Disseminating Study Findings: Scientific Writing
Objective: To present a systematic approach to writing the journal manuscript.
Speaker: Forest Arnold, DO
Department of Medicine, Division of Infectious Diseases

Class 12. Clinical Research: Putting It All Together
Objective: To summarize the most important concepts discussed during the course.
Speaker: Julio Ramirez, MD, FACP
Department of Medicine, Division of Infectious Diseases

Clinical Research

Step by Step
From Idea to Publication

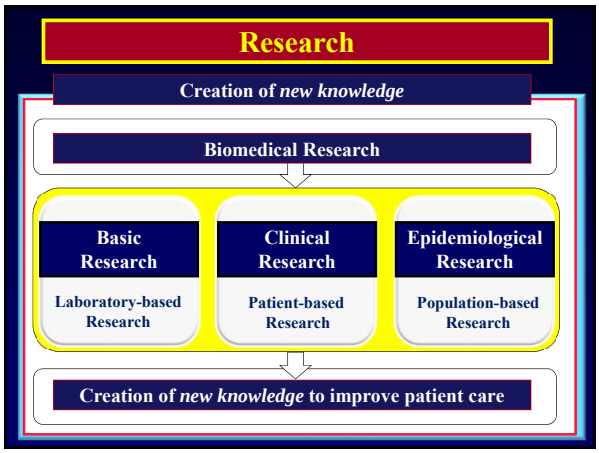
Julio A. Ramirez, MD, FACP
Professor of Medicine
Chief, Infectious Diseases Division,
University of Louisville
Louisville, Kentucky, USA

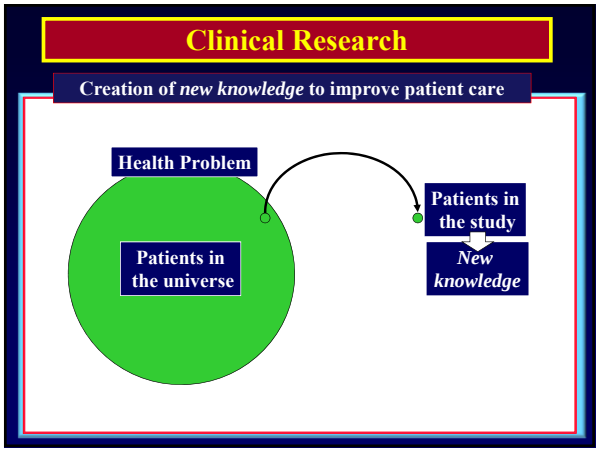
Clinical Research

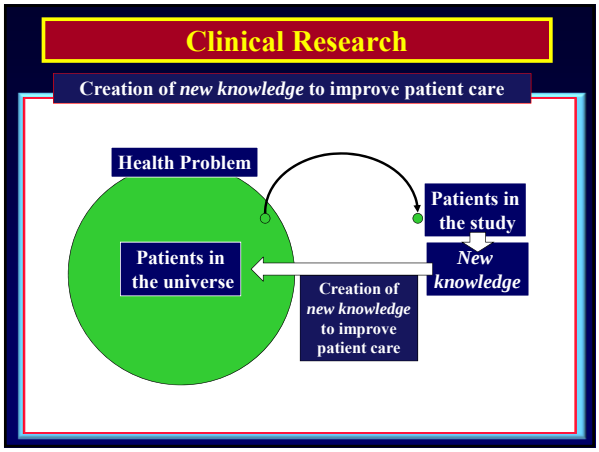
- A. Research: Definitions
- B. Step 1: Planning the Study
- C. Step 2: Performing the Study
- D. Step 3: Analyzing Study Results
- E. Step 4: Publishing Study Findings

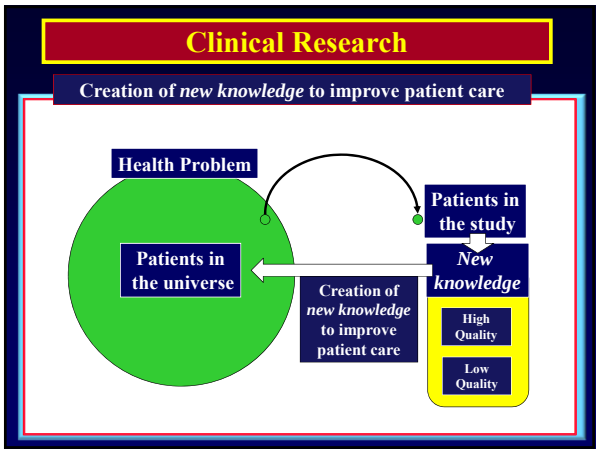
Clinical Research

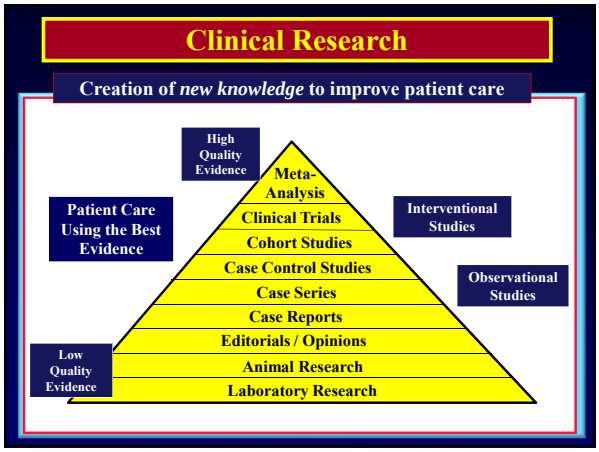
- A. Research: Definitions
- B. Step 1: Planning the Study
- C. Step 2: Performing the Study
- D. Step 3: Analyzing Study Results
- E. Step 4: Publishing Study Findings

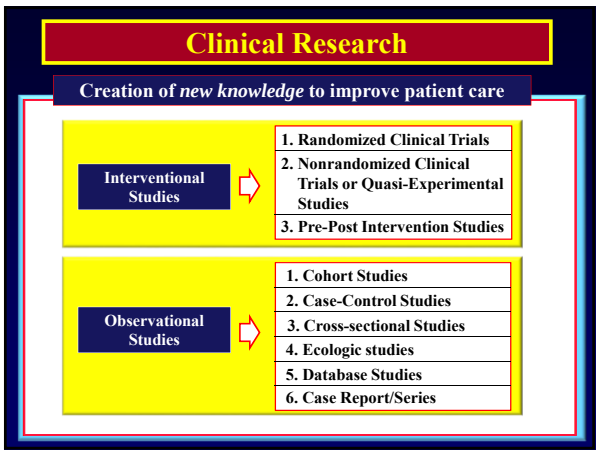

Research
Creation of *new knowledge*
Biomedical Research
Basic Research
Laboratory-based Research
Clinical Research
Patient-based Research
Epidemiological Research
Population-based Research
Creation of *new knowledge* to improve patient care

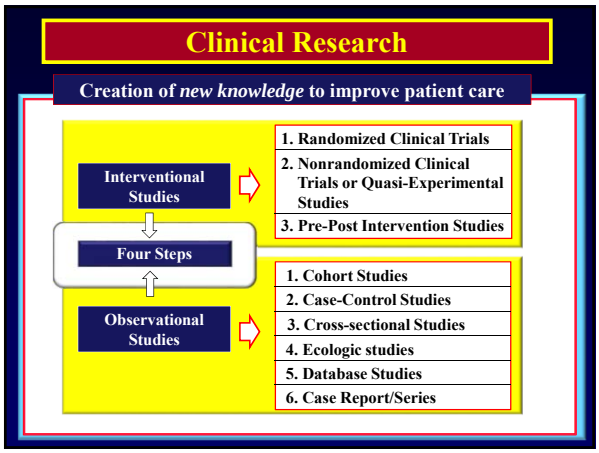

Clinical Research
Creation of *new knowledge* to improve patient care
Health Problem
Patients in the universe
Patients in the study
New knowledge

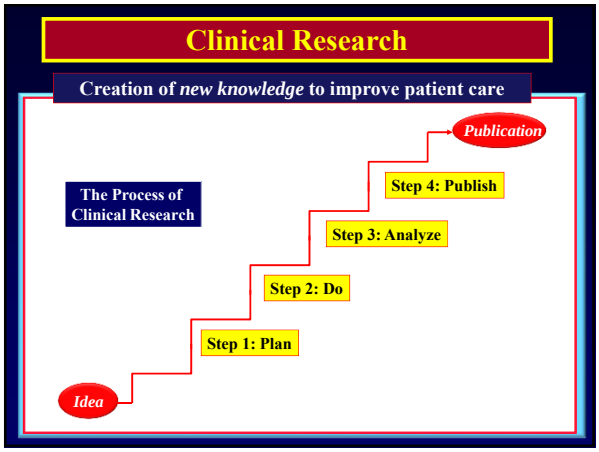

Clinical Research
Creation of *new knowledge* to improve patient care
Health Problem
Patients in the universe
Patients in the study
New knowledge
Creation of *new knowledge* to improve patient care

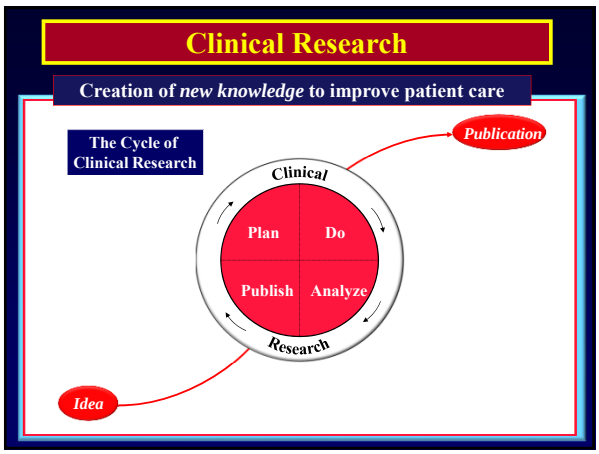

Clinical Research
Creation of *new knowledge* to improve patient care
Health Problem
Patients in the universe
Patients in the study
New knowledge
High Quality
Low Quality
Creation of *new knowledge* to improve patient care


Clinical Research
Creation of *new knowledge* to improve patient care
High Quality Evidence
Meta-Analysis
Clinical Trials
Cohort Studies
Case Control Studies
Case Series
Case Reports
Editorials / Opinions
Animal Research
Laboratory Research
Low Quality Evidence
Patient Care Using the Best Evidence
Interventional Studies
Observational Studies


Clinical Research
Creation of *new knowledge* to improve patient care
Interventional Studies
1. Randomized Clinical Trials
2. Nonrandomized Clinical Trials or Quasi-Experimental Studies
3. Pre-Post Intervention Studies
Observational Studies
1. Cohort Studies
2. Case-Control Studies
3. Cross-sectional Studies
4. Ecologic studies
5. Database Studies
6. Case Report/Series


Clinical Research
Creation of *new knowledge* to improve patient care
Interventional Studies
1. Randomized Clinical Trials
2. Nonrandomized Clinical Trials or Quasi-Experimental Studies
3. Pre-Post Intervention Studies
Four Steps
Observational Studies
1. Cohort Studies
2. Case-Control Studies
3. Cross-sectional Studies
4. Ecologic studies
5. Database Studies
6. Case Report/Series


Clinical Research
Creation of *new knowledge* to improve patient care
The Process of Clinical Research
Publication
Step 4: Publish
Step 3: Analyze
Step 2: Do
Step 1: Plan
Idea


Clinical Research
Creation of *new knowledge* to improve patient care
The Cycle of Clinical Research
Publication
Clinical
Plan
Do
Publish
Analyze
Research
Idea

Clinical Research

A. Research: Definitions

B. Step 1: Planning the Study

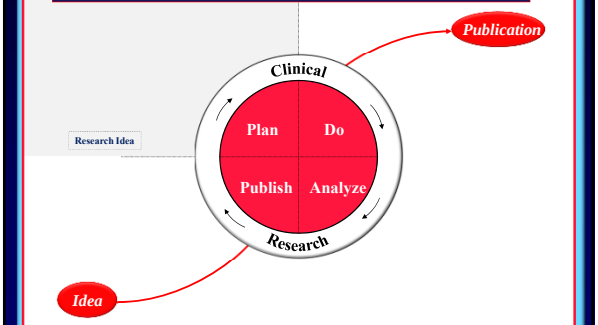
C. Step 2: Performing the Study

D. Step 3: Analyzing Study Results

E. Step 4: Publishing Study Findings

Clinical Research

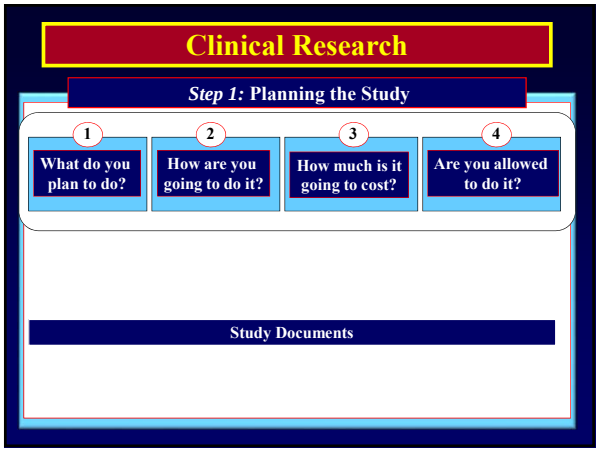
Creation of *new knowledge* to improve patient care

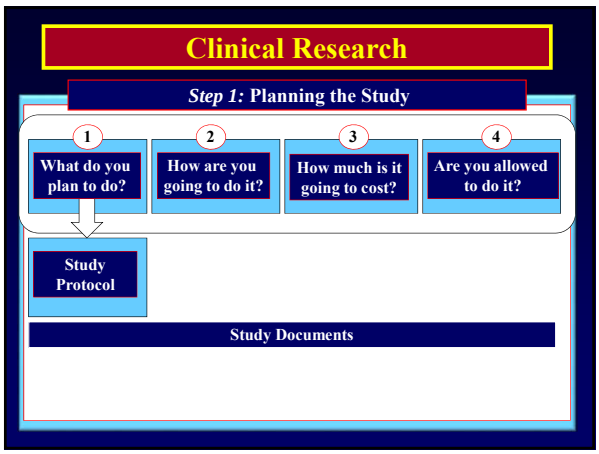


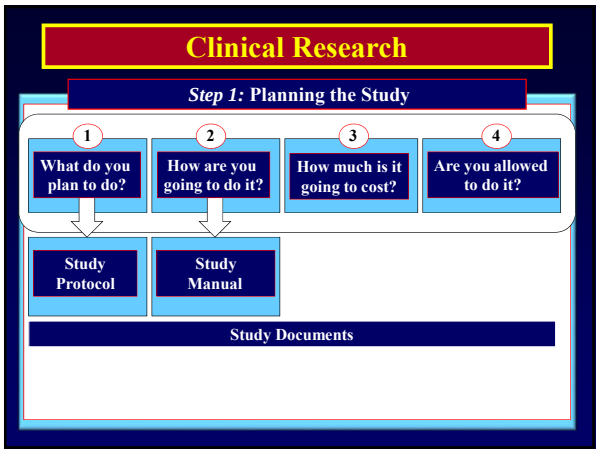
Clinical Research

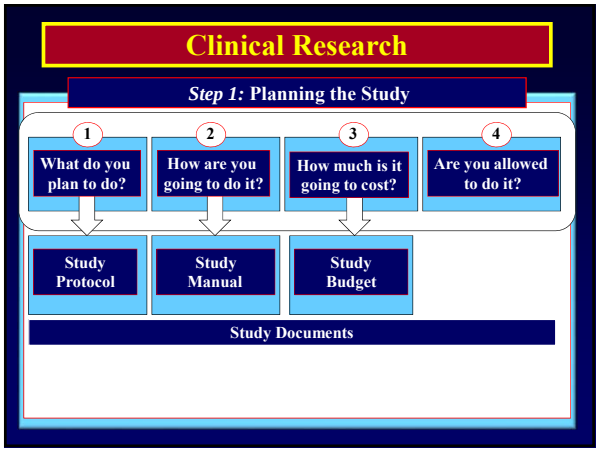
Step 1: Planning the Study

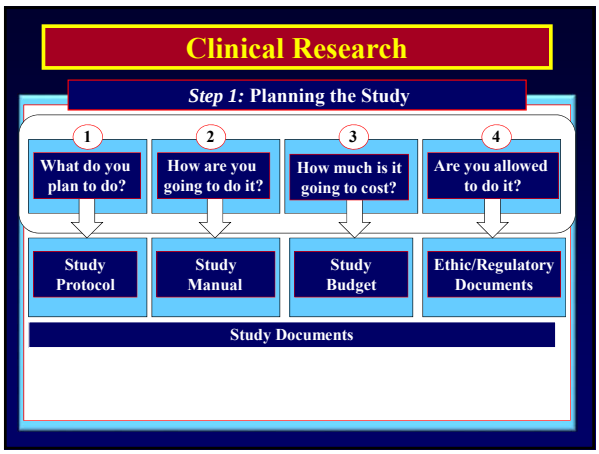

Clinical Research
Step 1: Planning the Study
Health Problem
Patients in the Universe
Health Problem
Lack of knowledge
Research Question
Study Documents

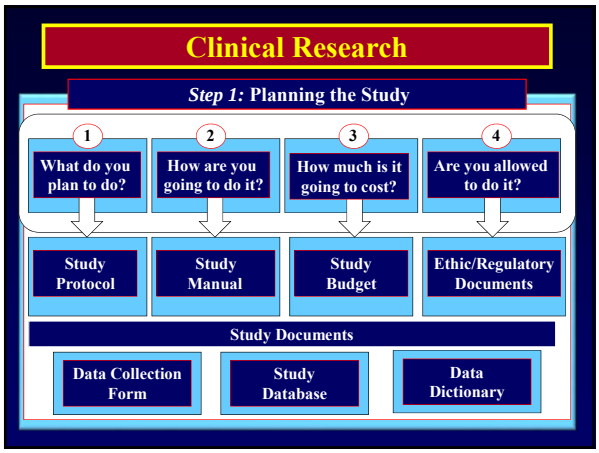

Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Documents

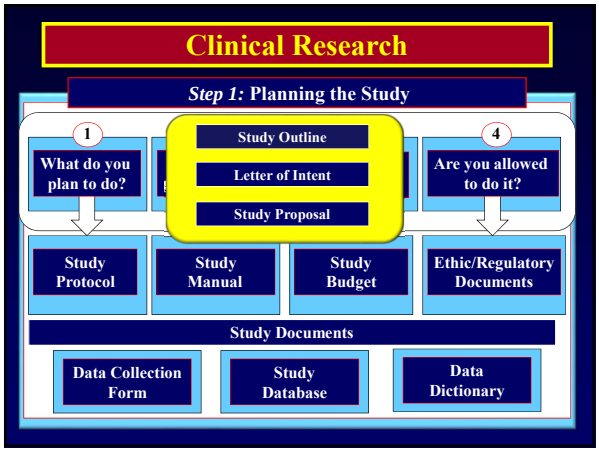

Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Protocol
Study Documents

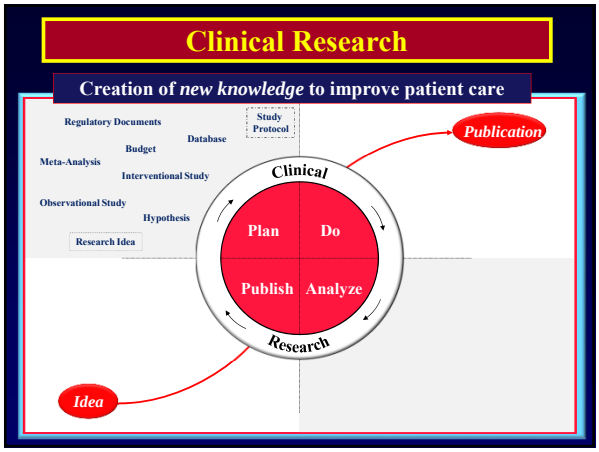

Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Protocol
Study Manual
Study Documents


Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Protocol
Study Manual
Study Budget
Study Documents


Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Protocol
Study Manual
Study Budget
Ethic/Regulatory Documents
Study Documents


Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
2
How are you going to do it?
3
How much is it going to cost?
4
Are you allowed to do it?
Study Protocol
Study Manual
Study Budget
Ethic/Regulatory Documents
Study Documents
Data Collection Form
Study Database
Data Dictionary


Clinical Research
Step 1: Planning the Study
1
What do you plan to do?
Study Outline
Letter of Intent
Study Proposal
4
Are you allowed to do it?
Study Protocol
Study Manual
Study Budget
Ethic/Regulatory Documents
Study Documents
Data Collection Form
Study Database
Data Dictionary


Clinical Research
Creation of new knowledge to improve patient care
Regulatory Documents
Database
Budget
Meta-Analysis
Interventional Study
Observational Study
Hypothesis
Research Idea
Study Protocol
Publication
Clinical
Plan
Do
Publish
Analyze
Research
Idea

Clinical Research

A. Research: Definitions

B. Step 1: Planning the Study

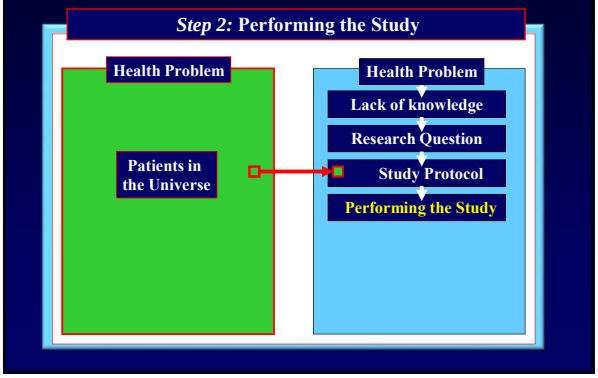
C. Step 2: Performing the Study

D. Step 3: Analyzing Study Results

E. Step 4: Publishing Study Findings

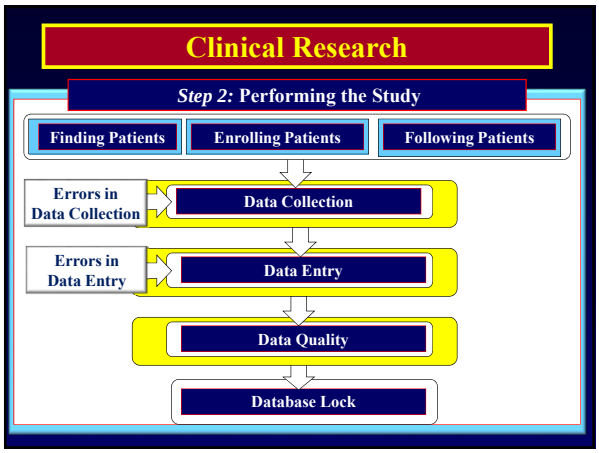
Clinical Research

Step 2: Performing the Study

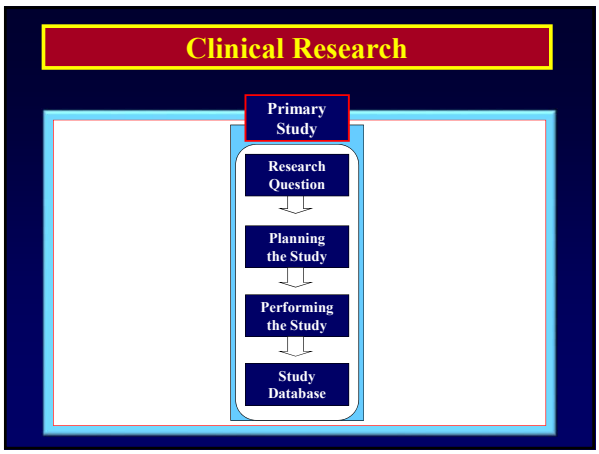


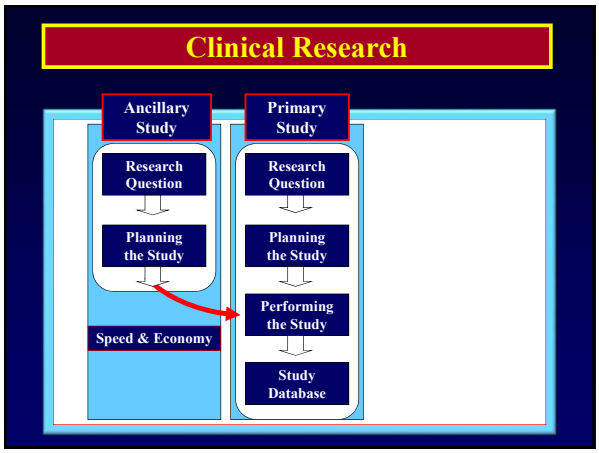
Clinical Research

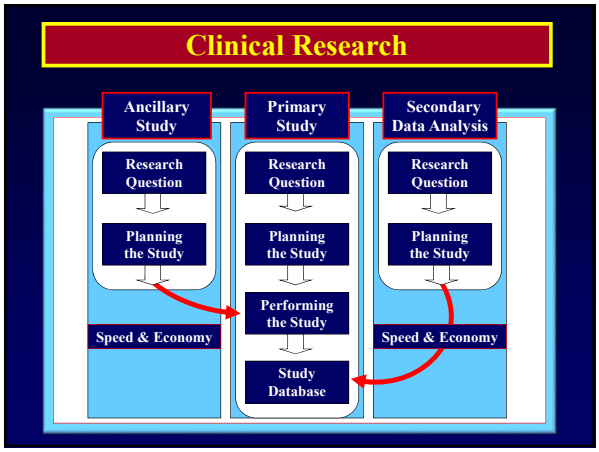
Step 2: Performing the Study

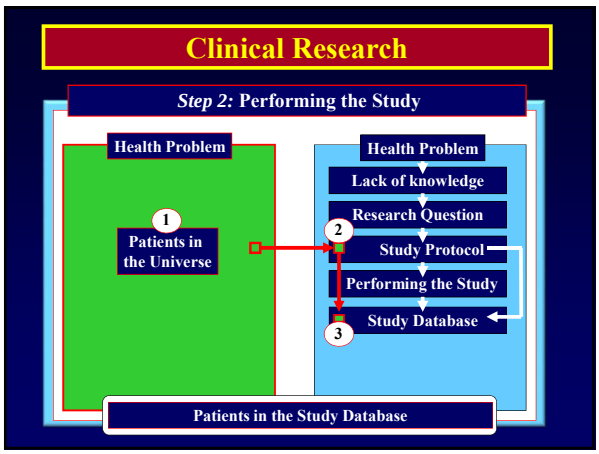

Clinical Research
Step 2: Performing the Study
Finding Patients
Enrolling Patients
Following Patients
Errors in Data Collection
Data Collection
Errors in Data Entry
Data Entry
Data Quality
Database Lock

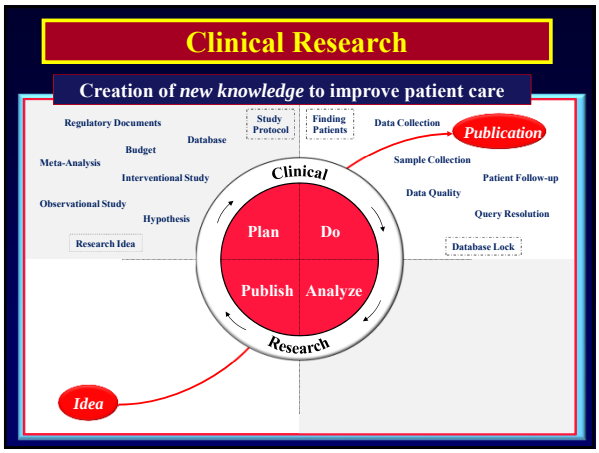

Clinical Research
Step 2: Performing the Study
Finding Patients
Enrolling Patients
Following Patients
Errors in Data Collection
Data Collection
Errors in Data Entry
Data Entry
Data Quality
Database Lock
"To err is human, but to really mess things up you need a computer"
Paul Ehrlich


