MATHEMATISCHES FORSCHUNGSINSTITUT OBERWOLFACH

T a g u n g s b e r i c h t 8/1987

Medical Statistics - Design and Analysis of Clinical Trials

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The conference was organized by M. Schumacher (Freiburg) and A. Neiß (Innsbruck). There were 37 participants from West Germany, Austria, England, France, Denmark, USA and Canada. The 35 talks given covered a wide range of topics within the field of design and analysis of clinical trials.

Some of the talks focussed on practical issues of the design and conduct of particular clinical trials. Many others discussed various aspects of statistical methodology in clinical trial design and analysis. A third category of talks concentrated on more theoretical and mathematical aspects.

In the following some of the important topics of the conference are summarized. A whole day was devoted to survival analysis, one of the main topics of the conference. Another large group of talks was gathered under the heading "analysis of clinical trials". It comprised a great variety of topics: the analysis of particular trials (cardiology, pediatrics), subgroup analysis and the search for prognostic factors, meta-analyses, a fundamental discussion on the adequacy of classical hypothesis testing for treatment comparisons and some further topics. Among the topics covering both design and analysis, crossover trials and sequential procedures were discussed extensively. A further topic of general interest was the relation between costs and benefits of treatments. There were a few "outliers" among the talks not quite fitting into the clinical trials framework, e.g. a survey of cancer mortality. However, these talks helped elucidating the close links between the different branches of medical statistics.

Abstracts

U. ABEL:

Two exploratory methods for evaluating quantitative variables V in follow-up studies

The first method assesses the discriminatory power of V with respect to prognosis. For all sample values v of V one compares the subsamples $S_{\leq v,m}$ and $S_{>v,m}$ defined by the m variable values next to v (m fixed). A distance measure, e. g., a monotonic transform of the log-rank statistic, is then plotted versus v. Simulations indicate that the Bonferroni procedure may be too conservative for correcting for the multiplicity of tests.

The second method deals with two-group comparisons in irregular follow-ups. A weak smoothness assumption for the time-dependence of V leads to interval data for V. For each follow-up time t, a generalized Wilcoxon statistic is calculated and transformed to ridits that are plotted versus t. An inequality is proposed for testing the null hypothesis that, for all t, the distributions of V in the two groups do not differ.

K. ABT:

Multivariate medians and related significance tests

The deficiencies of the arithmetic and geometric median are discussed. The "rotation"-median ("R") as proposed previously (Abt, Oberwolfach 1985) is shown to exist. In case of N = 2 dimensions the definition of R is based on the line integral

$$\Phi(u_\varphi^*) = \int_0^\pi \left| \int_{-\infty}^{u_\varphi^*} f_{u_\varphi} \, du_\varphi - 1/2 \right| d\varphi$$

where f_{u_φ} is the marginal density of the continuous density $f(x,y)$ on the axis u_φ at angle φ and where the common intersection point of all lines rectangular to u_φ and going through u_φ^*, $0 \leq \varphi \leq \pi$, defines the point R^*. R, then, is defined by the curve $\{u_\varphi^*\}_0$ which yields

$\text{Min } \Phi(u_\varphi^*) = \Phi(\{u_\varphi^*\}_0)$.

R is estimated by the tolerance region construction principle

(Abt, Biom. J. 1982) and $\hat{R}$ is shown to be invariant to affine transformations as well as to rotations of the coordinate system.

Using $\hat{R}$ in medical applications where, in general, the $N \geq 2$ variables have different scales opens possibilities to perform N-variate non-parametric significance tests for the k-sample case based on contingency tables ("median test") and on rank statistics on the circle.

D. G. ALTMAN:

Covariate imbalance and prognostic variables - a bootstrap investigation

The results of a randomised controlled trial of azathioprine versus placebo for primary biliary cirrhosis are discussed. A significant benefit of azathioprine was found, but only after adjustment for prognostic variables. It is shown that this effect of adjustment is due to slight imbalance in one highly prognostic variable, and that this imbalance ist not removed by performing a stratified analysis.

