Clinical Research Design

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Clinical research design

- Types of research
- Bias and random error
- Strong and weak aspects of each design type
- Basic indicators/outcome measures
- Calculation of some basic indicators
- Relationship between question – type of research – type of publication
- Secondary publications

Question on Therapy

- treatment
- prevention and control
- quality of care improvement
- Does administration of vitamin A to HIV+ pregnant women reduce MTCT?

Bias and Random Error

- We never know with certainty the real value of treatment effect because of random error. It is inherent in all measurement. We get only a sample of all possible results (for the whole population)
- Bias - a systematic tendency to produce an outcome that differs from the underlying truth

Bias

- **channeling bias** (treatment prescribed based on prognosis)
- **data completeness bias**
- **detection bias** (in one of two groups)
- **incorporation bias**
- **interviewer bias**
- **publication bias**
- **recall bias**
- **surveillance bias**
- **verification bias**

RCT - main characteristics

- **randomization** (random allocation to study groups)
- **blinding** (masking) (which group patient is assigned)
- **follow-up** (at least 80% of all participants)

- Comparison of **outcomes** (ethiology, cause, clinical effectiveness) in interventional group and control group **after** the intervention

- The best method for evaluating clinical effectiveness

RCT - study design
Outcome
- How we can measure and present outcomes?

RCT - understanding statistics
- absolute risk reduction
- relative risk reduction
- NNT
- confidence interval

- **Risk/event rate** (percentage) – proportion of patients in whom event is observed compared to the whole group

Absolute Risk difference (ARD)
- **Absolute difference** - **arithmetic difference** between the rates of events in the intervention group and the control group
- **Risk difference = 0** means no difference between intervention and control groups
- **ARR** - **risk of bad event decreases** (used for beneficial intervention/exposure)
- **Absolute benefit increase** - risk of good event increases when intervention is compared with control
- **Absolute risk increase -** risk of bad event increases when intervention is compared with control
- **Absolute benefit decrease -** benefit of good outcome decreases

Relative Risk (RR) (risk ratio)

- RR - ratio of the risk of the event in the intervention group to risk in the control group (exposed vs. unexposed)
- RR=1 means no difference between two compared groups

- for bad event - **RR< 1** means that intervention for reducing the risk of this outcome is successful

Relative Risk Reduction
- **Relative Risk Reduction -**calculated by dividing the absolute risk reduction by the absolute risk in the control group
- ARR/AR control group

Interpreting the results
Number Needed to Treat (NNT)
NNT - the number of patients who need to be treated over a specific period of time to prevent one bad outcome (inverse of ARR) (1/ARR)

NNH - Number Needed to Harm - the number of patients who would need to be treated over a specific period of time before one adverse side affect of the treatment will occur (inverse of ARI)

Confidence Interval (CI)

CI - range of two values within which it is probable that the true value lies for the whole population of patients from whom the study patients were selected

quantifies the uncertainity of a result or statistic

95% CI - the range of values whithin which we can be 95% sure that the result given falls whithin the range if we repeated the study

Calculation of indicators – an example

- White woman, age 50, with no family history of breast cancer, but with family history of cardio-vascular disease. Decision on hormone-replacement therapy (estrogen + progesterone, particular regimen)
- Calculate AR, RR, NNT/NNH
- Study data: Grady, D. et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117:1016-37

Study data (D. Grady)

RCT - strong points /limits

- **Strong points**
  - eliminates selection bias;
  - shows that intervention preceeds the outcome;
  - shows adverse outcomes rates
  - most reliable design;
  - blinding is possible;

- **Limits**
  - not always ethical;
  - not always practical;
  - needs time and money;
  - doesn't eliminate all bias

RCT of good quality

- randomization (properly done)
- follow up (80% is the goal for strong research)
- blind (triple - double -single)
- proved baseline similarities at the start of the trial
- large numerical differences between the study groups at the end of the trial

Therapy - levels of evidence

- RCT (large numerical difference)
- RCT
- non-randomized controlled trial
- case series ("before/after") with historic control (or compared with other trials)
- case series (without control)
- case report