Clinical Research
Primary Study
Research Question
Planning the Study
Performing the Study
Study Database

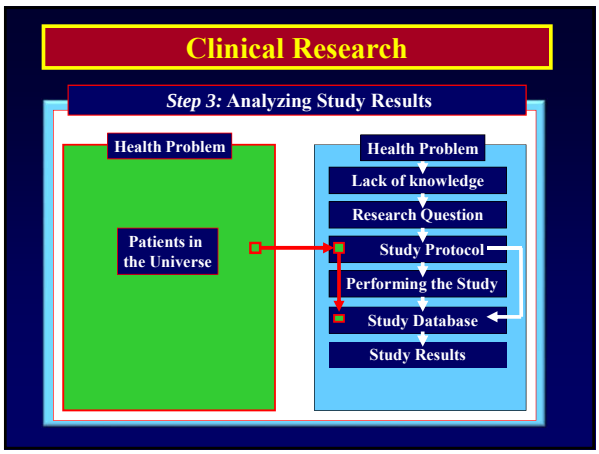

Clinical Research
Ancillary Study
Primary Study
Research Question
Planning the Study
Performing the Study
Study Database
Speed & Economy

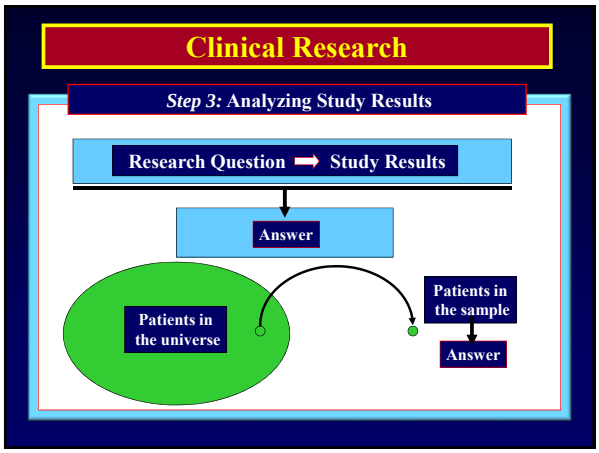

Clinical Research
Ancillary Study
Primary Study
Secondary Data Analysis
Research Question
Planning the Study
Performing the Study
Study Database
Speed & Economy
Speed & Economy

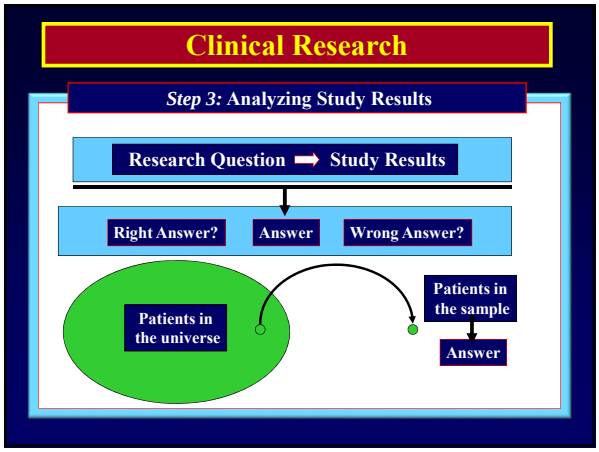

Clinical Research
Step 2: Performing the Study
Health Problem
1
Patients in the Universe
Health Problem
Lack of knowledge
Research Question
2
Study Protocol
Performing the Study
Study Database
3
Patients in the Study Database

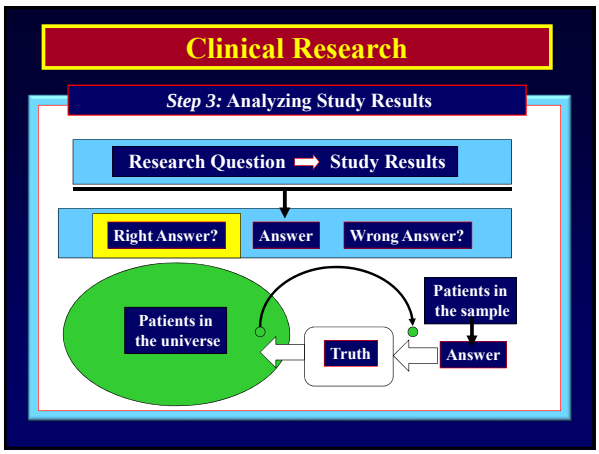

Clinical Research
Creation of *new knowledge* to improve patient care
Regulatory Documents
Budget
Database
Meta-Analysis
Interventional Study
Observational Study
Hypothesis
Research Idea
Study Protocol
Finding Patients
Data Collection
Publication
Sample Collection
Patient Follow-up
Data Quality
Query Resolution
Database Lock
Clinical
Plan
Do
Publish
Analyze
Research
Idea

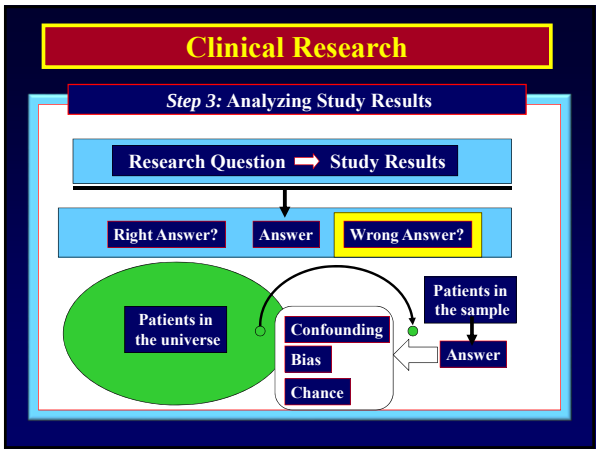

Clinical Research
A. Research: Definitions
B. Step 1: Planning the Study
C. Step 2: Performing the Study
D. Step 3: Analyzing Study Results
E. Step 4: Publishing Study Findings

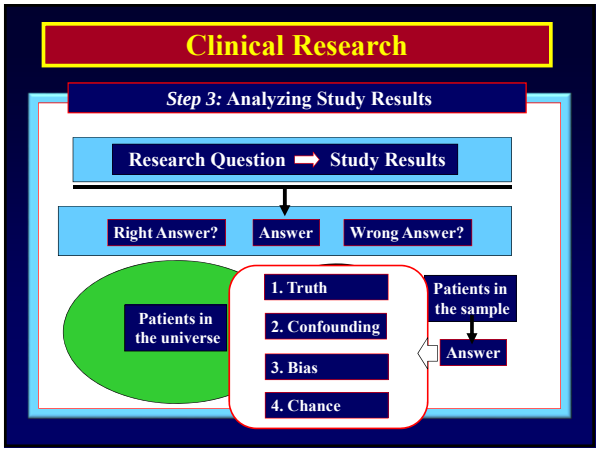

Clinical Research
Step 3: Analyzing Study Results
Health Problem
Patients in the Universe
Health Problem
Lack of knowledge
Research Question
Study Protocol
Performing the Study
Study Database
Study Results

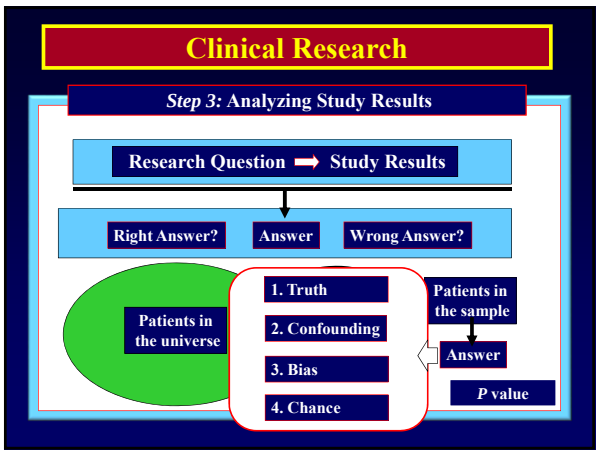

Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Answer
Patients in the universe
Patients in the sample
Answer


Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Right Answer?
Answer
Wrong Answer?
Patients in the universe
Patients in the sample
Answer


Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Right Answer?
Answer
Wrong Answer?
Patients in the universe
Truth
Patients in the sample
Answer

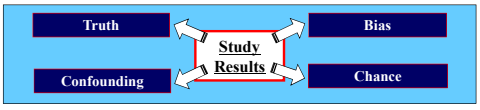

Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Right Answer?
Answer
Wrong Answer?
Patients in the universe
Confounding
Bias
Chance
Patients in the sample
Answer


Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Right Answer?
Answer
Wrong Answer?
Patients in the universe
1. Truth
2. Confounding
3. Bias
4. Chance
Patients in the sample
Answer


Clinical Research
Step 3: Analyzing Study Results
Research Question
Study Results
Right Answer?
Answer
Wrong Answer?
Patients in the universe
1. Truth
2. Confounding
3. Bias
4. Chance
Patients in the sample
Answer
P value

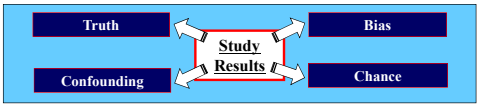
Clinical Research

Step 3: Analyzing Study Results



Clinical Research

Step 3: Analyzing Study Results



What is the meaning a low *P* value?

A: High probability that the result of the study is true or correct

B: Low probability that the result of the study is due to bias

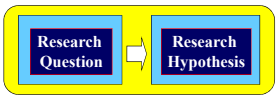
C: Low probability that the result of the study is due to chance

D: Low probability that the result of the study is due to confounding

E: All of the above

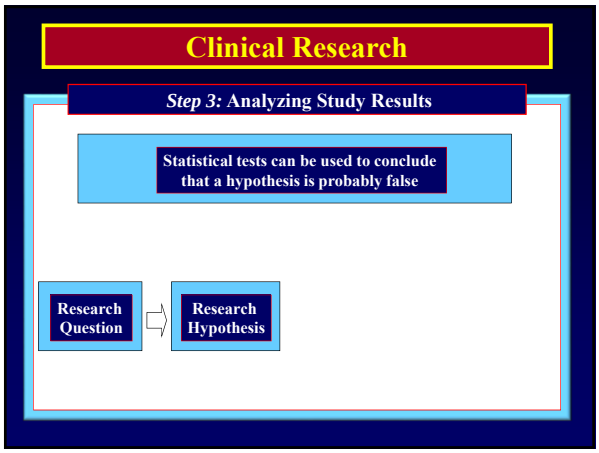
Clinical Research

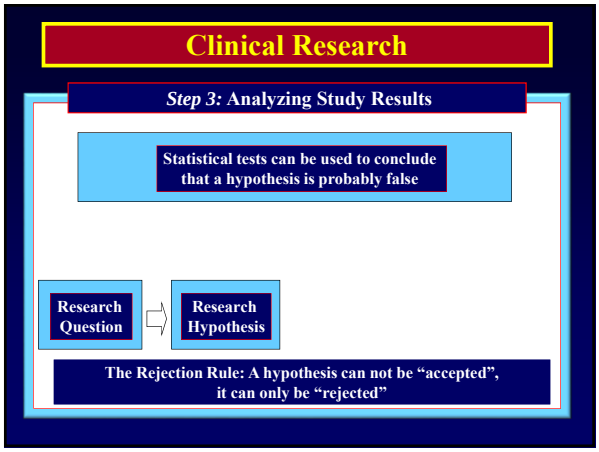
Step 3: Analyzing Study Results

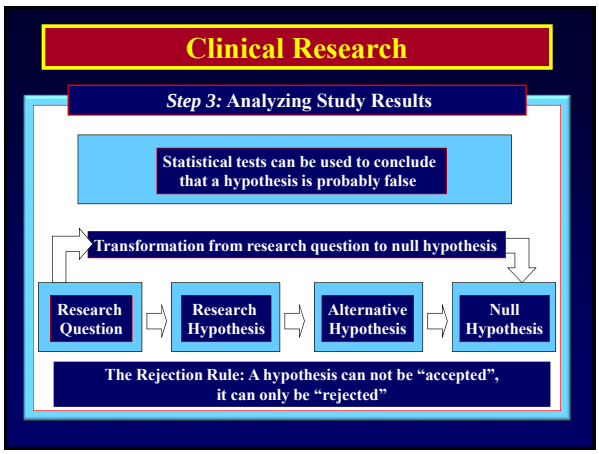


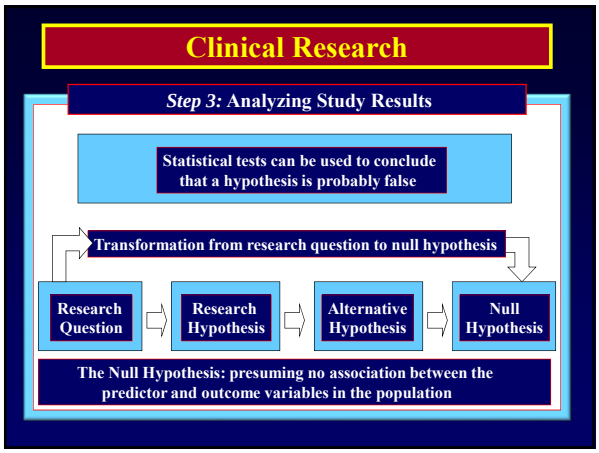
Statistical tests **can not be used** to conclude that a hypothesis is probably **true**

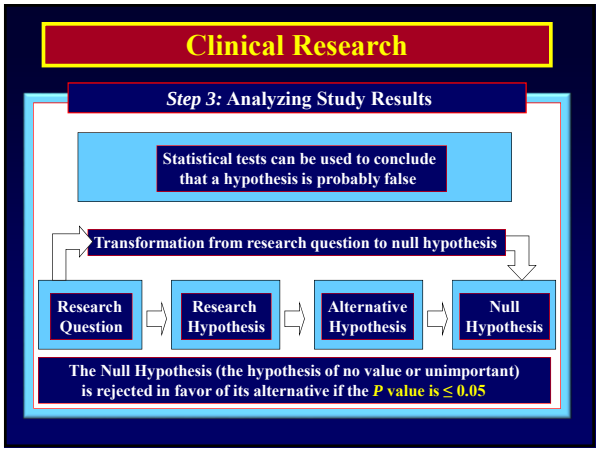
Statistical tests **can be used** to conclude that a hypothesis is probably **false**

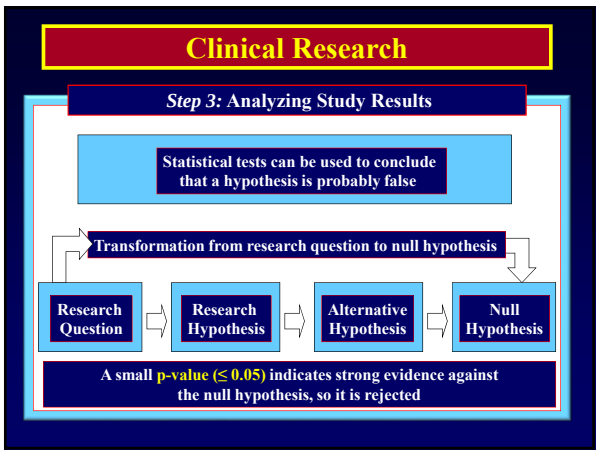

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Research Question
Research Hypothesis

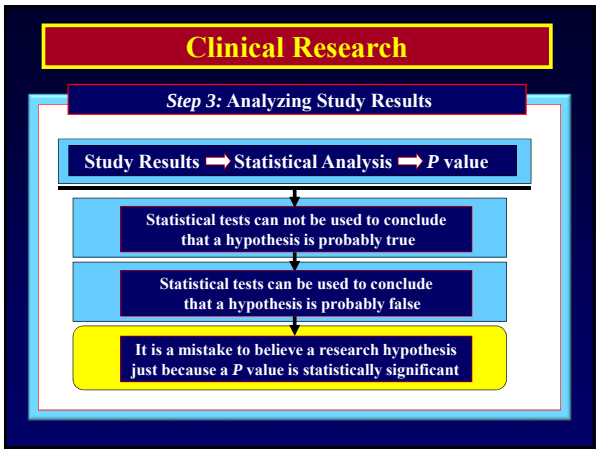

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Research Question
Research Hypothesis
The Rejection Rule: A hypothesis can not be "accepted", it can only be "rejected"

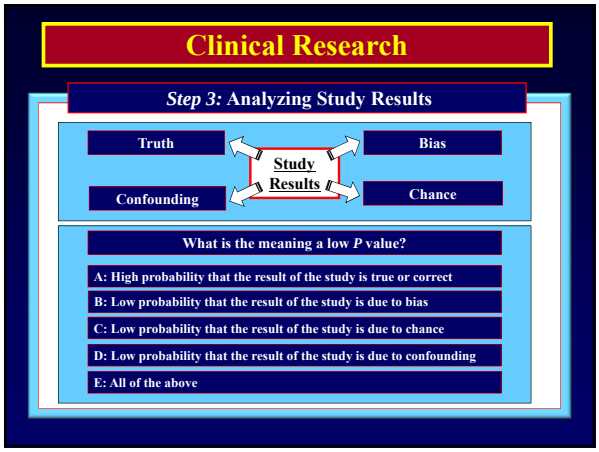

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Transformation from research question to null hypothesis
Research Question
Research Hypothesis
Alternative Hypothesis
Null Hypothesis
The Rejection Rule: A hypothesis can not be "accepted", it can only be "rejected"

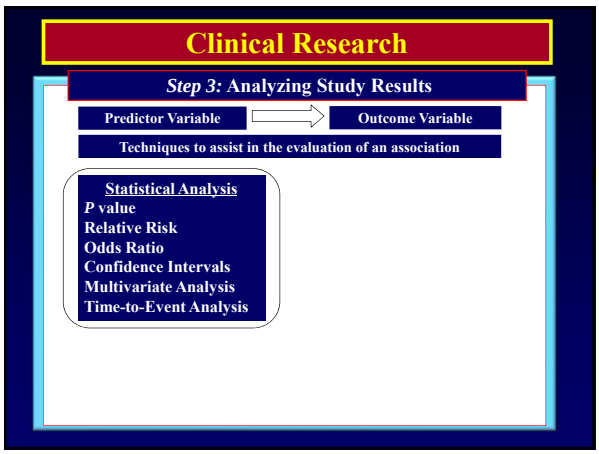

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Transformation from research question to null hypothesis
Research Question
Research Hypothesis
Alternative Hypothesis
Null Hypothesis
The Null Hypothesis: presuming no association between the predictor and outcome variables in the population

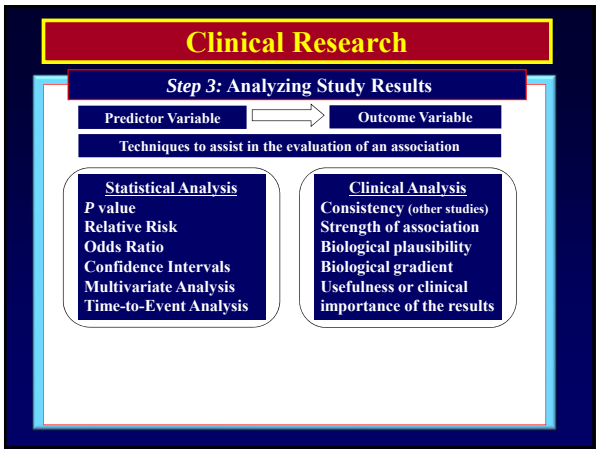

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Transformation from research question to null hypothesis
Research Question
Research Hypothesis
Alternative Hypothesis
Null Hypothesis
The Null Hypothesis (the hypothesis of no value or unimportant) is rejected in favor of its alternative if the P value is ≤ 0.05

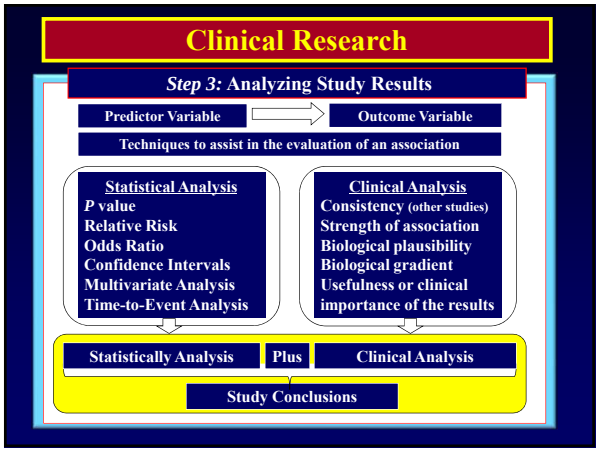

Clinical Research
Step 3: Analyzing Study Results
Statistical tests can be used to conclude that a hypothesis is probably false
Transformation from research question to null hypothesis
Research Question
Research Hypothesis
Alternative Hypothesis
Null Hypothesis
A small p-value (≤ 0.05) indicates strong evidence against the null hypothesis, so it is rejected

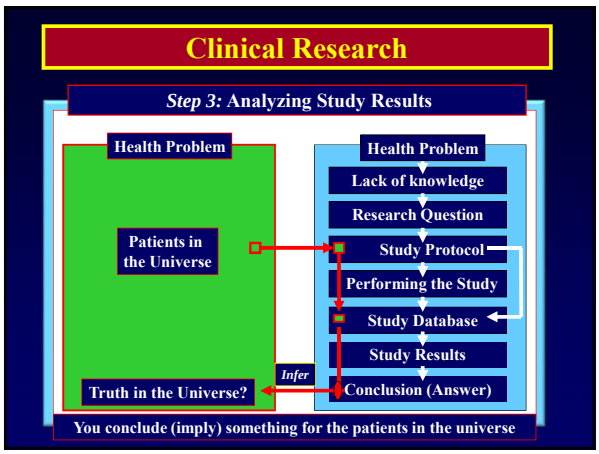

Clinical Research
Step 3: Analyzing Study Results
Study Results ➡ Statistical Analysis ➡ P value
Statistical tests can not be used to conclude that a hypothesis is probably true
Statistical tests can be used to conclude that a hypothesis is probably false
It is a mistake to believe a research hypothesis just because a P value is statistically significant

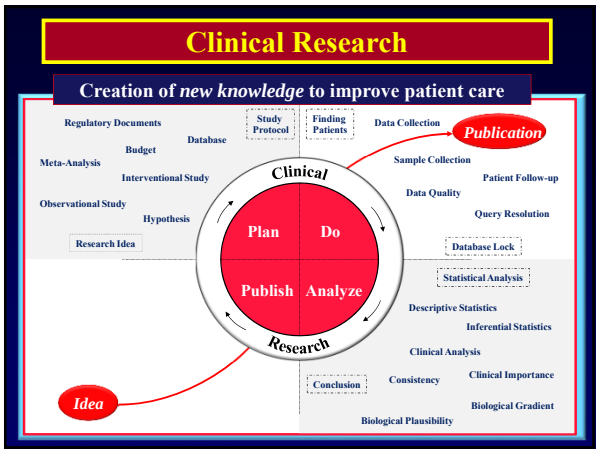

Clinical Research
Step 3: Analyzing Study Results
Truth
Bias
Study Results
Confounding
Chance
What is the meaning a low P value?
A: High probability that the result of the study is true or correct
B: Low probability that the result of the study is due to bias
C: Low probability that the result of the study is due to chance
D: Low probability that the result of the study is due to confounding
E: All of the above


Clinical Research
Step 3: Analyzing Study Results
Predictor Variable
Outcome Variable
Techniques to assist in the evaluation of an association
Statistical Analysis
P value
Relative Risk
Odds Ratio
Confidence Intervals
Multivariate Analysis
Time-to-Event Analysis

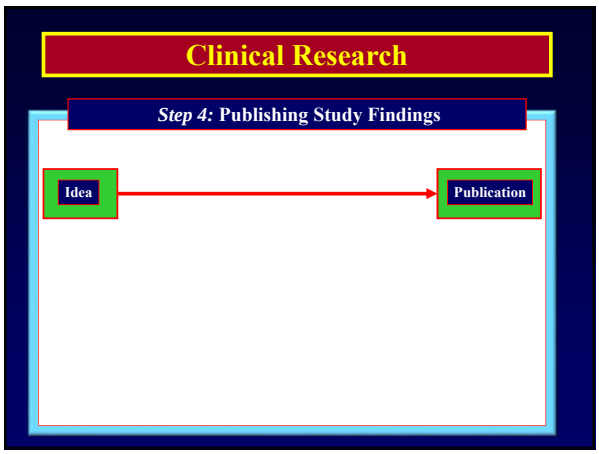

Clinical Research
Step 3: Analyzing Study Results
Predictor Variable
Outcome Variable
Techniques to assist in the evaluation of an association
Statistical Analysis
P value
Relative Risk
Odds Ratio
Confidence Intervals
Multivariate Analysis
Time-to-Event Analysis
Clinical Analysis
Consistency (other studies)
Strength of association
Biological plausibility
Biological gradient
Usefulness or clinical importance of the results


Clinical Research
Step 3: Analyzing Study Results
Predictor Variable
Outcome Variable
Techniques to assist in the evaluation of an association
Statistical Analysis
P value
Relative Risk
Odds Ratio
Confidence Intervals
Multivariate Analysis
Time-to-Event Analysis
Clinical Analysis
Consistency (other studies)
Strength of association
Biological plausibility
Biological gradient
Usefulness or clinical importance of the results
Statistically Analysis
Plus
Clinical Analysis
Study Conclusions


Clinical Research
Step 3: Analyzing Study Results
Health Problem
Patients in the Universe
Truth in the Universe?
Infer
Health Problem
Lack of knowledge
Research Question
Study Protocol
Performing the Study
Study Database
Study Results
Conclusion (Answer)
You conclude (imply) something for the patients in the universe

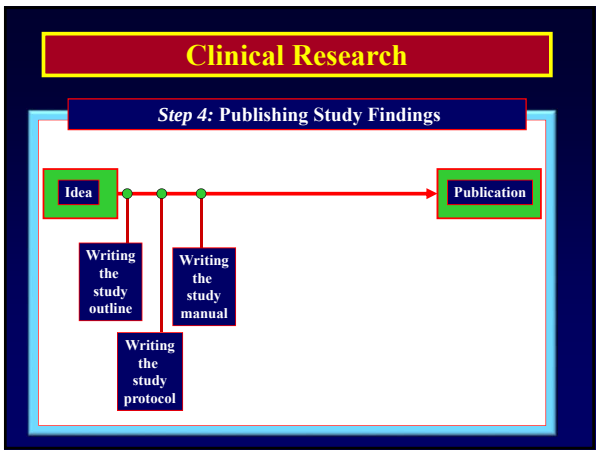

Clinical Research
Creation of *new knowledge* to improve patient care
Regulatory Documents
Budget
Database
Meta-Analysis
Interventional Study
Observational Study
Hypothesis
Research Idea
Study Protocol
Finding Patients
Data Collection
Publication
Sample Collection
Patient Follow-up
Data Quality
Query Resolution
Database Lock
Statistical Analysis
Descriptive Statistics
Inferential Statistics
Clinical Analysis
Clinical Importance
Biological Gradient
Biological Plausibility
Consistency
Conclusion
Idea
Clinical
Plan
Do
Publish
Analyze
Research


Clinical Research
A. Research: Definitions
B. Step 1: Planning the Study
C. Step 2: Performing the Study
D. Step 3: Analyzing Study Results
E. Step 4: Publishing Study Findings