The choice of variables in the stepwise Cox regression model, including the treatment effect, were investigated in 100 bootstrap samples. It is shown that fitting the same model to each of the 100 samples as had been fitted to the real data produces estimated coefficients and standard errors very similar to the usual asymptotic values. Stepwise regression models fitted to the 100 samples yielded models with from 4 to 10 variables, with all variables in the original model appearing in over 60 % of the models. Bootstrap percentile confidence limits based on fixed variable selection and stepwise selection are compared.

P. BAUER:

Multiple Sequential Tests for the Elimination of Inferior Treatments

The different situations for sequential simultaneous testing are discussed. A general sequential procedure for the elimination of inferior treatments based on the simultaneous tests of all pairwise comparisons is proposed. A treatment is eliminated, if it appears to be inferior in an individual comparison by, e.g., a repeated significance test. The individual significance levels

can be enlarged after every elimination of a treatment. The procedure provides a confidence set for the "best" treatments, irrespective of how many treatments being best. The procedure can be improved, if the confidence set, with probability $1-\alpha$, does not contain all the best, but at least one of the best treatments.

J. BERGER:

How to evaluate the drug safety

Beside the main aim of a clinical trial, to prove the efficacy of a therapy, another aim is to come to a judgement about the tolerance and safety of the treatment. This judgement is based on the side effects reported by the patients and the development of the clinical laboratory data. In this process you have to take into consideration statistical arguments such as missing value problems, power considerations, multiple tests and, what is quite important, non random changes in the data over the follow-up period. In some examples it is demonstrated that after the number of reported side effects has decreased in the course of time the majority of all counts belongs to only few people and that the movement of the clinical-chemical parameters are parallel to the in- or decrease of the internal quality control sample. But these control values are mostly not available for the data analysis. Therefore especially in the so-called tolerance studies, where patients are followed up over one or two years without an adequate control group, the conclusions drawn from these data can only be of restricted value and are based on subjective feelings rather than on statistical arguments.

E. BRUNNER:

Rank methods for the two-period cross over design

Eine verteilungsfreie Analyse für den Zwei-Perioden Cross-over-Plan (Grizzle, 1965) wurde zuerst von Koch (1972) vorgeschlagen und von Hills und Armitage (1979) diskutiert. Da bei diesem Verfahren bekannte Rangtests auf Summen oder Differenzen der Daten angewandt werden, sind einerseits die Ergebnisse nicht invariant unter monotonen Transformationen der Daten und andererseits ist das Verfahren nur korrekt für Modelle mit additiven Effekten. Daher werden hier ohne die Annahme eines linearen Modells verallgemeinerte Effekte im Zwei-Perioden-Cross-over-Plan definiert und dann Rangtests angegeben, die diese Effekte

testen, ohne daß Summen oder Differenzen der Daten benötigt werden. Die Äquivalenz der Hypothesen für die verallgemeinerten Effekte zu den bekannten Hypothesen im linearen Modell wird gezeigt. Die asymptotische Verteilung der Rangstatistiken wird angegeben. Für weitere Einzelheiten wird auf die Literatur verwiesen (Brunner/Neumann, 1986).

D. BYAR:

Design of cancer prevention studies

Carcinogenesis is believed to occur in at least two stages, initiation and promotion, followed by a preneoplastic lesion which develops into cancer. Cancer prevention trials can be classified as primary (1°) if the intervention precedes initiation, secondary (2°) if it occurs during promotion, and tertiary (3°) if it is applied to a preneoplastic lesion. The 3° trials resemble treatment trials, but 1° and 2° trials may be very different in size, duration, and cost. The designs of six such trials will be reviewed briefly to illustrate these differences and the design approaches adopted to deal with them. These include spezial sample size calculations needed because of competing risks, use of cluster randomization and factorial designs, and case-cohort monitoring.

