Trials & Biometry:

Statistical Basis of Clinical Trials & Epidemiology

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Textbook

Reference Book

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Statistical Basis of Clinical Trials, Biometry & Epidemiology

DEFINITIONS

Incidence rate of a disease: the rate at which new cases of the disease occur.
Prevalence rate: the proportion having that disease at a point in time.
Mortality rate: the rate at which the population is dying rather than becoming ill.

If n denotes the number of individuals in the epidemiological population,
n_{new} denotes the number of new cases in a specified interval,
n_{present} denotes the number of cases present at any one point in time, and
n_{dying} denotes the number dying during the specified interval, then

Incidence rate is

$$I = 1000 \times \frac{n_{\text{new}}}{n}.$$

Prevalence rate is

$$P = 1000 \times \frac{n_{\text{present}}}{n}.$$

Mortality rate is

$$M = 1000 \times \frac{n_{\text{dying}}}{n}.$$

CLINICAL TRIALS

PHASE I: eg dosage? safe? S/E?
small
5–10 pts

Phase II: prelim: effect.ⁿ of trtmt
(More effective than others)
20–30 pts

Phase III: large scale verification.
no. of centres. 1,000 – 10,000 pts

Phase IV: estd. trtmt MONITORED
long term toxicities, immunity, resistance eg. Parkinsonism

S.E.E.R. = SURVIVAL ANAYSIS

HOTELLING T^2 DISTRI

MAHALANOBIS D^2 DISTRI

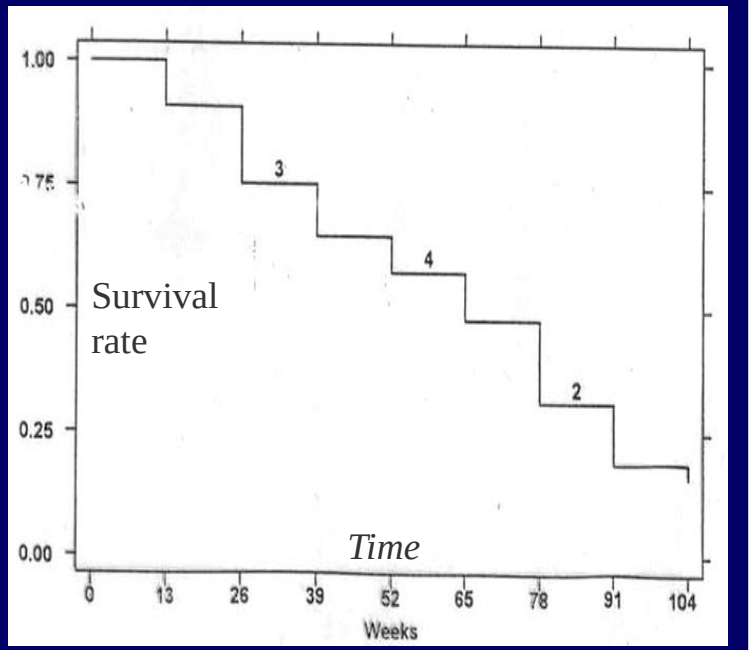
difference

Survival Analysis

Effect of Cerebral Malaria: 2 yrs

Life Table on Malaria (*Plasmodium falciparum*) Morbidity of 155 Infants

Interval (weeks)	*begin*	*died*	*lost*	*end*	*S* (survival rate)
0 (outset)	155	0	0	155	1.0000
>0–13	155	14	0	141	0.9097
>13–26	141	23	0	118	0.7613
	118	0	3	115	
>26–39	115	17	0	98	0.6488
>39–52	98	11	0	87	0.5760
	87	0	4	83	
>52–65	83	14	0	69	0.4788
>65–78	69	24	0	45	0.3123
	45	0	2	43	
>78–91	43	17	0	26	0.1888
>91–104	26	4	0	22	0.1598



Kaplan-Meier survival curve

The Concept of Meta-analysis

Meta-analysis is a pooling of data from various journal articles in order to enlarge the sample size and thus reduce the sizes of the Types I and II errors. It treats the different articles as replications of a single study, wherein lies its hazard. The crucial questions are (1) which articles to pool and (2) how to pool them.