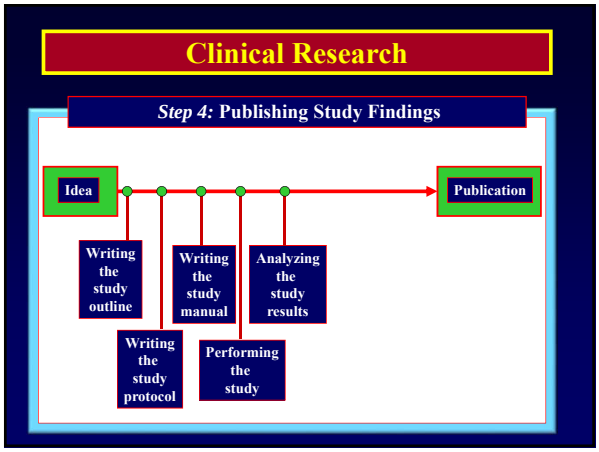

Clinical Research
Step 4: Publishing Study Findings
Idea
Publication

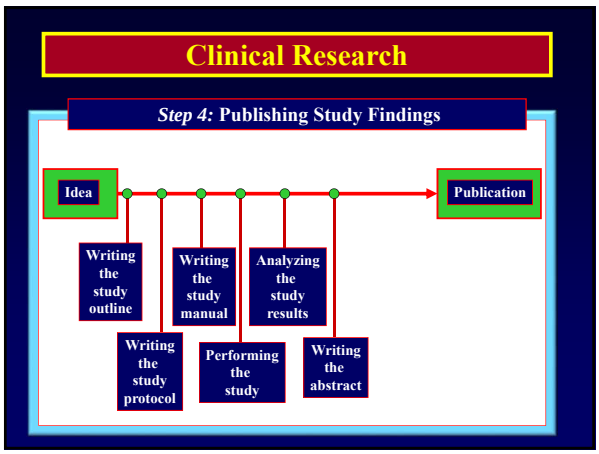

Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study protocol


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Writing the study protocol


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Writing the study protocol
Performing the study


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Analyzing the study results
Writing the study protocol
Performing the study

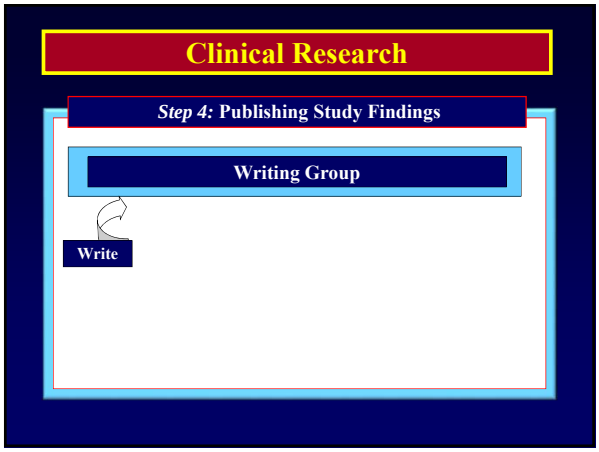

Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Analyzing the study results
Writing the study protocol
Performing the study
Writing the abstract


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Analyzing the study results
Writing the poster
Writing the study protocol
Performing the study
Writing the abstract


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Analyzing the study results
Writing the poster
Writing the article
Writing the study protocol
Performing the study
Writing the abstract

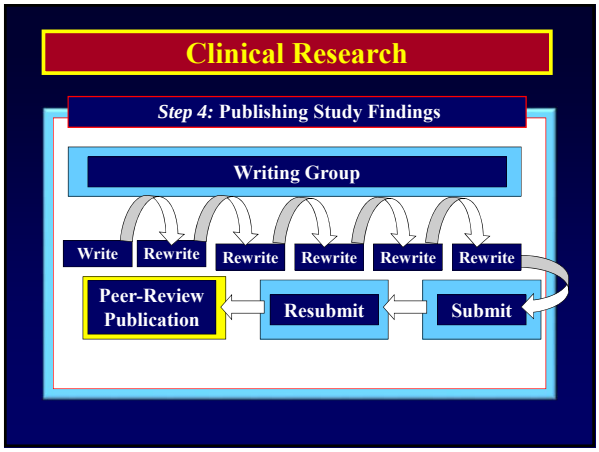

Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing the study outline
Writing the study manual
Analyzing the study results
Writing the poster
Writing the article
Writing the study protocol
Performing the study
Writing the abstract


Clinical Research
Step 4: Publishing Study Findings
Idea
Publication
Writing
Writing
Analyzing
Writing
You can not do good clinical research without mastering medical writing
Writing the study protocol
Performing the study
Writing the abstract
the article

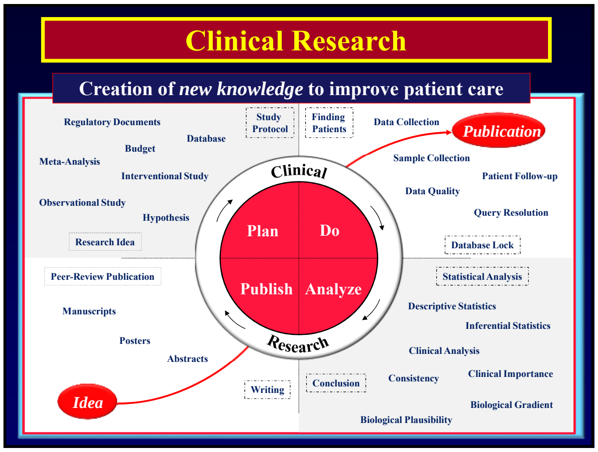

Clinical Research
Step 4: Publishing Study Findings
Writing Group
Write

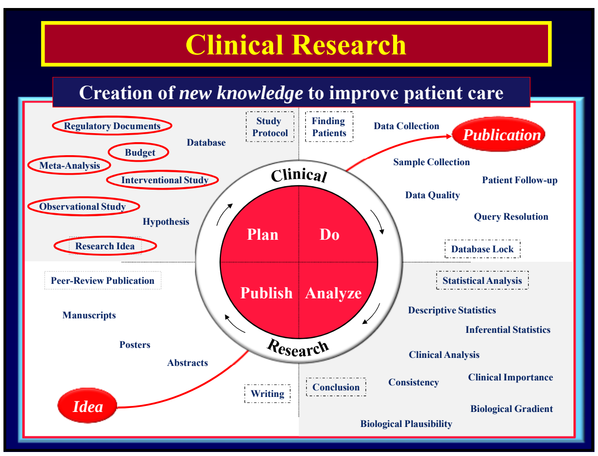

Clinical Research
Step 4: Publishing Study Findings
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Submit

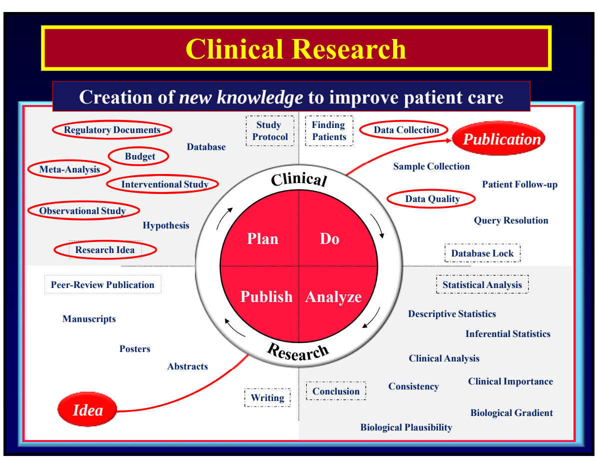

Clinical Research
Step 4: Publishing Study Findings
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Resubmit
Submit

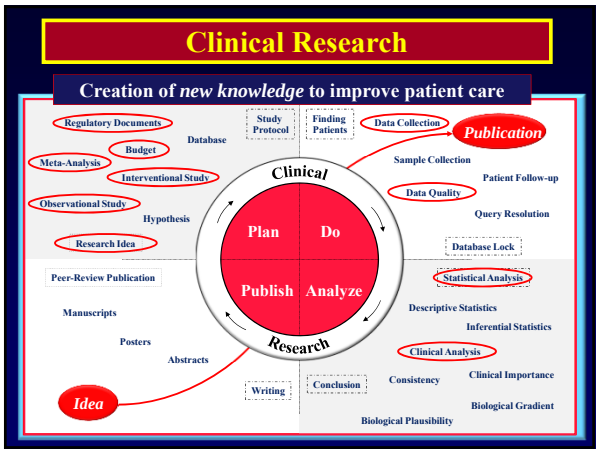

Clinical Research
Step 4: Publishing Study Findings
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Peer-Review Publication
Resubmit
Submit

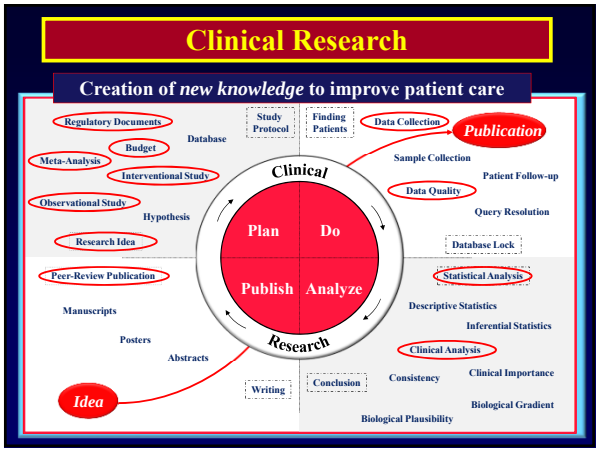

Clinical Research
Step 4: Publishing Study Findings
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Peer-Review Publication
Resubmit
Submit
A clinical study is not completed until the results are published
Investigators are measured by their publications
Without prior publications there is no grant


Clinical Research
Creation of new knowledge to improve patient care
Regulatory Documents
Database
Study Protocol
Finding Patients
Data Collection
Publication
Budget
Meta-Analysis
Interventional Study
Sample Collection
Patient Follow-up
Observational Study
Data Quality
Hypothesis
Query Resolution
Research Idea
Database Lock
Clinical
Plan
Do
Publish
Analyze
Research
Peer-Review Publication
Statistical Analysis
Manuscripts
Descriptive Statistics
Inferential Statistics
Posters
Clinical Analysis
Abstracts
Consistency
Clinical Importance
Writing
Conclusion
Idea
Biological Gradient
Biological Plausibility


Clinical Research
Creation of new knowledge to improve patient care
Regulatory Documents
Database
Study Protocol
Finding Patients
Data Collection
Publication
Budget
Meta-Analysis
Interventional Study
Sample Collection
Patient Follow-up
Observational Study
Data Quality
Hypothesis
Query Resolution
Research Idea
Database Lock
Clinical
Plan
Do
Publish
Analyze
Research
Peer-Review Publication
Statistical Analysis
Manuscripts
Descriptive Statistics
Inferential Statistics
Posters
Clinical Analysis
Abstracts
Consistency
Clinical Importance
Writing
Conclusion
Idea
Biological Gradient
Biological Plausibility


Clinical Research
Creation of new knowledge to improve patient care
Regulatory Documents
Database
Study Protocol
Finding Patients
Data Collection
Publication
Budget
Meta-Analysis
Interventional Study
Sample Collection
Patient Follow-up
Observational Study
Data Quality
Hypothesis
Query Resolution
Research Idea
Database Lock
Clinical
Plan
Do
Publish
Analyze
Research
Peer-Review Publication
Statistical Analysis
Manuscripts
Descriptive Statistics
Inferential Statistics
Posters
Clinical Analysis
Abstracts
Consistency
Clinical Importance
Writing
Conclusion
Idea
Biological Gradient
Biological Plausibility


Clinical Research
Creation of *new knowledge* to improve patient care
Regulatory Documents
Budget
Meta-Analysis
Interventional Study
Observational Study
Hypothesis
Research Idea
Database
Study Protocol
Finding Patients
Data Collection
Publication
Sample Collection
Patient Follow-up
Data Quality
Query Resolution
Database Lock
Statistical Analysis
Descriptive Statistics
Inferential Statistics
Clinical Analysis
Clinical Importance
Consistency
Biological Gradient
Biological Plausibility
Conclusion
Writing
Peer-Review Publication
Manuscripts
Posters
Abstracts
Idea
Clinical
Plan
Do
Publish
Analyze
Research


Clinical Research
Creation of *new knowledge* to improve patient care
Regulatory Documents
Budget
Meta-Analysis
Interventional Study
Observational Study
Hypothesis
Research Idea
Database
Study Protocol
Finding Patients
Data Collection
Publication
Sample Collection
Patient Follow-up
Data Quality
Query Resolution
Database Lock
Statistical Analysis
Descriptive Statistics
Inferential Statistics
Clinical Analysis
Clinical Importance
Consistency
Biological Gradient
Biological Plausibility
Conclusion
Writing
Peer-Review Publication
Manuscripts
Posters
Abstracts
Idea
Clinical
Plan
Do
Publish
Analyze
Research

"The Research Question"

Ruth Carrico PhD DNP FSHEA CIC
Associate Professor
Division of Infectious Diseases
University of Louisville

Clinical & Translational Research

The Research Question

1. Sources of the Research Question
2. Characteristics of a Good Research Question

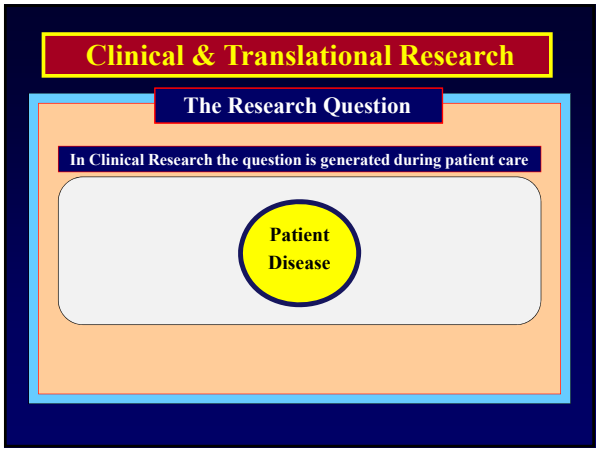
Clinical & Translational Research

The Research Question

1. Sources of the Research Question
2. Characteristics of a Good Research Question


Clinical & Translational Research
The Research Question
Sources for the Research Question
Prior Studies
Meetings
The Literature
Brainstorming


Clinical & Translational Research
The Research Question
Sources for the Research Question
Prior Studies
Meetings
The Literature
Brainstorming
Patient Care
In Clinical Research the important question is generated by the "health care worker" during patient care
In Clinical Research the important question is generated by the "patient" during patient care


Clinical & Translational Research
The Research Question
In Clinical Research the question is generated during patient care
Patient
Disease

Clinical & Translational Research

The Research Question

In Clinical Research the question is generated during patient care

Clinical & Translational Research

The Research Question

In Clinical Research the question is generated during patient care

Translational Research
Applying knowledge from basic research into the prevention and treatment of human disease

Clinical & Translational Research

The Research Question

1. Sources of the Research Question
2. Characteristics of a Good Research Question

Clinical & Translational Research

The Research Question

Characteristics of a Good Research Question

- F
- I
- N
- E
- R

Clinical & Translational Research

The Research Question

Characteristics of a Good Research Question

- F Feasible
- I Interesting
- N Novel
- E Ethical
- R Relevant

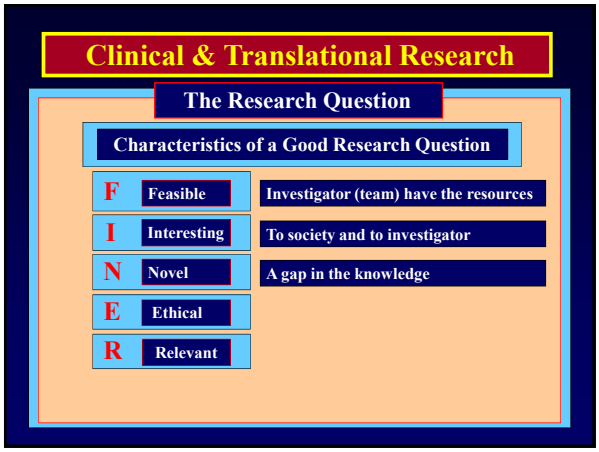
Clinical & Translational Research

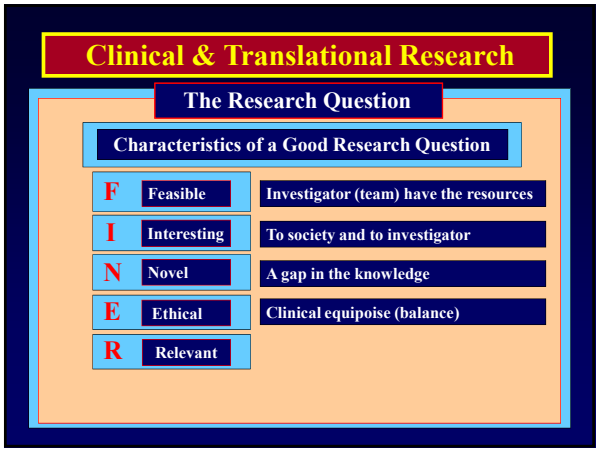
The Research Question

Characteristics of a Good Research Question

- F Feasible — Investigator (team) have the resources
- I Interesting
- N Novel
- E Ethical
- R Relevant


Clinical & Translational Research
The Research Question
Characteristics of a Good Research Question
F Feasible
Investigator (team) have the resources
I Interesting
To society and to investigator
N Novel
E Ethical
R Relevant


Clinical & Translational Research
The Research Question
Characteristics of a Good Research Question
F Feasible
Investigator (team) have the resources
I Interesting
To society and to investigator
N Novel
A gap in the knowledge
E Ethical
R Relevant


Clinical & Translational Research
The Research Question
Characteristics of a Good Research Question
F Feasible
Investigator (team) have the resources
I Interesting
To society and to investigator
N Novel
A gap in the knowledge
E Ethical
Clinical equipoise (balance)
R Relevant

Clinical & Translational Research

The Research Question

Characteristics of a Good Research Question

F	Feasible	Investigator (team) have the resources
I	Interesting	To society and to investigator
N	Novel	A gap in the knowledge
E	Ethical	Clinical equipoise (balance)
R	Relevant	Pass the "so what" test

Clinical & Translational Research

The Research Question

Characteristics of a Good Research Question

F	Feasible	Investigator (team) have the resources
I	Interesting	To society and to investigator
N	Novel	A gap in the knowledge
E	Ethical	Clinical equipoise (balance)
R	Relevant	Pass the "so what" test

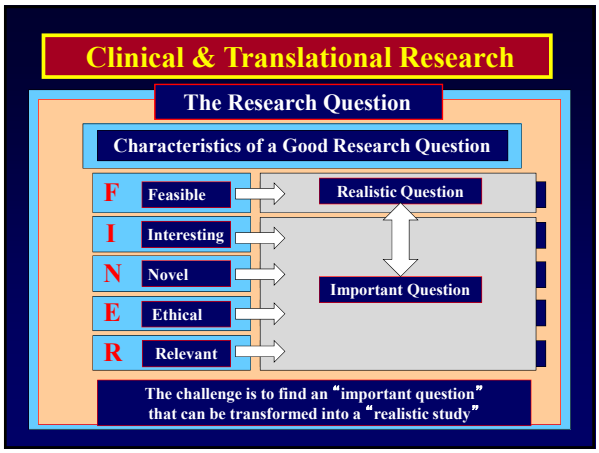
Your research question should not reiterate what is already established

Clinical & Translational Research

The Research Question

Characteristics of a Good Research Question

F	Feasible	Realistic Question
I	Interesting	
N	Novel	Important Question
E	Ethical	
R	Relevant	


Clinical & Translational Research
The Research Question
Characteristics of a Good Research Question
F
Feasible
I
Interesting
N
Novel
E
Ethical
R
Relevant
Realistic Question
Important Question
The challenge is to find an "important question" that can be transformed into a "realistic study"

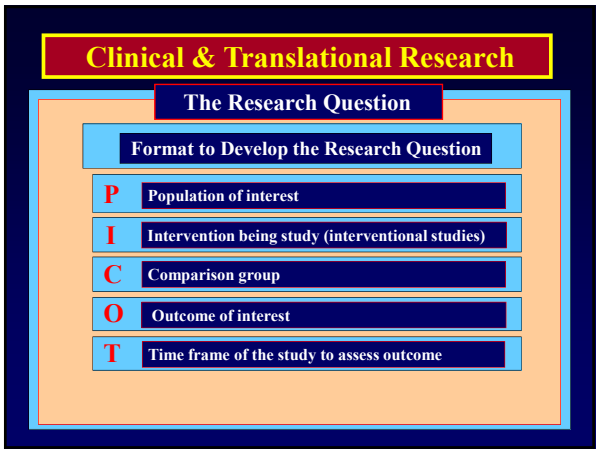

Clinical & Translational Research
The Research Question
Problems with the Research Question
Not Feasible


Clinical & Translational Research
The Research Question
Problems with the Research Question
Not Feasible
* Not enough subjects available


Clinical & Translational Research
The Research Question
Problems with the Research Question
Not Feasible
* Not enough subjects available
* Resources not available


Clinical & Translational Research
The Research Question
Problems with the Research Question
Not Feasible
* Not enough subjects available
* Resources not available
* Not enough time


Clinical & Translational Research
The Research Question
Format to Develop the Research Question
P
I
C
O
T


Clinical & Translational Research
The Research Question
Format to Develop the Research Question
P
Population of interest
I
Intervention being study (interventional studies)
C
Comparison group
O
Outcome of interest
T
Time frame of the study to assess outcome

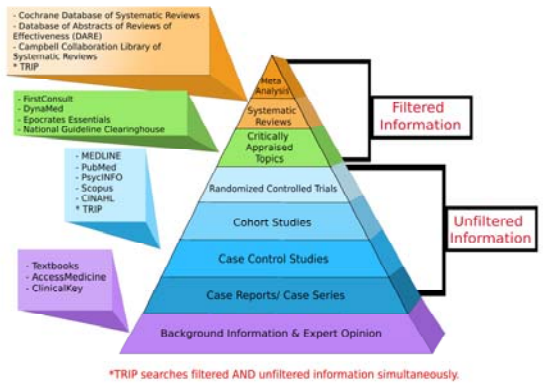

Clinical & Translational Research
The Research Question
1. Sources of the Research Question
2. Characteristics of a Good Research Question

Observational Studies

Maxwell Boakye, MD, MPH, MBA, FAANS, FACS
Professor of Neurosurgery
Ole A.,Mabel Wise&Wilma Wise Nelson Endowed Chair
Chief of Spinal Neurosurgery
Director Spine Fellowship
Clinical Director, Kentucky Spinal Cord Injury Center

Agenda

- Types of Observational studies
- Threats to Validity of Observational studies
  - Bias
  - Confounding
  - Generalizability
- Analysis of Observational studies



Establishing Causality

- Causality cannot be established when the therapeutic selection is influenced by patient characteristics, including severity and acuteness of illness and comorbidity

Bradford Hill criteria for causality

1) temporal relationship—the cause must always come before the effect
2) strength of association
3) dose–response relationship
4) consistency of the relationship
5) biological plausibility
6) consideration of alternatives
7) experimental verification
8) specificity (a specific cause for a specific effect)
9) coherence (compatibility with existing knowledge)

Establishing causality

- Establishing causality requires consideration of these criteria but also
- General acceptance by the scientific community, subject matter experts, and society at large.

Cochrane Database Syst Rev. 2014 Apr 29;(4):MR000034. doi: 10.1002/14651858.MR000034.pub2.

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials.

Anglemyer A[1], Horvath HT, Bero L

Author information

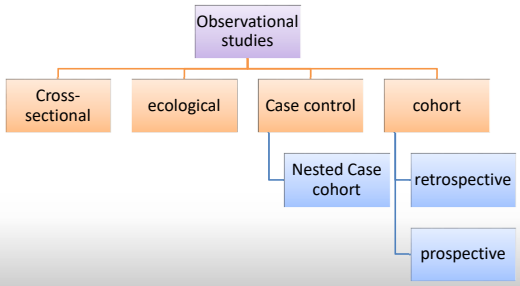
1 Global Health Sciences, University of California, San Francisco, San Francisco, California, USA, 94105.

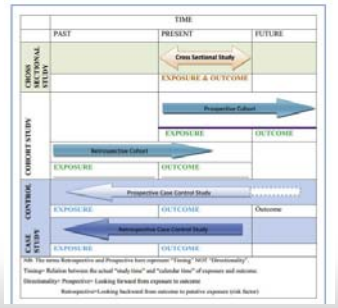
"Our results across all reviews (pooled ROR 1.08) are very similar to results reported by similarly conducted reviews.

On average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions.

Factors other than study design per se need to be considered when exploring reasons for a lack of agreement between results of RCTs and observational studies"

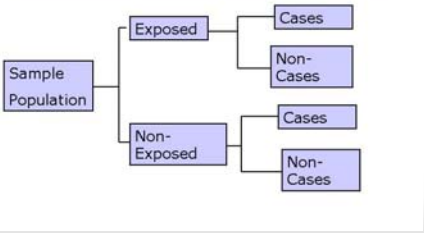
Types of observational studies





Esene et.al., World Neurosurg. 2018 Apr;112:233-242

Cross-Sectional Study Design



LOUISVILLE.EDU

Ecological studies

- Inferences made at group or population level e.g infection rates in a state correlated to opioid consumption rates
- Subject to significant fallacies

LOUISVILLE.EDU

Case control vs Cohort studies

Case Control	Cohort
Retrospective	Prospective
Fewer subjects	Large number of subjects
Less time	More time-years
Inexpensive	More expensive
Rare disease-Good for	Not so good for rare disease
Odds ratio-estimate of relative risk	Incidence rates, relative risk

LOUISVILLE.EDU

Misclassification of Case-Control Studies in Neurosurgery and Proposed Solutions

Ignatius Ngene Esene[1,2], Lawrence Mbuagbaw[3], Gilbert Dechambenoit[4], Wael Reda[3], Kazadi K. Kalangu[5]

Key words
- Case-control study
- Cohort study
- Neurosurgery
- Observational studies
- Research methods

Abbreviations and Acronyms
CCS: Case-control study
CI: Confidence interval
CS: Cohort studies
OR: Odds ratio
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

From the [1]Department of Neurological Surgery, University of Wisconsin-Madison, Madison, Wisconsin, USA, [2]Science Knife Center, Nasser Institute, Cairo, Egypt, [3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada, [4]African Journal of Neurological Sciences, Ivory Coast, and [5]Department of Neurosurgery, University of Zimbabwe, Harare, Zimbabwe

To whom correspondence should be addressed: Ignatius Ngene Esene, M.D., Ph.D., M.PH.
E-mail: esenengene@yahoo.co.uk; ignatiusesene@yahoo.co.uk

Citation: World Neurosurg. (2018) 112:233-242
https://doi.org/10.1016/j.wneu.2018.01.171
Journal homepage: www.WORLDNEUROSURGERY.org
Available online: www.sciencedirect.com
1878-8750/$ - see front matter © 2018 Elsevier Inc. All rights reserved

OBJECTIVE: Case-control studies (CCS) and cohort studies (CS) are common research designs in neurosurgery. But the term case-control study is frequently misused in the neurosurgical literature, with many articles reported as CCS, even although their methodology does not respect the basic components of a CCS. We sought to estimate the extent of these discrepancies in neurosurgical literature, explore factors contributing to mislabeling, and shed some light on study design reporting.

METHODS: We identified 31 top-ranking pure neurosurgical journals and searched them for articles reported as CCS, either in the title or in the abstract. The articles were read to determine if they really were CCS according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Article assessment was conducted in duplicate (agreement [κ statistics] = 99.82%).

