Types of Research

Research – Theory and Practice
Brussels, Belgium
March 4-5, 2010

Types of research

Animal studies

Human cell, tissue and fluid analyses

Primary human studies

- **Randomized controlled trials**
- **Other controlled trials**
- **Cohort studies (prospective, retrospective)**
- **Case control studies**
- Cross-sectional studies and surveys
- Case series and case reports

Synthesis: **narrative reviews, systematic reviews**, decision analysis, economic analysis, guidelines

Types of Research

Background	Types of studies	Assessment, Application
• History • Purpose of research • Intervention development	• Treatment • Diagnosis • Prognosis • Harm	• Role of bias • Quality of evidence • Using evidence in practice

Research

- Function: *noun*
- Etymology: Middle French *recerche*, from *recercher* to go about seeking, from Old French *recerchier*, from *re-* + *cerchier*, *sercher* to search
- Date: 1577
- **1 :** careful or diligent search
  2 : studious inquiry or examination; *especially* **:** investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws
  3 : the collecting of information about a particular subject

http://www.merriam-webster.com/

Types of Research

Background

- History of medical research
- Research and knowledge translation
- Sequence of clinical research studies
- When trials are not necessary

Types of clinical studies

Assessment and application

History of medical research

- John Hunter FRS, (13 February 1728 – 16 October 1793) was a Scottish surgeon regarded as one of the most distinguished scientists and surgeons of his day. He was an early advocate of **careful observation and scientific method** in medicine. The Hunterian Society of London was named in his honour.

Early Trials

Sir James Lind 1747 - 12 sailors with scurvy, groups of two

1. 1 qt cider,
2. 25 gtts elixir vitriol,
3. 2 tsp vinegar *t.i.d.*,
4. sea water *ad lib*,
5. **2 oranges + 1 lemon**,
6. nutmeg, garlic, mustard seed, raphan, balsam of Peru and gum myrrh.

Only group 5 recovered.

Benjamin Rush 1775

purges and bleeding for yellow fever. No control group, no evidence of benefit.

7

Chalmers TC. 1987. The Clinical Trial. Millbank Memorial Find Quarterly / Health and Society. 59:324-3239.

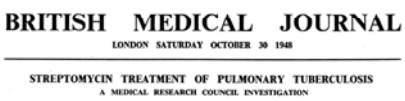
Historical trends in America

Evidence-based medicine is the **judicious** and **conscientious** use of **current** best evidence from **medical care research** for making medical decisions. Sackett et al BMJ 1996; 312:56-7.

Mulrow & Lohr 2001. J Health Politics, Policy Law, 26:249-66.

First modern RCT

1948: MRC trial of tuberculosis therapy[1]



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

1962: FDA required new drug applications to show efficacy by adequate and well-controlled interventions.

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[1]MRC 1948. Streptomycin treatment of pulmonary tuberculosis. BMJ II:769-82.

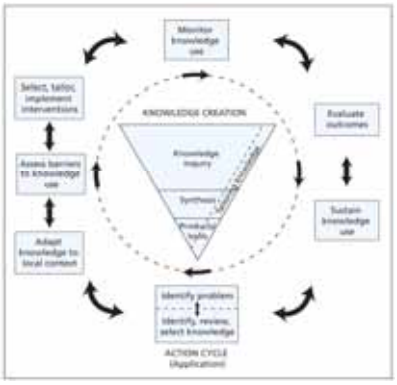
Research and knowledge translation

First generation knowledge	Primary research studies
Second generation knowledge	Synthesis of research reports
Third generation knowledge	Guidelines, decision aids, economic analyses

10 Straus et al, 2009. CMAJ. 181:165-8.

Knowledge Translation

Straus et al, 2009. CMAJ. 181:165-8.



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Knowledge translation

- Knowledge translation is about turning knowledge into action and encompasses the processes of knowledge creation and knowledge application.
- Related terms: knowledge transfer, knowledge exchange, research utilization, implementation, diffusion, and dissemination.

