Use of Bayesian statistics in drug development: Advantages and challenges

Sandeep K Gupta

Department of Medical Affairs and Clinical Research, Ranbaxy Laboratories Ltd., Gurgaon, Haryana, India

Abstract

Mainly, two statistical methodologies are applicable to the design and analysis of clinical trials: frequentist and Bayesian. Most traditional clinical trial designs are based on frequentist statistics. In frequentist statistics prior information is utilized formally only in the design of a clinical trial but not in the analysis of the data. On the other hand, Bayesian statistics provide a formal mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage. It is easier to implement adaptive trial designs using Bayesian methods than frequentist methods. The Bayesian approach can also be applied for post-marketing surveillance purposes and in meta-analysis. The basic tenets of good trial design are same for both Bayesian and frequentist trials. It has been recommended that the type of analysis to be used (Bayesian or frequentist) should be chosen beforehand. Switching to an analysis method that produces a more favorable outcome after observing the data is not recommended.

Key words: Adaptive trial, Bayesian statistics, drug development

Introduction

Clinical trials are very expensive and their outcomes are crucial to the concerned stakeholders and, hence, there is considerable pressure to optimize them. One route of optimization is to make better use of all available information, and Bayesian statistics provides this opportunity. Mainly, two statistical methodologies are applicable to the design and analysis of clinical trials: frequentist and Bayesian. Most traditional clinical trial designs are based on frequentist statistics. In frequentist statistics prior information is utilized formally only in the design of a clinical trial but not in the analysis of the data. However, Bayesian statistics provide a formal mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage.[1–4]

Address for correspondence: Dr. Sandeep Kumar Gupta, House No. 660, First Floor, Sector-22B, Gurgaon 122 015, Haryana, India.
E-mail: drsandeep_gupta@rediffmail.com

Access this article online	
Quick Response Code:	Website: www.ijabmr.org
	DOI: 10.4103/2229-516X.96789

The roots of Bayesian statistics lies in Bayes' theorem. Bayes' theorem arose from a publication in 1763 by Thomas Bayes. This theorem of Bayes was not published during his lifetime but only after his death, when his work was found in his desk by a friend. Bayesian statistics starts with a prior belief (expressed as a prior distribution), which is then updated with the new evidence to yield a posterior belief (also a probability distribution). Bayesian statistics provides a mathematical method for calculating the likelihood of a future event, given the knowledge from prior events. These methods, thus, directly address the question of how new evidence should change what we currently believe.[1,2,5]

Components of The Bayesian Approach

Prior distribution

The prior distribution is usually based on data from previous trials. It has been recommended that appropriate prior information should be carefully selected and incorporated into the analysis correctly. It is recommended that as many sources of good prior information as possible should be identified.[3,6]

Likelihood principle

Basically, two sources of information about the unknown parameters of interest are used in Bayesian analysis. The

first of these is the sample data, expressed formally by the likelihood function. The second is the prior distribution, which represents the additional (external) information that is available. The likelihood function is also an essential component of frequentist statistics, but the prior distribution is used only in the Bayesian approach.[3]

The likelihood principle essentially states that all evidence obtained from an experiment about an unknown quantity θ is contained in the likelihood function of θ for the given data. In the Bayesian approach the prior distribution for θ is updated using the information provided by the trial through the likelihood function and nothing else. The posterior distribution is the product only of the prior and the likelihood function.[3]

Posterior probabilities

The prior distribution is updated after data from the trial become available. This updated distribution is called the posterior distribution. Thus the Bayesian approach requires previous information (the prior probabilities) and current data to arrive at the 'posterior.' Conclusions from a Bayesian trial are based only on the posterior distribution. It should be borne in mind that today's posterior probabilities become tomorrow's prior probabilities.[3,7,8]

A better illustration of how Bayes' theorem works is a Bayesian 'triplot,' in which the prior distribution, the likelihood, and the posterior distribution are all plotted on the same graph. The triplot is useful to show how the two types of information (data and prior) are combined. It gives a graphical representation of prior to posterior updating.[9]

