Nat. Volatiles & Essent. Oils, 2021; 8(4): 10574-10584

NVEO
Natural Volatiles &
Essential Oils

Bayesian Decision Procedures For Dose-Escalation Studies With Cohort Effects

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Abstract: This paper considers the methods of modelling for the dose escalation process using the Bayesian hierarchical models. The phase I clinical trial data is analysed to find the optimum Maximum Tolerated Dose (MTD). In this paper we have considered the mixed logistic linear regression model to predict the dose limiting event with respect to the cohort effects and the doses. We have also developed a mixed linear regression model to predict the desirable outcome response in the study. The illustrations of the models have been conducted which is then analysed to find the MTD for the clinical trial study.

Keywords: Maximum Tolerated Dose, Dose Limiting Event, Desirable Outcome, Cohort Effects, Dose Response.

1. Introduction

Dose escalation procedures in phase I trials is to avoid exposing too many patients to subtherapeutic doses while preserving safety and maintaining rapid accrual. (Ashby(2006)).

Whitehead et.al (2006) studied in the setting of the Bayesian decision theoretic procedures which considersthe doses which are chosen in a specific way such that it will maximise therapeutic effects and minimise side effects. The Dose Escalation studies considers the subjects which are repeatedly dosed,and the pharmacodynamic measurements relating to the pattern of the concentration of the drug during the hours following the clinical trial administration. Bayesian dose-escalation procedures for early phase I clinical trials in oncology are developed in this paper andthey are based on the measures of undesirable events and continuous measures of therapeutic benefit.

Senn et.al (2007) examines the state of Bayesian thinking as Statistics in Medicine which considers the applicability and uses in medical research. It then looks at each subsequent five-year epoch, with a focus on papers appearing in Statistics in Medicine, putting these in the context of major developments in Bayesian

thinking and computation with reference to important books, landmark meetings and seminal papers. It charts the growth of Bayesian statistics as it is applied to medicine and makes predictions for the future.

Ethical considerations suggest that randomized trials are more suitable than uncontrolled experimentation in protecting the interests of patients in the cohorts.Randomized clinical trials remain the most reliable method for evaluating the efficacy of therapies. (Thall(1998), Bailey(2007)).

Whitehead et.al(1998) considers the Phase I clinical trials and describes a systematic approach to their implementation in dealing with the dose-escalation studies in which two responses are observed on each subject. One of these was referred to as a Dose limiting Event[DLE] and the other was a DO [Desirable Outcome] measures of Therapeutic benefit.

Bailey(2007) illustrates that a small groups of subjects, known as "cohorts", where the treatment of one cohort being completed and assessed before the next cohort begins. Within each cohort,there are a small number of treatment periods,and each subject is administered a treatment in each period.

To the best of our knowledge the study on the Bayesian procedures to find the MTD exists, however the Bayesian models for dose escalation studies with the cohort effects are not considered in the literature in the setting of Phase I clinical trials,

Cohort Effects are uncorrelated random variables with a common variance. Cohort effects study modelling is important as it includes the reactions within the treatment periods and it is done by evaluating the posterior modal estimates.

In the paper , Section 2 gives a general illustration of the parameters considered in the clinical trial. It also shows the Models that are considered for the extension study along with the results of the simulation runs. Section 3, gives the conclusions of the trial study.

2. Methodology:

In this paper we have considered cohort effects in the model while escalating MTD.

Zhou(2006) considered that the Regression Models for the dose limiting event and desirable event outcomes. The subjects in this trial are denoted as $(S_i), i = 1 \dots n$ and the dosing periods are denoted as $(P_{ij}), j = 1 \dots k$. The dose administered to S_i in P_j is denoted as d_{ij} for those combinations of i and j for which an active dose is administered. Suppose that at the start of the study a number of doses $d^1 < \cdots d^m$ are available for administration to successive cohorts of subjects and that we can express our opinions about the likely value of the

MTD by specifying a prior distribution which corresponds to the initial estimate of the MTD.

2.1.Bayesian Models considered for the study:

We develop 2 models to model the cohort effects in this paper. First model is the dose limiting event model and the second model developed considers the Desirable Outcome Event.

Dose Limiting Event Model

Model Specification:

The basic set up is to consider the 3 parameter logistic regression model with the predictor variables (Independent variables) and the response variables (outcome variables).

$$p_{DLE} = \frac{\exp(\beta_1 + \beta_2 \log d_{ij} + \beta_3)}{1 + \exp(\beta_1 + \beta_2 \log d_{ij} + \beta_3)} \quad \ldots(1)$$

where,

p_{dle} denotes the probability of dose limiting event.

d_{ij}represents the doses considered in the clinical trial study.