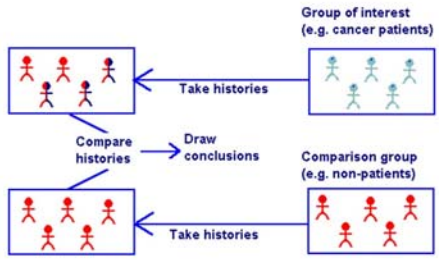
RESULTS: Two hundred and twenty-four articles met our inclusion criteria, 133 of which (59.38%) correctly labeled the case-control design, whereas 91 (40.62%) misclassified this study design. Cohort studies (CS) were the most common design mislabeled as case-control studies in 76 articles (33.93%), 57 of which (25.45%) were retrospective CS. The mislabeling of CCS impairs the appropriate indexing, classification, and sorting of evidence. Mislabeling CS for CCS leads to a downgrading of evidence as CS represent the highest level of evidence for observational studies. Odds ratios instead of relative risk are reported for these studies, resulting in a distortion of the measurement of the effect size, compounded when these are summarized in systematic reviews and pooled in meta-analyses.

CONCLUSIONS: Many studies reported as CCS are not true CCS. Reporting guidelines should include items that ensure that studies are labeled correctly. STROBE guidelines should be implemented in assessment of observational studies. Researchers in neurosurgery need better training in research methods and terminology. We also recommend accrued vigilance from reviewers and editors.

INTRODUCTION

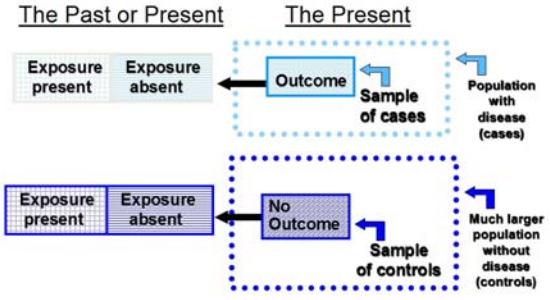
Case-control studies (CCS) and cohort studies (CS) are well-known research designs in contemporary use in neurosur-

Case Control Studies

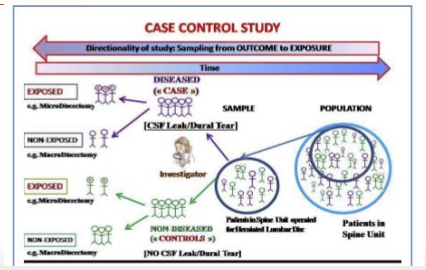


Statisticshowto.com

Case-Control Design



Case control, surgery example



Esene et.al., World Neurosurg. 2018 Apr;112:233-242

Odds Ratio Calculation

Exposure	Cases	Controls
	Outcome	
Exposed	A	B
Not Exposed	C	D

$$\text{Odds of exposure for cases} = \frac{A / C}{B / D} = \text{Odds Ratio}$$

Odds of exposure for controls

(estimates the relative risk)

Odds Ratio Example

	Autism		
MMR Vaccine?	Yes	No	Total
Yes	130	115	245
No	120	135	255
Total	250	250	500

$$OR = \frac{a \times d}{b \times c} = \frac{130 \times 135}{115 \times 120} = 1.27$$

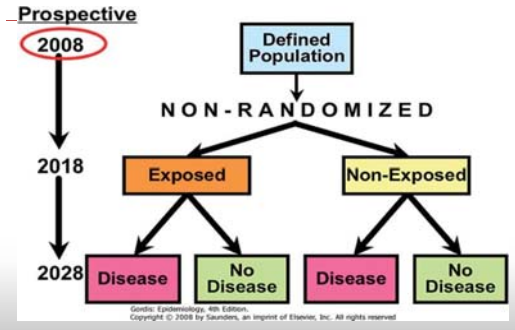
Case Control, example

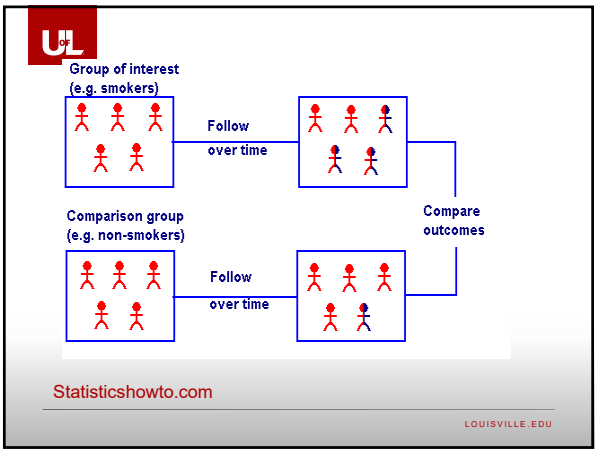
- Does intramuscular vit K cause childhood cancer?
- Select cases-107 children with leukemia
- Select controls-107 age and sex matched kids from same town as case at the time of diagnosis
- Review medical records-to see which cases and controls received Vit K

Case Control, example

- Founds 69/107 64% of cases and 63 of 107 59% of controls received IM Vit K odds raio 1.2 with confidence interval 0.7 to 2.3 therefore did not support that IM Vit K associated with childhood cancer-
- Von Kries et. al, BMJ,313(7051):199-203, 1996

Cohort Studies

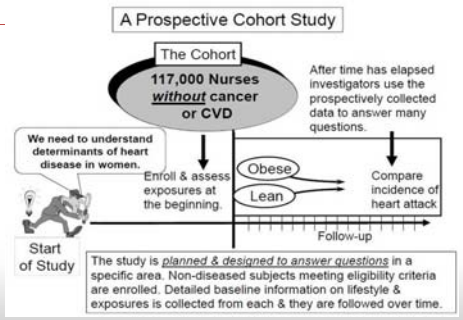




Statisticshowto.com

LOUISVILLE.EDU

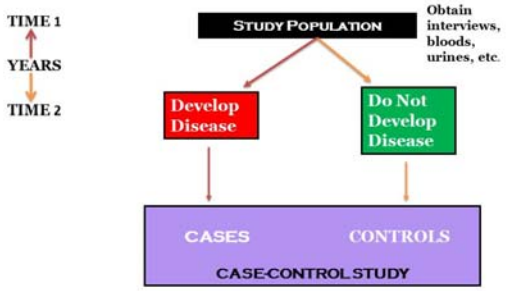
Cohort Study-example



http://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_analyticoverview/ProspectiveCohortStudy.jpg

LOUISVILLE.EDU

Nested Case Control Study Design



Relative Risk;

RR is the ratio of the incidence of the disease among exposed and the incidence among non exposed. It is a direct measure of the strength of association b/w cause and effect.

	Disease	No Disease
Exposed (Smoking)	a →	b
Non Exposed (Non Smoking)	c →	d

RR = a/a+b ÷ c/c+d

RR of 1 indicates no association, RR greater than 1 suggest positive association and RR less than 1 indicates negative association b/w exposure and disease.

Relative Risk Example

	Food Poisoning		
Russian Salad	Yes	No	**Total**
Yes	23	10	33
No	7	60	67
Total	30	70	100

$$RR = \frac{a / (a + b)}{c / (c + d)} = \frac{23 / 33}{7 / 67} = 6.67$$

Database studies

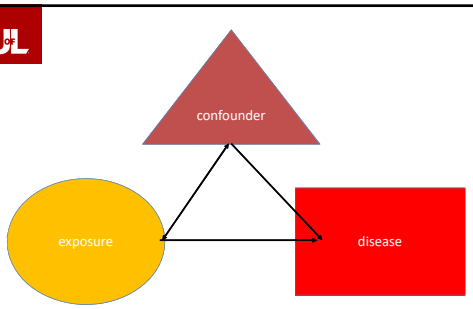
- Many opportunity exists to use existing data-Marketscan, Medicare, SEER-Medicare
- Retrospective cohort studies
- Age and complication rate after neurosurgery
- Compare surgical approaches
- Treatment approaches

Database studies

- Selection bias
- Measured and Unmeasured confounders
- Confounding by indication
- Measurement/Information biases
- Cohort and Data extraction dependent on ICD and CPT codes
- Generalizability
- Large sample sizes

Methods to reduce bias

- Multivariable methods
- Propensity score methods
- Instrumental variables methods



Multivariate regression

TABLE III Appropriate Multivariable Adjustment Models for Common Types of Outcomes

Type of Outcome	Example	Model	Estimate of Effect
Binary	Prevalence of postoperative infection	Logistic regression	Odds ratio
Continuous	Range of motion or functional outcome score (i.e., SF-36)	Linear regression	Mean difference
Time-to-event	Time to reoperation following total hip arthroplasty	Cox proportional hazards	Hazard ratio
Rate	National rates of total joint replacement	Poisson regression	Rate ratio

Propensity score

- The propensity score is the probability of treatment assignment conditional on observed baseline characteristics
- PS is a balancing score-treated and untreated subjects with the same propensity score will have equal distribution of measured baseline covariates.
- most often estimated scores obtained using a logistic regression model, in which treatment status is regressed on observed baseline characteristics.

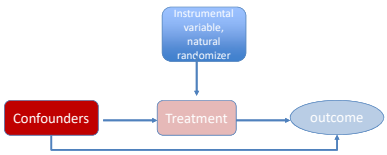
Propensity score methods

- Propensity score matching
- Stratification on the propensity score
- Inverse probability of treatment weighing using the propensity score
- Covariate adjustment using the propensity score

Instrumental variable

- Both multivariable and propensity score method will eliminate bias if all confounders are measured
- If there are unmeasured confounders, instrumental variables are used
  - IV is used to determine the level of exogenous variation, which is how much the variation in the treatment variable affects the outcome variable
  - They cause variation in the treatment variables

- Instrumental variable

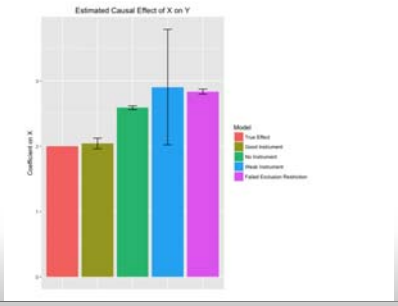


do not have a direct effect on the outcome variable (only indirectly through the treatment variable).

Some instrumental variables

- Physician preference
- Patients, by their choice (or referral)
- Distance to hospital-Patients treated at a hospital with a cardiac catheterization laboratory would have a higher chance of receiving PCI than those treated at a hospital without a cardiac catheterization laboratory-distance is a natural randomizer
- Parents educational level (nonmedical)

Weak vs strong instruments



Emily Glassberg Sands, Head of Data Science at Coursera, Jan 2018

TABLE I Relative Strengths and Weaknesses of Methods of Analysis of Therapeutic and Prognostic Nonrandomized Studies

Methods	Strengths	Weaknesses
Matching	Simple	Limits sample size
	Efficient sampling method, especially in case-control studies	Unable to fully explore associations with matched factors
		Potential for overmatching
Stratification	Simple	Difficult to interpret with multiple subgroups
	Easy to see effect modification	
Multivariable adjustment	Efficient simultaneous adjustment for multiple confounders	Quality of estimates subject to fit and assumptions of model
	Ability to easily assess effects of individual factors	
Propensity scores	Ability to directly see confounding through distribution of the propensity score	Potential remains for bias from unknown confounding
	Intuitive and simplified means of matching on single number	Possible to miss effect modification
	Rare outcomes	
	Confounding adjustment more robust to modeling assumptions	
Instrumental variables	Ability to get unconfounded estimates despite not having observed all possible confounders	Cannot test all instrumental variable assumptions
		Inference restricted only to subjects whose treatment is impacted by the instrumental variable

JNS

CLINICAL ARTICLE

Effect of decompressive craniectomy in the postoperative expansion of traumatic intracerebral hemorrhage: a propensity score–based analysis

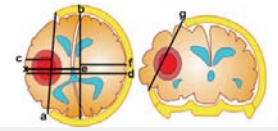
Santiago Cepeda, MD,[1,3] Ana María Castaño-León, MD,[2,3] Pablo M. Munarriz, MD,[2,3] Igor Paredes, MD, PhD,[2,3] Irene Panero, MD,[2,3] Carla Eiriz, MD,[2,3] Pedro A. Gómez, MD, PhD,[2,3] and Alfonso Lagares, MD, PhD[2,3]

[1]Department of Neurosurgery, University Hospital Río Hortega, Valladolid; [2]Department of Neurosurgery, University Hospital 12 de Octubre, Instituto de Investigación i+12, Madrid; and [3]University Complutense, Madrid, Spain

J Neurosurg. 2019 Apr 26:1-13

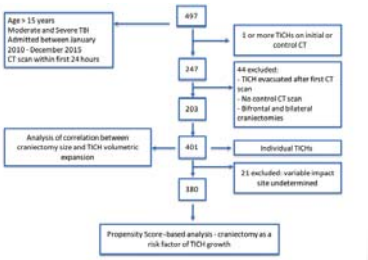
Question of interest

- Does Decompressive craniectomy cause hemorrhagic progression of intracranial hematoma?



Outcomes and variables

- Exposure = Decompressive Craniectomy
- Outcome=Hemorrhagic progression (any increase ≥ 33% of the initial volume of the ICH)



Create propensity score

- Binary logistic regression model
  - the exposure variable was craniectomy
  - demographic
  - variables such as age and sex
  - clinical variables: mechanism of injury, GCS admission score, systemic injury (shock and hypoxia), activated partial thromboplastin
  - time (aPTT), prothrombin activity (PA), platelet count, and radiological variables (initial volume of TICH, presence of multiple contusions, radiological pattern of TICH, cranial fracture, and presence of ASDH)

Statistical analysis

- Multivariate Regression model based on a generalized estimating equation
- A propensity score (PS)–based analysis

PS method 1-matching

- Greedy algorithm using the nearest-neighbor method with a ratio of 1:1 within a specified caliper distance of 0.2
- select a single unexposed match for each exposed case
- Match without replacement, once control participant was matched, was not matched with other treated participants

PS method 2-stratification

- grouped individuals with similar or equal PS ensures the distributions of measured covariates are sufficiently balanced in the treatment groups within each stratum
- five subsets of equal size by quintiles on the basis of the estimated PS

PS-method 3 (Inverse probability treatment weighting)

- The IPTW method applies weighting to participants to creates a new sample in which the distribution of measured baseline covariates is independent of exposure assignment.
- The weight (w) of the participant is equal to the inverse of the probability of receiving the treatment actually received

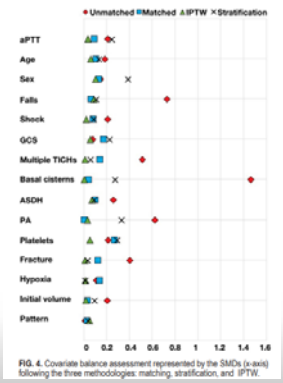


FIG. 4. Covariate balance assessment represented by the SMDs (x-axis) following the three methodologies: matching, stratification, and IPTW.

TABLE 4. Analysis of craniectomy effect on TICH HP

Analysis Method	OR	95% CI	p Value
Unadjusted	3.41	1.73–6.7	0.001
Adjusted using logistic regression	2.77	1.45–5.75	0.004
Adjusted by GEE	2.33	1.05–5.17	0.036
PS methods			
Matching	2.66	1.06–7.17	0.043
IPTW	2.43	1.03–5.73	0.043
Stratification			0.005
Outcome rates	2.08	1.27–3.49	
Mantel-Haenszel	2.15	1.25–3.67	

"In the present observational study, we demonstrated that craniectomy is a risk factor for the growth of brain contusions and that there is also an association between the size of the craniectomy and the magnitude of the volume increase in TICHs"

PLOS ONE

RESEARCH ARTICLE

Surgical Clipping versus Endovascular Intervention for the Treatment of Subarachnoid Hemorrhage Patients in New York State

Kimon Bekelis[1]*, Symeon Missios[2], Shannon Coy[3], Redi Rahmani[2], Robert J. Singer[1], Todd A. MacKenzie[4,5,6]

1 Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States of America, 2 Department of Neurosurgery, Louisiana State University Health Sciences Center, Shreveport, LA, United States of America, 3 Geisel School of Medicine at Dartmouth, Hanover, NH, United States of America, 4 Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States of America, 5 Department of Community and Family Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, United States of America, 6 The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH, United States of America

* bekelis@gmail.com

PLoS ONE 10(9): e0137946. 2015

Database: New York Statewide Planning and Research Cooperative System (SPARCS)

ruptured cerebral aneurysms(ICD-9-CM diagnosis code 430)

Surgical clipping (ICD-9-CM procedure code 39.51) or endovascular coiling 39.52, 39.72, 39.75, 39.76

The primary outcome variable was mortality during the initial hospitalization after treatment of a ruptured cerebral aneurysm.

Demographic Covariates: age, gender, race (African-American, Hispanic, Asian, Caucasian, other), and insurance (private, Medicare, Medicaid, uninsured, other).

Comorbidities: diabetes mellitus (DM), smoking, chronic lung disease, hypertension, hypercholesterolemia, peripheral vascular disease (PVD), congestive heart failure (CHF), coronary artery disease (CAD), history of ischemic stroke, transient ischemic attack (TIA), alcohol abuse, obesity, chronic renal failure (CRF), and coagulopathy.

Instrumental variable: regional ratio of coiling (county level coiling ratio—defined as the number of coiled patients divided by the total number of interventions for cerebral aneurysms in a county) was used as an instrument

Methods: A two stage least squares (2SLS) method
The value of the F statistic in the first stage of the 2SLS approach was 30, which is consistent with a strong instrument (F statistic>10), based on a practical rule, published before in the literature

Propensity score was calculated using the following variables: sex, race, insurance, medical comorbidities

Results: No association of treatment technique with mortality (ME, -0.56; 95% CI, -1.03 to 0.02) after using a probit regression with instrumental variable analysis.

Alternative methods: Results persisted in a mixed effects logistic regression model (OR, 0.88; 95% CI, 0.69 to 1.14) and a propensity score adjusted model (OR, 0.83; 95% CI, 0.65 to 1.04).

Table 3. Multivariable models examining the association of surgical clipping with outcomes.

	Inpatient Mortality		Discharge to rehabilitation		30-day readmission		Length-of-stay§	
	ME (95% CI)	P-value	ME (95% CI)	P-value	ME (95% CI)	P-value	ME (95% CI)	P-value
Instrumental variable analysis*	-0.56 (-1.03 to 0.02)	0.130	0.63 (0.24 to 1.01)	<0.001	-0.30 (-0.82 to 0.22)	0.259	1.72 (-3.39 to 6.84)	0.509
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	Beta (95% CI)	P-value
Mixed effects logistic regression†	0.88 (0.69 to 1.14)	0.200	1.65 (1.39 to 1.95)	<0.001	1.05 (0.81 to 1.38)	0.694	1.26 (0.10 to 2.42)	0.334
Propensity score adjusted logistic regression¶	0.83 (0.65 to 1.04)	0.110	1.69 (1.45 to 1.96)	<0.001	1.05 (0.82 to 1.35)	0.707	1.16 (-0.02 to 2.33)	0.070

Conclusion: "Using a comprehensive all-payer cohort of patients in New York State with aneurysmal SAH we did not identify an association of treatment method with mortality, LOS, or 30-day readmission"

Summary

- Overview of observational studies and limitations and pitfalls
- Thx to Dr. Ramirez for great course
- Thx to neurosurgery outcomes research group

Planning the Study: Systematic Reviews and Meta-Analyses

Rodrigo Cavallazzi, MD
Associate Professor of Medicine
University of Louisville

Planning the Study: Systematic Reviews and Meta-Analyses

- Objective
- ✓ Provide a guidance on how to conduct a systematic review

Planning the Study: Systematic Reviews and Meta-Analyses

- Outline
- ✓ Introduction
- ✓ Framing the question
- ✓ Literature search
- ✓ Study selection
- ✓ Risk of bias or quality reporting assessment
- ✓ Meta-analysis
- ✓ Discussion
- ✓ Limitations of systematic review
- ✓ Take-home message

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

- Problems with narrative review:
- ✓ Inherent subjectivity
- ✓ Lack of transparency

Planning the Study: Systematic Reviews and Meta-Analyses

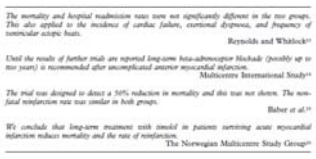
Introduction

- Pretend we are in 1981
- During rounds, there is bedside discussion on the use of beta-blockade after myocardial infarction
- The attending asks the resident physician to look up the literature.

Egger M, Smith GD, O'Rourke. Rationale, potentials, and promise of systematic Reviews. In: Egger M, Smith GD, Altman DGSystematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction



The mortality and hospital readmission rates were not significantly different in the two groups. This also applied to the incidence of cardiac failure, exertional dyspnoea, and frequency of ventricular ectopic beats.

Reynolds and Whitlock[10]

Until the results of further trials are reported long-term beta-adrenoceptor blockade (possibly up to two years) is recommended after uncomplicated anterior myocardial infarction.

Multicentre International Study[11]

The trial was designed to detect a 50% reduction in mortality and this was not shown. The non-fatal reinfarction rate was similar in both groups.

Baber et al.[12]

We conclude that long-term treatment with timolol in patients surviving acute myocardial infarction reduces mortality and the rate of reinfarction.

The Norwegian Multicentre Study Group[13]

Egger M, Smith GD, O'Rourke. Rationale, potentials, and promise of systematic Reviews. In: Egger M, Smith GD, Altman DGSystematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

Regular Review

Timolol after myocardial infarction: an answer or a new set of questions?

Thus, despite claims that they reduce arrhythmias, cardiac work, and infarct size, we still have no clear evidence that beta-blockers improve long-term survival after infarction despite almost 20 years of clinical trials.[1]

Egger M, Smith GD, O'Rourke. Rationale, potentials, and promise of systematic Reviews. In: Egger M, Smith GD, Altman DG. Systematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

European Heart Journal (1981) 2, 259-266

The use of beta blockers for the reduction of mortality after myocardial infarction

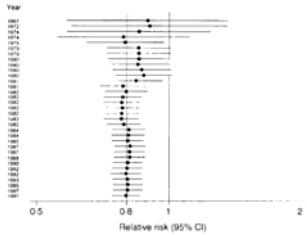
J. R. Hampton

Department of Medicine, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH

"It seems perfectly reasonable to treat patients who survived an infarction with timolol"

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction



Egger M, Smith GD, O'Rourke. Rationale, potentials, and promise of systematic Reviews. In: Egger M, Smith GD, Altman DGSystematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

- Systematic reviews
- ✓ Clear set of rules to:
  - ✓ Search for studies
  - ✓ Determine which studies will be included or excluded from the analysis

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

- Meta-analysis
- ✓ Statistical synthesis of the data
- ✓ Weights assigned to each study are based on mathematical criteria
- ✓ Results are replicable

Planning the Study: Systematic Reviews and Meta-Analyses

Introduction

- Synthesize the evidence (not only clinical trials)
- Support policy and guidelines
- Form the core of the evidence-based medicine
- Used by pharmaceutical companies (internal research, submission to governmental agencies, and marketing)
- Synthesize adverse events
- Used in other fields (e.g. psychology, criminology, business)

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Framing the question

- Problem addressed in the form of clear and structured questions before the onset of the review
- May use PICO (acronym for population, intervention, comparison, outcomes)

Uman LS. Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry. 2011 Feb;20(1):57-9.

Planning the Study: Systematic Reviews and Meta-Analyses

Framing the question

Intensive Care Med (2008) 34:2147–2156
DOI 10.1007/s00134-008-1214-5

REVIEW

Rodrigo Cavallazzi
Abhilash Nair
Tajender Vasu
Paul E. Marik

Natriuretic peptides in acute pulmonary embolism: a systematic review

"The purpose of this systematic review is to evaluate the available evidence on (a) the accuracy of BNP and NT-proBNP for the diagnosis of RVD and (b) their value as a prognostic factor of all-cause in-hospital or short-term mortality in patients with acute PE."

Planning the Study: Systematic Reviews and Meta-Analyses

Framing the question

- Patient population
  - ✓ Patients admitted to the hospital with acute pulmonary embolism
- Intervention, Prognostic Factor, Exposure
  - ✓ Brain natriuretic peptide level
- Comparison
  - ✓ High vs normal BNP level
- Outcomes
  - ✓ In-patient mortality

Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008 Dec;34(12):2147-56.

Planning the Study: Systematic Reviews and Meta-Analyses

Literature search

- Search at least two electronic databases (Medline, EMBASE, ISI Web of Knowledge)
- AND and OR Boolean terms
  - ✓ pulmonary embolism OR thromboembolic disease AND brain natriuretic peptide
- Truncation symbol
- Screen articles by reading title and abstract
- Additional searches (references, manual journal search…)
- No restriction language

Siddaway AP, Wood AM, Hedges LV. How to Do a Systematic Review:
A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses.
Annu Rev Psychol. 2019 Jan 4;70:747-770.

Planning the Study: Systematic Reviews and Meta-Analyses

Study selection

- Ideally two separate reviewers conduct the search
- Studies that may meet inclusion criteria should be fully reviewed
- Keep a log of all screened studies, fully reviewed studies, included studies, and excluded studies (use a software such as Refworks)

Planning the Study: Systematic Reviews and Meta-Analyses

Study selection

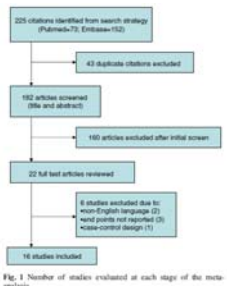


Fig. 1 Number of studies evaluated at each stage of the meta-analysis

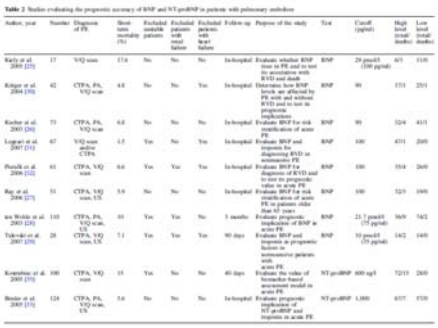
Cavallazzi R, Nair A, Vasu T, Marik PE.
Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008 Dec;34(12):2147-56.

Planning the Study: Systematic Reviews and Meta-Analyses

Data extraction

- Use a data extraction form or table to organize the information
- Ideally performed by two reviewers
- Author, year, journal, setting, purpose, inclusion and exclusion criteria, follow up, data needed for synthesis

Planning the Study: Systematic Reviews and Meta-Analyses



Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008 Dec;34(12):2147-56.

Planning the Study: Systematic Reviews and Meta-Analyses

Risk of bias or quality reporting assessment

- Checklists
- ✓ STROBE
  - ✓ Observational studies
- ✓ QUADAS-2
  - ✓ Studies of diagnostic accuracy tests
- ✓ Cochrane risk of bias tool for randomized trials
  - ✓ Randomized clinical trials

Planning the Study: Systematic Reviews and Meta-Analyses

Risk of bias or quality reporting assessment

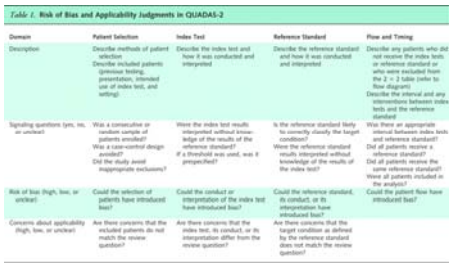


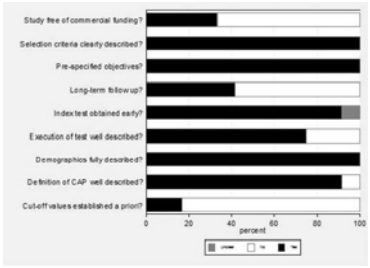
Table 1. **Risk of Bias and Applicability Judgments in QUADAS-2**

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

Planning the Study: Systematic Reviews and Meta-Analyses

Risk of bias or quality reporting assessment



Cavallazzi R, El-Kersh K, Abu-Atherah E, Singh S, Loke YK, Wiemken T, Ramirez J. Midregional proadrenomedullin for prognosis in community-acquired pneumonia: a systematic review. Respir Med. 2014 Nov;108(11):1569-80.