Predictive probability

Predictive probability is a special type of posterior probability; namely, the probability of unobserved outcomes (future or missing). Collectively, the probabilities for all possible values of the unobserved outcome are called the predictive distribution. Predictive distributions have many uses; for example for deciding when to stop a trial, for helping the physician and the patient make decisions by predicting the patient's clinical outcome (given the observed outcomes of patients in the clinical trial), and for predicting a clinical outcome from an earlier or more easily measured outcome for that patient, etc.[3,7,10]

Exchangeability of trials

The assumption of trial exchangeability enables the current trial to 'borrow strength' from previous trials. Thus, exchangeability of trials is important in the development of realistic models for combining trial data with prior information. Bayesian hierarchical modeling is a specific methodology used to combine results from multiple studies to obtain estimates of safety and effectiveness parameters. The name hierarchical model derives from the hierarchical manner in which observations and parameters are structured. Some Bayesian analysts refer to this approach as 'borrowing strength.'[3,11,12]

Decision rules

For Bayesian trials one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if the posterior probability is large enough. For Bayesian hypothesis testing the posterior distribution may be used to calculate the probability that a particular hypothesis is true, given the observed data.[3]

Advantages of Bayesian Methods

Incorporation of prior information

The Bayesian statistics augments and increases the precision of the information from a current trial by the incorporation of prior information. When good prior information exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial. When the prior information is based on empirical evidence, such as data from clinical studies rather than information based mainly on personal opinion, then the Bayesian methods are usually less controversial.[3,13]

Adaptive trial design

Accumulating data are used to modify certain aspects of a trial according to a prespecified plan, without undermining the validity and integrity of the trial in adaptive designs. It is easier to implement adaptive trial designs using Bayesian methods than frequentist methods.[3,14]

The flexibility of adaptive design methods, however, may introduce possible operational biases and consequently have an impact on the overall type I error rate.[14] Even though the control of the type I error rate is not a relevant property of a Bayesian design, simulations can be used to design a Bayesian adaptive trial that may achieve good power and control of type I error.[2]

Phase I dose-finding study

The continual reassessment method (CRM) was one of the first clinical applications of Bayesian methodology for determining the maximum tolerated dose (MTD) of a drug molecule. The doses given to subjects are determined by prior and historical data, and data obtained from previously dosed subjects are used to determine the range of doses to be explored. A probability of toxicity is assigned to each dose based on historical data or investigator input; these probabilities represent prior information and are the starting point for the search for the MTD. A model is defined that represents the dose–response relationship, and subjects

are treated at the starting dose, dose is increased steadily and dose-limiting toxicities are observed. Then, the next best estimate of the MTD is calculated based on the prior information and the new information from the study. Based on this approach, subjects are treated up to the dose that currently available evidence indicates to be the best estimate of the MTD. The CRM is flexible and allows different numbers of subjects to be treated per dose, and accommodates specific dose-limiting toxicity rates that are expected in different therapeutic areas.[14–16]

Phase II proof-of-concept studies

Decision making in a proof-of-concept study could be improved with Bayesian methodology. Proof-of-concept studies are carried out to obtain early evidence of clinical efficacy using a small, targeted, number of subjects, the aim being to obtain evidence to justify full-fledged clinical development. Traditional designs might unnecessarily expose an excessive number subjects to an ineffective arm before concluding the utility of the drug and, moreover, conclusions can only be drawn once the study is completed. Two-stage Simon designs, three-stage designs, optimal flexible two-stage designs, or adaptive two-stage designs can address these limitations. These studies are implemented in stages, as suggested by their names. The data from subjects in the study are examined at each stage and, depending on the results, a decision is made to stop the study early or to enroll additional subjects into the next stage.[14,15]

Seamless phase II–III trials

A phase II and a phase III clinical trial can be integrated into a single confirmatory study to shorten the development time. These seamless phase II/III trials involve complex interim adaptations, such as treatment selection, sample size reassessment, and stopping for futility. Bayesian predictive power can help in these interim adaptations and can make this decision-making process more efficient.[17]