K. DAVIS:

Design and analysis of the randomized trial from the Coronary Artery Surgery Study (CASS)

The design of the CASS study will be described. Briefly, CASS consists of a registry of all patients who were studied angiographically for suspected ischemic heart disease at fifteen participating institutions in the United States and Canada between 1974 and 1979. Within this registry of 24,959 patients, 2099 patients were in the population defined to be eligible for a randomized trial of coronary bypass surgery and medical therapy. Of these patients, 780 agreed to participate in the randomized trial. The analysis of the randomized study will be discussed, including the ways in which the registry patients and the 1319 patients who declined randomization have been used to confirm and extend the results of the randomized study.

L. EDLER:

Determination and Evaluation of Response in Clinical Trials

Reviews of results on response in clinical cancer studies reveal often so an immense variation that attempts for combination of trials become doubtful. The present contribution tries to identify explanatory factors for this variability of published response rates. Prerequisites and criteria of response, sources of misclassification and uncertainities of definitions are discussed. Based thereupon, it is shown how differentiation with respect to measurability of the disease and complete registration of all patients considered for a trial can lead to aconsiderable improvement. In general, this would lead to a multistate model for the analysis of response data. Two aspects of the evaluation of response rates are considered in more detail: Wilcoxon type tests proposed for ordered alternatives for the comparison of response rates are examined by a small simulation study. Survival by response, possible misinterpretations, and inadmissible conclusions are discussed within the multistate frame and methods of unbiased analyses are reviewed.

S. M. GORE:

Clinical trials in paediatrics

Two randomized clinical trials are described in which statistical design was chosen to abet evolutionary paediatric research. The first example is a multicentre trial of preterm formula versus banked human milk (in 3 centres) or term formula (2 centres). The design was group sequential to allow early publication of short term anthropometric advantage (but not cessation of randomization) and early application for funds to follow infants to 18 months to compare Bayley scores for physical and mental development. Randomization to more than 900 babies was ethical because longer term outcome might offset initial advantage.

The second example concerns extension of a Cambridge-Nottingham trial which compared respiratory scores between surfactant treated and control infants less than 34 weeks. Extension occurred after 94 very premature infants (less than 30 weeks) had been randomized (2/3 through C-N trial); mortality favoured surfactant; 10 neonatal units each randomized 20 25-29 week babies within 1 yaer; 2-stage trial had 74 % conditional power to detect plausible mortality reduction from 36 % to 21 %. Bias in the reporting of 2-stage designs is discussed and implications for meta-analysis reviewed.

J. HILDEN:

Decision Analysis in the Design and Analysis of Clinical Trials: A Case Study Involving Severe Surgical Disfigurement

An unusual design was adopted for a trial comparing local excision and full vulvectomy for in-situ vulvar carcinoma. In view of the pilot finding that no invasive recurrences developed after local excision a conventional comparative trial was deemed unethical. Instead, patients are allocated to local excision as long as no such recurrences are seen. Should one occur (which has not happened in over 300 woman-years of observation), the trial may switch to an alternation scheme, depending on the information then accumulated (which is now, after nine years, very unlikely). The utility-theoretic loss assessment involved, and its proper role in the design and analysis of this trial and in trials in general, will be discussed. In particular, it is shown that with an asymmetrical loss structure some classical null hypotheses and tests are beside the point; this includes for instance the conventional null hypothesis of equal success rates. In our study asymmetry arises because of vulvectomy having the "fixed handicap" of disfigurement.

C. HILL:

Trends in cancer mortality over the last 35 years in France

In France, the age standardised (world standard) cancer mortality has increased by 66 % for males and decreased by 11 % for females between 1950 and 1984. These trends are the result of different evolutions for the different sites of cancer, some of which are discussed here. The causes of death in old age are much better known in 1984 than in 1950. To eliminate, at least partly, this artefact in the study of trends, rates truncated to the age 35 to 64 will be considered.

Alcohol and alcohol plus tobacco related sites show a very large excess mortality for males compared to females, an increase for males until 1976, followed after 1976 by either stability or a decrease. This is at least partly a consequence of steady decline in alcohol consumption since world war II (mortality from cirrhosis is also decreasing after 1976).