$\beta_1, \beta_2, \beta_3$ represents the parameters in the study and they are assumed to follow the normal priors.

Bayesian approach is implemented based on the assumption that the effect parameters change gradually. A Bayesian setting with priors is introduced for the selection of the optimal model.

We then go on to develop a Bayesian approach for projecting the cohort parameters, which allows fully for uncertainty in the recent parameters due to the lack of information in the dose escalated data.

2.2 Bayesian Hierarchical setting and estimation of the model parameters

To derive the posterior distribution, the traditional Bayes theorem together

with the application of the product of the normal prior probability and thelogistic likelihood function for the observed data.

Let $\beta_3 \sim c_{ij}$

$\beta_1, \beta_2, \beta_3$ follow the Normal priors.

The Bayesian prior is given by the following equation

$$P\left(\frac{D}{\beta_1,\beta_2,\beta_3}\right)\sim \frac{1}{\sqrt{2\pi}\sigma_j} e^{\left(\frac{-1}{2}\left(\frac{\beta_j-\mu_j}{\sigma_j}\right)\right)^2} \qquad \ldots(2)$$

The Likelihood is given by

$$P(\beta_1,\beta_2,\beta_3)\sim \prod_{i,j=1}^{n} \frac{e^{(\beta_1+\beta_2 \log d_{ij}+\beta_3)}}{1+e^{(\beta_1+\beta_2 \log d_{ij}+\beta_3)}} \qquad \ldots(3)$$

The posterior is given by

$$P\left(\frac{\beta_1,\beta_2,\beta_3}{D}\right) \sim \prod_{i,j=1}^{n} \frac{e^{(\beta_1+\beta_2 \log d_{ij}+\beta_3)}}{1+e^{(\beta_1+\beta_2 \log d_{ij}+\beta_3)}} \times \frac{1}{\sqrt{2\pi}\sigma_j} e^{\left(\frac{-1}{2}\left(\frac{\beta_j-\mu_j}{\sigma_j}\right)\right)^2} \qquad \ldots(4)$$

The posterior distrbution involves the absolute mean and the optimisation of the loss function. Explicitly we cannot integrate out the posterior parameters hence the Gibbs sampler is considered.

Bayesian Markov chain Monte Carlo methods considers modelling of the unknown parameters from their conditional (posterior) distribution given those stochastic nodes that have been observed in the clinical trial. The basic idea behind the Gibbs sampler is to generate posterior distribution of the unknown quantities. Empirical summary statistics formed from these samples and used to draw inferences about their true values.

The current Gibbs sampler algorithm is based on a symmetric normal proposal distribution, whose standard deviation is tuned over the first 20000 iterations in order to get an acceptance rate of between 20% and 40%. All summary statistics for the model will ignore information from this adapting phase.

Hence the 20 % risk of toxicity level is determined from the threshold of the convergence pattern of the DLE burn in phase of iterations.

The Hastings Algorithm leads to the Gibbs sampler teachnique with the transition probability function such as the event of toxicity in our case.

The advantage is to eliminate dependency on the initial values which considers the missing data values as well in the burn in phase.

2.3 Model comparison:

Within a simple Bayesian framework simultaneous parameter estimation and model comparison can be performed.

Zhou's model (2006) considered the 2 parameter Bayesian regression model settings for efficacy and toxicity levels. The accuracy measures for the toxicity settings is measured by the cohort variable effect which happens in a clinical trial.

Hence we propose the model for setting the probability of our proposed dose limiting event modeland desirable outcome model with cohort effects. The dose limiting event model to get probability of toxicity is using the following method

logit(p) is denoted as $\beta_1 + \beta_2 \log d_{ij} + \beta_3$

which is obtained by

$\ln[p/(1-p)] = \beta_1 + \beta_2 \log d_{ij} + \beta_3$

or

$p/(1-p) = e^{\beta_1+\beta_2 \log d_{ij}+\beta_3}$

(Where:

"ln" is the natural logarithm, $\log_{exp}$, where e=2.71828

"p" is the probability that Y for cases equals 1, p (Y=1)

"1-p" is the probability that Y for cases equals 0,

"p/(1-p)" is the odds

ln[p/1-p] is the log odds, or "logit")

Simplifying the above equations we get,

$p = e^{\beta_1+\beta_2 \log d_{ij}+\beta_3} (1- p)$

$p (1+ e^{\beta_1+\beta_2 \log d_{ij}+\beta_3}) = e^{\beta_1+\beta_2 \log d_{ij}+\beta_3}$

Hence the equation for the probability of toxicity is obtained as

$$p_{DLE} = \frac{\exp(\beta_1 + \beta_2 \log d_{ij} + \beta_3)}{1 + \exp(\beta_1 + \beta_2 \log d_{ij} + \beta_3)} \quad \ldots (5)$$

Cohort effects follow the Normal priors with the mean = 0 and precision follows a uniform prior.