Decision can be taken in an efficient way

In the Bayesian approach decisions can be taken in an efficient way due to the following reasons: (1) there is continuous learning as the data accumulate; (2) hierarchical modeling allows 'borrowing' of information across therapies or disease subtypes, etc., where the strength of borrowing depends on the homogeneity of the data; (3) it allows calculation of predictive probabilities of future outcomes and permits one to make inferences using the trial's currently available data; and (4) direct estimation of evidence is possible for the effect of interest, using posterior probability.[18,19]

Postmarketing surveillance

The Bayesian approach can be applied for postmarketing surveillance purposes. Today's posterior distribution is tomorrow's prior distribution. The Bayesian approach allows the use of the posterior distribution from a premarketing study as a prior distribution for surveillance purposes. Information provided by clinical trials can be updated with postmarketing data if exchangeability can be justified between pre- and postmarketing data.[3]

Meta-analysis

The flexibility of the Bayesian approach makes it very suitable for combining data from various sources. This meta-analysis of multiple data sets is of course more properly the domain of Bayesian statistics.[20]

Challenges in Using The Bayesian Approach

Preplanning of design, conduct, and analysis of trial

The basic tenets of good trial design are the same for both Bayesian and frequentist trials. It has been recommended that the type of analysis to be used (Bayesian or frequentist) should be chosen beforehand. Switching to an analysis method that produces a more favorable outcome after observing the data is not recommended.[3]

For a Bayesian trial, planning of design, conduct, and analysis is crucial. In a Bayesian trial decisions have to be made at the design stage regarding the prior information, the information to be obtained from the trial, and the mathematical model to be used to combine the two. Any change in the prior information at a later stage of the trial may hamper the scientific validity of the trial results.[3]

Mathematical modeling

Extensive mathematical modeling of a clinical trial is involved in the Bayesian approach; for example, the probability distributions chosen to reflect the prior information, the relationships between multiple sources of prior information, etc.[3,21–23]

Computational issues

Special computational algorithms are often used to analyze trial data, check model assumptions, assess prior probabilities at the design stage, perform simulations to assess the probabilities of various outcomes, and estimate sample size. Although Bayesian analyses are often computationally intense, recent breakthroughs in computational algorithms and computing speed have made it possible to carry out calculations for very complex and realistic Bayesian models.[3,24,25]

The flexibility of Bayesian models and the complexity of the computational techniques for Bayesian analyses can create greater possibility for errors and misunderstandings. It has

been recommended that a Bayesian adaptive trial be planned in advance. Switch from a frequentist to a Bayesian analysis (or *vice versa*) is not recommended once a trial has been initiated.[3]

Ethical considerations

Implementation of Bayesian adaptive designs may be challenging because the confidentiality of the data needs to be maintained to avoid operational biases. For instance, if the investigator knows that one treatment is doing better at an interim analysis, he or she may assign it with a higher probability to future patients. In order to minimize operational biases, the design should be well planned in advance and the adaptive algorithm should be prespecified. The details of the adaptive design that may reveal evolving treatment differences is best referred to Institutional Review Boards (IRBs).[3,26]

Conclusion

In frequentist statistics prior information is utilized formally only in the design of a clinical trial but not in the analysis of the data. On the other hand, Bayesian statistics provide a formal mathematical method for combining prior information with current information at the design stage, during the conduct of the trial, and at the analysis stage. It is easier to implement adaptive trial designs using Bayesian methods than frequentist methods. Bayesian designs provide an efficient and effective method for evaluating new molecules during the early phases of drug development. The Bayesian approach can also be applied for postmarketing surveillance purposes and in meta-analysis. The basic tenets of good trial design are the same for both Bayesian and frequentist trials. It has been recommended that the type of analysis to be used (Bayesian or frequentist) should be chosen beforehand; switching to an analysis method that produces a more favorable outcome after observing the data is not recommended.

Acknowledgment

I gratefully acknowledge the help of my colleagues in the Department of Medical Affairs and Clinical Research, Ranbaxy Laboratories Ltd.