12 Lost in knowledge translation: time for a map? Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, Robinson N. J Contin Educ Health Prof. 2006 Winter;26(1):13-24.

Intervention development sequence

Pre-clinical studies: animal and laboratory research

Phase I studies: safety in 20-30 healthy volunteers

Phase II studies: effects, safety and dose ranging (100s)

Phase III studies: RCTs in patients (100s to 1000s)

Phase IV studies: post marketing surveillance, health economic studies, safety studies (1000s)

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http://www.centerwatch.com/clinical-trials/overview.aspx

The ART regulatory viewpoint

Spectrum of evidence

Horizon Scanning	Innovative Practice	Established Practice
Animal studies	Case reports, case series	RCTs show effectiveness
Human cell & tissue studies	Initial RCTs	Continuing research on safety

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Pre-regulation studies

In 1921 Frederick Banting, an orthopedic surgeon, tied the pancreatic ducts in dogs and cows, and extracted insulin.

JJR MacLeod provided lab space, Charles Best was a student assistant and chemist James Collip purified insulin in 1922.

After treating one teenage boy, insulin was mass produced, and used to treat millions of diabetics allowing many to survive and live fairly normal lives.

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When trials are not necessary

- Salicin for acute rheumatism (Maclagan 1876)
- Insulin for diabetes (Banting, 1922)
- Blood transfusion for haemorrhagic shock (Blundell, 1930s)
- Sulphanilimide for puerperal sepsis (Colebrook 1937)
- Streptomycin for tuberculous meningitis (MRC 1948)
- Defibrillation for ventricular fibrillation (Beck 1947)
- Neostigmine for myasthenia gravis (Walker 1934)
- Tracheostomy for tracheal obstruction (Adams et al 1969)
- **[IVF for tubal obstruction** (Steptoe & Edwards, 1976)]

16

Glasziou & Chalmers, 2007. Picking signal from noise. BMJ 334:349-51.

What is common to these interventions?

The effectiveness is dramatic.
The results are self-evident.

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A current example

Preimplantation genetic diagnosis
- 2396 citations since 1991
- No RCTs

Preimplantation genetic screening
- 825 citations since 1991
- 10 RCTs since 2004

18

It's not the intervention, it's the application

Pre-implantation genetic diagnosis

- Couples with a specific genetic defect
- Polymerase chain reaction (PCR) for genetic defect, or
- Fluorescent in situ hybridization (FISH) for chromosome analysis
- RCTs necessary?

Pre-implantation genetic screening

- IVF candidates with risk of aneuploidy (eg, female age)
- FISH for limited chromosome analysis or
- comparative genomic hybridization (CGH) for 23 chromosomes
- RCTs necessary?

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Types of Research

Background

Types of clinical studies

- RCTS
- Cohort studies
- Case control studies

Assessment and application

Types of clinical studies

Diagnosis	Prognosis	Treatment	Harm*
Dx test studies	Cohort studies	RCTs	Case reports Case control studies Cohort studies RCTs

* Ordered from most to least common and most to least bias.

21

Proof and policy from medical research evidence. Mulrow C, Lohr KN. Journal of Health Politics, Policy and Law, 26:249-66, 2001.

Study Designs for Treatment Questions

Design	Advantage	Disadvantage
RCT: parallel	Less bias	Narrow range
RCT: cross-over	Less variance	Few indications
N of one RCT	Least variance	Only relevant to subject
Prospective cohort	Inobtrusive	Bias between groups
Historical cohort or CC	Ready made data	Many sources of bias
Case series	Simple and direct	Not evaluable unless insulin

22 Spitzer 1973. Ten tips on preparing research proposals. Can Nurse 17:30-3.

Treatment studies: types of RCT

Rationale: efficacy or effectiveness
Design architecture: parallel, crossover, factorial
Logistics: single or multicentre
Sample size: fixed or sequential sample size
Aim: superiority, equivalence, non-inferiority

23 Arce et al, 2005. Hum Reprod 20:1757-71.

Rationale for randomized controlled trials

Terminology		Authors
Explanatory	Pragmatic	Schwartz & Lellouch, 1967
Efficacy	Effectiveness	Cochrane, 1972
Fastidious	Pragmatic	Feinstein & Horwitz, 1982
Can it work?	Does it work?	Haynes, 1999.

