Teaching Statistical Principles and Methods in Medical Applications

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SUMMARY

Biostatistics is undesirably perceived as a mathematical science. Time now is to reorient the subject so that it enjoys its rightful place into medical disciplines instead of being treated as an alien subject. The following is a brief outline of the plan of teaching this subject that can be very convincing to medical undergraduates as the one that fulfills their medical need.

Establish the perimeter of biostatistics: Variation is spice of life. This enjoyable feature in human beings is also a source of enormous uncertainties in clinical decisions. Besides genetic, biological, environmental, observer, instrumental and sampling variability, factors such as incomplete information on the patient, inadequacy of medical knowledge, poor compliance with the regimen, and imperfect medical tools contribute to the spectrum of uncertainty. Some times these uncertainties are so profound that medicine digresses from science to an art. Clearly, tools are needed that help to keep a handle on these uncertainties. They must be properly measured and strategies should be adopted to minimise their impact on clinical decisions. *(Define biostatistics as the science to manage medical uncertainties, and keep this theme alive all through the course.)*

Measurement of uncertainty: Uncertainty is measured through its complement, namely, the probability. Sensitivity, specificity, positive and negative predictive values are the examples of probability that are used every day in clinical practice. *(Explain clinical relevance of these concepts and illustrate their calculation though a real life example.)* Sensitivity and specificity are easy to calculate but move in a reverse direction from disease to symptoms. Predictive values rightly move from symptoms to disease but are difficult to obtain in a direct manner. Indirectly they can be obtained from sensitivity and specificity by using Bayes' rule. *(Give a practical clinical example of how*

sensitivity could be very different from positive predictivity, and how predictions depend on the prevalence rates.)

Form and magnitude of variation: Since different individuals — healthy or sick — have different levels of parameters such as blood glucose and cholesterol, it is useful to know what percentage of subjects fall into different categories of level. This gives rise to form of distribution. *(Discuss the Gaussian form and contrast it with other forms such as bath-tub.)* Because of inter-individual variation, it is imperative that a central value such as mean is used and the magnitude of variation is assessed. *(Describe situations where each of mean, median, and mode is appropriate and give a heuristic explanation of the formula for calculating SD).* Also, since variations are prominent even in healthy subjects, it is essential that a range of normal or reference values be used for evaluating the parameter of an incoming patient. Ideally, such references should be related to the likelihood of absence of diseases but generally are obtained such that very few (say, less than 5%) healthy subjects fall outside. When the distribution is Gaussian, this leads to ±2SD limits. *(Explain the risks of using such statistical limits on healthy subjects and separately for patients.)*

Clinical trials: Clinical trials essentially entail comparison of a new regimen (experimental) with an existing (control) regimen with regard to its efficacy in providing relief or in increasing the period of relief or survival. Because of the risks involved, the trials are done in phases. *(Explain various phases of a clinical trial, along with the significance of each.)* Present-day trials are enormously expensive and it is essential that they are carefully planned and meticulously executed. *(Discuss various sources of bias and features such as matching, blinding, and randomisation. Also discuss one-way, two-way and cross-over designs with regard to the merits and demerits of each with emphasis on how these help to control uncertainties.)* They must be carried out on adequate number of subjects so that sampling fluctuation could be effectively ruled out as an explanation of the observed difference. *(Give principles for determining the sample size.)*

Comparison of groups: To rule out any major role of sampling fluctuation, chance of obtaining the observed (or more extreme) difference (in means or proportions) between the experimental and the control regimen is calculated starting with the assumption that there is no difference. *(Explain the null*

hypothesis and the alternative hypothesis with the help of court-judgement analogy.) If this probability is small (say, less than 5%), the evidence is considered sufficient against the null hypothesis of no difference. *(Contrast between the statistical and the medical significance.)* The method to obtain this probability is not straight forward and depends on a host of factors such as whether means are being examined or the proportions, whether the sample size is small or large, whether the underlying distribution is approximately Gaussian or grossly nonGaussian, etc. *(Give an outline of the Student's t and chi-square tests.)* The method also depends on whether only two regimens are being compared, or several doses or several variants of the regimen. *(Refer to ANOVA-F and extension of chi-square.)*

Medical relationships: Medicine is greatly helped by the knowledge about dependence (causal or incidental) of one parameter on one or more of the others. For example, it is very useful to know that BP level depends on heredity, age, sex, stress and personality profile of a person — and that systolic and diastolic levels are highly correlated. The extent and form of dependence varies greatly from person to person. Whereas relationships in an individual subject are difficult to assess, it can be easily obtained for groups of subjects. *(Discuss the concepts of regression and correlation and indicate how the group relationships are still useful for individual case management.)*

Quality control in medicine: In an empirical science such as medicine, obtaining information on a group of subjects is *sine-qua-non* for studying uncertainties. Validity of conclusions depends on the quality of such data. The instruments used to obtain information — be these questionnaires or schedules, sphygmomanometer or stethoscope, laboratory procedures or x-rays — should be valid and reliable. *(Discuss measures of validity and reliability.)* An additional dimension is the quality control of medical errors. No medical centre can remain error-free all the time. The key is to keep these errors under control, and to take rectifying steps if they get out of control. *(Describe quality control charts, particularly for maintaining quality of laboratory investigations.)*

Clinimetrics: Whereas some clinicians depend mostly on subjective assessment of the sign-symptom syndrome, others believe in quantitative aspects that can be more objective. Clinimetrics requires that signs-symptoms are assigned scores based on previous experience and the chance of a disease is evaluated on the basis of this score. *(Give examples such as that of thyroid scoring system for*

differential diagnosis.) Clinimetrics is also used to assess the severity of disease. *(Mention about scores such as APACHE and Apgar.)* Some clinicians believe in using aids such as expert systems that can provide immense help in reminding about the investigations required in a particular case and in providing a narrow spectrum of diagnostic entities that are likely for a particular patient. Some believe in using flow charts such as etiology diagram. *(Give examples of expert systems and etiology diagrams used in medicine.)* All these should be used as aids and not as guides.

Final Comment: Successful empiricism is proper discernment of trends from fluctuation and segregation of focus from turbulence. Biostatistics plays a very significant role in achieving this objective in medical sciences. *(Advise to the students to rely on biostatistical methods only to a limit, and not replace common sense with any such method.)*