Planning the Study: Systematic Reviews and Meta-Analyses

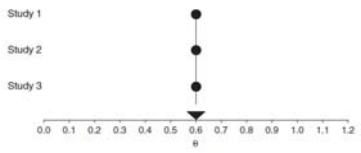
Meta-analysis

- Two statistical models
- Fixed-effect model: Assumes there is one true effect size. All differences in observed effects are due to sampling error.
- Random-effects model: True effect varies from one study to study.

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

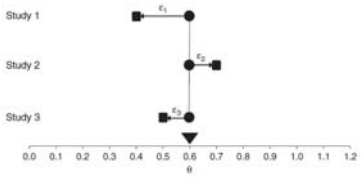
Meta-analysis
Fixed-effect



Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Fixed-effect



Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

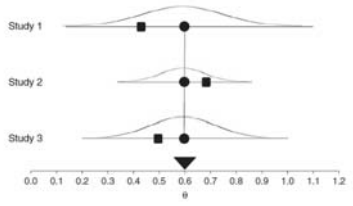


Figure 11.3 Fixed-effect model – distribution of sampling error.

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Fixed-effect

- Weight assigned to each study is the inverse of the study's variance

$$W_i = 1/V_{yi}$$

V_{yi} is within-study variance for study.

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Fixed-effect

- The weighted mean is the sum of the effect size multiplied by the weight of each study, divided by the sum of weights

$$M = \Sigma W_i Y_i / \Sigma w_i$$

W_i is weight of each study.
Y_i is the effect of each study.

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Fixed-effect

- Variance of the summary effect is estimated as the reciprocal of the sum of the weights

$$V_m = 1/\Sigma W_i$$

- Standard error is the square root of the variance

$$SE_m = \sqrt{V_m}$$

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Fixed-effect

- 95% lower and upper limits for the summary effect are estimated as:

$$LL_m = M - 1.96xSE_m$$
$$UL_m = M + 1.96xSE_m$$

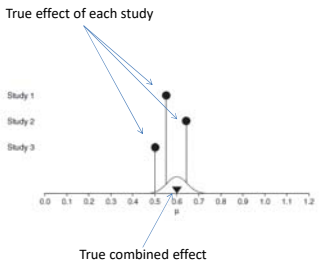
- Z-value to test the null hypothesis that the common true effect is zero:

$$Z = M/SE_m$$

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

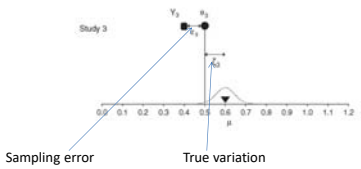
Meta-analysis
Random-effects



Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

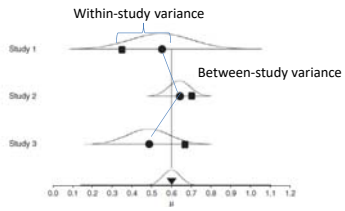
Meta-analysis
Random-effects



Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects



Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects

- Estimating between-studies variance (tau-squared)

$$T^2 = (Q - df)/C$$

$$Q = \Sigma W_i Y_i^2 - (\Sigma W_i Y_i)^2/\Sigma w_i$$

$$C = = \Sigma W_i - \Sigma w_i^2/\Sigma w_i$$

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects

- Each study will be weighed by the inverse of its variance

$$W_i = 1/Vy_i$$

Vy_i is within-study variance for study plus the estimate of the between-studies variance (T2).

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects

- The weighted mean is the sum of the effect size multiplied by the weight of each study, divided by the sum of weights

$$M = \Sigma W_i Y_i / \Sigma w_i$$

W_i is weight of each study.
Y_i is the effect of each study.

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects

- Variance of the summary effect is estimated as the reciprocal of the sum of the weights

$$V_m = 1/\Sigma W_i$$

- Standard error is the square root of the variance

$$SE_m = \sqrt{V_m}$$

Introduction to Meta-Analysis Borenstein, Michael, Hedges, Larry V., Higgins, Julian P.T.,Rothstein, Hannah R. Wiley , 2009

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Random-effects

- 95% lower and upper limits for the summary effect are estimated as:

$$LL_m = M - 1.96 \times SE_m$$
$$UL_m = M + 1.96 \times SE_m$$

- Z-value to test the null hypothesis that the common true effect is zero:

$$Z = M/SE_m$$

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis

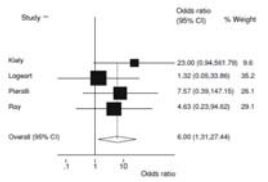
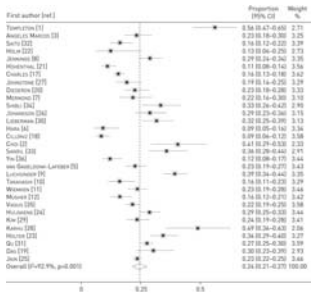


Fig. 3 Effect of elevated BNP on short term mortality (cutoff 100 pg/ml). Weight is the relative contribution of each study to the overall odds ratio (fixed effects model with 95% confidence interval)

Cavallazzi R, Nair A, Vasu T, Marik PE. Natriuretic peptides in acute pulmonary embolism: a systematic review. Intensive Care Med. 2008 Dec;34(12):2147-56.

Planning the Study: Systematic Reviews and Meta-Analyses



Burk M, El-Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. Eur Respir Rev. 2016 Jun;25(140):178-88.

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Assessment of heterogeneity/Subgroup analysis

- Studies that obtained lower respiratory tract sample
  - ✓ Prevalence: 44.2% (95% CI 35.1–53.3%; I^2=0%)
- Other studies
  - ✓ Prevalence: 23.5% (95% CI 20.5–26.6%; I^2=93%)
- Studies with an inpatient population
  - ✓ Prevalence: 25.5% (95% CI 22–29%; I^2=93.6%)
- Studies with outpatient population
  - ✓ Prevalence: 12.1% (95% CI 7.7–16.5%; I^2=0.0%)

Burk M, El-Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. Eur Respir Rev. 2016 Jun;25(140):178-88.

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Assessment of heterogeneity/Subgroup analysis

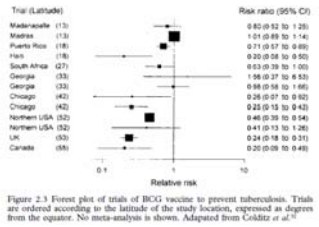
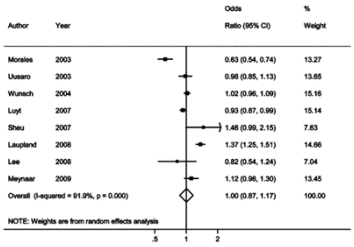


Figure 2.3 Forest plot of trials of BCG vaccine to prevent tuberculosis. Trials are ordered according to the latitude of the study location, expressed as degrees from the equator. No meta-analysis is shown. Adapted from Colditz *et al.*[4]

Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman DG. Systematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Assessment of heterogeneity/Subgroup analysis



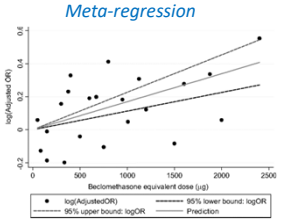
No intensivist (OR, 1.05 [95% CI, 0.79-1.41]; P = .73)

Intensivist (OR, 0.93 [95% CI, 0.87-0.99]; P = .02)

Cavallazzi R, Marik PE, Hirani A, Pachinburavan M, Vasu TS, Leiby BE. Association between time of admission to the ICU and mortality: a systematic review and metaanalysis. Chest. 2010 Jul;138(1):68-75

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis
Meta-regression



Each 500 µg increase in beclomethasone dose equivalents was associated with a 9% increase in the likelihood of fractures, OR 1.09 (95% CI 1.06 to 1.12; p<0.001)

Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. Thorax. 2011 Aug;66(8):699-708.

Planning the Study: Systematic Reviews and Meta-Analyses

Meta-analysis

Sensitivity analysis

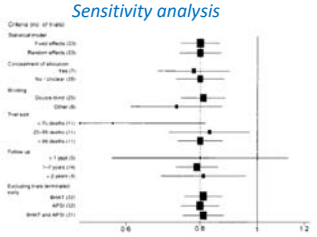


Figure 2.4 Sensitivity analyses examining the robustness of the effect on total mortality of beta-blockers in secondary prevention after myocardial infarction. The dotted vertical line corresponds to the combined relative risk from the fixed effects model (0·8).

Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman DG. Systematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Discussion

- Summary of the results
- Overall completeness and applicability
- Quality of the evidence
- Potential biases in the review process
- Agreements and disagreements with other studies or reviews

Planning the Study: Systematic Reviews and Meta-Analyses

Discussion

- Present information rather than offer advice
- Implications for practice
  - ✓ Practical and unambiguous
  - ✓ Supported by the data
  - ✓ No evidence of effect different from evidence of no effect

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews

- Publication bias
- ✓ Probability that an article is published depends on the results

Table 1. Outcomes of Tests of Significance for Four Psychology and Three Medical Research Journals

Journals	No. of articles reviewed in 1986–87	% articles reviewed that use tests in 1986–87	% articles using tests that reject H_0 in 1986–1987	No. of articles reviewed that used tests in 1958	% articles using tests that reject H_0 in 1958
Experimental Psychology (four journals)	165	92.73	93.46	106	99.06
Comparative & Physiological Psychology (two journals)	119	88.24	97.14	94	96.81
Consulting & Clinical Psychology	83	96.39	97.50	62	95.16
Personality & Social Psychology	230	97.83	95.56	32	96.88
Psychology Journals Total	**597**	**94.30**	**95.56**	**294**	**97.28**
American Journal of Epidemiology	141	81.56	80.87	N/A	N/A
American Journal of Public Health	97	43.30	88.10	N/A	N/A
New England Journal of Medicine	218	75.69	87.88	N/A	N/A
Medical Journals Total	**456**	**69.25**	**85.40**	N/A	**N/A**

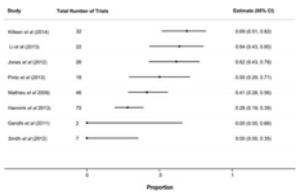
Publication Decisions Revisited: The Effect of the Outcome of. Statistical Tests on the Decision to Publish and Vice Versa. Sterling TD, Rosenbaum WL, Weinkam JJ. The American Statistician, Vol. 49, No. 1 (Feb., 1995), pp. 108-112

Egger M, Smith GD, O'Rourke. Rationale, potentials, and promise of systematic Reviews. In: Egger M, Smith GD, Altman DGSystematic reviews in health care : meta-analysis in context

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews

- Choice of outcomes reported can be influenced by the results



Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC Med. 2015 Nov 18;13:282.

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews

- Criteria for inclusion of studies in the systematic review can be influenced by knowledge of these studies
- ✓ Register a protocol:

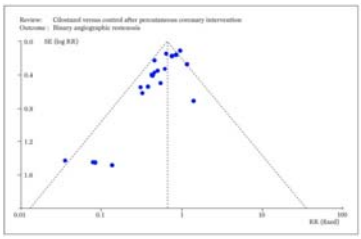
https://www.crd.york.ac.uk/prospero/

https://community.cochrane.org/review-production/production-resources/proposing-and-registering-new-cochrane-reviews

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews

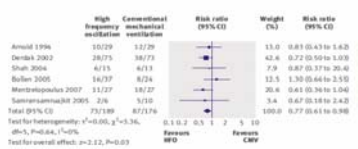
- Single center studies tend to provide higher magnitude effects
- Small single center studies with positive effects often refuted by large multicenter studies



Biondi-Zoccai G, Lotrionte M, Landoni G, Modena MG. The rough guide to systematic reviews and meta-analyses. HSR Proc Intensive Care Cardiovasc Anesth. 2011;3(3):161-73.

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews



BMJ. 2010 May 18;340:c2327.

Planning the Study: Systematic Reviews and Meta-Analyses

Limitations of systematic reviews

The NEW ENGLAND JOURNAL of MEDICINE

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

Multicenter, randomized, controlled trial, 39 ICUs
New onset, moderate to severe ARDS (PaO/FiO2 < 200 on a PEEP of at least 10)
HFOV vs. control ventilation with low tidal volume and high PEEP
Enrolled 571 of planned 1200
In-hospital mortality:
✓47% in the HFOV
✓35% in the control group; P value = 0.005

N Engl J Med. 2013 Feb 28;368(9):795-805

Planning the Study: Systematic Reviews and Meta-Analyses

Take-home message

- Formulate the review question
- Define the inclusion and exclusion criteria
- Locate studies
- Extract data
- Asses study quality
- Analyze and present results
- Interpret results

THANKS

Planning the Study: Ethics & Regulations

Rebecca Redman, MD
Clinical Research Course
August 20, 2019

1932: Public Health Service began the "Tuskegee Study of Untreated Syphilis in the Negro Male"

https://www.cdc.gov/tuskegee/timeline.htm

Timeline of Rules & Regulations

1948

Nuremberg Code
- In response to Nazi medical experiments in WWII
- Stated that voluntary consent was absolutely essential

1964

Declaration of Helskinki
- Governs international research ethics
- Basis for Good Clinical Practice

1974

National Research Act
- Established the Commission that drafted the Belmont Report:
  - Respect for persons
  - Beneficence
  - Justice

1991

Federal Policy for the Protection of Human Subjects: "Common Rule"
- Formal adoption of DHHS regulations (based on Belmont Reports):
  - Research institution requirements re: assuring compliance
  - Informed consent requirements
  - IRB requirements
  - Protection for vulnerable subjects
- Revised Jan 2019

IRB and Common Rule

- Serve to protect the rights and welfare of human subjects in research

What qualifies as research?

DHHS 45 CFR 46.102(d): A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge

- Institutional Review board or designee will make determination regarding whether or not a project meets "Common Rule" definition of human subjects research.

Research vs. Quality Assurance/Improvement

	Research	QA/QI
Purpose	To test a hypothesis OR establish clinical practice standards where none are accepted	To assess or promptly improve a process, program, or system; OR improve performance as judged by accepted/established standards
Starting Point	To answer a question or test a hypothesis	To improve performance
Benefits	Designed to contribute to generalizable knowledge and may or may not benefit subjects	Designed to promptly benefit a process, program or system and may or may not benefit patients
Risks/Benefits	May place subjects at risk and states such	By design, does not increase patient risk, with exception of possible privacy/confidentiality concerns
Data Collection	Systematic data collection	Systematic data collection
Testing/Analysis	Statistically prove or disprove a hypothesis	Compares a program/process/system to an established set of standards

https://louisville.edu/research/humansubjects/lifecycle/initial-submissions/what-is-qa-qi

Case Report vs. Case Series

- Both require HIPAA (Health Insurance Portability and Accountability Act) authorization unless the author firmly believes information is not identifiable
- General rule is that series of ≥ 3 patients is considered to be a systematic investigation designed to contribute to generalizable knowledge (i.e., research) and should be reviewed by the IRB

IRB Review

FULL BOARD "CONVENED"	EXPEDITED	EXEMPT

• Involve more than minimal risk
• Does not meet criteria for Expedited or Exempt
• Requires continuing annual review
	• No more than minimal risk (including risks related to breach of confidentiality or privacy)
	• Requires IRB continuing review
		• Requires initial review for determination of exempt status
		• Examples:
		  • Research involving educational practices
		  • Surveys (unless breach of confidentiality could place subject at risk)
		  • Source of data is publicly available or recorded such that subject data is not identifiable

IRB Review Expedited Categories

*For studies involving no more than minimal risk to subject AND one or more of the following….

1. Clinical studies of drugs/medical devices not requiring IND/IDE and being used in accordance with labeling
2. Collection of blood samples (dependent upon volume/frequency of collection)
3. Noninvasive collection of biological specimens
4. Collection of data through noninvasive procedures (e.g., MRI, audiogram)
5. Research involving materials that have been or will be collected solely for non-research purposes (e.g., chart review)
6. Collections of data from recordings (voice, video, etc.)
7. Research on individual or group characteristics or behavior

Principal Investigator Responsibilities:

EVERYTHING

FDA Investigational New Drug Applications

A clinical investigation of a ***marketed*** drug is exempt from the IND requirements if ***all*** of the criteria for an exemption in § 312.2(b) are met:

- The drug product is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
- In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-exemptions-ind-requirements

FDA Investigational New Drug Applications

- The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
- The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

Informed Consent

1. **Information**
   Disclose purpose of research, risks, anticipated benefits, and alternative
2. **Comprehension**
   Allow sufficient time, translation and assent where applicable
3. **Voluntariness**
   No undue influence or excessive reward

Exceptions to Informed Consent Process

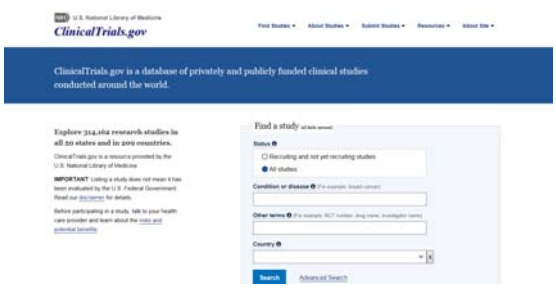
- Generally few and far between
- Emergency research or use of a test article; must apply for waiver
- Expedited/exempt protocol may qualify for waiver
- Research could not be carried out in practice without waiver

- If granted waiver of consent or documentation of consent, you must also request a waiver/partial waiver of HIPAA authorization assuming you plan to collect or use protected health information (PHI)

Requesting Waiver of HIPAA Authorization

1. Adequate plan to protect and destroy PHI
2. Research could not reasonably be conducted without waiver
3. Research could not be conducted without use of PHI

Clinicaltrials.gov



Study is up and running….

…but there is no rest for the weary.

Ongoing Study Responsibilities

- Continuing Review
  - DHHS and FDA require continuing IRB review of all non-exempt studies at least annually
- Event Reporting
  - Adverse events: IRB reporting requirements vary by site as well as the following:
    - Local or external event
    - Expected or unexpected
    - Seriousness
    - Relationship to study participation
  - Deviations: Major vs. Minor
  - Changes in protocol or risk

When in doubt….ask!

- IRB analysts are here to help
- FDA website
- Chances are that colleagues have faced similar questions or challenges

GOOD LUCK!

Clinical Research "Sources of Research Funding"

Craig J. McClain, M.D., Professor
Division of Gastroenterology/Hepatology/Nutrition
Departments of Medicine, Pharmacology and Toxicology
Associate Vice President for Translational Research
Associate Vice President for Health Affairs/Research
Director, Clinical Trials Unit
Louisville VA Medical Center
University of Louisville

Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

Funding Your Clinical Research

Your Mentor

Have a Mentor!

Funding Your Clinical Research

- Mentoring is a relationship – a journey mentors and mentees embark on together. Throughout this journey, two or more individuals help each other arrive at a destination called professional excellence.
- Mentors are:
  - *Advisors* who have career experience and share their knowledge
  - *Supporters* who give emotional and moral encouragement
  - *Tutors* who provide specific feedback on performance
  - *Masters* who serve as employers to 'apprentices'
  - *Advocates* who are willing to interact with others on their behalf
  - *Role models* who lead by example

Funding Your Clinical Research

Some effective mentoring behaviors

- Introduce you to collaborators
- Help set up collaborations
- Encourage presentations at meetings
- Introduce at meetings
- Arrange opportunities for talks, give talks in mentor's place
- Talk about you to colleagues
- Ask you to help review journal articles
- Ask to help write a major part of publication
- Help with lab budget
- Ask to write part of research grant
- Be an advocate with the administration

Funding Your Clinical Research

Is there a mentoring gene?

Great Mentors

M^+M^+

Good Mentors

M^+M^-

Bad Mentors

M^-M^-

Effective mentoring can be learned!

Funding Your Clinical Research

Work with Your Mentor and Become Familiar with Granting Agencies

Funding Your Clinical Research

Have your mentor help with grant writing

Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

Funding Your Clinical Research

Intramural Support

UofL EVPRI Internal Grants Programs

To assist faculty in the initiation of new research projects

https://louisville.edu/research/support/internal

Funding Your Clinical Research

Intramural Support

Associate Chair for Research

Associate Dean for Research

Associate Vice President for Research

Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

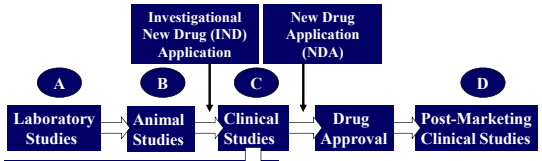
Funding Your Clinical Research

Industry Support

- Company-initiated study
  - Phase 2 studies
  - Phase 3 studies
- Investigator-initiated study
  - Phase 4 studies

Funding Your Clinical Research

Industry: Drug Research & Development



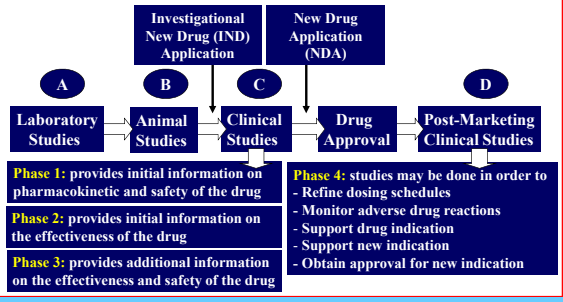
Phase 1: provides initial information on pharmacokinetic and safety of the drug

Phase 2: provides initial information on the effectiveness of the drug

Phase 3: provides additional information on the effectiveness and safety of the drug

Funding Your Clinical Research

Industry: Drug Research & Development



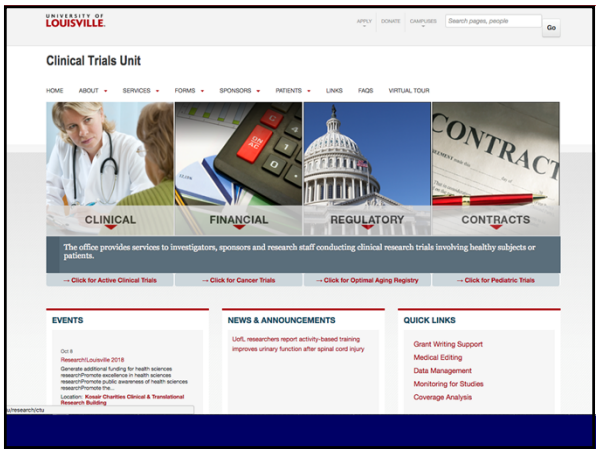
Funding Your Clinical Research

Clinical Trials Unit

The Clinical Trials Unit (CTU) is a central research unit operated under the Executive Vice President for Health Affairs (EVPHA). The unit provides services to investigators, sponsors and research staff conducting clinical research trials involving healthy subjects or patients. CTU operates in four locations on the Health Sciences Center: The Outpatient Research Clinic - HCOC building, the Administrative Office - MedCenter One Building, the Coordinator Pool - MDA building, and the Coordinator Pool - Heart and Lung Building.

Departmental research support

- Feasibility analysis
- Financial services
  - Budget negotiation
  - Billing compliance plan
  - Post-award account management
- Contract submission
- Regulatory services
- Data monitoring and management
- Standard Operating Procedure writing
- Clinical services
  - Recruitment
  - Data collection



Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

Funding Your Clinical Research

Private Foundations

Investigator-initiated	Institute-initiated
Grant application	Request for grant application

Funding Your Clinical Research

Private Foundations

- Early Career Investigators
  - Focused programing for fellows and post-training hepatologists
  - Professional and career development programing
- Special Interest Group Leadership Opportunities
  - Steering Committee Member
    - Work with SIG leadership to represent all SIG members

Funding Your Clinical Research

Private Foundations

Mentee Training opportunities

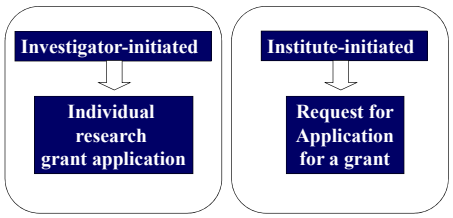
- Seminars by leading researchers in the field
- Workshops, seminars, case-conferences and on-line training modules
- Training in specific techniques, whether laboratory or clinical
- Workshops on professional writing, including manuscript and grant writing
- Short courses and seminars
- Career development counseling by senior clinicians/investigators

Funding Your Clinical Research

1. Support from your Mentor
2. Intramural Support
3. Industry Support
4. Private Foundations
5. Government

Funding Your Clinical Research

Government: NIH / VA / CDC / DOD



Funding Your Clinical Research

1st Grant - Trainee

- Career plan
- How K Award will lead to independent investigator status
- Mentor
- Environment
- Good Proposal
- Contact granting organization – NIH, VA, etc.

Funding Your Clinical Research

1st Grant - Mentor

- Record of mentoring
- NIH funding
- Involvement in project
- Strong letter of support

Funding Your Clinical Research

1st Grant - Environment

- Mentoring
- Institutional Commitment
- Start up/resources
- Protected time
- Career Development Plan
- Letters

Funding Your Clinical Research

NIH K-Awards: Research Career Development Awards

- To provide individual research training opportunities (including international) to trainees

Funding Your Clinical Research

K23: Mentored Patient-Oriented Research Career Development Award

- To provide support for the career development of clinically trained professionals who have made a commitment to patient-oriented research, and who have the potential to develop into productive, clinical investigators
- U.S. citizen or permanent resident, with research or clinical doctoral degree
- Postdoctorate/Residency, Early Career, Established Investigator

Funding Your Clinical Research

K08: Mentored Clinical Scientist Research Career Development Award

- To provide the opportunity for promising clinician scientists with demonstrated aptitude to develop into independent investigators, or for faculty members to pursue research, and aid in filling the academic faculty gap in health profession's institutions
- U.S. citizen or permanent resident, with a clinical doctoral degree
- Postdoctorate/Residency, Early Career, Established Investigator

Funding Your Clinical Research

K99/R00:

- To support both an initial mentored research experience (K99) followed by independent research (R00) for highly qualified, postdoctoral researchers, to secure an independent research position. Award recipients are expected to compete successfully for independent R01 support during the R00 phase
- U.S. citizen or non-citizen, with research or clinical doctoral degree, and no more than 4 years of Post-Doctoral research experience
- Postdoctorate/Residency, Early Career

Funding Your Clinical Research

NIH Loan Repayment Programs (LRPs)

- established by Congress to recruit and retain highly qualified health professionals into biomedical or biobehavioral research careers.
- repay up to $50,000/yr. of a researcher's qualified educational debt in return for a commitment to engage in NIH mission-relevant research
- five areas for researchers not employed by NIH (Extramural)
- not intended to fund research projects, but rather, LRP awards are based on an applicant's potential to build and sustain a research career

Funding Your Clinical Research

Qualifications, continued

- **Qualified Research (Extramural programs only) -** You must agree to conduct only research that is not prohibited by Federal law, regulations, or policies of the U.S. Department of Health and Human Services (HHS) or National Institutes of Health (NIH). Additionally, you must engage in qualified research for an average of at least 20 hours per week during each quarterly service period of your LRP award.
- **Domestic, nonprofit research funding (Extramural programs only)** - Your research must be supported by a domestic, nonprofit foundation, university, professional association, or other nonprofit institution, or a U.S. government agency (Federal, State, or local).

Research Success!

