Review Article

Development of statistics as a discipline for clinical research: Past, present and future

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Abstract

This article traces the history and evolution of statistics in the era of evidence based medicine, and focuses on the Indian perspective of this growth of statistics as a discipline for clinical research. Statistics will assume a more inter disciplinary form. Use of software other than SAS likely to grow further. In India, innovative statistical methods will help propel the development of biosimilars. The future is exciting with statistics being used for real world evidence, development of biosimilars, mining of adverse event data and becoming a core function in medicinal product development and lifecycle maintenance.

Keywords: Biostatistics, clinical research, real world evidence, risk-based monitoring

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INTRODUCTION

The development of statistical methodology in the context of clinical research and biomedical research, in general, has been tremendous over the past couple of decades. Biostatistics is well established as a discipline of its own, which integrates the quantitative sciences (statistics, mathematics, computing) with biology and medicine.

The fillip that statistics received in the early 1960s for scientific testing towards new drug approvals gradually led to statistics being the basis for establishing the efficacy of a drug. This was due to the enactment of the 1962 Drug Amendments, following a worldwide drug disaster in 1961, which explicitly stated that the Food and Drug Administration (FDA) would require "substantial evidence" of the impact of a drug in a clinical trial setting and that new drug approvals would not be based only on proof of safety.[1] Clinical trials designed as per statistical principles became the norm in the USA following World War II.

The applications and methodologies continued to evolve with a lot of important developments over the next three decades. The 1990s provided the next major inflection point, and the past few years have witnessed explosive growth in applications of computationally intensive methods founded on statistical principles, due to the focus on translational research, personalized medicine, and the relevance of real-world data. Statistical and mathematical modeling has become more complex, and big data analytics is the buzzword.

The Western world (USA and Europe) has primarily driven the phenomenal growth and sophistication in terms of how statistics is being applied for clinical research and beyond;

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/2229-3485.198548

How to cite this article: Lele C. Development of statistics as a discipline for clinical research: Past, present and future. Perspect Clin Res 2017;8:41-4.

advances in statistical methodology and computing have been both the cause and the effect. While the past couple of decades have seen especially remarkable contributions, the globalization which happened in parallel, gave an international dimension to the development of statistics in pharmaceutical research. We will trace how statistical methodologies and techniques evolved, and will focus on the impact is has had in the Indian scenario.

EVOLUTION OF STATISTICAL METHODOLOGY AND APPLICATION

The discipline of biostatistics, or statistics in biomedical research, has developed by drawing on quantitative methods from other fields such as mathematics, operations research, and economics. In addition to clinical research, statistics is routinely applied to genomics, population genetics, epidemiology, ecology, nutrition, etc. Diverse research questions from these various fields have enriched the discipline.[2] Statistical methods such as generalized linear models, categorical data analysis, and survival analysis, quite the staple methods used in clinical research, have seen enhancements to handle new situations, just as Bayesian methods have become more prevalent and sophisticated, and nonparametric and computationally intensive methods are widely used. A few examples of the emerging scenarios and areas of emphasis that have influenced the development of methods are: (1) Increased relevance of pharmacometrics (PK-PD modeling) in drug development, (2) importance of adaptive designs to make the drug development programs more efficient and effective, (3) the reliance on meta-analysis for cumulative evidence, (4) advances in diagnostic systems and the data they generate, (5) emergence of oncology as one of the most important therapeutic areas to target and the complexities of its clinical trial designs as well as endpoints, (6) greater use of biomarkers, (7) availability of longitudinal data and repeated measurements, (8) incorporation of genetic testing in many clinical trials, and (9) shift of focus to benefit: Risk evaluation, emphasis on comparative effectiveness and real world evidence.