24 Haynes 1999. Can it work? Does it work? Is it worth it? BMJ 319:652-3.

RCT design architecture

Parallel design

Cross-over design

- chronic, incurable diseases
- effects have rapid onset and short duration
- condition must be stable

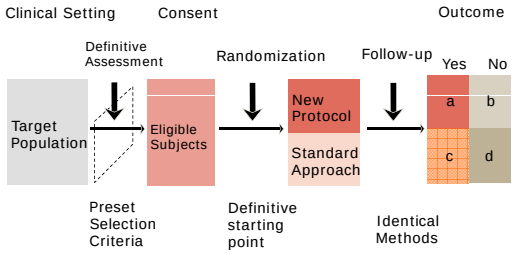
Factorial design

- placebo, a, b, a + b

N of 1 trials

25

Parallel design randomized controlled trial



26 Clinical Epidemiology: How to Do Clinical Practice Research. by David L. Sackett, R.B. Haynes, P. Tugwell, and G. Guyatt. Lippincott, London, 2004.

Crossover RCT design

Treatment	Period 1	Washout	Period 2
A	Group 1		Group 2
B	Group 2		Group 1

Chronic, incurable diseases

Variable but not steadily worsening condition

Drug effects have rapid onset and short duration

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Factorial design

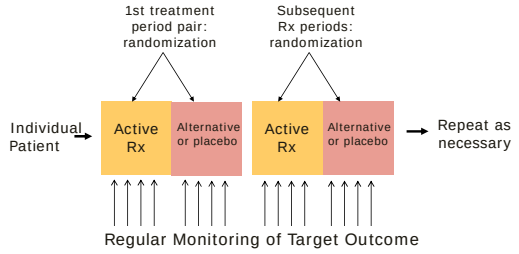
Both placebos	**FSH +placebo IUI**
IUI + placebo FSH	**FSH + IUI**

Power for at least three comparisons:
p:a, p:b, p:ab
Allows more comparisons

28

Guzick et al, 1999. N Eng J Med 340:177-83.

N of 1 RCT Design



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Pairs of treatment periods are repeated until the physician and patient are convinced that the treatment is effective, or harmful, or useless.

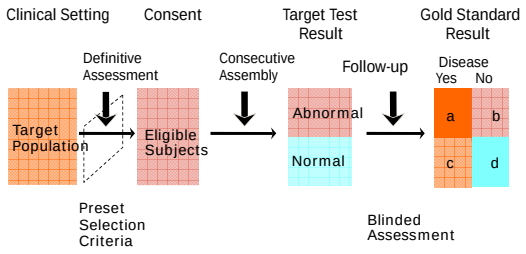
Study Designs for Diagnosis Questions

Design	Purpose	Problems
RCT	Is test effective?	Can't do accuracy
Prospective cohort	Assess accuracy	Possible bias
Historical cohort	Assess accuracy	Additional bias
Case series	Pilot study	Not evaluable

30

Spitzer 1973. Ten tips on preparing research proposals. Can Nurse 17:30-3.

Design for a Diagnostic Study



31 Clinical Epidemiology: How to Do Clinical Practice Research. by David L. Sackett, R.B. Haynes, P. Tugwell, and G. Guyatt. Lippincott, London, 2004.

Criteria for a diagnostic study

1. Patients: typical clinical features that indicate use of this diagnostic test.
2. Assembly: consecutive assembly of patients.
3. Intervention: the cohort is divided by the test result into two groups, with either abnormal or normal results.
4. All patients receive the gold standard test to determine which ones truly have the disease.

