



Tessella in Action:

The Opportunities and Advantages of Using Bayesian Statistics in Clinical Trials

Bayesian Statistics focuses on the key question: “How does this new bit of evidence change what we believe?” In this article we are in particular interested in the question “what do we believe the effect of this drug or treatment is?”

Bayesian Statistics starts with your prior belief (expressed as a probability distribution), which is then updated with the new evidence to yield a posterior belief (also a probability distribution).

The Bayesian approach allows all evidence to be taken into account in an explicit way. Different forms of evidence can be combined in the overall probability model or included via the prior belief. Analyzing the data using different priors allows the data to be interpreted from different points of view – regulatory, therapeutic and business.

The Bayesian framework more naturally allows for the modelling of biases or systematic error, and for modelling any hierarchical structure in the data. For instance in a trial with 200 subjects at 5 different hospitals, we can model

not just the overall effect of the treatment studied, but also variations in outcome due to the different hospitals.

The result of a Bayesian analysis are direct statements about the quantities of interest, for instance a mean and variance for the mean therapeutic effect of the treatment, providing more intuitive results and feeding naturally into a decision making process.

These general benefits of Bayesian Statistics lead to some specific opportunities in randomized clinical trials, and related areas of observational studies, evaluation and regulation.

Use of Prior Data

The most obvious, but contentious, use of the Bayesian approach in clinical trials is to include a prior belief for the effect of the treatment in a clinical trial. Normally we would have to include a sceptical prior in order that the posterior results are convincing to a regulatory body such as the FDA. But the FDA have suggested informative priors *could* be used in certain circumstances such as: the development of an antibiotic (where trials are required for its use in different treatment sites), replacement therapies which seek to restore a compound in the body to its normal levels, and paediatric studies (where data from studies on adults could be used). Another possible area where prior data could be used is for the response of the control population, where this could lessen the number of subjects required in the placebo arm of a trial.

Judging Success

In order to include a prior, the final determination of the result of the trial must be Bayesian. But a Bayesian approach can bring benefits even if a non-informative prior is used. It introduces more flexibility than the standard evaluation techniques – for instance not merely proving superiority to placebo but showing a clear clinical superiority, or when comparing not with placebo but an existing treatment and needing to show ‘non-inferiority’. The analysis can be based simply on the posterior probability of the drug’s effect, but if this is not the final clinical trial in the drug’s development, the analysis could use a decision theoretic approach based for instance on whether it is cost effective to continue the drug’s development.

Sizing Studies

Bayesian statistics can also be used to calculate the required size of the study – this will be necessary if we are using a Bayesian approach elsewhere, but could be done for a conventional trial if we want to take into account the *inevitable uncertainty* over the required initial assumptions (the alternate hypothesis and the variability in response) that even the conventional approach has to make.

Adaptive Randomization

Unique to the Bayesian approaches to Clinical Trials is the ability to adapt the randomization during the trial based on the responses seen so far. There are two reasons to do this; one is ethical where the desire is to reduce the subjects’ exposure to the less efficacious treatments, and the other is efficiency where the desire is to favour allocation to the treatment arm that will most quickly bring the trial to a conclusion.

Adaptive randomization requires the use of a central randomization facility, and a means to quickly capture response data (though not necessarily the whole CRF). It updates a model of the dose response and uses a pre-programmed method to determine the next dose or doses to be used. This could be as simple as allocating to the most effective dose in proportion (up to some limit) to the degree to which it appears to be the most effective dose. It could be as complicated modelling the dose response curve over a number of doses using forward simulation and a decision theoretic approach to determine which dose is most likely to reduce our uncertainty about the result.

Study Termination

Some trials can draw from a ready pool of suitable subjects, others can only recruit subjects over a period of time as they present with the disease. In this case, as results become available, we can update a rolling estimate of the likely success of the trial. This rolling estimate of the likely success can be used to determine whether to continue the trial. It is natural to make provision for stopping early for futility, efficacy or toxicity. The more this can be automated the less the risk of unblinding those conducting the trial and tainting the result. ***This early termination offers huge potential savings for pharmaceutical companies – in time, cost and effort.*** The gains are so great that trial designs using conventional statistical have evolved that also allow early termination. The Bayesian approach is more natural and straightforward because we can simply use the current posterior probability. It also allows the monitoring to be continuous and not limited to specific, pre-planned points in the study.

More Complex Models

Clinical trials are so expensive and their outcomes so crucial to the success of pharmaceutical companies, that there is considerable pressure to optimize them. One route to optimization is to make better use of all the information available. The Bayesian approach makes this much easier because the Bayesian framework allows us to more easily check the correctness of more complex statistical models, and from the adoption of Markov Chain Monte Carlo methods to evaluate them. Some of the models that are being considered are:

Hierarchical models can be used to incorporate the results from several trials – where an overall rate of response is modelled as well as individual rates for each trial. This allows for systematic bias occurring in some trials.

Longitudinal models model the subjects' response over time, they allow early response data to be used to estimate the final response which increases the amount of information available for taking decisions such as early termination or to adapt the randomization.

Biomarker models allow a relationship to be established between a biomarker and the final response. The biomarker is usually a less noisy measure than the final response, which is available earlier. A biomarker model can be used like the longitudinal model above, and can be used to establish the biomarker as a quicker, cheaper more accurate end point for later trials than the original final response. For example the establishment of 'lowered cholesterol level' as a biomarker for 'reduced incidence of heart attack' has allowed trials for Statins to be much smaller and shorter than they would have otherwise been.