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Interventional Clinical Trials

Janice E. Sullivan, M.D., FAAP, FCCM
Professor
Vice Chair for Research
Department of Pediatrics
Medical Director, Pediatric Clinical Research Unit
Division of Pediatric Clinical & Translational Research
University of Louisville
August 20, 2019

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Overview

- Definitions
- Interventional studies (also called clinical trials)
- Clinical trials design
- Cautions
- Responsibility
- References

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

Definitions

- Types of clinical studies
  - Observational study:
    - A type of study in which people are observed or certain outcomes are measured. No attempt is made by the researcher to affect the outcome.
  - **Clinical trial (interventional study; prospective):**
    - During clinical trials, researchers learn if a new test or treatment works and is safe.
    - Treatments studied in clinical trials might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments.
  - Medical records research:
    - Medical records research involves the use of information collected from medical records. By studying the medical records of large groups of people over long periods of time, researchers can see how diseases progress and which treatments and surgeries work best.

NIH Clinical Trials

- Definition clarified October 2014 which resulted in more studies being classified as clinical trials
- Encompasses a wide range of types of trials:
  - Mechanistic
  - Exploratory/Developmental
  - Pilot/Feasibility
  - Behavioral
  - Other Interventional

Interventional study (clinical trial)

- NIH: A research study in which one or more human subjects are prospectively assigned to one or more interventions/treatments (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
  - Assignments are determined by study protocol
    - Experimental Group
    - Control Group
    - Not all clinical trials have a control group
  - Participants may receive diagnostic, therapeutic, or other types of interventions
  - Researchers evaluate the effects of the interventions on biomedical or health-related outcomes
    - Cause/effect relationship
    - Analytical study
- ***The best study design to demonstrate causality***

Interventional study (clinical trial)

- Prospectively Assigned: a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
- Intervention: a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints.
  - Examples include:
    - Drugs/small molecules/compounds, biologics, devices
      - Drug trials are frequently described by phases defined by FDA
      - May include multiple dose groups and may be staged by age group
    - Procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews)
    - Strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits)
    - Treatment strategies, prevention strategies, or diagnostic strategies

Interventional study (clinical trial)

- Health-related Biomedical or Behavioral Outcome: the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life.
  - Examples include *positive or negative changes* to:
    - Physiological or biological parameters (e.g., improvement of lung capacity, gene expression, etc.)
    - Psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers, reading comprehension and/or information retention, etc.)
    - Disease processes
    - Health-related behaviors
    - Quality of life

Interventional study (clinical trial)

- Control Group
  - Historical control
  - Sequential control (crossover; patient serves as own control)
  - Concurrent control (no treatment to one group)
  - Randomized concurrent control (clinical trial; one group given treatment and the other group a different treatment or placebo)

Interventional study (clinical trial)

- What is the role of:
  - Randomization

Interventional study (clinical trial)

- What is the role of:
  - Randomization
  - *Prevention of influence of confounding variables*

Interventional study (clinical trial)

- What is the role of:
  - Randomization
  - *Prevention of influence of confounding variables*
- What is the role of blinding:
  - Blinding (double-blind, single-blind, unblinded, etc.)
    - Investigators
    - Study team
    - Subjects/Family

Interventional study (clinical trial)

- What is the role of:
  - Randomization
  - *Prevention of influence of confounding variables*
- What is the role of blinding:
  - Blinding (double-blind, single-blind, unblinded, etc.)
    - Investigators
    - Study team
    - Subjects/Family
  - *Prevention of biased assessment of outcomes*

Interventional study (clinical trial)

- Who conducts clinical trials:
  - Principal investigator (often an MD)
  - Study team
- Who sponsors clinical trials:
  - Pharmaceutical companies, academic medical centers/investigators, NIH, DOD, Foundations, consortiums, etc.
- Where are clinical trials conducted:
  - Hospitals, universities, clinics, communities, etc.

Why do clinical trials FAIL?

Interventional study (clinical trial)

- Who designs clinical trials:
  - Principal investigator(s)
    - Consortiums
    - Teams of investigators (MDs, RNs, DNPs, Dentists, Psychologists, Social Workers, etc.)
  - Pharmaceutical companies
  - Networks

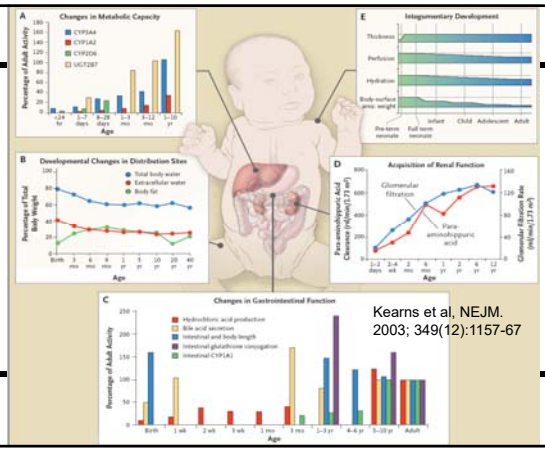
Interventional study (clinical trial)

- *PICOT* criteria: help frame research question*
  - **P**opulation
  - **I**ntervention
  - **C**omparison group
  - **O**utcome of interest
  - **T**ime
- *FINER* criteria for a good research question*
  - **F**easible (# subjects, technical expertise, affordable, manageable)
  - **I**nteresting (getting the answer is intriguing)
  - **N**ovel (confirms, refutes, or extends previous findings)
  - **E**thical (amenable to IRB approval)
  - **R**elevant (to scientific knowledge, clinical/health policy, future research)
- *SPIRIT* (guidelines for writing a protocol)**
- *Clinical Trials Recruitment*: Trial design/protocol development, Trial feasibility and site selection, and Communication***

* Ref 1
** Ref 2
*** Ref 3

Interventional study (clinical trial)

- **Study design**
  - Protection of human subjects at forefront
  - Engaged study team (multi-disciplinary)
    - Investigators, study coordinators, research nurses, pharmacists, etc.
    - Thought leaders
    - Feasibility
      - Inclusion/exclusion criteria
      - Population
      - Potential obstacles
        - Blood volume
        - Staff/patient/parent buy-in
      - Staff to conduct study
      - Budget
  - Well-developed protocol
    - Hypotheses and specific aims
    - Methods including study schedule
      - Outcome variables and measurements
      - Risks
      - Statistical analyses (power analysis, appropriate statistical plan, etc.)
  - **Regulatory and Contract support**
  - **Implementation and conduct of study at site**



Kearns et al, NEJM. 2003; 349(12):1157-67

Is it a Clinical Trial?

- Does your study involve:
  - Human subjects
  - Prospectively assigned intervention
  - Evaluate the effect of an intervention
  - Have a health-related biomedical or behavioral outcome
- If "yes" to ALL questions your study is a clinical trial (NIH)

Interventional study (clinical trial)

- **CAUTION**:
  - Trials performed during drug development are carefully controlled and protocol driven
  - Patient populations are carefully selected and the "environment" tightly regulated
  - Concomitant medications are limited and sometimes even prohibited
  - Compared with anticipated population (usually a large number) to be treated, trials are performed in small numbers of subjects (usually 1000-3000)
  - Duration of exposure to drug during clinical trials is short compared to anticipated use for chronic conditions

Interventional study (clinical trial)

- **Why study drugs in children?**
  - Drug studies in adults or animal models may not adequately predict their actions in children
  - Growth, differentiation and maturation (ONTOGENY) can alter the disposition, response and toxicities of drugs
  - Administration of drugs without adequate information may place children at more risk than if the drug was given as part of a well-controlled clinical trial
  - **Is it ethical NOT to study drugs in children?**

LACK OF PEDS DATA

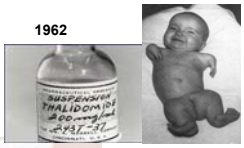
- Lack of adequate data to support dosing, efficacy and precautions for use of drugs used in pediatrics
  - **60-70%** of all FDA approved drugs that are used in children DO NOT have indications for children
  - *BUT* **90% for neonates**
- Lack of standardized, validated pediatric **formulations** for many drugs
- **"Disclaimer" in labeling** despite wide-spread pediatric use
  - **"Not recommended for children less than 12 years of age"**

Pediatric Misadventures

1937

107 deaths

(DEG solvent)



1962

1990's

1950's

1980's

38 died

Therapeutic Misadventures Resulting from Inadequate Information in Children

Our Responsibility

- Design and conduct properly performed research to ensure safe and effective therapy in humans from in utero and throughout the lifespan
- Assure that all studies are conducted under the highest ethical and medical standards
  - ICH E-11
  - GCP
  - CFR

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

References

1. Bandholm T, Christensen R, Thorborg K, Treweek S, Henriksen M. Preparing for what the reporting checklists will not tell you: the PREPARE Trial Guide for planning clinical research to avoid research wastes. Br J Sports Med Sept 2017 as 10.1136/bjsports.
2. Chan AW,Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krlez˝a-Jeric´ K, Hro´bjartsson A, Mann H, Dickersin K, Berlin JA, Dore´ CJ, Parulekar WR, Summerskil WSM, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, and Moher D. Intern Med. 2013;158:200-207
3. Huang GD, Bull J, McKee KJ, Mahon E, Harper B, Roberts JN, for the CTTI Recruitment Project Team. Contemporary Clinical Trials 66 (2018) 74–79.
4. Ramirez JA. Clinical Research Step by Step from Idea to Publications "Study Designs" presentation 2018.
5. NIH Clinical Trial Initiatives: "Putting it all Together". NIH Office of Extramural Research; 2018.
6. Clinical Trials.gov. US National Library of Medicine. Learn about Clinical Studies.
7. GlobalHealthTrials.org. Research, Guidance, Training, Professional Development & Resources.

UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE

UNIVERSITY OF LOUISVILLE.
SCHOOL OF MEDICINE

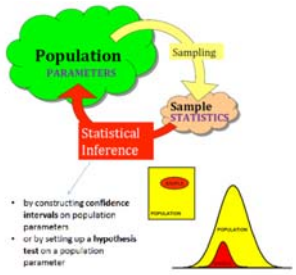
Clinical Research

Performing the study

Beatrice Ugiliweneza, PhD, MSPH
Assistant Professor
Kentucky Spinal Cord Injury Research Center
Department of Neurosurgery
Louisville, KY, USA

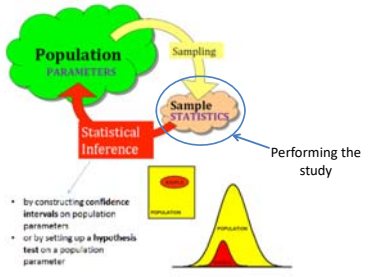
UNIVERSITY OF LOUISVILLE. SCHOOL OF MEDICINE

Schema of the goal

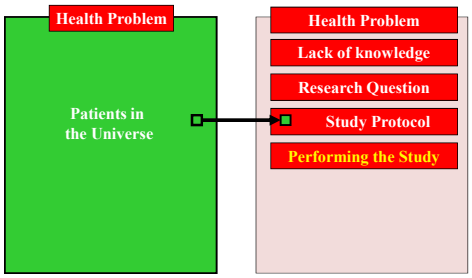


UNIVERSITY OF LOUISVILLE. SCHOOL OF MEDICINE

Schema of the goal



Study sample



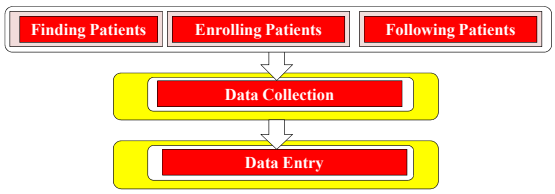
Different types of samples

- Random sample
  Each individual in the population has the same probability of being selected
- Systematic sample
  Every kth participant is chosen
- Convenient sample
  People who are easy to reach, willing to volunteer, etc
- Cluster sample
  Individuals are divided into groups (called clusters) and then clusters are selected
- Stratified sample
  Individuals are divided into stratas and then participants are drawn from those stratas randomly

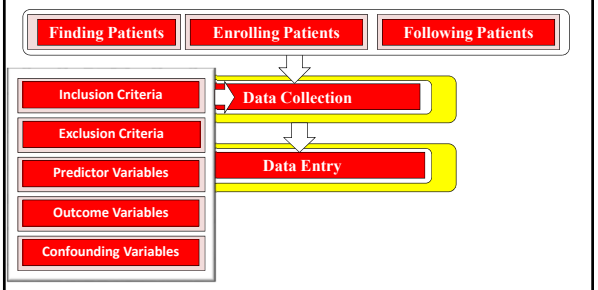
Finding the participants, enrolling them and following them

Finding Patients	Enrolling Patients	Following Patients
Understanding the population Targeting the best sample for the question Planning for potential difficulties in finding the best sample	Following protocol for enrollment Planning for potential loss of patients (withdrawal or loss to follow up)	Following protocol for follow up Putting safeguards in place to minimize loss to follow up Considering the potential burden of the study on the participant

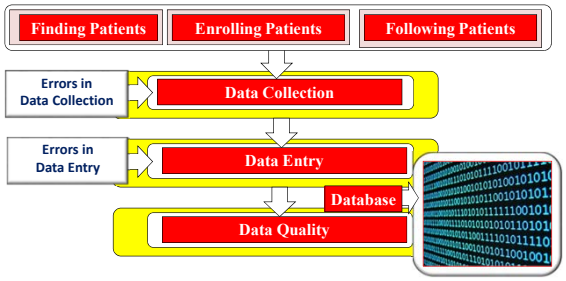
Data collection and Data entry



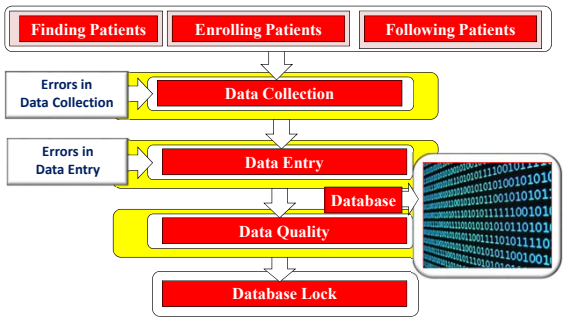
Data collection and Data entry



Data collection and Data entry



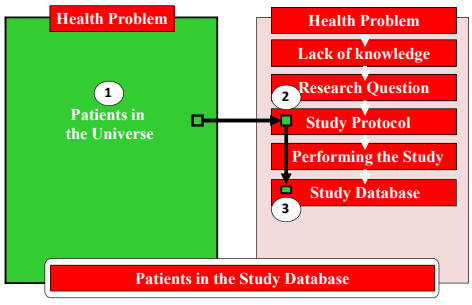
Data collection and Data entry



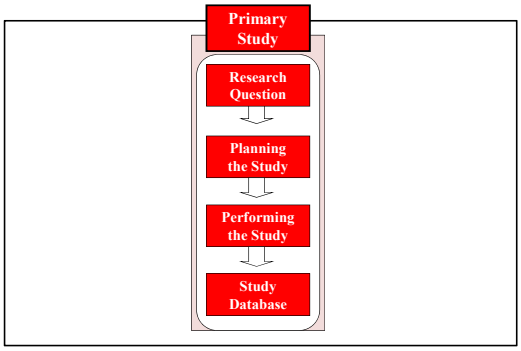
REDCap and other platforms

- REDCap (Research Electronic Data Capture)
  - Powerful platform for data collection and data management for research database
  - HIPAA compliant
  - Free
- Other platforms: depending on the type of the study, you may find other platforms
  - For example: SurveyMonkey for surveys
  - Other field specific platforms

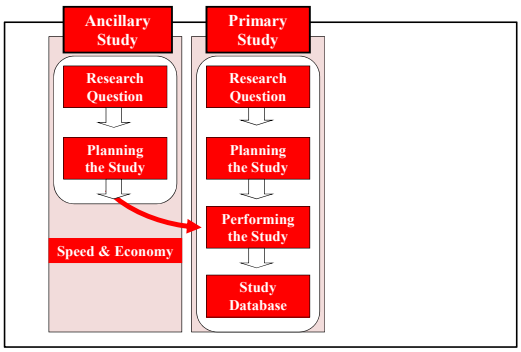
Study database



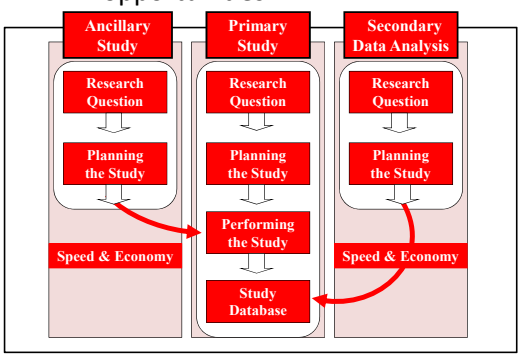
Primary study and additional opportunities



Primary study and additional opportunities



Primary study and additional opportunities



Statistical Significance

Stephen Furmanek, MS MPH
Biostatistician
Division of Infectious Diseases
University of Louisville, KY
stephen.furmanek@Louisville.edu

What are statistics?

- Statistics concern transforming our raw data into information that we can process
- Statistics can be descriptive or analytical by nature

Why do we use statistics?

- Statistics are used in clinical research because:
  - They help us understand the data we've collected
  - They help us manage uncertainty
  - They allow us to make conclusions about interventions
  - Under the right conditions, they allow us to make conclusions about broader populations based on a smaller sample

Statistics in Clinical Research

- We are primarily concerned with two kinds of statistics:
  - Descriptive Statistics
  - Inferential/Analytical Statistics
- While not always a "kind" of statistic, data visualization is helpful for interpreting both kinds

Descriptive Statistics

Table 1

Participant characteristics.

	All participants	Placebo	Azithromycin	p value
N	30	15	15	
Clinical parameters				
Age, mean (SD); range	70.8 (7.6)	69.9 (8.9)	71.7 (6.2)	0.535
Sex, Male/Female	19/11	10/5	9/6	0.705
Ex-smokers, n (%)	22 (73.3%)	11 (73.3)	11 (73.3)	1.0
Pack years, mean (SD)	46.11 (36.61)	56.2 (43.2)	36.0 (26.9)	0.202
FEV_1% predicted, mean (SD)	53.69 (13.74)	51.1 (13.7)	56.5 (13.7)	0.297
FEV_1/FVC, mean (SD)	57.79 (11.24)	51.3 (11.3)	52.3 (11.6)	0.811
Atopy, n (%)	14 (46.67%)	8 (53.3)	6 (40.0)	0.464
ICS dose, BDP equivalent, µg/day, mean (range)	1011, (400–2000)	800 (500–1000), N=15	1000 (800–2000), N=11	0.196
CCQ total score, mean (SD)	16.0 (17.6)	16.5 (6.97)	15.4 (8.47)	0.692
SGRQ total score, mean (SD)	34.2 (16.0)	33.8 (15.7)	34.5 (16.8)	0.907
mMRC dyspnea score, mean (SD)	0.90 (0.80)	0.87 (0.92)	0.93 (0.70)	0.825

Descriptive Statistics: Why

We use descriptive statistics to ***describe*** our data

Descriptive Statistics: Data Types

Descriptive statistics vary depending on the kind of data:

- Categorical Data
- Continuous Data

Categorical Data

- Categorical data is generally *qualitative*
- Examples:
  - County of residence: *Jefferson, Clark, New Albany, Oldham*
  - Location in hospital: *ICU, Ward*
  - Site of respiratory culture: *Sputum, Tracheal Aspirate, BAL*

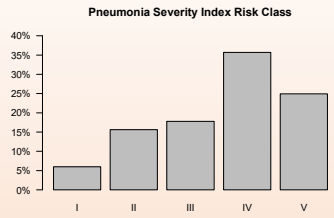
Categorical Data: Ordinal Data

- Ordinal data is *qualitative* but has an *ordered* element
  - Examples:
  - The Pneumonia Severity Index Risk Class Categorization: I, II, III, IV, V
    - Higher risk classes -> higher probability of morbidity/mortality
  - Stages of cancer: Stage 0, I, II, III, and IV
    - Higher stages -> further progression

Categorical Data

- Categorical data are almost universally represented by frequency (counts) and percent
  - Often denoted as n(%)

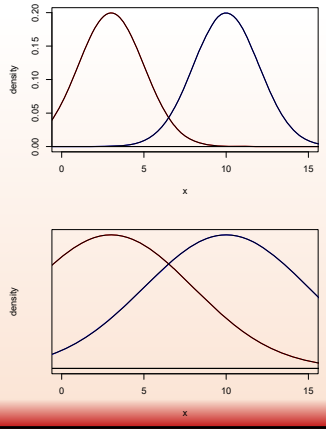
Categorical Data Visualization



Continuous Data

- Continuous data is *measurable* by some scale
- Examples
  - Temperature (degrees)
  - Age (Years, months)
  - Weight (Pounds, kilograms)

- Continuous data has two main aspects:
  - Central tendency
  - Variation



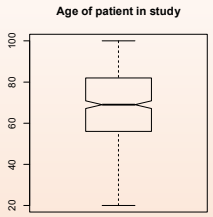
Continuous Data

- Common measures of central tendency
  - Mean
  - Median
  - Mode
- Common measures of variability
  - Variance / Standard Deviation
  - Interquartile Range

Continuous Data

- Means are reported with standard deviations
  - For “normal” data
- Medians are reported with interquartile ranges
  - For skewed or otherwise “non-normal” data
- Modes are rarely reported in clinical research

Continuous Data Visualization



Inferential/Analytical Statistics

Table 2

End of treatment clinical and inflammatory outcomes.

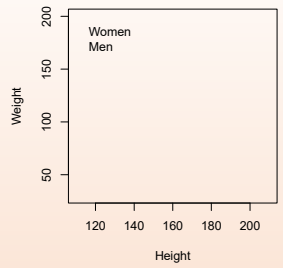
	Placebo	Azithromycin	p value
Clinical outcomes		N=15	
FEV_1% predicted, mean (SD)	52.17 (14.3)	57.79 (13.90)	0.285
FEV_1/FVC, mean (SD)	50.19 (10.33)	54.70 (13.03)	0.409
CCQ total score, mean (SD)	15.1 (9.2)	16.9 (10.1)	0.614
SGRQ total score, mean (SD)	28.1 (13.2)	34.2 (15.9)	0.259
mMRC dyspnea score, median (q1,q3)	1 (0,1)	1 (0,2)	0.695
VAS Breathlessness, median (q1,q3)	27 (0,43)	27 (7,68)	0.676
VAS Wheeze, median (q1,q3)	2 (0,31)	2 (0,28)	0.829
VAS Cough, median (q1,q3)	18 (8,42)	14 (0,63)	0.868
VAS Chest tightness, median (q1,q3)	5 (0,31)	8 (0,31)	0.542

Inferential/Analytical Statistics

We use inferential statistics to ***make inferences or conclusions*** about our data

We use analytical statistics to ***make predictions*** with our data

Data Visualization



Inferential Statistics

- Depends on type of data (continuous / categorical)
- Often uses hypothesis testing
- May be used for
  - Associations
  - Differences

Measures/Tests of Association

For categorical data:

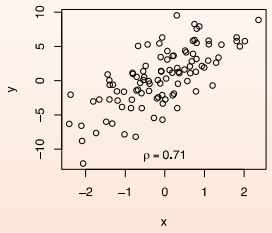
- Odds Ratio
- Relative Risk
- Chi-squared tests
  - Homogeneity
  - Independence
- Logistic Regression

	Dead at 1 year	Alive at 1 year
Aspirin Group	106	394
Placebo Group	153	347

Measures/Tests of Association

For continuous data:

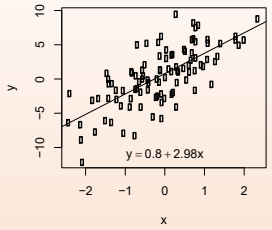
- Correlation



Measures/Tests of Association

For continuous data:

- Correlation
- Simple Regression



Measures/Tests of Differences

- Z-test; T-test; Mann-Whitney U test
- Chi-squared tests
- ANOVA
- Linear Regression
- Logistic Regression
- Survival Analyses
- and lots more!

Inferential Statistics

- More robust statistical tests and procedures allow you to account and control for other variables
- Examples of these include:
  - Multiple regression (logistic or linear)
  - ANCOVA
  - Proportional hazards regression

Hypothesis Testing

- It is near-impossible and/or implausible to study *ALL* people at risk
- Thus, we must test a hypothesis in a target population
- Your research question will guide your hypotheses

Hypothesis Testing

- It is very hard to prove something
- It is much easier to show that something is implausible or very unlikely
- We use hypothesis testing to set up and frame our statistical tests
  - You have a Null Hypothesis, H_0 that we gather data against
  - You have an Alternative Hypothesis, H_A

The Null Hypothesis

- The first hypothesis is called ***the Null hypothesis***
- The data we gather can be seen as "evidence" against this hypothesis
- The Null Hypothesis can be viewed as follows: "these two groups are the same" or "there is no association"
- If we set up our hypotheses correctly, then if we "disprove" ***the Null hypothesis***, our only option is to conclude ***the alternative hypothesis*** is true

The Alternative Hypothesis

- When we formulate a research question, usually we are thinking of the alternative hypothesis
- Often noted as H_1, H_A, or H_a

Hypothesis Testing: Example

- Lets say we want to see if the mean age between two groups of patients is different.
- We will call μ_1 our mean age in group 1
- We will call μ_2 our mean age in group 2
- Our hypothesis is as follows:

$$H_0: \mu_1 = \mu_2$$
$$H_1: \mu_1 \neq \mu_2$$

Hypothesis Testing: Example

- In this setup, the data we gather will be used as "evidence against" the null hypothesis
- When we have enough evidence, we can then reject the null hypothesis and conclude that the alternative is true
- It is always possible that we fail to gather sufficient evidence
- We could also erroneously reject the null hypothesis due to chance

Hypothesis Testing: Error

- There are two situations in hypothesis testing where ***error*** may occur

Test Conclusion	H_0 is actually: TRUE	H_0 is actually: FALSE
Fail to Reject H_0	Correct	**ERROR**
Reject H_0	**ERROR**	Correct

Hypothesis Testing: Error

- ***Type I error*** (α) occurs when we reject $\boldsymbol{H_0}$ when it is actually *true*
- ***Type II error*** (β) occurs when we fail to reject $\boldsymbol{H_0}$ when it is actually *false*
- In both cases, we are making the wrong conclusion about $\boldsymbol{H_0}$

Hypothesis Testing: Error

- Historically, it has been deemed that a type I error rate of 5% is justified
- We may lower it if making a type I error is incredibly detrimental
- This is why we use 0.05 for the cut-off for p-values

Hypothesis Testing: Error

- The type II error rate is directly related to ***Power***
- Power is defined as the probability you would reject $\boldsymbol{H_0}$ when it is *false* $(1 - \beta)$
- Typically, we want power to be at 80%

Hypothesis Testing: Error

- As we never know the *truth* about our null hypothesis, we don't know for certain our error rates
- Typically, we set what we expect are our type I and type II error rates before the study start
- This helps us determine our sample size

Statistical Tests

- Statistical tests are the mathematical process by which we test our hypotheses
- A statistical test summarizes our data into a ***test statistic***

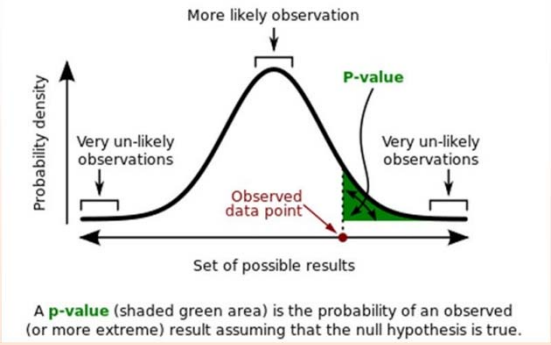
Statistical Tests

- The ***test statistic*** is calculated based on our data
- You can think of it as the amount of evidence that we have against H_0
- Test statistics (T) often take the following form:

$$T = \frac{Amount\ of\ association\ or\ difference}{Amount\ of\ variability}$$

Statistical Tests

- The ***test statistic*** will follow a ***probability distribution***
- From this ***probability distribution*** we get a p-value
  - E.g. A z-test gives us a statistic that follows a standard normal distribution



A **p-value** (shaded green area) is the probability of an observed (or more extreme) result assuming that the null hypothesis is true.

