Epidemiology and Clinical Trials: A Methodological Approach

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Outline

What is epidemiology?
Study design
Advantages and drawbacks
Measures of association
Causality, counterfactuals

What are clinical trials?
Measuring treatment effect
The need for standardization

―Life can only be understood backwards, but it must be lived forwards.― Søren Kierkegaard (1813-1855)

The epidemiological way of thinking

One definition (Cates, 1982), among many others:

• A quantitative basic science built on a working knowledge of probability, statistics, and sound research methods;
• A method of causal reasoning based on developing and testing hypotheses pertaining to occurrence and prevention of morbidity and mortality;
• A tool for public health action to promote and protect the public’s health based on science, causal reasoning, and a dose of practical common sense

Shortly, “Epidemiology is the study of the distribution and determinants of disease frequency in man.” (MacMahon and Pugh, 1970)

Various fields of research

For example,

• Psychiatric epidemiology is concerned with the study of prognosis and treatment of psychiatric disorders. Study on mental health related pathology does not always involve biological events or signals, thus emphasizing the need to build questionnaire or dedicated interview that might lead to some useable manifest variables. (Prince et al., 2003)
• Genetic epidemiology is the study of the joint action of genes and environmental factors in causing disease in human populations and their pattern of inheritance in families. (Thomas, 2004)

A common goal

The design and analysis of a study aims at maximizing the precision and validity of its findings. Avoiding bias or confounding effect is thus the primary goal of any epidemiologist, especially because most of the studies under consideration are observational per se. Strict control over experimental factors or exposure, like in a randomized controlled trial (RCT), are thus generally lacking.

The main objectives are generally one of explaining, monitoring, or forecasting.
Examples (Ahrens et al., 2006)

The Doll and Hill’s study on smoking and lung cancer (1948–1952) was one of the first case-control study where 1,357 male and 108 female with lung cancer were recruited from several hospitals in London and matched with respect to age and sex to the same number of patients hospitalized for non-malignant conditions. A positive association between smoking and lung cancer was reported.

The Framingham Heart Study (1949–1999) included 5,127 participants free from coronary heart disease (CHD), aged 30 to 59 years, that were followed during 50 years to determine the rate of occurrence of new cases among persons free of disease at first observation. This study allowed to develop innovative statistical models and predictive risk measures. http://www.framinghamheartstudy.org/

During the Salk vaccine field trial (1954), nearly one million school children were randomly assigned to one of two groups, a vaccination group that received the active vaccine and a comparison group receiving placebo. A 50 percent reduction of the incidence of paralytic poliomyelitis was observed in the vaccination group as compared to the placebo group.

GenomeWide Association Studies (http://pgc.unc.edu/)

Advantages and drawbacks

- **Ecological studies**: Association on group level may be used for development of broad hypotheses; possible ‘ecological fallacy’ effect.
- **Cross-sectional surveys**: no direct evidence of causality but individual association may be used for development and specification of hypotheses; representative sampling frame, response rate, not applicable to rare disorders.
- **Case-control study**: Mainly retrospective, subjects defined by outcome, can handle multiple exposures, odds-ratio approximately equal to relative risk in a cohort study for rare disorders (prevalence < 10%), prone to several form of bias (selection, information, i.e. observer and recall).
- **Cohort study**: Longitudinal (prospective) design or historical cohort or population cohort, subjects designed by their exposure, not well-suited for rare disorders, can handle multiple outcomes/exposures, no information bias and an increased risk of disease among exposed will indicate a causal relationship.
- **Intervention study**: Allocating exposure to subjects and comparing the outcome of interest in different random groups, no information bias provided trials are double-blind; reduction of the incidence rate of the disease will confirm a causal relationship.

See also Ahrens et al., 2006, Table 1.2, p. 19.
The phenomena or variables in question must covary spurious. The relationship must not be attributable to any other variable or with or be only with the supposed cause. The supposed cause must precede simultaneous longitudinal. In intervention studies not demonstrating general health benefits. Insufficient attention to evaluation of error.

Evidence for intervention research may not be ethical and/or feasible for many cause-effect relationships. Frequently a highly subjective judgement, given the volume of the biological literature. Sufficient to cause depression with no influence of further events. Of little use for cross-sectional data. Of course, the situation becomes more complex in case of a non-recursive causal relationship.

The causality dilemma (Hill, 1965)

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Recreating a virtual lab for health outcomes

Clinical trials

Clinical trials are clinical research studies to determine whether biomedical or behavioral interventions are safe, efficacious, and effective. A more formal definition is available on NIH: http://www.nichd.nih.gov/health/clinicalresearch/. Compared to observational studies, we aim at controlling all nuisance factors, much like in a designed experiment. Moreover, RCTs are registered, monitored, and their results should be reported according to standard guidelines.

Key concepts

- Use a prospective and comparative approach, with a control group and accounting for possible confusion factors.
- Use randomization and double-blinding to ensure that observed differences between groups come from treatment allocation only.
- No missing values and analysis by the intention-to-treat (ITT) approach. (No excluded patients, patients analyzed according to the randomization principle.)

“The effect of any treatment for a given patient is the difference between what happened to the patient as a result of giving the treatment and what would have happened had treatment been denied.” (Senn, 2007)

Types of clinical trial

Apart from the distinction between therapeutic trials (a new therapy is compared to a conventional one) and placebo-controlled trials (patients treated with a new treatment are compared to a group receiving a placebo), the pharmaceutical industry has established the following taxonomy: (Everitt and Wessely, 2004, Chap. 2)

- Phase I trials: clinical pharmacology and toxicity. Concerned with drug safety, not efficacy; usually performed on healthy, human volunteers (n = 20 – 80); characterization of the drug or treatment.
- Phase II trials: initial clinical investigation for treatment effect. Usually non randomized trials, with individual follow-up, to identify the patient population and study the effectiveness of the dosing regimen determined in Phase I.
- Phase III trials: full-scale evaluation of treatment. Comparison of the new drug with standard treatment in a large scale clinical trial; assessment of treatment efficacy and/or effectiveness.
- Phase IV trials: postmarketing surveillance. Monitoring for adverse effects, long-term studies of morbidity and mortality.

Common errors (Clark and Mulligan, 2011)

1. Failure to specify the inclusion and exclusion criteria.
2. Failure to determine and report the error of your measurement methods.
3. Failure to specify statistical assumptions made in the analysis.
4. Failure to perform sample size analysis before the study begins.
5. Failure to implement adequate bias control measures.
6. Failure to report missing data, dropped subjects and use of an intention to treat analysis.
7. Failure to perform and report power calculations.
Participant disposition

1. Methods of recruitment and number obtained if multiple methods
2. Number excluded and reasons for exclusion
3. Number of candidates who refuse to enroll and reason(s) why (if after randomization from each treatment group)
4. Number of participants who withdraw from each treatment group and reasons why
5. Rate and nature of incidence of adherence with each treatment
and reasons for nonadherence
6. Number lost to follow-up from each treatment group and reasons why

Summary

- To ensure the validity of any findings, we must control for potential sources of bias and confounding.
- Statistical methodology comes into play when we design a study, not after data are observed.
- Although not discussed here, data collection, cleansing, pre- and post-processing are an important (and usually long) process.
- Data collected from groups can be used to formulate decision at the individual level.
- The choice of the outcome or phenotype to study is not always easy (e.g., genetic or psychiatric studies).

Bibliography