Diagnosis and screening
- **Effectiveness of diagnostic intervention** (symptomatic patients)
- **Selection of tests for screening programs** (asymptomatic patients)

Diagnosis study design
- gold standard procedure available
- laboratory personnel blinding
- including patients with different stages of disease
- each participant has both tests
- 2x2 table
- measuring positive and negative results based on sensitivity and specificity; positive and negative predictive values; positive and negative likelihood ratios; false positive and false negative rates

2x2 Table

Sensitivity and specificity
- **Sensitivity**
  (Se) = A/(A+C) - proportion of patients with the disease who have positive results
- **Specificity**
  (Sp) = D/D+B - proportion without the disease who have negative results

Predictive value
- What test actually tells about the probability of disease in specific setting where the test was evaluated
- **Positive pedictive value** is the proportion of patients with postive test results who have the disease A/A+B
- **Negative predictive value** is the proportion of patients with negative test results who do not have the target disease D/D+C

Likelihood ratios
- **Likelihood ratio** indicates how much the probability of disease changes from baseline when the test result is positive (+LR) or negative (-LR)

- **+LR= Se/1-Sp**
- **-LR=1-Se/Sp**

Post-test probability

- Pre-test odds=Prevalence/1- prevalence
- Post-test odds= Pre-test odds x LR
- Post-test probability= Post-test odds/post-test odds+1
- Predictive values are affected by prevalence of the disease: if a disease is rare, the positive predictive value will be lower

Nomogram for likelihood ratios

Diagnostic test calculations

- Suspected acute pancreatitis
- standard - careful observation
- OR new test - serum lipase test
- Panzer RJ., et al. Diagnostic strategies for common medical problems. Philadelphia: American College of Physicians, 1991, p.160
- 200 patients - 53 with P, 147 - no P (standard)
- of 53 with P. - 50 with lipase test positive
- of 147 no P. - 7 with lipase test positive

Etiology, Cause, Harm

- Evaluation of exposures or risk factors and the related disease outcomes
- Increased risk for development and protection against a disease or condition
- Side effects of treatment/diagnostic interventions

- **Does keeping pet birds cause lung cancer?**

Etiology - types of research design

- RCT
- cohort studies
- case-control studies
- cross-sectional studies

Etiology - cohort studies

- Follow a group of people with common charecteristics over time and measure outcomes
- cohort formed based on exposure (yes/no) and followed over time for incidence of disorder/complications (yes/no)
- no randomization
- groups formed based on exposure
- Two types:
  - prospective
  - retrospective

Cohort studies

- sometimes it takes years to get outcomes
- more expensive than case-control

Cohort studies - strengths/limits

- **Strengths**
  - exposure before disease;
  - can calcualte incidence in both groups, relative risk, risk ratio;
  - can research multiple outcomes of one intervention/exposure;
  - ethical;
  - easier and less expensive than RCT
- **Limits**
  - bias
  - need large groups of people;
  - still expensive;
  - following groups for a long time;
  - not siuitable for rare diseases;
  - different to find two identical groups (other confounders);
  - blinding is difficult;
  - no randomization

Etiology - case-control study

- have a control (comparison) group
- control group formed based on the absence of disease, then informtaion about exposure is evaluated (yes/no)

Etiology - case-control study

- **Cases** - group of patients with disease (condition)
- Match cases with **control group** with no disease but similar in other features or confounding factors
- **Goes back in time** to assess exposure for the people who are being evalutaed - absence or presence of the causative agent

Case-control - strengths/limits

Strengths

- applicable for rare diseases/side effects;
- relatively cheap;
- ethicaly safe;
- relatively quick;
- easier to organize than RCT

Limits

- depends on memory of participants;
- difficult to form control group;
- con-founder factors;
- difficult to provide blinding;
- no randomization
- **recall bias**

