

METHODOLOGICAL ASPECTS OF IDENTIFYING RECRUITING CRITERIA FOR DRUG TRIALS AND RISK FACTORS FOR THE DISEASE. Ursula Kellhammer, Dept. of Medical Statistics and Data Processing, Volker Pfaffenrath, Dept. of Neurology, Ludwig-Maximilians-University, Munich, FRG.

There is no doubt, that randomized clinical trials are the best way to collect information on the efficacy of therapies. But before starting the drug trial, one should know (1) the profile of the typical patient, (2) the frequency of these typical patients in the population out of which the recruitment of the drug trial is done.

To answer these questions as well as to investigate more generally the epidemiology of the disease (e.g. etiology, risk factors) we have two statistical instruments, namely the cohort study and the case control study.

With a cohort study one can answer questions like 'risk factors for common migraine (CM)?', 'precipitating factors for the CM-attack?', 'profile of the typical CM-case?', 'symptom patterns of CM?', 'standard therapy of CM?'. The cohort study is a prospective study, which is usually set up to generate new hypotheses for diseases with a sufficiently high prevalence (resp. incidence). One defines the study population, the so-called 'cohort' by conditions, which all the members of the cohort fulfill. Then one has to specify the disease events, one is interested in, the so-called 'endpoints' for the analysis, e.g. frequency of attacks, occurrence of vision disturbances..., and the observation period (same for all patients, counting from entry into the study). The cross-sectional evaluation of a cohort study consists of exploratory data analysis and of estimation of risk factors for the disease and of estimation of relative risks in subgroups of the cohort. If one has enough cases, one can do a stratified analysis (e.g. estimate the relative risk separately for young and old women). Typical problems of cohort studies are dropouts during the observation period and errors in the cohort recruitment, esp. if the cohort is defined as a random sample. When interpreting the findings, one has to assess the generalizability of the results. There the main consideration is if the sample was drawn out of the general population or if it was taken from a patients' universe (ambulatory care, hospital). A hospital-based migraine study, for instance, would probably give a rather biased impression of the epidemiology of the disease, since it is estimated, that only about half of all migraine cases consult a physician and of these only the patients with graver symptoms would be seen in the hospital.

The case control study is a retrospective study, starting from occurrence of the endpoint event (i.e. being a 'case'). Case control studies are used, whenever the disease under investigation is so rare as to render the prospective approach (cohort study) unfeasible (e.g. cluster headache). One defines first the cases and then the controls. The controls should be equal to the cases except for not having the disease. The dilemma lies in defining the variables, which make a control equal to a case. Usually one tries to achieve similar age- and sex-structure for the case- and the control group. But there are quite a lot of conditions, which might violate the strict separation of the group having the disease and the disease-free group. If the endpoint is stroke, for instance, then hypertension as a well

established risk factor for stroke could be regarded as a step in the direction of the disease and its occurrence in the control group should at least be taken into account. There are two not infrequent situations, which pose even graver problems: (1) One is unsure about the number of relevant risk factors and of their interaction. (2) One knows the really important risk factors, but these are not suitable for the definition of the control group's recruiting criteria (because of being too many or having a wide variation of values in a small case group). A way out of problem (1) is to select more than one control group. The solution of problem (2) lies in choosing a matched design. Matching can be done in pairs (to each case belongs one control person with (nearly) the same values in the matching criteria) or in triples (1 case, 2 controls) or with more than 2 controls per case. One should keep in mind, that the evaluation of a matched study permits no conclusions on the importance of the matching criteria. This can be rather a big draw-back, esp. when risk factors for the disease are used as matching criteria. Once the cases and controls are identified (recruited), their history is compared. The odds ratio (an estimator of the relative risk) is calculated. For the assessment of the generalizability of the findings two points have to be considered: (1) The source of the data. (2) The quality of the data. If the source of the data is some kind of nationwide statistics (e.g. death certificates), then one may under favourable conditions expect fairly unbiased conclusions on the epidemiology of the investigated disease. If, on the other hand, the data come out of a hospital based registry of morbidity, the presence of various selection biases is highly probable. The data-quality of case-control studies is generally lower than that of cohort studies for two reasons, inherent to the case-control approach: (1) Since the evaluation is done retrospectively, some important exposure variables may not be documented at all or in such an unstandardized fashion, that they cannot be used. That happens frequently in the field of behaviour variables (e.g. smoking history, when the cases are lung cancer deaths). (2) It is often impossible, to control for completeness of the data source. In unicausal mortality statistics one misses all cases, in which the diagnosis under investigation is listed as an accompanying disease on the death certificate. In hospital-based case-control studies it is seldomly feasible to check the completeness of patient records' archives. If the missing records are a homogeneous group (e.g. all cases with a bad prognosis), then the conclusions of the case-control study are automatically biased and the investigator has no means of assessing the selection effect.