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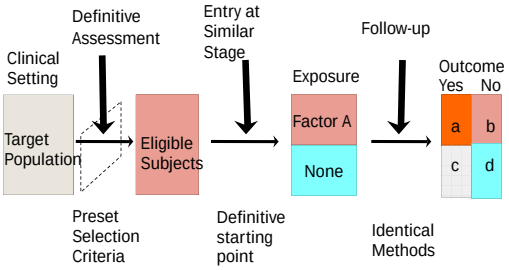
Study Designs for Prognosis Questions

RCT	Not practical just for prognosis
Prospective cohort	Takes time, allows comparisons
Historical cohort	Takes less time, but more biased
Case control	Limited to single outcome
Case series	Takes time, comparisons post hoc

33 Spitzer 1973. Ten tips on preparing research proposals. Can Nurse 17:30-3.

Prospective Cohort Study



34 Clinical Epidemiology: How to Do Clinical Practice Research. by David L. Sackett, R.B. Haynes, P. Tugwell, and G. Guyatt. Lippincott, London, 2004.

Criteria for a cohort study

- Investigator starts with a group of individuals apparently free of the disease(s) of interest.
- Determine exposure status.

  The cohort is divided into those exposed and not exposed to the factor of interest.
- Measurement of the disease.

  The cohort is followed to determine the incidence rate or mortality from the disease(s) of interest.

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Cohort Study Advantages

Advantages

- Can evaluate rare events
- Can use a large administrative database

Disadvantages

- Exposed and unexposed subjects may have different baseline risk of disease
- Can adjust for the effect of known prognostic factors, but not those that remain unknown
- Prospective cohort studies are expensive

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Study designs for questions about harm

Design	Issues
RCT	Not solely for harm (WHI)
Prospective cohort	OK if adverse events common
Historical cohort	Subject to bias
Case control	Most likely design, risk of bias
Case series, case reports	Often the first alarm

37 Spitzer 1973. Ten tips on preparing research proposals. Can Nurse 17:30-3.

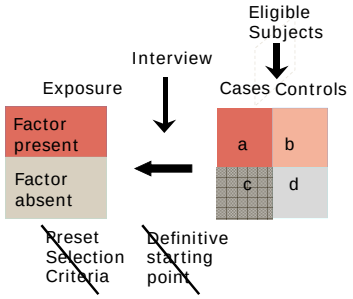
Does causation exist?

Proof of causation requires:

1. Is there evidence from true experiments in humans?
2. Is the association strong?
3. Is the association consistent from study to study?
4. Is the temporal relationship correct (exposure precedes disease?
5. Dose-response relationship?
6. Does the association make biological sense?
7. Does the association make epidemiological sense?
8. Is the association specific to this exposure and disease?
9. Is the association analagous to a previously proven causal association?

38 Sackett et al, 2004. From Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–30.

Case Control Study



39 Clinical Epidemiology: How to Do Clinical Practice Research. by David L. Sackett, R.B. Haynes, P. Tugwell, and G. Guyatt. Lippincott, London, 2004.

Case control study criteria

1. Investigator starts by identifying cases
   - Cases are persons with the disease of interest
2. Controls without the disease are selected
   - Controls should come from the same population that gave rise to the cases: population, hospital
3. Measurement of exposures
   - Cases and controls are interviewed to ascertain background characteristics and exposures. Ideally interviewers are blind to the question of interest

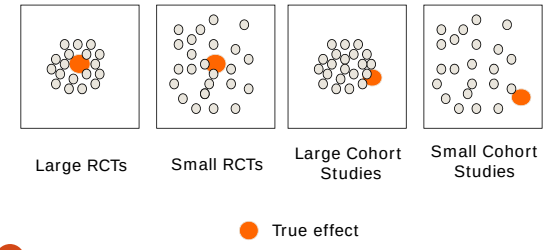
Strengths and Weaknesses of Different Designs

Design	Start with	Ascertain	Strengths	Weaknesses
RCT	Randomization	Outcome event	Low susceptibility to bias	Expensive, may not generalize
Cohort	Beginning of exposure	Outcome event	May be feasible if RCT is not possible	Expensive, bias limits validity
Case Control	Outcome status	Exposure status	Quicker, smaller sample size	Bias very likely to limit validity

Types of Research

- Background
- Types of clinical studies
- Assessment and application
  - Bias
  - Quality of evidence
  - Evidence in practice

Effect of Bias and Random Error



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Study Design, Random Error and Bias

Large sample size
- reduces the effect of random error
- but does not rule out bias.