The consequences of tobacco smoking, a recent habit for French females, are not yet detectable on female lung cancer mortality (lung cancer kills as many women as breast cancer in the US). The reduction in lung cancer mortality, observed in some countries for young males, is not seen in France where tobacco sales are still increasing and tar levels high.

The conclusion is that avoidance of known carcinogens like tobacco or cocarcinogens like alcohol could reduce notably cancer mortality in France by year 2010. Predictions for the next 10 to 20 years are rather pessimistic.

R. HOLLE:

Strategies for the analysis of prognostic factors in clinical trials

The analysis of prognostic factors from clinical trial data is often done for unclear reasons or by inadequate methods. In this talk different objectives for the analysis of prognostic factors in clinical trials will be discussed. The general adequacy of standard methods like stepwise variable selection in Cox's proportional hazard model is questioned and problems are pointed out which arise in the case of continuous predictor variables. As an alternative, the use of methods from the field of medical decision making, such as sensitivity-specifity-analysis and utility functions, is proposed for a wider application.

H. IMMICH:

Studies and physician's experience

Cohort studies suffer from the insufficient presentation of raw or original data. So the reader cannot scrutinize the data; transparency is not given. The reader has the possibilities either to believe in the results or to remain critical.

If the physician tries to repeat the examinations of cohort studies and if he gets divergent results, the problem remains unsolved. The interpretation of data depends on the observer.

Therefore the following rule is recommended. Forget yourself and your opinions and look on the data exclusively.

T. JOHNSON:

The trade-off between seizure recurrence and drug side effects: a multicentre clinical trial of withdrawal of antiepileptic drugs

People with a history of epilepsy are frequently prescribed drug treatment for many years despite side-effects and complete absence of seizures. Driving regulations stipulate that such people may not be able to stop drug treatment without risk of loosing their licences or motor insurance. The difficulties of applying current philosophy for large and simple radomised controlled trials, and the practical problems encountered in organisation and recruitment are illustrated against the background of an ongoing, multi-national clinical trial, assessing the risk of seizure recurrence in patients undergoing slow withdrawal of anti-epileptic drugs.

R. KAY:

The analysis of cancer markers and disease states in survival studies

This presentation concerns models to isolate the effects of a cancer marker on survival time. Levels of the cancer marker define a series of marker states and patients can move between these states and to a death state. The model assumes that transition rates between the states are constant and data from patients is of the form of a series of marker states at arbitrary points during follow-up. A likelihood function for the transition rateparametersis formed via the transition probabilities for each patient and each possible transition and maximised. The hypothesis that the marker level has no effect on survival is tested using a Wald's test. Goodness of fit methods for the model are presented. More generally the validity of the likelihood methods depends on the sampling scheme and considerations concerning what sampling schemes are appropriate are presented.

N. KEIDING:

Confirmatory analysis of survival data using left truncation of the life times of primary survivors

In survival analysis as in other branches of applied statistics, confirmatory analysis is often requested before an initial finding can be cleared of a suspicion of being due just to mass

significance. This note points out that the special temporal structure of the classical clinical trial with staggered entry allows the re-use of the initial survivors by left-truncating their remaining survival times. This procedure can often save a considerable amount of calendar time.

The procedure is illustrated by data from the Danish Breast Cancer Cooperative Group.

G. KEMMLER:

Optimality of crossover designs when the competing designs have different numbers of periods

In most work on optimal design of crossover trials it is assusmed that the number of periods has been fixed beforehand. However, in practical situations this may be open to the experimentor.

In this paper a suggestion is given on how the effectivity of crossover designs with different numbers of periods may be compared. The considerations are based on the notion of cost. For a class of intuitively appealing cost functions (linear in the number of periods) conditions for the existence of optimal designs and a characterization of these designs are given. Some practical consequences are drawn for the cases of two and three treatments.