Steps to Conduct a Meta-analysis

A meta-analysis should be developed as follows:

(1) Define the inclusion–exclusion criteria for admitting articles.
(2) Search exhaustively and locate all articles addressing the issue.
(3) Assess the articles against the criteria.
(4) Quantify the admitted variables on common scales.
(5) Aggregate the admitted databases. The reader may see one of several aggregation methods referenced, including nonparametric or omnibus combination, vote counting, weighted pooling, ANOVA combining

Criteria for an Acceptable Meta-analysis

As a meta-analysis depends a great deal on the investigator's judgment, clear criteria are crucial. A minimum list of criteria follows, and the reader should verify so far as possible that each criterion has been met.

(1) The study objectives were clearly identified.
(2) Inclusion criteria of articles in general and data to be accepted in specific were established prior to selection.
(3) An active effort was made to find and include all relevant articles.
(4) An assessment of publication bias was made.
(5) Specific data used were identified.
(6) Assessment of article comparability (controls, circumstances, etc.) was made.
(7) The meta-analysis was reported in enough detail to allow replication.

Even after a careful meta-analysis, limitations remain: innate subjectivity, aggregation of data of uneven quality, and forcing results into a mold for which they were not intended.

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Causation form statistical epidemiological testing

Criteria of evidence supporting causality:

(1) Size of effect. Relative risk >2.0.
(2) Strength of association. p-value <0.05.
(3) Consistency of association. Reproducible effect.
(4) Specificity of association. Effect from a single cause.
(5) Temporality. Cause precedes effect.
(6) Biologic gradient. Evidence of dose–response effect.
(7) Biologic plausibility. Reasonable explanatory model.

Biological data analysis: Bootstrap method

A method for obtaining information about population parameters or characteristics by first taking a random sample of N observations from a population, and then forming from this initial sample further random samples, called bootstrap samples. These are also of size N, and are obtained by sampling with replacement. The method is especially useful when there is insufficient information to specify the population distribution, or when there is little analytic theory about properties of estimators.

If B bootstrap samples are taken, they may be used to estimate standard errors of estimators of parameters such as means, medians, or correlation coefficients obtained from the original sample without the need to make any assumption about the population distribution. For e.g., if the sample median M is used to estimate the population median, then if the median of the B^{th} bootstrap sample is M_b^*, with b=1,2……., B, then the bootstrap-estimated standard error of M is given by

$$\mathbf{Se(M)= \sqrt{(1/B-1\Sigma(M_b^* - <M^*>)^2)}}$$

where <M*> is the mean of the M_b^*. *In practice, good estimates of Se(M) may be obtained with B=50, but values of B=1000 or B=2000 are usually required for reliable estimates of confidence intervals.*

Bias : Unbaised estimator

An estimator T is said to be an unbaised estimator of a parameter θ if $E(T) = \theta$.

However, if $E(T) - \theta = b \neq 0$

then b is called the bias in T.

Jack-Knife procedure

A statistical procedure used primarily for estimating bias in a sample estimator of a population parameter. The method, which is computer-intensive, is particularly useful when there is no analytic theory to estimate bias, e.g. in determining bias in the sample correlation coefficient r for a sample of n pairs as the estimator of a population correlation coefficient ρ. The procedure here is to compute successively the values $r'_{(i)}$, i= 1,2,…..,n, for samples identical to the original except that the i^{th} sample value is omitted.

If r' is the mean of the $r_{(i)}$, then the jack-knife estimator of bias is B= (n-1) (r'-r). In general, B is not an exact measure of bias, but it is usually a good approximation. Jack-knifing may also be used to obtain estimated standard errors. ***While the* Jack-knife *involves only n samplings of the original data, each of a specified form, the* Bootstrap *in practice often requires N samples, where N is considerably greater than n.*** Jack-knife solutions to many, but not all, problems are approximations to their bootstrap equivalents, but the method lacks the versatility of the bootstrap.