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Redefining Biostatistics – Managing Medical Uncertainties

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From the epitome of crunching numbers, statistical science has traveled a long distance. It is time that it is realized as a management science. This is especially true for biostatistics. I seek to define biostatistics as the science of managing medical uncertainties[1]. This can provide a completely new orientation to the subject and integrate it fully well into medical disciplines. How is this new definition justifiable?

Medical Uncertainties

Health differs greatly from person to person and in the same person from time to time. The variations are so prominent that no two individuals have ever been exactly alike. Differences in facial features and morphologic appearance help us to identify people uniquely. But more important for medicine are the profound variations in physiologic functions. We all know that measurements such as hemoglobin level, cholesterol level, and heart rate differ from person to person even in perfect health. Variations occur not only between individuals but also within individuals from time to time. Diurnal variations in body temperature, blood pressure, and blood glucose levels are normal. In addition, states such as shock, anger, and excitement affect most of us temporarily but have the potential to produce long-term sequelae. In the presence of such large variation, it is not surprising that a response to a stimulus such as a drug can seldom be exactly reproduced even in the same person. Uncertainties resulting from these variations are an essential feature of the practice of medicine and deserve to be recognized.

Medicine is not just ingesting a drug. It involves intimate interaction with the patient. More often than not, a large number of steps are taken before reaching to a treatment regimen. The patient's history is taken; measurements such as weight, blood pressure, and heart rate are recorded; physical examination is carried out; and investigations such as the electrocardiogram (ECG), x-ray studies, blood glucose measurements, and stool examination are done. In passing through these steps, the patient sometimes encounters many observers and many instruments. Variations among them contribute their bit to the uncertainties in clinical practice. The assessment of diagnosis, treatment, and prognosis can all go wrong. In order to highlight the large magnitude of these uncertainties, a list of specific contributing factors is provided below. This shows how profound uncertainties are and how important it is to delineate them and to contain their effect.

Biologic variability
Genetic variability
Variation in behavioural and other host factors
Environment variability
Chance variability
Sampling fluctuation
Observer variability
Variability in treatment strategies
Instrument and laboratory variability
Imperfect tools
Incomplete information on the patient
Poor compliance of the regimen
Inadequate knowledge (epistemic, diagnostic, therapeutic and prognostic uncertainties, predictive and other uncertainties)

Medical uncertainty at individual level is the potential fallibility of decisions regarding diagnosis, treatment and prognosis of health conditions. At the group or community level, this comprises lack of assurance regarding the role of primordial and proximal risk factors of various conditions of ill-health, and regarding the effect of various preventive and moderating interventions. In both setups, a prominent component is the uncertainty regarding the present state and future course of events.

Medical uncertainty is easy to handle when divided into aleatory and epistemic types. These terms may sound new to medicine but are commonly used in seismic science and economics. Aleatory uncertainty in medicine arises from endogenous factors such as inherent biological variation, environmental factors, socio-cultural and psychological factors, random variation due to observers, instruments and laboratories, etc. Epistemic uncertainty arises from lack of knowledge, conceptual errors, non-availability of tools, and biases of various types. These sources are exogenous in nature.

Management of Uncertainties

Since the uncertainties are glaring, one wonders how medicine has been successful, sometimes very successful, in giving succor to mankind. The silver lining is that a trend can still be detected among these variations, and following this trend yields results within clinical tolerance in most cases. The term clinical tolerance signifies that the medical intervention may not necessarily restore the system to its homeostatic level but tends to bring it closer to that level so that the patient feels better, almost cured. Also note the emphasis on 'most cases'. Positive results are not obtained in all cases, nor is this expected. But a large percentage responds to medical intervention. Thus, the statement is doubly probabilistic and truly statistical.

Essentially, management is a value addition process that tries to optimize the output by properly organizing the inputs. It involves elements such as goal setting; identifying quality and quantity of inputs such as men, machine, methods, material and money in a production line, and their adequate and timely provision; minimizing risk opportunities and maximizing conducive environment for optimal functioning of the inputs; gauging performance; and taking rectifying and promoting steps—thus starting the cycle all over again. Management is a

flexible process instead of adhering to consistency and conformity. It is an art of accomplishing an assignment by translating complexity, specialization and talents into performace[2].

Value addition in the case of management of medical uncertainties is in terms of their control so that the impact of such uncertainties on decisions is minimal. Their description and assessment are integral part of the process. Performance is the key in this case also as is for management anywhere else. The inputs are the aleatory variations and epistemic bottlenecks. Study design is a tool that seeks to organize these inputs. A perfect design, when immaculately executed, would minimize the risk of reaching to an invalid or unreliable conclusion, and maximize the power of the study, for fixed inputs. Considerations such as definition of study units and variables, sample size, method of selection, confounders, potential sources of bias including reliability and validity of medical assessment, and the method of analysis of data, are the elements that provide definite help in reducing the risk of reaching to an invalid conclusion. With tools such as probability and its derivatives that include frequency distribution, sensitivity, specificity, relative risk and odds ratio; estimation methods in terms of confidence interval and meta-analysis; test of hypothesis for absence of medically important difference; and trend analysis that sieves clear signals from noise; biostatistics fits the bill quite admirably. By considering various options, it awards flexibility instead of consistency and conformity that could mar a management process. Decision analysis that allows infusion of value judgements regarding utility of various possible outcomes to the evidence-based risk assessments at the stage of diagnosis and treatment, is also an important function of biostatistical methods for managing medical uncertainty at individual level.

The sources of intrinsic variation listed earlier are mostly beyond control but their impact can still be managed. Other sources of uncertainty also contribute but investigations can be designed such that their influence on decisions is minimized. Elementary concepts are given in the following paragraphs as illustration. The quality of decisions in the long run can also be enhanced by devising and using improved medical methods. Both require substantial statistical inputs.