Valid study designs
- minimize bias,
- but small valid studies are still subject to random error.

44 Guyatt & Rennie 2002. Users' Guides. AMA Press Chicago. 224, 330.

Reducing Bias in RCTs and Epi Studies (1)

Source of Bias	RCTs	Epidemiological Studies
1. Groups differ in prognosis	Randomization	Statistical adjustment for prognostic factors
2. Placebo effects	Blinding of patients	Choose unarguable outcomes (birth, death)
3. Co-intervention	Blinding of caregivers	Documentation and statistical adjustment

Reducing Bias in RCTs and Epi Studies (2)

Source of Bias	RCTs	Epidemiological Studies
4. Biased outcome assessment	Blinding of outcome assessors	Choose unarguable outcomes (birth, death)
5. Loss to follow-up	Ensure complete follow-up	Ensure complete follow-up

Assessment of medical evidence

It is time to write up your results. How will the journal assess your research? (See Friday morning with Prof Van Steirteghem)

Then your publication will join a body of similar clinical evidence.

How will that body of evidence be assessed by other researchers?

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Assessment of medical evidence

The value of the evidence about a given clinical intervention depends on

1. the quality of the individual research studies
2. the strength of the body of evidence comprising all studies relevant to the intervention

48

Lohr, KN. Rating the strength of scientific evidence. International Journal for Quality in Health Care 2004; 16(1): 9-18.

Published Systems For Grading Quality

Quality of individual articles	Number of systems
Systematic reviews and meta-analyses	20
Randomized controlled trials	49
Observational studies	19
Diagnostic test studies	18
Overall strength of a body of evidence	40

www.ahrq.gov/clinic/epcix.htm

1. Quality of the individual studies

Level	Study types
I	Randomized controlled trials
II	Cohort studies, prospective or retrospective Case control studies
III	Case series, case reports

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Harbour & Miller, 2001. BMJ 323:334-40.

2. Quality of the body of evidence

Criterion	Description
Quality	the aggregate of quality rankings for the individual studies.
Quantity	the number of individual studies the sample size or power of those studies the size of the effects of the intervention
Consistency	the extent of agreement among studies that make use of different types of patients, different clinical settings and different study designs

51

www.ahrq.gov/clinic/epcix.htm.
Lohr KN, 2004. Int J Qual Health Care 16:9-18.

Application of research in patient care

In your research a counselling intervention increased IVF birth rates.

Now that your research has been published, how will it affect patient care?

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How is evidence used?

Medical Evidence	Patient's Preferences	Clinician's recommendations
Imposes society's values	Education, beliefs, social resources, financial resources	Knowledge, skills, experience, and beliefs
Is of variable quality	Severity of disease, concurrent conditions	Health care system rules and resources

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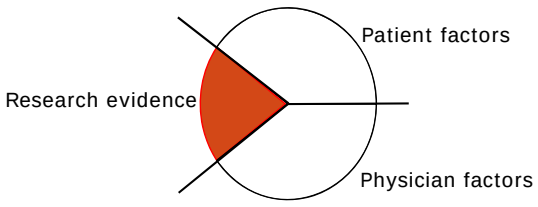
Clinical Judgments and Decisions



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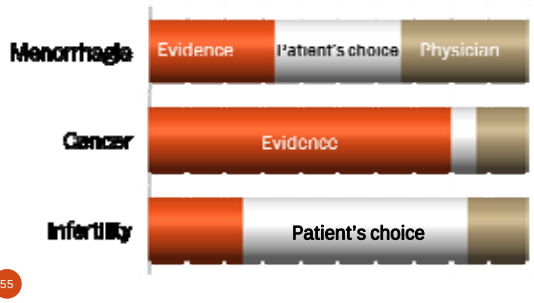
Application of Evidence



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