Statistical significance

- The ***probability distribution*** of our test statistic assumes that the null hypothesis is *true*
- If our p-value is small, we have shown our data is very unlikely given the null hypothesis
  - Reject the null hypothesis!

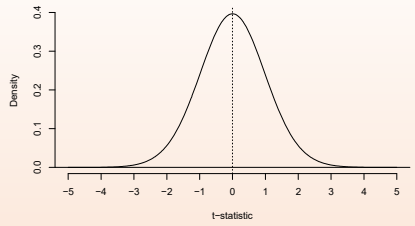
Statistical significance: example

- Back to our age example
- Group 1: 20 patients, mean age 33
- Group 2: 20 patients, mean age 38
- Standard deviation is 15 in both groups
- Lets assume each sample is *independent*

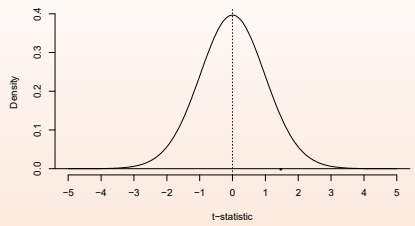
Statistical significance: example

- The most appropriate test for this example is a two-sample t-test
- The *t*-statistic for this is 1.49
- This follows a *t*-distribution with 38 degrees of freedom

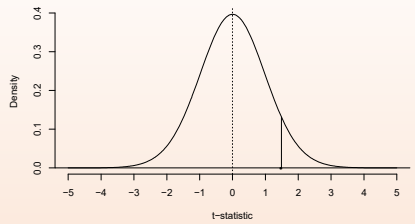
Statistical significance: example



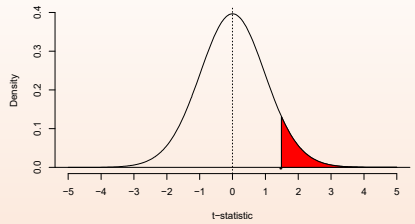
Statistical significance: example



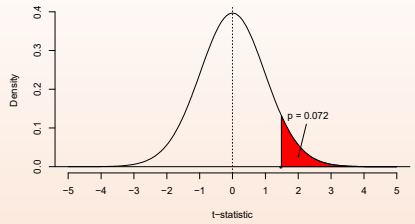
Statistical significance: example



Statistical significance: example



Statistical significance: example



Statistical significance: example

- In this example, because we have $p > 0.05$, we fail to reject H_0
- We have not gathered enough evidence to show there was a statistically significant difference

Considerations

- If we fail to reject the null hypothesis, that does not necessarily mean the null hypothesis is true
- If we fail to reject the null hypothesis comparing two groups, *it does not mean they are the same*
  - Tests of equivalence are used to show this!

Scenario 1: fail to reject

- Your study could be underpowered
  - Sample size is too small
  - Your data may be more varied than you thought
  - Your data may not have as large of an effect size as you thought
  - Your data may have other sources of error (e.g. measurement error)

Scenario 2: Reject the null!

- Never report your p-value alone!
  - How big is the difference?
  - How big is the measure of association?
- Check your effect size!
  - Statistical significance ≠ clinical significance
  - You could be overpowered!
- Your results could still be due to confounding or unmeasured variables

Scenario 2: Reject the null!

- Mathematically, it is possible to find ANY difference between groups statistically significant
  - This is especially a risk when performing secondary analyses on large administrative databases

Scenario 2: Reject the null!

- Mathematically, it is possible to find ANY difference between groups statistically significant
  - This is especially a risk when performing secondary analyses on large administrative databases
- *"All we know about the world teaches us that the effects of A and B are always different—in some decimal place—for any A and B. Thus asking 'are the effects different?' is foolish."* – John Tukey

Back to our example…

- Statistical significance does not always imply clinical significance
- Even if we did find our difference statistically significant, the mean age difference between groups was 5 years
  - Depending on what we're studying, 5 years may be clinically negligible
  - 5 years may be more relevant in children than adults

Final considerations

A p-value *does not and can not* determine if a hypothesis is **true**!

Final considerations

Your results are still in the context of your study. How ***generalizable*** they are will depend on your study design, inclusion/exclusion, etc.

Clinically Significant *vs.* Statistically Significant

Ozan Akca, MD, FCCM
Department of Anesthesiology & Perioperative Medicine
Comprehensive Stroke Center & Neuroscience ICU
University of Louisville

UNIVERSITY OF LOUISVILLE.

Disclosure

- Nothing to be disclosed related to this presentation

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Ángel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Estruch at the Department of Internal Medicine, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain, or at restruch@clinic.ub.es, or to Dr. Martínez-González

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Person-yr of follow-up	11,852	10,365	9763		
Primary end point‡					
No. of events	96	83	109		
Crude rate/1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)	0.009	0.02
Secondary end points					
Stroke					
No. of events	49	32	58		
Crude rate/1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)	0.03	0.003
Myocardial infarction					
No. of events	37	31	38		
Crude rate/1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)	0.31	0.25

UNIVERSITY OF LOUISVILLE

Table 3. Outcomes According to Study Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)	P Value†	
				Mediterranean Diet with EVOO vs. Control Diet	Mediterranean Diet with Nuts vs. Control Diet
Hazard ratio for each Mediterranean diet vs. control (95% CI)					
Primary end point					
Unadjusted	0.70 (0.53–0.91)	0.70 (0.53–0.94)	1.00 (ref)	0.009	0.02
Multivariable-adjusted 1§	0.69 (0.53–0.91)	0.72 (0.54–0.97)	1.00 (ref)	0.008	0.03
Multivariable-adjusted 2¶	0.70 (0.54–0.92)	0.72 (0.54–0.96)	1.00 (ref)	0.01	0.03
Secondary end points‖					
Stroke	0.67 (0.46–0.98)	0.54 (0.35–0.84)	1.00 (ref)	0.04	0.006
Myocardial infarction	0.80 (0.51–1.26)	0.74 (0.46–1.19)	1.00 (ref)	0.34	0.22
Death from cardiovascular causes	0.69 (0.41–1.16)	1.01 (0.61–1.66)	1.00 (ref)	0.17	0.98
Death from any cause	0.82 (0.64–1.07)	0.97 (0.74–1.26)	1.00 (ref)	0.15	0.82

UNIVERSITY OF LOUISVILLE

CORRESPONDENCE

This article has been retracted: N Engl J Med 2018;378(25):2441-2.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

UNIVERSITY OF LOUISVILLE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

R. Estruch, E. Ros, J. Salas-Salvadó, M.-I. Covas, D. Corella, F. Arós, E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, R.M. Lamuela-Raventos, L. Serra-Majem, X. Pintó, J. Basora, M.A. Muñoz, J.V. Sorlí, J.A. Martínez, M. Fitó, A. Gea, M.A. Hernán, and M.A. Martínez-González, for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND

Observational cohort studies and a secondary prevention trial have shown inverse associations between adherence to the Mediterranean diet and cardiovascular risk.

METHODS

In a multicenter trial in Spain, we assigned 7447 participants (55 to 80 years of age, 57% women) who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was a major cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes). After a median follow-up of 4.8 years, the trial was stopped on the basis of a prespecified interim analysis. In 2013, we reported the results for the primary end point in the Journal. We subsequently identified protocol deviations

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Martínez-González at the Department of Preventive Medicine and Public Health, Facultad de Medicina–Clínica Universidad de Navarra, Irunlarrea 1, 31008 Pamplona, Spain, or at mamartinez@unav.es.

*The PREDIMED study investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Estruch and Martínez-González contributed equally to this study.

This article was published on June 13, 2013, at NEJM.org.

Table 3. Estimates of Cardiovascular Events, According to Intervention Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
No. of person-yr of follow-up	11852	10365	9763
Primary end point†			
No. of events	96	83	109
Incidence rate per 1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)
5-yr absolute risk — % (95% CI)‡	3.6 (2.8–4.5)	4.0 (3.1–5.0)	5.7 (4.6–6.9)
Secondary end points			
Stroke			
No. of events			
Incidence rate per 1000 person-yr (95% CI)			
5-yr absolute risk — % (95% CI)	1.7 (1.3–2.4)	1.5 (1.1–2.3)	3.0 (2.3–3.9)
Myocardial infarction			
No. of events	37	31	38
Incidence rate per 1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)
5-yr absolute risk — % (95% CI)	1.4 (1.0–2.1)	1.6 (1.1–2.3)	2.1 (1.5–2.9)

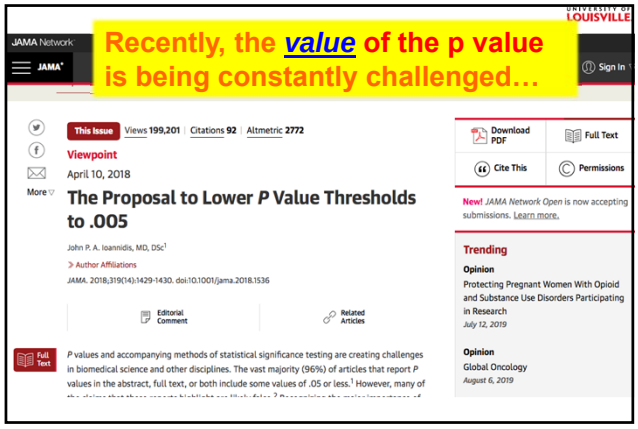
Results are the same…but no p values reported!!!

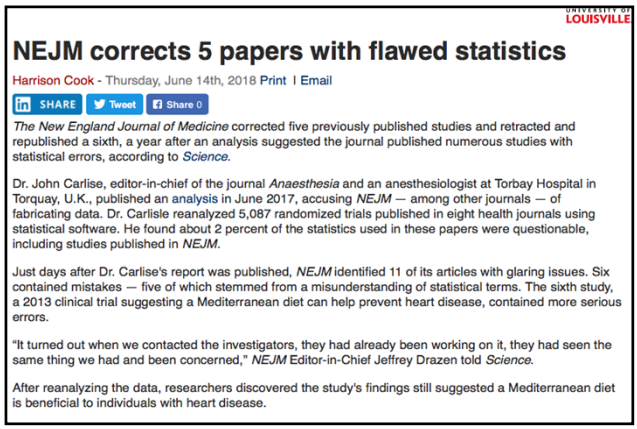
Table 3. Estimates of Cardiovascular Events, According to Intervention Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
No. of person-yr of follow-up			9763
ITT analysis: hazard ratio for Mediterra combined vs. control (95%			
Primary end point			
Unadjusted		0.70 (0.55–0.89)	1.00 (ref)
Adjusted¶		0.70 (0.55–0.89)	1.00 (ref)
Secondary end points¶			
Stroke		0.58 (0.42–0.82)	1.00 (ref)
Myocardial infarction		0.80 (0.53–1.21)	1.00 (ref)
Death from cardiovascular causes		0.80 (0.51–1.24)	1.00 (ref)
Death from any cause		0.98 (0.77–1.24)	1.00 (ref)

Am I missing something?!
No p values reported!!!

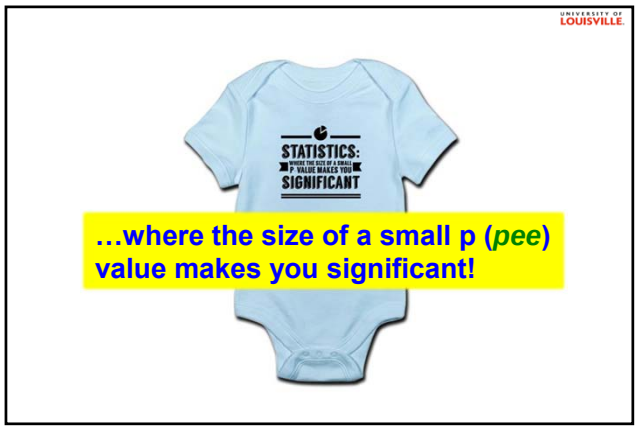
We are so much into the *p values*…
…Not even looking into the *differences* between the groups at all…


Recently, the value of the p value is being constantly challenged…
JAMA Network
JAMA
Sign In
This Issue Views 199,201 | Citations 92 | Altmetric 2772
Viewpoint
April 10, 2018
More
The Proposal to Lower P Value Thresholds to .005
John P. A. Ioannidis, MD, DSc[1]
Author Affiliations
JAMA. 2018;319(14):1429-1430. doi:10.1001/jama.2018.1536
Editorial Comment
Related Articles
Full Text
P values and accompanying methods of statistical significance testing are creating challenges in biomedical science and other disciplines. The vast majority (96%) of articles that report P values in the abstract, full text, or both include some values of .05 or less.[1] However, many of
Download PDF
Full Text
Cite This
Permissions
New! JAMA Network Open is now accepting submissions. Learn more.
Trending
Opinion
Protecting Pregnant Women With Opioid and Substance Use Disorders Participating in Research
July 12, 2019
Opinion
Global Oncology
August 6, 2019


NEJM corrects 5 papers with flawed statistics
Harrison Cook - Thursday, June 14th, 2018 Print | Email
SHARE
Tweet
Share 0
The New England Journal of Medicine corrected five previously published studies and retracted and republished a sixth, a year after an analysis suggested the journal published numerous studies with statistical errors, according to Science.
Dr. John Carlise, editor-in-chief of the journal Anaesthesia and an anesthesiologist at Torbay Hospital in Torquay, U.K., published an analysis in June 2017, accusing NEJM — among other journals — of fabricating data. Dr. Carlisle reanalyzed 5,087 randomized trials published in eight health journals using statistical software. He found about 2 percent of the statistics used in these papers were questionable, including studies published in NEJM.
Just days after Dr. Carlise's report was published, NEJM identified 11 of its articles with glaring issues. Six contained mistakes — five of which stemmed from a misunderstanding of statistical terms. The sixth study, a 2013 clinical trial suggesting a Mediterranean diet can help prevent heart disease, contained more serious errors.
"It turned out when we contacted the investigators, they had already been working on it, they had seen the same thing we had and been concerned," NEJM Editor-in-Chief Jeffrey Drazen told Science.
After reanalyzing the data, researchers discovered the study's findings still suggested a Mediterranean diet is beneficial to individuals with heart disease.


Science
A study of the health benefits of a Mediterranean diet was rewritten after a statistical analysis set off alarm bells.
JOZEF POLC/500PX
Following charges of flawed statistics, major medical journal sets the record straight
By Jennifer Couzin-Frankel | Jun. 13, 2018 , 5:00 PM
One year after a damning review suggested that many published clinical trials contain statistical errors, The New England Journal of Medicine (NEJM) today is correcting five of the papers fingered and retracting and republishing a sixth, about whether a Mediterranean diet helps prevent heart disease. (Spoiler alert: It still does, according to the new version of the paper.) Despite errors missed until now, in many ways the journal system worked as intended, with NEJM launching an inquiry within days of the accusations.


FINANCIAL TIMES
HOME WORLD US COMPANIES TECH MARKETS GRAPHICS OPINION WORK & CAREERS LIFE & ARTS HOW TO SPEND IT
Sign In
Get a fresh start.
Choose your FT trial
Latest on Science
Brexit/trade: Frankenfarmers' market
Premium
The breakthrough that's reshaping our world
Physician Hugh Montgomery: 'Great leaps often need eccentric thought'
UK plans 'fast-track' visas to boost science
Opinion Science
Scientists strike back against statistical tyranny
Many claim the use of 'probability values' is confusing
ANJANA AHUJA


STATISTICS:
SIGNIFICANT
…where the size of a small p (pee) value makes you significant!


Keep it real
BANKSY

p < 0.05 …*statistically significant*…

- …suggests that the ***observed data is sufficiently inconsistent with the null hypothesis***, and that the ***null hypothesis may be rejected***.
- p value does ***not support reasoning***
- p value is ***only a tool*** for deciding whether to reject the null hypothesis

p < 0.05 …*statistically significant*…

…3 common errors when interpreting …

- By definition 1 in 20 comparisons in which the null hypothesis is true will result in p = 0.05
- Even a small difference will be statistically significantly if the sample-size is large
- Small studies may result statistically not significant…one needs to check the *effect size*

Effect Size

Strength of the relationship between two variables

A few different ways to assess the effect size:

- *Effect size* = Difference of Means / Pooled SD
- *Number-Needed-To-Treat* = 100 / Absolute Risk Reduction (ARR)
- Odds Ratio (OR), Hazard Ratio (HR), Relative Risk (RR) …always interpret with confidence intervals (CI)

UNIVERSITY OF LOUISVILLE

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

The ANDROMEDA-SHOCK Randomized Clinical Trial

Glenn Hernández, MD, PhD; Gustavo A. Ospina-Tascón, MD, PhD; Lucas Petri Damiani, MSc; Elisa Estenssoro, MD; Arnaldo Dubin, MD, PhD; Javier Hurtado, MD; Gilberto Friedman, MD, PhD; Ricardo Castro, MD, MPH; Leyla Alegría, RN, MSc; Jean-Louis Teboul, MD, PhD; Maurizio Cecconi, MD, FFICM; Giorgio Ferri, MD; Manuel Jibaja, MD; Ronald Pairumani, MD; Paula Fernández, MD; Diego Barahona, MD; Vladimir Granda-Luna, MD, PhD; Alexandre Biasi Cavalcanti, MD, PhD; Jan Bakker, MD, PhD; for the ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN)

JAMA. 2019;321(7):654-664. doi:10.1001/jama.2019.0071
Published online February 17, 2019.

UNIVERSITY OF LOUISVILLE

Hazard Ratio (HR) …~25% less mortality in the *Peripheral-Perfusion targeted group*

Table 2. Main Outcomes of the Study of Resuscitation Strategies in Septic S

Outcome	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)	Unadjusted Absolute Difference (95% CI)	Adjusted Relative Measure (95% CI)
Primary Outcome				
Death within 28 d, No. (%)	74 (34.9)	92 (43.4)	−8.5 (−18.2 to 1.2)[b]	HR, 0.75 (0.55 to 1.02)[a]
Secondary Outcomes				
Death within 90 d, No. (%)	87 (41.0)	99 (46.7)	−5.7 (−15.6 to 4.2)[b]	HR, 0.82 (0.61 to 1.09)[a]
Mechanical ventilation-free days within 28 d, mean (SD)[c]	14.6 (12.1)	12.7 (12.2)	1.9 (−0.6 to 4.3)	
Renal replacement therapy-free days within 28 d, mean (SD)[c]	18.5 (12.1)	16.9 (12.1)	1.7 (−1.5 to 4.8)	
Vasopressor-free days within 28 d, mean (SD)[c]	16.7 (12.0)	15.1 (12.3)	1.6 (−0.7 to 3.9)	

JAMA. 2019;321(7):654-664. doi:10.1001/jama.2019.0071
Published online February 17, 2019.

UNIVERSITY OF LOUISVILLE

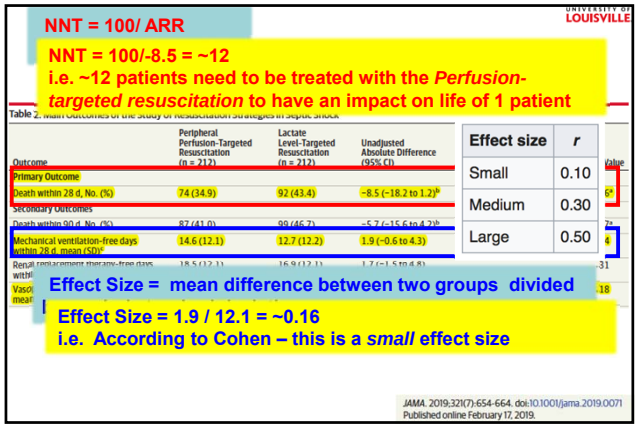
Not statistically significant! (p=0.06)

Table 2. Main Outcomes of the Study of Resuscitation Strategies in Septic Shock

Outcome	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)	Unadjusted Absolute Difference (95% CI)	Adjusted Relative Measure (95% CI)	*P* Value
Primary Outcome					
Death within 28 d, No. (%)	74 (34.9)	92 (43.4)	−8.5 (−18.2 to 1.2)[b]	HR, 0.75 (0.55 to 1.02)[a]	.06[a]
Secondary Outcomes					
Death within 90 d, No. (%)	87 (41.0)	99 (46.7)	−5.7 (−15.6 to 4.2)[b]	HR, 0.82 (0.61 to 1.09)[a]	.17[a]
Mechanical ventilation-free days within 28 d, mean (SD)[c]	14.6 (12.1)	12.7 (12.2)	1.9 (−0.6 to 4.3)		.14
Renal replacement therapy-free days within 28 d, mean (SD)[c]	18.5 (12.1)	16.9 (12.1)	1.7 (−1.5 to 4.8)		.31
Vasopressor-free days within 28 d, mean (SD)[c]	16.7 (12.0)	15.1 (12.3)	1.6 (−0.7 to 3.9)		.18

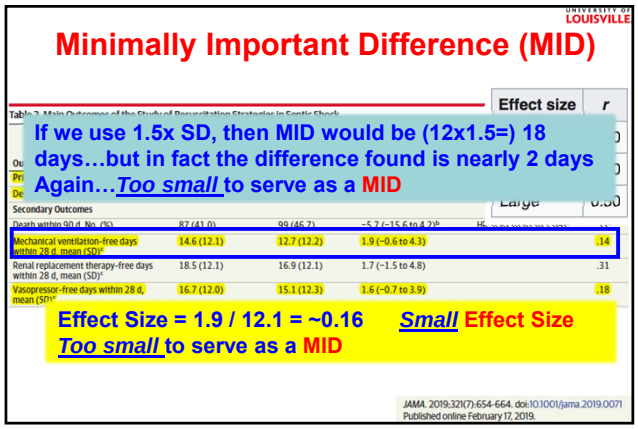
…Easier to interpret a CI without a P-value, than a P value without a CI…

JAMA. 2019;321(7):654-664. doi:10.1001/jama.2019.0071
Published online February 17, 2019.



Minimally Important Difference (MID)

- …smallest change in a treatment outcome that an individual patient would identify as important and which would indicate a change in the patient's management…
  - 1.5x SD
  - Effect size ~ 0.20 – 0.40
  - Panel of experts decide on a difference



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts

R. Estruch, E. Ros, J. Salas-Salvadó, M.-I. Covas, D. Corella, F. Arós, E. Gómez-Gracia, V. Ruiz-Gutiérrez, M. Fiol, J. Lapetra, R.M. Lamuela-Raventos, L. Serra-Majem, X. Pintó, J. Basora, M.A. Muñoz, J.V. Sorlí, J.A. Martínez, M. Fitó, A. Gea, M.A. Hernán, and M.A. Martínez-González, for the PREDIMED Study Investigators*

ABSTRACT

BACKGROU… Observati… ciations b…

METHODS

In a multicenter trial in Spain, we assigned 7447 participants (55 to 80 years of age, 57% women) who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was a major cardiovascular event (myocardial infarction, stroke, or death from cardiovascular causes). After a median follow-up of 4.8 years, the trial was stopped on the basis of a prespecified interim analysis. In 2013, we reported the results for the primary end point in the Journal. We subsequently identified protocol deviations

Let's get back at this paper and calculate the *Effect Size*…

…academic de… …e listed in the … requests to Dr. … Department of … Preventive Medicine and Public Health, Facultad de Medicina–Clínica Universidad de Navarra, Irunlarrea 1, 31008 Pamplona, Spain, or at mamartinez@unav.es.

*The PREDIMED study investigators are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Estruch and Martínez-González contributed equally to this article.

This article was published on June 13, 2018, at NEJM.org.

Table 3. Estimates of Cardiovascular Events, According to Intervention Group.*

End Point	Mediterranean Diet with EVOO (N=2543)	Mediterranean Diet with Nuts (N=2454)	Control Diet (N=2450)
No. of person-yr of follow-up	11852	10365	9763
Primary end point†			
No. of events	96	83	109
Incidence rate per 1000 person-yr (95% CI)	8.1 (6.6–9.9)	8.0 (6.4–9.9)	11.2 (9.2–13.5)
5-yr absolute risk — % (95% CI)‡	3.6 (2.8–4.5)	4.0 (3.1–5.0)	5.7 (4.6–6.9)
Secondary end points			
Stroke			
No. of events	49	32	58
Incidence rate per 1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)
5-yr absolute risk — % (95% CI)	1.7 (1.3–2.4)	1.5 (1.1–2.3)	3.0 (2.3–3.9)
Myocardial infarction			
No. of events	37	31	38
Incidence rate per 1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)
5-yr absolute risk — % (95% CI)	1.4 (1.0–2.1)	1.6 (1.1–2.3)	2.1 (1.5–2.9)

Let's use NNT to represent the effect size in this case

NNT = 100/ ARR **ARR = ARC-ART**

NNT = 100 / (5.7 – 3.6) = 100 / 2.1 = ~ 50

i.e. 50 patients need to be on the Mediterranean Diet to have an impact on cardiovascular events of 1 patient

---

Table 3. Estimates of Cardiovascular Events, According to Intervention Group.*

End Point	Mediterranean Diet with EVOO	Mediterranean Diet with Nuts	Control Diet
Secondary end points			
Stroke			
No. of events	49	32	58
Incidence rate per 1000 person-yr (95% CI)	4.1 (3.1–5.5)	3.1 (2.1–4.4)	5.9 (4.5–7.7)
5-yr absolute risk — % (95% CI)	1.7 (1.3–2.4)	1.5 (1.1–2.3)	3.0 (2.3–3.9)
Myocardial infarction			
No. of events	37	31	38
Incidence rate per 1000 person-yr (95% CI)	3.1 (2.2–4.3)	3.0 (2.0–4.2)	3.9 (2.8–5.3)
5-yr absolute risk — % (95% CI)	1.4 (1.0–2.1)	1.6 (1.1–2.3)	2.1 (1.5–2.9)

Biological Plausibility

Biological Plausibility

- Proposal of a causal association
- Relationship between a putative cause and an outcome — that is consistent with existing biological and medical knowledge
- Method of reasoning that can establish a cause-and-effect relationship between a biological factor and a particular disease

Biological Plausibility

Table 3. Estimates of Cardiovascular Events, According to Intervention Group.*

- How does Mediterranean diet decrease cardiovascular events?
- Is there a causal relationship between such diet and cardiovascular events? Can we prove it? How do we know patients' compliance with the diet for 5 years?

Summary

- ***p value***, in itself, ***does not say much*** about study results
- ***Effect size*** helps to ***interpret study results***
- **Differences of Means/SD, NNT, OR, RR, and HR** are preferred methods to calculate the effect size
- If an established **Minimally Important Difference (MID or MCID)** is available, it may help interpreting results and also helps to plan new study
- If there's no ***biological plausibility***, there's not much meaning of the statistical associations calculated…

Medical Writing: The Abstract & Journal Article

Forest Arnold, D.O., M.Sc., FIDSA
Associate Professor, Division of Infectious Diseases, University of Louisville
Hospital Epidemiologist, University of Louisville Hospital

1

The Process of Clinical Research

Medical Writing

1. General Principles
2. Writing the Abstract
3. Writing the Article

2

The Process of Clinical Research

Medical Writing

1. General Principles
2. Writing the Abstract
3. Writing the Article

3

The Process of Clinical Research

Medical Writing

What makes it so hard?