Real challenge in research is thrown by epistemic uncertainties that arise from inadequate medical knowledge. Statements are sometimes made without realizing that they are assumptions. Gastric ulcer was thought to be caused by acidity till it was established that the culprit is *Helicobacter pylori* in many cases. Thus even fully established 'facts' should be continuously evaluated and replaced by new ones where needed.

Proper Design

A clinical trial aims to evaluate the efficacy of one or more treatment procedures—generally different drugs or different dosages of the same drug—relative to one another. The 'another' could be 'no treatment' or 'existing treatment' and termed control. Among the precautions sometimes taken is matching of the subjects in various groups so that the known sources of variability have less influence on the outcome. Another very effective strategy is randomization, which equalizes the chance of the presence of different sources of uncertainty in various groups including the unknown sources. The techniques of observation and measurement are standardized and uniformly implemented to minimize the diverse influence of these techniques on the outcome. If identifiable sources of uncertainty still remain uncontrolled, they are taken care of at the time of analysis by suitable adjustments.

Appropriate statistical methods help to come to a conclusion that has only a small likelihood of being wrong.

These preliminaries are stated in the context of clinical trials, but other medical investigations, be it in a community, in a clinic, or in a laboratory, have the same basic structure and require similar statistical inputs. Descriptive research, such as to estimate the magnitude of the problem or to delineate normal levels of, say, a hematological parameter in a specific population, also requires similar care in selection of subjects and similar quality control of the instruments. The investigations into cause and effect or association also need similar inputs to minimize the influence of uncertainty and thus to increase the reliability of the conclusions.

Improved Medical Methods

Although health of each individual is important, and clinical practice must use the best available methods, but research endeavors generally require especially improved methods that are more accurate and more exact. This makes medical research an expensive proposition but compromise on improved methods can substantially affect the quality of research. If such improved methods are not available, research may have to be redirected to devise such methods.

Incomplete knowledge about a patient's condition can be substantially overcome by research into new methods that are quicker, safer, and more accurate and that can be performed more easily. To fill gaps in medical knowledge, research into more exact delineation of factors responsible for specific conditions of ill health and their mechanism is required. All this will help devising strategies to minimize the uncertain space.

Some epistemic uncertainties can be minimized by using appropriate scoring system. Newer treatment regimens or other modes of patient management need to be discovered so that better relief can be provided. Inadequacies in medical tools such as diagnostic tests can be removed only by research on newer, more, valid, and more reliable tools. Compliance with prescribed regimens can be improved by devising regimens that are simple to implement, less toxic, and more effective. Instrument and observer variability can be controlled mostly by adhering to strict standards and by training. Thus, improving the methods can minimize the uncertainties arising from these deficiencies. Research into these requires scientific investigations so that the conclusions arrived at are valid as well as reliable. Proper design of the investigation helps to achieve this aim.

Analysis and Synthesis

Because of the uncertainties involved at every stage of a medical investigation, the conclusion can seldom be drawn in a straightforward manner. In almost all cases, the data obtained are carefully examined to find the answers to the questions initially proposed. For this, it is generally necessary that the data be collated in the form of tables, charts, or diagrams. Some summary measures are also chosen and computed to draw inferences. Because of the inherent variations in the data and because only a sample of the subjects is investigated rather than the entire target population, some special methods are required to draw valid conclusions— collectively called techniques of statistical inference. These techniques depend on the type of questions asked, on the design of the study, on the kind of measurements used, on the number of groups investigated, on the number of subjects studied in each group, etc. These techniques are primary focus of biostatistics. The role of statistical analysis is to help draw valid and reliable conclusions.

Although statistical analysis is acknowledged as an essential step in empirical research, the importance of synthesis is sometimes overlooked. Synthesis is the process of combining and reconciling varied and sometimes conflicting evidence. The findings of an investigation do not often

match those in another investigation. Diabetes, smoking habits and blood pressure levels were found to be significant factors in mortality in Italy in one study but not in other studies in the same country[3]. Prevalence of hypertension in India was found to range widely from 0.36 to 30.92 percent in a general population of adults[4]. These differences occur for a variety of reasons such as genuine population differences; sampling fluctuation; differences in definitions, methodology, and instruments; and differences in the statistical methods used. A major scientific activity is to synthesize these varying results and arrive at a consensus. The discussion part of most articles published in medical journals tries to do such a synthesis. The objective of most review articles is basically to present a holistic view after reconciling the varying results in different studies. In addition, techniques such as meta analysis seek to combine evidence from different studies. This text does not discuss the synthesis methods, although these methods too are primarily statistical in nature and are important for medical research.

Aleatory uncertainties are the basic ingredient of statistical methods. These can be very adequately managed by these methods. The same can not be stated about epistemic uncertainties. Sensitivity analysis[5] can be effectively used to delineate the impact of some epistemic uncertainties. However, they can be rarely minimized. There are epistemic bottlenecks for which apparently there is no solution except further research. If the underlying process of emergence and progression of a health condition is unclear, modeling will have to be based on conjectures. They may or may not stand the test of the time. No science is available that can adequately deal with the unknown except, to some extent, statistics that pools all these together under 'error term', and provides methods to examine them.

Conclusion

Considering all this, it seems very appropriate to define biostatistics as the science of managing medical uncertainties. No definition is perfect, nor one that is convincing to every one, but this definition seems to describe the subject in a very appropriate manner. Incidentally, this definition emphasizes that "bio" is an integral part of biostatistics and exemplifies fusion of medicine with statistics that Feinstein[6] emphasized so much. Conventionally, biostatistics has come to be identified with medicine rather than other biological disciplines such as agriculture or fisheries—thus restricting it to the medical uncertainties looks appropriate.

References

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