References

1. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Methods in health service research. An introduction to bayesian methods in health technology assessment. BMJ 1999;319:508-12.
2. Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR. Bayesian methods in health technology assessment: A review. Health Technol Assess 2000;4:1-130.
3. Food and Drug Administration. Guidance for Industry and FDA Staff: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials; 2010. Available from: http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm071121.pdf [Last accessed on 2011 Jan 25].
4. Howard G, Coffey CS, Cutter GR. Is Bayesian analysis ready for use in phase III randomized clinical trials? Beware the sound of the sirens. Stroke 2005;36:1622-3.
5. Freemantle N. The Reverend Bayes - was he really a prophet? J R Soc Med 2005;98:546.
6. Sterne JA, Davey Smith G. Sifting the evidence-what's wrong with significance tests? BMJ 2001;322:226-31.
7. Petrie A, Bulman JS, Osborn JF. Further statistics in dentistry. Part 9: Bayesian statistics. Br Dent J 2003;194:129-34.
8. Kulkarni UP. The Bayesian clinician. J Postgrad Med 2007;53:267-9.
9. O'Hagan A. Bayesian statistics: Principles and benefits. Available from: http://library.wur.nl/frontis/bayes/03_o_hagan.pdf [Last accessed on 2011 Jan 25].
10. Kpozèhouen A, Alioum A, Anglaret X, Van de Perre P, Chêne G, Salamon R. Use of a Bayesian approach to decide when to stop a therapeutic trial: The case of a chemoprophylaxis trial in human immunodeficiency virus infection. Am J Epidemiol 2005;161:595-603.
11. Morita S, Thall PF, Bekele BN, Mathew P. A Bayesian hierarchical mixture model for platelet derived growth factor receptor phosphorylation to improve estimation of progression-free survival in prostate cancer. J R Stat Soc Ser C Appl Stat 2009;59:19-34.
12. Braun TM, Wang S. A hierarchical Bayesian design for phase I trials of novel combinations of cancer therapeutic agents. Biometrics 2010;66:805-12.
13. Bland JM, Altman DG. Bayesians and frequentists. BMJ 1998;317:1151-60.
14. Chow SC, Chang M. Adaptive design methods in clinical trials - A review. Orphanet J Rare Dis 2008;3:11.
15. Chung SC, Schulz M. Bayesian designs for clinical trials in early drug development. J Clin Res Best Practice 2007;3:1-5.
16. Mahajan R, Gupta K. Adaptive design clinical trials: Methodology, challenges and prospect. Indian J Pharmacol 2010;42:201-7.
17. Schmidli H, Bretz F, Racine-Poon A. Bayesian predictive power for interim adaptation in seamless phase II/III trials where the endpoint is survival up to some specified timepoint. Stat Med 2007;26:4925-38.
18. Biswas S, Liu DD, Lee JJ, Berry DA. Bayesian clinical trials at the University of Texas M. D. Anderson Cancer Center. Clin Trials 2009;6:205-16.
19. Coory MD, Wills RA, Barnett AG. Bayesian versus frequentist statistical inference for investigating a one-off cancer cluster reported to a health department. BMC Med Res Methodol 2009;9:30.
20. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med 1999;130:1005-13.
21. Crespi CM, Boscardin WJ. Bayesian Model Checking for Multivariate Outcome Data. Comput Stat Data Anal 2009;53:3765-72.
22. Krishna A, Bondell HD, Ghosh SK. Bayesian variable selection using an adaptive powered correlation prior. J Stat Plan Inference 2009;139:2665-74.
23. Hu J, Johnson VE. Bayesian model selection using test statistics. J R Stat Soc Series B Stat Methodol 2008;71:143-58.
24. Jackson CH, Sharples LD, Thompson SG. Structural and parameter uncertainty in Bayesian cost-effectiveness models. J R Stat Soc Ser C Appl Stat 2010;59:233-53.
25. Leuenberger C, Wegmann D. Bayesian computation and model selection without likelihoods. Genetics 2010;184:243-52.
26. Berry DA. Bayesian statistics and the efficiency and ethics of clinical trials. Stat Sci 2004;19:175-87.

How to cite this article: Gupta SK. Use of Bayesian statistics in drug development: Advantages and challenges. Int J App Basic Med Res 2012;2:3-6.

Source of Support: Nil. **Conflict of Interest:** None declared.