1. Lack of training

2. Lack of practice

Writing is a skill necessary for researchers to do their job

4

The Process of Clinical Research

Medical Writing

What are the benefits?

1. Helps to put your ideas in a coherent and sequential structure

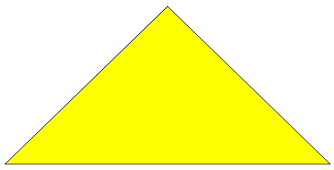
2. The act of writing helps to clarify thinking

5

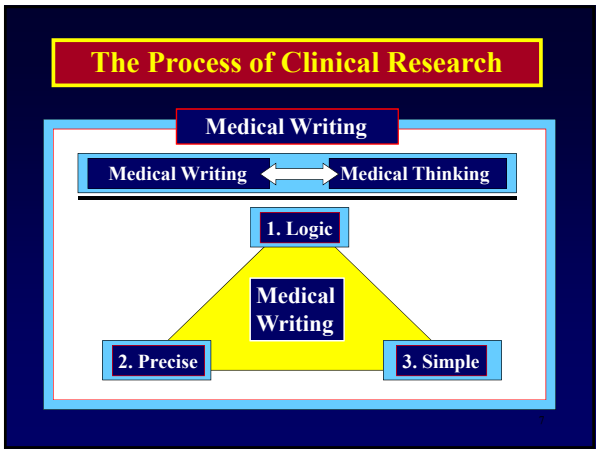
The Process of Clinical Research

Medical Writing

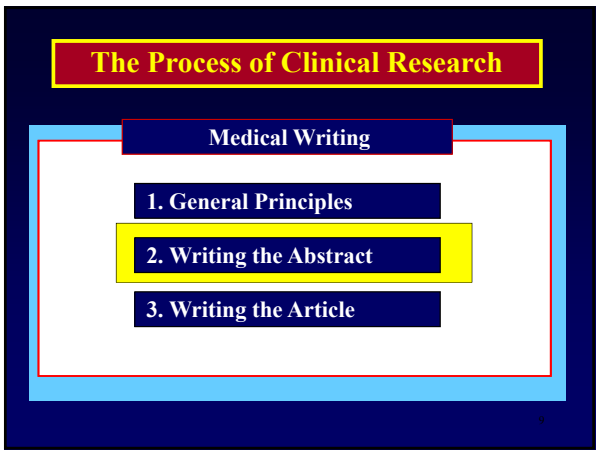
Medical Writing ⟷ Medical Thinking



6


The Process of Clinical Research
Medical Writing
Medical Writing
Medical Thinking
1. Logic
Medical Writing
2. Precise
3. Simple


The Process of Clinical Research
Medical Writing
Medical Writing
Medical Thinking
1. Logic
Medical Writing
2. Precise
3. Simple
A good article is brief and clear


The Process of Clinical Research
Medical Writing
1. General Principles
2. Writing the Abstract
3. Writing the Article

The Process of Clinical Research

Medical Writing

The Abstract

- 1. To be considered for presentation at a meeting
- 2. To summarize a paper for a journal

Length: Usually 250 words or less

10

The Process of Clinical Research

Medical Writing

The Abstract

- 1. To be considered for presentation at a meeting
- 2. To summarize a paper for a journal

Length: Usually 250 words or less

Starting is always the hardest part of any writing effort

It is much more difficult to describe the key aspects of a study in an abstract, than to write the paper for publication

11

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

1. Introduction	1. What is the problem?
2. Objective	2. What is the question?
3. Materials & Methods	3. How did you do it?
4. Results	4. What did you find?
5. Conclusion	5. So what? & Who cares?

12

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

- 1. Introduction — 1. What is the problem?
  - 1A. Background: Importance of the field of research
  - 1B. Problem: Importance of the problem
  - The primary goal of the introduction or background is to set the stage for the research question or hypothesis
  - Introduction: Brief logical lead in to the objective

13

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

- 2. Objective — 2. What is the question?
  - 2. Objective: The question that will be answered

14

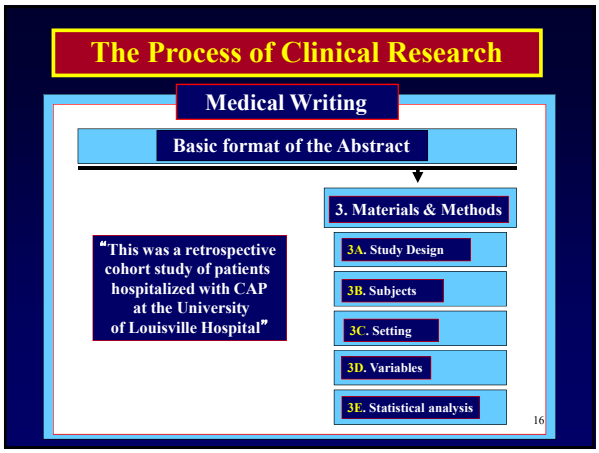
The Process of Clinical Research

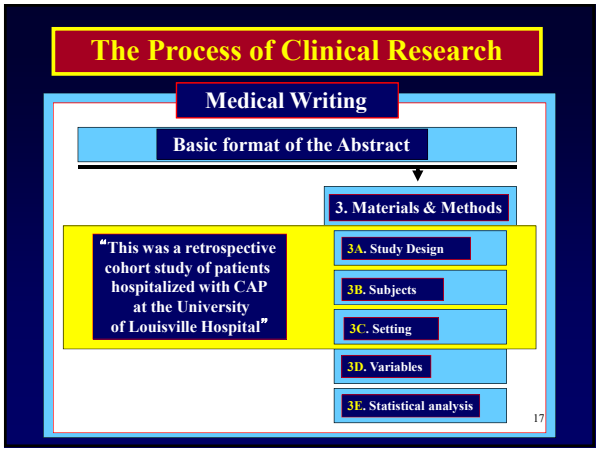
Medical Writing

Basic format of the Abstract

- 3. Materials & Methods — 3. How did you do it?
  - 3A. Study Design
  - 3B. Subjects
  - 3C. Setting
  - 3D. Variables
  - 3E. Statistical analysis

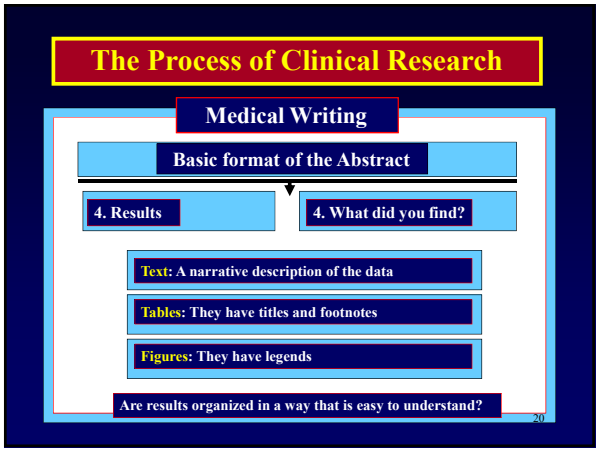
15

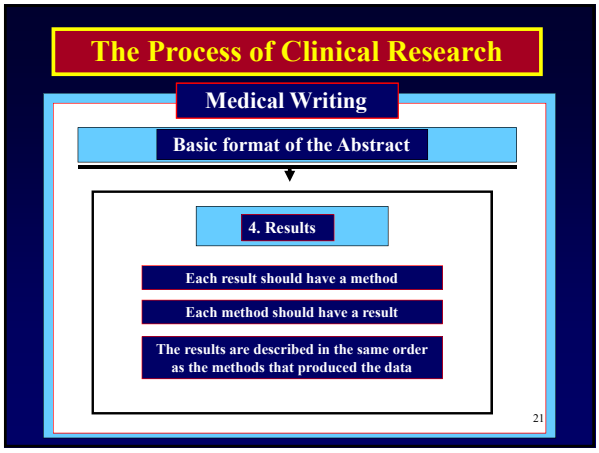

The Process of Clinical Research
Medical Writing
Basic format of the Abstract
"This was a retrospective cohort study of patients hospitalized with CAP at the University of Louisville Hospital"
3. Materials & Methods
3A. Study Design
3B. Subjects
3C. Setting
3D. Variables
3E. Statistical analysis
16


The Process of Clinical Research
Medical Writing
Basic format of the Abstract
"This was a retrospective cohort study of patients hospitalized with CAP at the University of Louisville Hospital"
3. Materials & Methods
3A. Study Design
3B. Subjects
3C. Setting
3D. Variables
3E. Statistical analysis
17


The Process of Clinical Research
Medical Writing
Basic format of the Abstract
3. Materials & Methods
3A. Study Design
3B. Subjects
3C. Setting
Predictor, Outcome, Confounders
3D. Variables
3E. Statistical analysis
18


The Process of Clinical Research
Medical Writing
Basic format of the Abstract
3. Materials & Methods
3A. Study Design
3B. Subjects
3C. Setting
3D. Variables
Statistical tests
3E. Statistical analysis
19


The Process of Clinical Research
Medical Writing
Basic format of the Abstract
4. Results
4. What did you find?
Text: A narrative description of the data
Tables: They have titles and footnotes
Figures: They have legends
Are results organized in a way that is easy to understand?
20


The Process of Clinical Research
Medical Writing
Basic format of the Abstract
4. Results
Each result should have a method
Each method should have a result
The results are described in the same order as the methods that produced the data
21

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

- **5. Conclusion**
  - **5A.** Answer to the question
  - **5B.** Implications of the results
- **5. So what? & Who cares?**

22

The Process of Clinical Research

Anesthesiology. 2004 August ; 101(2): 279–283.

Anesthetic Requirement is Increased in Redheads

Edwin B. Liem, M.D.[*], **Chun–Ming Lin, M.D.**[†], **Mohammad–Irfan Suleman, M.D.**[‡], **Anthony G. Doufas, M.D., Ph.D.**[*], **Ronald G. Gregg, Ph.D.**[§], **Jacqueline M. Veauthier, Ph.D.**[¶], **Gary Loyd, M.D.**[#], and **Daniel I. Sessler, M.D.**[**]

* *Assistant Professor, Outcomes Research™ Institute and Department of Anesthesiology, University of Louisville*

† *Research Fellow, Department of Anaesthesiology, Chang Gung Memorial Hospital,*

‡ *Resident, Department of Anesthesiology, University of Louisville*

§ *Associate Professor, Department of Biochemistry, University of Louisville,*

¶ *Research Associate, Department of Chemistry and Biochemistry, University of Texas, Austin*

\# *Associate Professor, Department of Anesthesiology, University of Louisville*

** *Associate Dean for Research, Director Outcomes Research™ Institute, Distinguished University Research Chair, Lolita & Samuel Weakley Professor of Anesthesiology and Pharmacology, University of Louisville*

23

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

1. Introduction	**1. Present tense**
2. Objective	**2. Past / Present tense**
3. Materials & Methods	**3. Past tense**
4. Results	**4. Past tense**
5. Conclusion	**5. Present tense**

24

The Process of Clinical Research

Medical Writing

Basic format of the Abstract

- Abstracts are written in the passive voice
- Length: Usually 250 words or less
- Form: Written as one paragraph
- Continuity: Use signals to indicate the parts of the abstract

25

The Process of Clinical Research

The Abstract: Reasons for Rejection

Review Criteria

The Process of Clinical Research

The Abstract: Reasons for Rejection

Review Criteria

1. Typographic, grammatical, and spelling errors

The Process of Clinical Research

The Abstract: Reasons for Rejection

Review Criteria

1. Typographic, grammatical, and spelling errors

2. Mixing materials and methods with results or conclusions. The integrity of each section should be maintained

The Process of Clinical Research

The Abstract: Reasons for Rejection

Review Criteria

1. Typographic, grammatical, and spelling errors

2. Mixing materials and methods with results or conclusions. The integrity of each section should be maintained

3. To promise an answer that is not provided

The Process of Clinical Research

The Abstract: Reasons for Rejection

Review Criteria

1. Typographic, grammatical, and spelling errors

2. Mixing materials and methods with results or conclusions. The integrity of each section should be maintained

3. To promise an answer that is not provided

4. Conclusions not justified by the data

The Process of Clinical Research

Medical Writing

1. General Principles
2. Writing the Abstract
3. Writing the Article

31

The Process of Clinical Research

Medical Writing

Basic format of the Article (The IMRaD Format)

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

32

The Process of Clinical Research

Medical Writing

Basic format of the Article (The IMRaD Format)

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

For each section of the article you should have an outline

33

The Process of Clinical Research

Medical Writing

Basic format of the Article (The IMRaD Format)

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

For each section of the article you should have an outline

The Process of Clinical Research

The Introduction (Present Tense)

Outline

A. Background

B. Problem

C. Objective

The Process of Clinical Research

The Introduction (Present Tense)

A. Background: Importance of the field of research

B. Problem: Needs to generate a question

C. Objective: The question that will be answered

The Process of Clinical Research

The Introduction (Present Tense)

"The Known"

A. Background: Importance of the field of research

B. Problem: Needs to generate a question

C. Objective: The question that will be answer

"The Unknown"

The Process of Clinical Research

The Introduction (Present Tense)

Review Criteria

The Process of Clinical Research

The Introduction (Present Tense)

Review Criteria

A. Background: Does the importance of the field of research build a logical case for the problem statement?

The Process of Clinical Research

The Introduction (Present Tense)

Review Criteria

A. Background: Does the importance of the field of research build a logical case for the problem statement?

B. Problem: Is the problem well articulated?
Is the literature appropriately analyzed?
Does it build a logical case for the study question?

40

The Process of Clinical Research

The Introduction (Present Tense)

Review Criteria

A. Background: Does the importance of the field of research build a logical case for the problem statement?

B. Problem: Is the problem well articulated?
Is the literature appropriately analyzed?
Does it build a logical case for the study question?

C. Objective: Is the question that will be answered clear, concise, and complete?

41

The Process of Clinical Research

Medical Writing

Basic format of the Article

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

For each section of the article you should have an outline

42

The Process of Clinical Research

Materials & Methods (Past Tense)

Outline

- A. Study Design
- B. Subjects
- C. Setting
- D. Study definitions
- E. Quality control
- E. Statistical analysis

43

The Process of Clinical Research

Materials & Methods (Past Tense)

Review Criteria

44

The Process of Clinical Research

Materials & Methods (Past Tense)

Review Criteria

Is the research design appropriate (or as optimal as possible) for the research question?

45

The Process of Clinical Research

Materials & Methods (Past Tense)

Review Criteria

- Is the research design appropriate (or as optimal as possible) for the research question?
- Does the research have internal validity to address the question rigorously?

46

The Process of Clinical Research

Materials & Methods (Past Tense)

Review Criteria

- Is the research design appropriate (or as optimal as possible) for the research question?
- Does the research have internal validity to address the question rigorously?
- Does the research have external validity? Are the results generalizable to subjects beyond the research situation?

47

The Process of Clinical Research

Materials & Methods (Past Tense)

Review Criteria

- Is the research design appropriate (or as optimal as possible) for the research question?
- Does the research have internal validity to address the question rigorously?
- Does the research have external validity? Are the results generalizable to subjects beyond the research situation?
- Are materials and methods clearly defined and sufficiently detailed to permit the study to be replicated?

48

The Process of Clinical Research

Medical Writing

Basic format of the Article

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

For each section of the article you should have an outline

49

The Process of Clinical Research

Results (Past Tense)

Outline

The outline of the results should be consistent with the outline of the other sections of the manuscript

Questions: A, B, C

M & M: A, B, C

Results: A, B, C

50

The Process of Clinical Research

Medical Writing

Basic format of the Article

4. Results

Each result should have a method and each method should have a result

The findings are described in the same order as the methods that produce the data

51

The Process of Clinical Research

Results (Past Tense)

- Text: A narrative description of the data
- Tables: They have titles and footnotes
- Figures: They have legends
- Statistics: A balance of descriptive and inferential statistics

Data should be presented without interpretation

The Process of Clinical Research

TABLE II Relationship Between Histological and Culture Findings in Proximal Bone Biopsy Specimens*

	Positive Histologically	Negative Histologically	Total
Positive culture	12	21	33
Negative culture	2	16	18
Total	14	37	51

*P = 0.09.

Data should be presented without interpretation

T ch

Tex
Tab
Fig
Sta ics

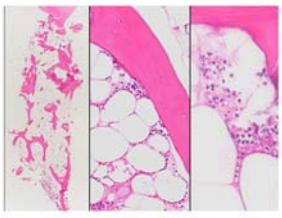


Fig. 2
Representative histological images of bone specimens taken from diabetic patients (hematoxylin and eosin). I = non-infectious changes in bone marrow of bone with perivascular fibrosis and plasmacytic infiltration in the absence of neutrophilic granulocytes (400×). II = possible osteomyelitis with <5 neutrophilic granulocytes (12.5× and 600×). III = definite osteomyelitis with ≥5 neutrophilic granulocytes, showing fatty marrow necrosis with loss of nuclear staining (image in the center) and microabscess-like infiltration accompanied by edema (image on the right) (20×, 200×, and 400×).

The Process of Clinical Research

Results (Past Tense)

- Review Criteria

55

The Process of Clinical Research

Results (Past Tense)

- Review Criteria
  - Are results organized in a way that is easy to understand?

56

The Process of Clinical Research

Results (Past Tense)

- Review Criteria
  - Are results organized in a way that is easy to understand?
  - Are tables and figures used judiciously?

57

The Process of Clinical Research

Results (Past Tense)

Review Criteria

- Are results organized in a way that is easy to understand?
- Are tables and figures used judiciously?
- Are data in text, tables, and figures consistent?

58

The Process of Clinical Research

Results (Past Tense)

Review Criteria

- Are results organized in a way that is easy to understand?
- Are tables and figures used judiciously?
- Are data in text, tables, and figures consistent?
- Is the amount of data presented sufficient and appropriate?

59

The Process of Clinical Research

Results (Past Tense)

Review Criteria

- Are results organized in a way that is easy to understand?
- Are tables and figures used judiciously?
- Are data in text, tables, and figures consistent?
- Is the amount of data presented sufficient and appropriate?
- Are interpretations or implications of the data presented?

60

The Process of Clinical Research

Medical Writing

Basic format of the Article

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

For each section of the article you should have an outline

61

The Process of Clinical Research

Discussion (Present Tense)

Outline

A. Answer to the question, key findings
B. Implications of the results
C. Possible mechanisms for the findings
D. Relate to other studies
E. Detail strengths and limitations
F. Assess generalizability
G. Suggest areas of research
H. Summary of the study & implications

The first sentence of each paragraph should guide the reader, by indicating what this paragraph will be about.
"Walking the reader through the manuscript"

62

The Process of Clinical Research

Discussion (Present Tense)

Outline

A. Answer to the question: "This study shows that …"
B. Implications of the results: "One important clinical implication…"
C. Possible mechanisms: "Our findings can be due to…"
D. Relate to other studies: "Our data support/contradict the study of …"
E. Detail strength & limitations: "The strength/weakness of this study …"
F. Assess generalizability: "The results can be generalized to a population…"
G. Suggest areas of research: "Future research is needed to define…"
H. Summary of the study: "In conclusion this study indicates that …"

63

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

64

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?

65

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?
- Are interpretations of results appropriate?

66

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?
- Are interpretations of results appropriate?
- Are alternative interpretations for the findings considered?

67

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?
- Are interpretations of results appropriate?
- Are alternative interpretations for the findings considered?
- Are statistical differences distinguished from clinical differences?

68

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?
- Are interpretations of results appropriate?
- Are alternative interpretations for the findings considered?
- Are statistical differences distinguished from clinical differences?
- Is guidance for futures studies offered?

69

The Process of Clinical Research

Discussion (Present Tense)

Review Criteria

- Are the conclusions clearly stated?
- Are interpretations of results appropriate?
- Are alternative interpretations for the findings considered?
- Are statistical differences distinguished from clinical differences?
- Is guidance for futures studies offered?

Failure to discuss the limitations of the study is considered a serious flaw

70

The Process of Clinical Research

Medical Writing

Starting is always the hardest part of any writing effort

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

71

The Process of Clinical Research

Medical Writing

Starting is always the hardest part of any writing effort

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

Flowchart

For each section of the article you should have an outline

72

The Process of Clinical Research

Medical Writing

Starting is always the hardest part of any writing effort

1. Introduction
2. Materials & Methods
3. Results
4. Discussion

Writing Plan

1. Materials & Methods
2. Results
3. Discussion
4. Introduction
5. Abstract

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?
- Is the vocabulary appropriate?

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?
- Is the vocabulary appropriate?
- Are simple ideas dressed up in complicated language?

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?
- Is the vocabulary appropriate?
- Are simple ideas dressed up in complicated language?
- Is the manuscript well organized?

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?
- Is the vocabulary appropriate?
- Are simple ideas dressed up in complicated language?
- Is the manuscript well organized?
- Are reference citations complete and accurate?

79

The Process of Clinical Research

Manuscript Presentation

Presentation refers to the clarity and effectiveness with which authors communicate their ideas

Review Criteria

- Is the text well written and easy to follow?
- Is the vocabulary appropriate?
- Are simple ideas dressed up in complicated language?
- Is the manuscript well organized?
- Are reference citations complete and accurate?

A poor presentation reflects poor content

80

The Process of Clinical Research

Manuscript Submission: Basic Requirements

- Type the manuscript double space
- Each component on a new page:
  1. Title (the shortest possible abstract) & Authors
  2. Abstract
  3. Text: Introduction/M&M/Results/Discussion
  4. Acknowledgments
  5. References
  6. Tables
  7. Figures
- Number pages consecutively, beginning with the title page

81

The Process of Clinical Research

Case Report Submission: Basic Requirements

Type the manuscript double space

Each component on a new page:
1. Title (the shortest possible abstract) & Authors
2. Abstract
3. Text: Introduction/Case Report/Discussion
4. Acknowledgments
5. References
6. Tables
7. Figures

Number pages consecutively, beginning with the title page

82

The Process of Clinical Research

Medical Writing

Writing Group

Write → Rewrite → Rewrite → Rewrite → Rewrite → Rewrite → Submit

The qualities of the manuscript and the journal must match

Read the instructions to authors carefully

83

The Process of Clinical Research

Medical Writing

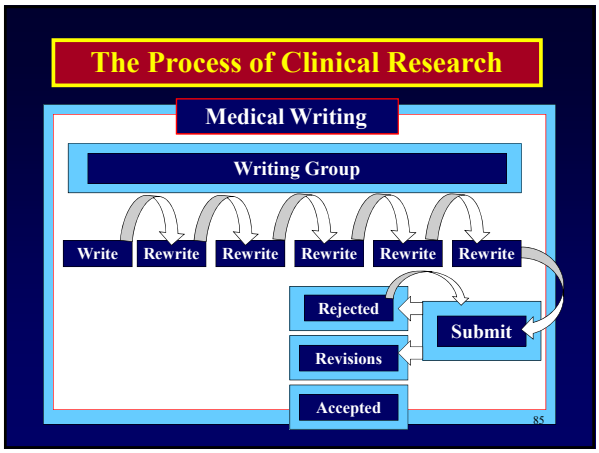
Writing Group

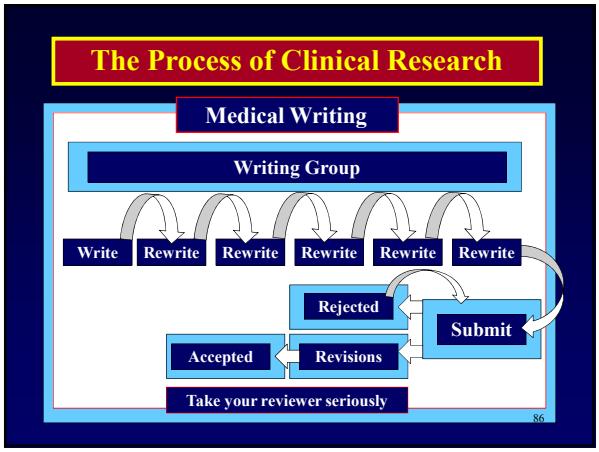
Write → Rewrite → Rewrite → Rewrite → Rewrite → Rewrite → Submit

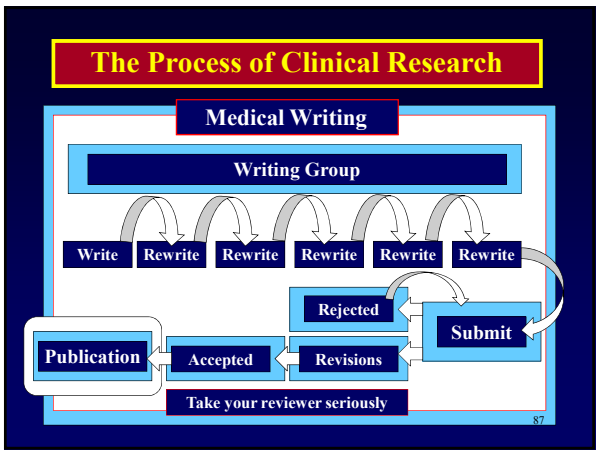
The qualities of the manuscript and the journal must match

Read the instructions to authors carefully

84


The Process of Clinical Research
Medical Writing
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Rejected
Submit
Revisions
Accepted
85


The Process of Clinical Research
Medical Writing
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Rejected
Submit
Accepted
Revisions
Take your reviewer seriously
86


The Process of Clinical Research
Medical Writing
Writing Group
Write
Rewrite
Rewrite
Rewrite
Rewrite
Rewrite
Rejected
Submit
Publication
Accepted
Revisions
Take your reviewer seriously
87

Course Accreditation

The University of Louisville is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Course Credit: Physicians

The University of Louisville Office of Continuing Medical Education & Professional Development designates this live activity for a maximum of 8.25 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Course Credit: Nurses

This program has been approved by the Kentucky Board of Nursing for 9.9 continuing education credits through University of Louisville Hospital, provider number 4-0068-7-20-1138. The Kentucky Board of Nursing approval of an individual nursing education provider does not constitute endorsement of program content. Completion criteria to obtain CE's: Attend entire session and complete the evaluation.

Course Accreditation

To claim CME credits and obtain your certificate, you must complete the online evaluation* by following the options below to access the website:

http://bit.ly/cmecert
Activity Code: 1279593

** Note: Signing-in or initialing a sign-in sheet at this course does not register you for CME credit; visit the above URL to claim credit.*

If you are a registered user of the UofL CME Tracker system, type or copy and enter the URL above into your Internet address bar, then on the landing page click the "Sign In to generate Certificate" button. Complete sign in by providing your email address and password and then click the "Sign In" button. You will then have to provide the activity code above to access the course evaluation and generate your certificate.

Note: If you cannot print from your Smart Phone, please access this procedure ONLY from a desktop or mobile device that has print capabilities.

If this is your first time accessing the UofL CME Tracker platform, type or copy and enter the URL above into your Internet address bar, then on the landing page click the "Sign In to generate Certificate" button. Then enter your email address and click the "Create New Account" button. Follow the step-by-step procedure to complete your personal profile. Once complete click the "Save Profile" button, "Continue" then provide the activity code above to access the course evaluation and generate your certificate.

Note: If you cannot print from your Smart Phone, please access this procedure ONLY from a desktop or mobile device that has print capabilities.

Subsequently, should you need to get a copy of your course transcript, you may follow the URL above, then click the "View/Print Transcript" button, click the "Sign In to generate Transcript" button and once you have completed sign in enter a transcript date range and click submit and the record will download. You may also view and print past certificates through this option. If you have any questions or difficulties, please contact the University of Louisville Continuing Medical Education & Professional Development Office at cmepd@louisville.edu.