3. Experimental Results for the probability of toxicity

The simulation results that were obtained by generating the toxicity responses using the logistic model is observed in Table 1, Table 2, andTable 3.

Probability of toxicity is around 0.2 for the cohort with less adverse events.

Analysis of the Cohort effects in the DLE model is obtained in the simulation process.

3.1 Desirable Outcome Model

The desirable outcome measure is modelled using the parameters of the cohort effects in the statistical model. The analysis leads to the separate assessments of cohort, treatment and the doses available in the data. The assessment of these three factors can possibly yield insights into the optimisation of the model.

Linear Mixed effects regression model

$$y_{ij} = \beta_0 + \beta_1 \log d_{ij} + \beta_3 \log d_{ij} \quad \ldots(6)$$

Where,

$y_{ij}$is the desirable Outcome response which is modelled along with the doses in the study which is denoted as $d_{ij.}$

β1, β2 ,β_3 represents the parameters in the study and they are assumed to follow the normal priors.

Bayesian Hierarchical setting of the model parameters involve the desirable outcome response with a Normal prior. The estimates of β_0 and β_1 have a normal prior distribution. The precision estimate takes a uniform prior.

In this section, we give an option Bayesian structure for the dose- response evaluation to the interim analysis of finding the way the desirable outcomes work with the cohort effect parameters included in the model for the study. The Bayesian system additionally considers a more careful surmising, utilizing all accessible data, which is ideal when settling on choices under uncertainty.We used MCMC via WinBUGS (Spiegelhalter, 2002) to simulate samples from posterior distributions of relevant parameters.

Initial values for the cohort effects are chosen as 2.6, β_0 = 3.2 ,β_1 = 2 after running the simulation trial runs.

InFigure 1 and Table 4 for the Dose Response curve shows the prediction values and data convergence.

The convergence pattern of the prediction values with the data in the Bayesian setting is observed when the

cohort parameters are fitted to the model with the dose combinations. In the comparitive study of Zhou (2006) we find that our Dose response curve estimation gives a more accurate response to the study of the escalation procedure.

The probability of toxicity is found to be 0.2 which gives an exact approximation for the 20 % risk of toxicity level that we want to achieve when implementing the model. The treatment and cohort effects are showing more convergence for the cohorts with the doses that causes more adverse events.

Extension of Zhou (2006) model was consistent when verified using the Bayesian hierarchical model settings. Using dose-limiting and low-level toxicity counts, which are obtained from data already collected, it is a promising way to improve the efficiency in finding the true maximum tolerated dose in phase I trials using the simulation run in hierarchical models.

4. Results and Conclusions

The dose limiting event model evaluates the posterior modal estimates of the parameters β_1 and β_2 which is given by $\tilde{\beta}_1$ = - 3.4 and $\tilde{\beta}_2$ = 0.36.

In the simulation study, we evaluate how often our models select the true maximum tolerated dose, and we compare our models with the Bayesian models optimal fit.

Simulation results based on 20000 iterations gives the estimator accuracy of the cohort effects and the precision for the dose-response curves. True parameter value of mean and standard deviation is shown in the table.

Across a variety of simulation settings, we find that our models compare well against the Logistic regression models in terms of selecting the true optimal dose. In particular, our models is to predict the probability of the dose-limiting toxicity levels and then check with the safety constraint scenario.

The posterior modal estimates are consistent with the paper of Zhou (2006) and the maximum safety constraint for a p(dle) is 0.2.

Here cohort 5 and cohort 6 has the safety constraints more than 0.2 and so the doses have to be de-escalated to minimize the risk in the trial.

Discussions on the Fitted Cohort Parameters:

We deal with this by using the general dose escalation procedure to sequentially select the doses for the study and then adding a set of cohort parameters to the model.

The cohort parameters should be stationary, in the sense that the variability of the cohort parameters around the central trend should not change with the dosing periods.

The outputs for the prior distribution gives the overall cohort effect value to be 0.6904 which is observed from the trace density plots.

So, the probability of toxicity is calculated for each of the cohorts individually and the aim is to check if the toxicity is more for the higher doses in the Bayesian hierarchical setting. The probability of toxicity increases with the doses.

The feasible values often lie outside the 95% prediction interval for the ultimate cohort parameters. The cohort parameters are checked with respect to the interim data in the trial. So, our cohort effect parameters clearly show the convergence of the responses for the prediction model.