Etiology - cross-sectional studies

- Observation of a defined population at a single point in time or during a specific time interval
- **exposure** and **outcomes** are assessed at the same time
- disease prevalence and incidence research
- statistically adjusted groups (balance the con-founders)

Etiology studies results

- **Relative Risk (RR) -** risk or rate of developing the disease in the exposed group divided by the risk or rate of developing the disease in those who were not exposed (RCT and cohort studies)

- **Odds ratio (OR) -** ratio of the rate among people who have disease of having been exposed in the past to the rate of exposure in the past among people who don't have the disease (case-control studies)

Relative risk - calculation

- Women who gained at least 20-25 pounds since they were 18 years old - have a risk of developing heart disease
- of 200 with a weight gain - 106 developed heart disease
- of 200 without weight gain - 58 developed heart disease
- **What is the relative risk of developing heart disease for women with weight gain?**

Study Designs in Etiology Research
Prognosis

- examining the possible outcomes of a disease and the probability with which they can be expected to occur
- help clinicians make the right diagnostic and treatment decisions
- help compare populations and adjust for differences in prognosis to obtain a more accurate indication of how management is affecting outcome
- prognostic studies may suggest factors that differentiate between those at low and high risk for a target outcome or adverse event
- use the results from therapy and etiology studies (RCT, cohort studies)

Prognosis - cohort study

- Representative sample of patients with the disease (disorder) at an early stage of their disease process (immediately after diagnosis) (inception cohort)
- the group is followed forward in time (completeness of follow-up)
- as in etiology studies - rates of disease progression, specific outcomes; risks of these outcomes

Prognosis study of high quality

- well-defined sample of patients at a similar point in the course of the disease
- length and completeness of follow-up (80%)
- objective and unbiased outcome criteria
- adjustment for important prognostic factors

Secondary publications

- Economic analyses
- Systematic reviews and meta-analyses
- Clinical practice guidelines

Economic Analyses

- Compare alternative interventions for their resource use and outcomes achieved (therapy, screening, prevention, diagnosis, quality improvement)
- Data on costs and benefits (including additional - incremental)

- cost analyses (only costs included)
- cost-benefit analysis
- cost-effectiveness analysis
- cost-utility analyses

Economic analyses - design

- RCT
- systematic reviews of cost effectiveness analyses
- retrospective analyses of a published RCT
- decision models that use data from trials or systematic reviews to estimate outcomes for a hypothetical group of patients

Systematic Reviews

- Type of study. 5 steps
- Clearly formulated clinical question
- Identification and selection articles for inclusion
- Data extraction for analysis
- Analysis and statistical confirmation
- Presentation of results

Why systematic reviews are done?

- To get a "bottom line" using all studies on a topic
- To increase the precision of estimates of the effects of treatment, of etiology and causation, or of another topic
- To increase a number of patients in clinically relevant subgroups
- To resolve discrepancies in findings (conflicting results)
- To plan new studies

Systematic reviews of good quality

- focused clinical question
- explicit inclusion and exclusion criteria
- strong retrieval methods (important relevant studies are not missed)
- individual studies assessed for validity
- meta-analyses of studies (if possible)

Meta-analyses

- An overview that incorporates a quantitative strategy for combining the results of several studies into a single pooled or summary estimates

Users' Guides to the Medical Literature , p.418

Qualitative Studies

- How people feel or experience certain situations
- surveys, unstructured interviews, focus-groups, observation, diaries, personal notes
- data analyses takes place concurrent with data collection process. Units of analyses - are thoughts or concepts
- findings are presented in narrative format (many direct quotations of participants included)

Research typology

- **Experimental research**
  - Randomized controlled trials
  - Randomized cross-sectional studies
- **Observational research**
  - Cohort studies
  - Case control studies
  - Cross-sectional studies
  - Case series
  - Individual case reports

Classification of clinical research
Types of questions and design of studies

References

- PDQ. Evidence-Based Principles and Practice/ Ann McKibon, Angela Eady, Susan Marks. Hamilton, 1999
- Users' Guides to Medical Literature: Essentials of Evidence-Based Clinical Practice. 2002