H. KLINGER:

Remark on the behaviour of estimators in Cox`s proportional hazards model

The results of simulation studies with one and two binary covariates , respectively, were presented in detail. It was demonstrated that the asymptotic normal approximations are very good in case of sample sizes n = 128 and n = 256. There seems to be a tendency for overestimating the parameters in absolute value. The relative frequencies of confidence intervals containing the true parameter values corresponded to the prescribed values. On the other hand the power is small. The parameters have to represent large effects in order to give significant results. Censoring with probabilities less than 0.3 does not affect seriously the above mentioned results.

W. KÖPCKE:

Patient Selection and Drop-outs in Clinical Trials

Patient selection takes place before randomization. The eligibility criteria for entry in a trial may affect the generalizability of the resulting treatment. However, because the exclusions occur prior to the randomization, the process of exclusion is not associated with treatment assignment and is therefore not a confounder.

Several patients are often removed after randomization and therefore have the potential to invalidate the comparison between the randomized treatment groups. It depends on whether there is a pragmatic or an explanatory trial what patients are removed from analysis. The impact of different views on the results is demonstrated on a trial for prophylactic sclerotherapy of oesophageal varices.

W. LEHMACHER:

The Analysis of Crossover Trials in the Presence of Residual Effects

The analysis of the two period and two treatment crossover design is discussed. If in the second period a residual (i. e. carry over) effect is present, the standard tests based on the differences of the two observations of an individual is biased. It is shown, how residual effects can influence the results and how these results have to be interpreted correctly. Further, as an alternative to Grizzle's pretest method, a procedure is suggested which combines several relevant tests to a strategy which controls the multiple (experimentwise) error and allows for a better yield of the information from a crossover experiment.

J. MAU:

On the construction and use of confidence distributions

To make Cox's notion of a confidence distribution, informally mentioned in his 1958 AMS paper, mathematically precise, I introduce it as a random measure on the parameter space R. One easily obtains central and symmetrical confidence intervals from a graph of an observed confidence distribution. The approach is illustrated in a context of clinical trials as a tool to assess the clinical equivalence of two treatments.

D. MORGENSTERN:

The k-point median

The usual onedimensional median and its d-dimensional generalization (geometric median), defined by the minimum property E (distance (X,B)) = Min(B), is generalized by taking k points, thus $E(\text{Min}(\text{dist}(X,B_i))=\text{Min}(B_1,\ldots B_k)$.
Another characterization (equivalent) is

$$\sum E(\text{dist}(X,B_i)\cdot \mathbb{1}_{\mathcal{L}_i}) = \text{Min}\,(B_1,\cdots,B_k\,;\ \text{partitionings } \mathcal{L}_1+\cdots+\mathcal{L}_k=\mathbb{R}^d)$$

Another geralization gives affin-invariant medians which also could be recommended for display of the distribution by some "typical" points (centers of clusters).

A. NEISS:

Tests in Clinical Trials

Comparing two treatments A and B in a clinical trial usually means testing H : "A and B are equal" against H : "A and B are not equal". Instead of this hypothesis it is proposed to test H : "A and B are equivalent" against H : "A and B are not equivalent". For normally distributed response variables in the two groups with means μ and ν standard deviation σ equivalence is defined as

$$\Delta_1 \leq (\mu-\nu)/\sigma \leq \Delta_2.$$

To test the equivalence hypothesis the usual t-test statistic is used. To derive the critical values for this test the non-central t distribution is needed.

For several sample sizes the critical values and the power function are presented. Further applications are disussed.

A. J. PETKAU:

Optimal Group Sequential Designs

Optimal group sequential designs are obtained for both the original and a truncated version of a model for clinical trials originally investigated by Anscombe and Cotton. The properties of these designs indicate the magnitude of the penalty incurred due to both the restriction to group sequential designs and the imposition of varying degrees of truncation, and provide a

baseline against which to assess the performance of suboptimal designs such as the different types of group sequential designs which have been proposed. Conclusions differ somewhat from those to which one is led in the classical hypothesis-testing framework and these results yield implications for the general problem of designing clinical trials.