ROLE OF REGULATIONS IN RECENT ADVANCES AND EXPANDED SCOPE OF STATISTICS

A lot of guidance around emerging statistical methods and how they can be used in clinical trials is provided through the USA FDA's critical path initiative which was launched in 2004, as its strategy to drive innovation in the scientific processes through which medical products are developed, evaluated, and manufactured.[3] This list includes several topics that have influenced the development of methods and expanded the scope of the application of statistics. Some of the relevant topics in the list pertain to: Biomarkers, enrichment design, handling missing data, analysis of multiple endpoints, development of data standards, adverse event data mining, modeling device performance, better predictive disease models, and pediatric trial design, animal models for vaccines, and drug metabolism and therapeutic response.

Application of statistical methods in development and product lifecycle maintenance of devices, diagnostics, and vaccines has also grown and has been guided by emerging regulations.

Clinical trials have become more global, with patient recruitment happening in several countries. The commercial relevance of countries other than the USA and those in Western Europe, especially of the emerging markets, has increased over the past decade. This is both due to the commercial potential of the emerging economies and the limited sales growth in developed regions. Due to these factors, the regulatory authorities in these other countries have also been active and are emulating the developed regions in terms of their clinical research-related regulations. This has led to greater and wider need for applying statistical methods. For example, regulatory requirement to establish the safety of a generic product on a certain number of patients in a particular country mandates local clinical trials.

Regulatory guidance is also available for establishing therapeutic equivalence for certain categories of generic products, which also requires complex clinical trial design and analysis. Thus, some generic manufacturers also need to conduct large trials and use advanced statistical techniques. It is expected that regulatory guidance for postapproval research and marketing claims from observational data will emerge, and this will reinforce the importance of statistical methods for real world evidence.

Increasing importance of observational research and statistical inference based on it has led to heightened statistical diligence around capture, analysis, and reporting of observational data. Statisticians also play a pivotal role in analyzing data for publications and in reviewing and approving statistical interpretations in publications.

As the industry and regulators are looking at ways to improve the efficiency of the drug development process and reduce the cost of bringing a new drug to the market, they have been looking at ways to use statistical principles to streamline the conduct of clinical trials. Risk-based monitoring (RBM) is a prime example.

IMPACT OF GLOBALIZATION

As the cost of drug development was rising in the late 1990s and the early part of the new century, the industry started looking at patient recruitment in a larger number of countries for speedy

completion of trials and cost reduction. India was an attractive destination, with its advanced medical fraternity, English language skills, a large treatment-naïve population, and cost efficiencies. The industry soon realized that India could also be an attractive destination for outsourcing data management and data analysis work which was rapidly increasing because more clinical trials had to be conducted, and the trials were getting larger and more complex. There was a large educated workforce in the metro cities of India and these cities were also focusing on improving network connectivity and other infrastructure. A little over a decade ago, with the concept already successfully piloted by a couple of large pharmaceutical companies for a few years by then, many companies started looking at getting data-related work for clinical trials done from India. Several companies also replicated this model in other countries such as China, a few countries in Eastern Europe and South Africa. Over the past decade, most large and mid-sized companies embraced this model, as have the large Contract Research Organizations (CROs). Depending on each company's outlook and priorities, certain countries were preferred more than others. The globalization of statistics and data-related work for clinical trials had happened.

THE INDIAN CONTEXT

With the advent of outsourcing of data-related work to India, there were changes in the Indian environment in response to the emerging trend. The first and foremost change was with respect to education. In the early part of the century, the preferred field of study for a student who was interested in quantitative sciences was computer science and programming. However, as students and parents started seeing good job opportunities for statistics graduates, more students, including the brighter ones, opted to study statistics at the Masters' level. Thus, statistics became a discipline of choice for many students.

However, the typical Masters' level courses in most Indian universities focused on theory and were not geared towards equipping the students to apply statistical principles to real-life data. Some universities started courses in biostatistics to provide students an understanding of the way statistics is used in clinical trials. Due to a dearth of teachers with hands-on and industry experience, these courses did not equip the students to apply statistics to design and analyze clinical trials, but they served the purpose of providing an orientation to the subject. Some academicians developed an interest in this area and started doing methodological research, or moved to the industry to practice statistics in clinical research, or started practicing in a hospital setting. Subsequently, some universities also started specialized Biostatistics programs.