Observational Studies

Sometimes we may wish to evaluate a drug or treatment without being able to run a randomized trial. Bayesian analysis is not predicated on randomization, and can be used to analyze data from studies in exactly the same way as for randomized trials. However the analysis of non-randomized data must explicitly address the risk of systematic bias. For the models of bias to be convincing there needs to be some supporting evidence for the bias.

Meta Analysis

For policy makers, they will frequently have data from a number of trials or studies that are relevant to a deciding issues such as the risks attendant on a particular treatment or the superiority of one treatment over another. The flexibility of the Bayesian approach – through the use of priors and complex models – makes it very suitable for combining data from disparate sources.

This meta analysis of multiple data sets is of course more properly the domain of Bayesian statistics and “what should we believe” than conventional statistics and its framework based on repeatable experiments.

To Be Bayesian or Not

With all these benefits why isn't Bayesian Statistics more widely deployed? As Bayesian Statistics is the only formal, coherent calculus of statistical inference, why is there any other form of statistics? The simple answer is that most Bayesian models are not analytically evaluable, and we need to use numerical methods that require computing power that is commonplace today, but has only been readily available since the late 1980s.

Following a blossoming of fundamental research and tool building Bayesian Statistics only became mainstream in the mid 1990s. So there is not yet an established body of procedures and guidance as has been built up for conventional statistics. Using Bayesian Statistics thus both permits and requires more innovation than conventional methods.

Removing the Barrier to Use

To be able to terminate early, response data needs to be returned to the centre quickly – ideally as soon as it is collected. This is also required to be able to use adaptive dose allocation, which in addition requires some form of adaptive drug supply distribution.

Capturing and filing response data quickly has other important benefits – in particular improved data quality and quicker results from the trial. So much so that even for conventional trials there has been a push to use Electronic Data Capture (EDC). Tessella has experience of the many techniques can be used – hand held computers, entering the data over the web, filing forms by fax, reporting via IVRS – in clinical trial and other contexts. A central EDC system can be developed to be extensible and support as many of these techniques as was required.

The problem of the drug distribution during the trial has largely been tackled already to reduce drug wastage. Many clinical trial central randomization systems already also perform drug supply management (through there is scope to improve the efficiency of the re-supply algorithms using Bayesian statistics).

There are broadly two approaches to enabling Bayesian Statistics to run clinical trials, one is to build from scratch, and the other is to integrate with existing systems. Tessella has been involved in successful projects using both approaches – the decision comes down to the quality and suitability of the existing systems. Whether you want to preserve existing investment, or seize the opportunity to replace a legacy application with something easier to maintain and extend.

Finally there is the issue of validation – the use of Bayesian routines in clinical trials is increasingly well received by regulators. At the Biotechnology Industry Organization annual international meeting June 21 in Philadelphia, FDA Regulatory Counsel Lisa Rovin indicated that the incorporation of Bayesian reasoning into clinical trial design is likely to be one component of the agency's forthcoming "Critical Path" opportunities list (reported in "The Pink Sheet", June 27, 2005)

Tessella has an almost unique combination of skills in software engineering, Bayesian statistics and regulatory validation (GLP, medical devices and 21 CFR part 11) that enable us to validate software that implements Bayesian algorithms for clinical trials.

Conclusions

Conventional statistics work, are widely accepted and for a lot of problems have well documented approaches to tackling them. Bayesian Statistics on the other hand has a better foundation, offers greater power and flexibility and provides results in a more natural and intuitive form. We expect its use to become well-established in areas not well covered by existing conventional statistics and in the long term become the dominant method for doing statistics.

The advances in areas of complex data analysis and decision-making, offer potentially great benefits in the area of health care in particular.

Examples of Bayesian Statistics at Tessella
A significant issue for a water company is the condition of a large number of fixed assets, many of which are in remote locations, or are underground. A consortium of companies commissioned Tessella and a leading statistician to design and implement a Bayesian asset model that could help them manage the investment in maintaining the condition of the assets using less monitoring of the assets than a conventional statistical model would have required.

Tessella worked with the Treasury department of a large multinational to develop an overnight investment decision support system. They wanted a system to track performance of the various decisions and to create a decision support tool that would help the investment staff move the funds at the appropriate time to

the appropriate market. This is one of a significant number of Bayesian Belief Network based projects Tessella have undertaken from financial investment decisions to decisions on where to drill for oil or gas.

For Pfizer, Tessella worked with leading academics from the US to enable an ambitious Bayesian model to be used to run the ASTIN Stroke trial. This allowed Pfizer to explore the dose response to 16 different doses of a drug rather than the usual 2 or 3, without requiring a larger trial than usual.

For a biotech company Tessella worked with an imaging expert to develop a Bayesian algorithm to first align and then analyze the differences in 2D protein peptide maps, resulting from a 2D chromatography process. This allowed the automation of what had been a labour intensive process.

References

"Bayesian Approaches to Clinical Trials and Health-Care Evaluation" Spiegelhalter, Abrams & Myles pub: Wiley 2004 – is not only an excellent and recent review of this area, but also has an extensive references section.

For details of the ASTIN trial see:
<http://ftp.isds.duke.edu/WorkingPapers/99-34.pdf> and
<http://stroke.ahajournals.org/cgi/content/abstract/34/11/2543>

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