S. J. POCOCK:

Statistical problems in the reporting of trials

Reports of clinical trials often contain a wealth of data comparing treatments which can lead to problems of interpretation,particulary with the extensive use of significance testing. A survey of 45 published comparative trials in the British Medical Journal, the Lancet and the New England Journal of Medicine has been undertaken to illustrate these statistical problems.

Issues considered include the analysis of multiple endpoints, analysis of repeated measurements over time, subgroup analyses, trials with multiple treatments and the overall number of significance tests in a trial report. Interpretation of such a multiplicity of data is further complicated by the failure of most reports to specify any pre-defined intended size of trial or statistical stopping rules for interim analyses. Also, there is a marked tendency for the trial summary to emphasize the more statistically significant endpoints.

Overall, the current state-of-the-art in reporting of clinical trials appears biassed towards an exaggeration of treatment differences. Trial publications need a clearer definition of the pre-defined policy for data analysis and reporting. In particular, one should specify a limited number of primary treatment comparisons in advance. Also, the obsession with arbitrary significance levels (eg P<.05) is detrimental to good scientific reporting and greater emphasis should be given to the magnitude of treatment differences and estimation methods such as confidence intervals.

R. REPGES:

Case Control Studies with exposure time going to zero

The population in a case control study is usually consideed to consist of two groups, exposed (Np) and non exposed (N(1-p)), N the population size.

The observed cases are modelled as $n_{11} = Np \cdot \mu_1 t$ for the exposed and $n_{12} = N(1-p) \cdot \mu_2 t$ for the non exposed. μ_i is the incidence for the adverse reaction. The control group consists of a random sample of size n and is drawn to estimate p, the part of the population being under exposure.

If the exposure time τ is not equal to t, the ovservation time, the above formulae do not hold. An example is the immediate reaction after the use of a drug, which occurs with a small probability, p_1 say.

It is proposed to define a flux $\varphi = \lim \Delta N/\Delta t$ of ΔN persons, who are exposed for the time Δt and then go back to the pool of non exposed people, or - with probability p_1 - contribute to the number n_{11} of cases.

These are then described by $n_{11} = p_1 N \int \varphi(t)\, dt$ instead of $n_{11} = p\, N \int \mu(t)\, dt$. The controls are to be chosen in such a way that they allow for estimating the flux φ. A practical example (Boston study) is given.

H. ROCKETTE:

Issues in Combining Data From Randomized Clinical Trials

The integration of findings from multiple clinical studies with similar treatment protocols is becoming increasingly popular in medical research. The major problems with such overviews result from the attempt to combine studies that may be diverse in design, quality control and analytic methods employed. This diversity creates problems relative to which studies should be included in the overview, formulation of a hypothesis, estimation of an average treatment effect and analysis of subgroups. The limitation of doing such overview analyses are discussed as well as recommendations for improving the current manner in which most of these trials are conducted.

M. SCHEMPER:

Subgruppen- und Wechselwirkungsanalysen in klinischen Lebensdauerstudien

Klinische Studien werden häufig mit heterogenen Patientenkollektiven durchgeführt, was dann meist Interesse an Subgruppenanalysen hervorruft. Abgesehen von der Berücksichtigung damit meist verbundener Multiplizitätsprobleme sollten signifikante Wechselwirkungstests die formale Rechtfertigung für getrennte Subgruppenanalysen und -aussagen liefern.

Der Beitrag beschäftigt sich daher genauer mit der Deskription von Wechselwirkungen und zur Verfügung stehenden nichtparametrischen Testverfahren, die jeweils auch für zensierte Daten geeignet sind. Auf theoretische Überlegungen folgt die Diskussion von Simulationsergebnissen mit einem "einfachen" Test, einem verallgemeinerten Patel-Hoel-Test unter Verwendung von Jackknife-Varianzen sowie mit dem Wald'schen Test im Rahmen des Cox-Modells. Die Präsentation alternativer Analysen einer Mammakarzinom-Studie weist auf kontroversielle statistische Schlüsse bei Vorliegen von Wechselwirkungen hin.