Statistics has thus become a good option as a discipline for higher studies.

Most of the work being done in India by the sponsor organizations or the CROs involves data management and programming. Over the past few years, some work related to the statistical planning of the design and analysis of clinical trials is being done from India, but this is still very small compared to the programming work. However, the past few years have seen an increase in statistical programming work involving efficacy analysis. This requires a sound statistical understanding, hence statistics graduates are largely employed for these roles.

Recently, there has also been growth in programming work related to data standards and RBM being done from India.

The majority of statistics and data-related work done from India is for global biopharmaceutical and contract research companies who have adopted an offshore delivery model. Although some increase in the volume can be expected in the future, it will be quite small compared to what India experienced over the past decade. This is partly due to the work being placed in other regions which are commercially more attractive, partly because many large companies have already outsourced most of the available work, and partly because some companies now prefer a blended onshore-offshore model for statistics and programming work, instead of a primarily offshore model. However, the variety and complexity of work is likely to increase.

There has not been much growth in statistics and data management work for clinical trials or postapproval studies done in India. Commercial attractiveness of some other markets in Asia-Pacific (such as China, Korea, and Japan) and their favorable regulatory environments has led to more products being tested for local approvals in these markets. Thus more trials are happening in these other countries. Indian generics manufacturers have to conduct studies for approval of their products in India, but these are usually simple safety studies which do not require much statistics. Indian affiliates of global biopharmaceutical companies conduct some local studies to help with their sales and marketing efforts, including some investigator-initiated studies and registries. They are typically interested in publishing the results, and with the growing emphasis on the statistical propriety of everything that's published, there's a role for statistics in analyzing and reporting these studies.

WHERE DO WE GO FROM HERE

Statistics will continue to be a critical aspect of clinical research, in view of the global trends outlined here and the evolving regulatory environment. It will assume a more inter-disciplinary form, while the emerging needs of clinical trials and postapproval research also fuel further methodological

advances in statistics. Statistics will continue to become more visible, i.e., statisticians will have to play a more prominent role as an integral part of product lifecycle maintenance teams, and will be called to weigh in on most aspects of development and maintenance. Thus, statisticians will need to have a better understanding of therapeutic areas and mechanisms of action etc., and will have to be effective communicators in cross-functional team discussions. Innovation will be the key to success as newer research problems, and business exigencies will demand new solutions.

Another development will be with respect to computational tools and software. SAS has been the preferred software for all clinical trial data analysis in the industry. However, as the variety of data to be analyzed increases, and more exploratory analysis and data mining are required, use of other tools and software (e.g., R) has seen an increase over the past few years. This is likely to grow further. With the need to manage and analyze data from various data sources and large databases (such as electronic health records, insurance databases), other tools for data standardization and mining will also assume a prominent role.

Closer home, statisticians, and programmers will have to gear up for the changes in terms of the kind of methods, analyses, and the tools to be used. Academic programs and training of the students of statistics will also have to evolve accordingly. Some of the Indian pharmaceutical companies that have embarked on the development of biosimilars will be looking for innovative statistical methods to help speed the development in a cost-effective manner.

CONCLUSION

Statistics as a discipline for clinical research has a history of over 50 years and has seen phenomenal development over the past two decades. The evolution has been with respect to new methods and improvisation of existing methods towards solving new research problems, as well as the scope and span of the application of statistics (all medicinal products including vaccines, devices etc., across the entire product lifecycle and not only limited to the traditional efficacy analyses, data mining and big data analytics). As a result, the prominence of the discipline witnessed a marked increase. India has been a beneficiary of this evolution, especially due to the large scale outsourcing of clinical trial analysis work to India. This led to increased importance of the discipline of statistics in the country. The future promises to be exciting as well, with statistics getting increasingly used for real world evidence, development of biosimilars, mining of adverse event data, etc., and becoming a core function in medicinal product development and lifecycle maintenance. The success of our capability building efforts will determine how much action India will experience. Increase in clinical trials in the region, including India, will also lead to further growth of this discipline in India.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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