Depending on how important the length of the trial is to the clinician and the institution, we recommend using cohort effects per dose level to avoid seeing simultaneous toxic events when a group of patients are treated at the same dose level as was the case in a recent phase I trial of the drug TGN1412. [Senn[2007]]. In that trial, six volunteers were given what was believed to be a safe dose of an anti-inflammatory drug TGN1412. Shortly after, all 6 were admitted into intensive care due to severe reactions including swelling of the head and neck. The cohort effects considered in this paper extends to the TGN1412 Bayesian setting of priors comparing the frequentist model approach.

References

[1] Ashby D. Bayesian statistics in medicine: A 25-year review. Statist. Med. 2006; 25:3589-3631.

[2] Bailey R.A. (2007).Design of dose-escalation trials presented at Statistical Models Design and Data Analysis,Conference to celebrate Anthony Atkinson's 70th Birthday .

[3] ChalonerK.(1984).Optimal Bayesian Experimental Design For Linear Models,The Annals of Statistics**12**,283-300.

[4] Senn S, Amin D, Bailey RA, Bird SM, Bogacka B, Colman P, Garrett A, Grieve A, LachmannP.(2007). Statistical issues in first-in-man studies. Journal of the Royal Statistical Society, Series A,**170**,517-579.

[5] Bailey R.A.(2009). Designs for dose-escalation trials with quantitative responses it Statistics in Medicine.1-18.

[6] ChalonerK.(1984).Optimal Bayesian Experimental Design For Linear Models, The Annals of Statistics**12**,283-300.

[7] Senn S, Amin D, Bailey RA, Bird SM, Bogacka B, Colman P, Garrett A, Grieve A, LachmannP.(2007) Statistical issues in first-in-man studies. Journal of the Royal Statistical Society, Series A,**170**,517-579.

[8] Thall, P.F., and Russell, K.E. (1998). A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. Biometrics, 54,251264.

[9] Whitehead, J.,andDavid,W.(1998).Bayesian decision procedures based on logistic regression models for dose-findingstudies.Journal of Biopharmaceutical Statistics,8,445467.

[10] Whitehead, J., Zhou,Y., Patterson, S., Webber, D., Francis,S. (2001). Easy-toimplement Bayesian methods for dose-escalation studies in healthy volunteers. Biostatistics, 2,47-61.

[11] Whitehead, J.,Williamson, D. (1998) An evaluation of Bayesian decision procedures for dose-finding studies. Journal of Biopharmaceutical Medicine, 8,445-467.

[12] Zhou, Y.,Whitehead, J.,Bonvini, E.,Stevens, J.W. (2006) Bayesian decision procedures for binary and continuous bivariate dose-escalation studies. Journal of Pharmaceutical Statistics. **5**125-133.

Table 1 :

6 cohorts with 10 subjects each

$\beta_1 = -2, \beta_2 = 0.2$

NODE	MEAN	SD	MSE
beta[1]	-2.33	1.417	0.07674
beta[2]	0.3013	0.2905	0.01586
pdle[1]	0.196	0.1033	0.005014
pdle[2]	0.2614	0.06909	0.001186
pdle[3]	0.3636	0.1042	0.003571
pdle[4]	0.2614	0.06909	0.001186
pdle[5]	0.2904	0.07204	8.14E-04
pdle[6]	0.3299	0.09237	0.002544
Cohort effect	0.65152	0.4069	0.008624

Table 2 :

6 cohorts with 30 subjects each

$\beta_1 = -3, \beta_2 = 0.2$

NODE	MEAN	SD	MSE
beta[1]	-3.33	1.269	0.05067
beta [2]	0.2222	0.2565	0.04597
pdle[1]	0.06954	0.03977	0.05055
pdle[2]	0.21001	0.02547	0.05632
pdle[3]	0.2214	0.04344	0.04246
pdle[4]	0.28661	0.02547	0.00623
pdle[5]	0.29557	0.02687	0.05569
pdle[6]	0.2992	0.0366	0.05091
Cohort effect	0.63421	0.4031	0.05071

Table 3:

6 cohorts with 60 subjects each

$\beta_1 = -4, \beta_2 = 0.2$

NODE	MEAN	SD	MSE
beta[1]	-4.034	1.2631	0.056932
beta[2]	0.2119	0.25625	0.054531
pdle[1]	0.03518	0.0208	0.055642
pdle[2]	0.24327	0.01318	0.056753
pdle[3]	0.26091	0.02304	0.057482
pdle[4]	0.274327	0.01318	0.052390
pdle[5]	0.284957	0.01402	0.057892
pdle[6]	0.29468	0.01899	0.056730
Cohort effect $(\boldsymbol{\beta_3})$	0. 6582	0.3983	0.058797

Table 4:

	MEAN	SD	MSE
cohort_effect(β_3)	3.34	1.880	0.067
β_0	2.990	0.97	0.075
β_1	1.23	1.034	0.053

Figure 1