B. SCHNEIDER:

Large sample methods and sequential triangular tests for design and analysis of clinical trials

Large sample methods are based on Taylor expansion of the log-likelihood function: $\ln L(x,\vartheta) = \sum \ln(x_i;\vartheta)$ about the point $\vartheta = 0$. The first order derivative (at point $\vartheta = 0$) can be considered as test-statistic Z for treatment differences ϑ, if ϑ is adequately chosen. This statistic is asymptotically normally distributed with mean ϑV and variance V, where V is a function of the second order derivatives of the log likelihood function at $\vartheta = 0$ and asymptotically equivalent to Fisher's information. Based on these two statistics sequential triangular tests for $H_0 : \vartheta = 0$ against $H_1 : \vartheta = \vartheta_R$ (with significance level α and power $1 - \alpha$) can be constucted. These tests have the continuation region:

$$Z \in (-a + \lambda V,\ a + \mu V) \text{ with } a = (2/\vartheta_R)\ln(1/2\alpha);\ \lambda = (3/4)\vartheta_R,\ \mu = (1/4)\vartheta_R .$$

The properties of these tests are discussed and their applications to various situations in clinical trials are demonstrated.

M. SCHUMACHER:

On the combined analysis of randomized and non-randomized patients in a clinical trial

A method for the combined analysis of randomized and non-randomized patients in a clinical trial is presented. It is based on a proportional hazards model relating the hazard function to the treatment actually given, the randomization status, and other covariates of prognostic relevance. It turns out that the interaction between the treatment indicator and the randomization status is the key for the interpretation of such an analysis. In the case that this interaction term is equal to zero, we can assume "stable conditions", i. e. the hazard ratio or relative risk of the treatments is equal for randomized and non-randomized patients. If this is not the case the generalization of the results obtained from the randomized part of the trial can be questioned. The procedure of analyzing such a "Comprehensive Cohort Study" is illustrated by the data from the Coronary Artery Surgery Study (CASS).

N. VICTOR:

On the "clinically relevant difference" in significance testing

It is proposed to discuss before starting a clinical trial with the clinician four different values of clinically relevant resp. important differences, instead of the one usual sample-size $\mathfrak{N}_0$:

Δ_1 : The clinically relevant difference in the individual patient

δ_1 : The clinically relevant difference between treatments ($\delta_1 = \Delta_1 p_1$, with p_1 : = minimal success rate).

Δ_2 : The clinically important difference in the individual patient

δ_2 : The clinically important difference between treatments ($\delta_2 = \Delta_2 p_2$, with p_2 : = desired success rate).

The proposal is to take into account these values in the process of analysis by testing the "shifted" null hypothesis (the "non-zero" null hypothesis) $H_0 : \delta = \delta_1$ vs. $H_1 : \delta > \delta_1$, with a fixed power at the point δ_2.

J. WAHRENDORF:

An Investigation of the Adequacy of a Radomization

A randomization actually performed in an individual-based double-blind intervention trial in cancer epidemiology is investigated concerning the resulting imbalance of treatment assignment. Complete randomization, permuted block procedures, and adaptive urn models are simulated in order to assess how representative the achieved distribution is for the procedure used and how other procedures would have performed on the given study population. The achieved randomization is deemed to be satisfactory and the different procedures are discussed in light of different logistic requirements. It is argued that such investigations should be carried out when debating the implications of a given randomization.

S. WELLEK:

A Nonparametric Model for Product-Limit Estimation Under Right Censoring and Left Truncation

We consider the problem of generalizing the product-limit estimator (PLE) to the case of survival data subject to both right censoring and left truncation. From a practical point of view the problem admits an easy solution: The usual Kaplan-Meier technique may be adapted by simply eliminating from the risk set to be assigned to an arbitrary time t, all items whose follow-up interval does not contain the point t. The model which we propose and call "independent random truncation model", is a natural generalization of the well-known random censorship model. Relying on this model, we state some theorems giving conditions which ensure consistency and asymptotic normality of the generalized PLE.

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