INDIAN JOURNAL OF SCIENCE AND TECHNOLOGY

RESEARCH ARTICLE

Bayesian Design Study of the TGN1412 Trial

Maria Daya Roopa[1]*, **Nimitha John**[1]

1 Department of Statistics, Christ University, Hosur Road, Bengaluru, 560029, Karnataka, India

OPEN ACCESS

Received: 30-07-2022

Accepted: 24-12-2022

Published: 23-01-2023

Citation: Daya Roopa M, John N (2023) Bayesian Design Study of the TGN1412 Trial. Indian Journal of Science and Technology 16(3): 223-229. https://doi.org/10.17485/IJST/v16i3.1554

* **Corresponding author**.

maria.roopa@res.christuniversity.in

Funding: None

Competing Interests: None

Published By Indian Society for Education and Environment (iSee)

ISSN
Print: 0974-6846
Electronic: 0974-5645

Abstract

Objective: This study considers the Bayesian design of clinical trials from the perspective of a comparative study of the Bayesian approach for the TGN1412 clinical trial. The Bayesian setting analyses the statistical issues of the TGN1412 trials' first in man studies, which include the details of the Northwick Park trial, and the clinical study design recommendations are implemented. **Methods:** The clinical trial data analysis was carried out to screen the structural evidence of the trial outcomes. Hierarchical modeling is implemented with structural priors to get the most efficient Bayesian outcomes. **Findings:** We concentrated on determining the best model for the clinical pathway of randomization and Bayesian design of experiments. **Novelty:** The Bayesian design of experiments is widely used for outcome prediction under various treatments in order to validate the trial's dosing periods. The purpose of this paper is to compare the growth models for Phase I trial results. Current research on Bayesian designs incorporates simulation studies on the effects of design variables.

Keywords: Clinical Trial; Bayesian; Efficacy; Dose Limiting Event; Desirable Outcome; Treatment Effects; Cohort Effects; Dose Response

1 Introduction

The TeGenero study analyses the new compound TGN1412, a monoclonal antibody that the targeted T cells, which was being developed for the potential treatment of various inflammatory diseases, such as rheumatoid arthritis, and possibly also for a type of leukemia. The Bayes factor hence gives a consistent proportion of proof. In the ongoing review, we will exhibit the qualities of the Bayesian reanalysis for drug preliminary studies.

The paper discusses a comprehensive simulation study, and puts forward recommendations on how to improve dose ranging in the clinical development, including, but not limited to, the use of adaptive dose-ranging methods. In the paper, Section 2 gives a general illustration of the design parameters considered in theTGN1412 clinical trial. It also shows the design models that are considered for the extension study along with the results of the simulation runs. Section 3 and Section 4, gives the conclusions of the clinical trial study for experimental and sensitivity analysis modeling.

TGN1412 trial was conducted by the RSS (Royal Statistical Society) in Northwick Park. In that trial, eight volunteers were given what was believed to be a safe dose of an anti-inflammatory drug TGN1412. Shortly after, all eight were admitted into intensive

care due to severe adverse reactions. We recommend using cohort effects and treatment 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 [(1)].

Cohort Effects are uncorrelated random variables with a common variance. Cohort effects study modeling is important as it includes the reactions within the treatment periods and it is done by evaluating the posterior modal estimates. The cohort effects and treatment effects considered in this paper extends to the TGN1412 Bayesian setting of priors comparing the frequentist model approach. In one form of dose-escalation trial, several cohorts of subjects are recruited. Each cohort takes part at a different time period. Higher doses may have more adverse side-effects [(2)].

If there are cohort effects, then more precise comparisons between doses can be made if half of each cohort receives placebo (sugar pill drug effect). A new design will be discussed that does at least as well as both of these, whether or not there are cohort effects, and whether or not within-cohort information is combined with between-cohort information [(3)].

Ethical considerations suggest that randomized trials are better suitable to preserving the interests of patients in cohorts than uncontrolled testing. Randomized clinical trials continue to be the most reliable method for evaluating the efficacy of therapies in drug development [(4)].

The Bayesian model parameters incorporate shape and scale boundaries for Gamma conveyance which are assessed based on the predefined enlistment rates. During the preliminary, all suitable data on noticed enlistments and site initiations is dynamically utilized for Bayesian updates of the Gamma parameters. The model has been approved by utilizing the past information from a few genuine clinical preliminaries.

2 Methodology

In this paper, we considered and addressed the cohort effects and treatment effects in the design model, as well as the doses that are monitored for the clinical trial. The RSS group recommends the halving design as the best design since it performs better in terms of blinding than the other two ideas.

2.1 Bayesian Models Considered for the Study:

2.1.1 Model Specification

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.

The Bayesian approach for projecting the cohort parameters and the treatment effect parameters considers the uncertainty in the recent parameters due to the lack of information in the dose escalated data. Since the TGN1412 trial, various databases (including Pub Med and CINAHEL) have been screened for studies. The design model for the doses that are considered for the analysis is hierarchically built with Bayesian priors. Model assumptions consider that the cohort effects occur and the results from the coding of the Bayesian decision framework illustrate that the cohort effects lie within in a favourable range of values and a comparative study with the classical designs of the RSS working party is conducted.

2.2 Bayesian Hierarchical setting and estimation of the model parameters

To derive the posterior distribution for the clinical data, the traditional approach which is based on a frequentist setting, a speculation test is utilized to decide whether there is a genuinely huge treatment impact between another treatment and a control. Model assumptions is done using WinBugs Bayesian sampler. The cohort effects and treatment effects are fitted and the designs are compared. The variance of the difference between the doses are computed.

The response model is for the TGN1412 phase I clinical trial.

$\mu_{ij} = \nu + \alpha_i \log d_{ij} + \beta_j + \varepsilon_{ij}$

where

α -the treatment effects of the cohort.

β - the cohort effects. μ_{ij} is the response of the patient i in cohort j.

α_i - treatment effects

β_j – cohort effects

The $\log d_{ij}$ is considered in the design models for the analysis which was not in the design model of the RSS.

Bayesian priors are set on the model to start with the vague prior information to compare the classical designs. In the Bayesian analysis the uncertainty can be expressed as prior and the posterior probabilities are updated. The Bayesian decision theoretic framework helps optimize the next given dose in the trial. Within a simple Bayesian framework simultaneous parameter

estimation and model comparison can be performed. Cohort effects and Treatment Effects follow the normal priors and the precision effect follows a Gamma prior.

$\beta_j \sim N(\mu_\beta, \frac{1}{\sigma_c^2})$

$\alpha_i \sim N(\mu_\alpha, \frac{1}{\sigma_\alpha^2})$

$\frac{1}{\sigma_\alpha^2} \sim \gamma(0.01, 0.01)$

$\frac{1}{\sigma_c^2} \sim \gamma(0.01, 0.01)$

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 15,000 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.

3 Result and Discussion

The results are shown and described according to the figures and tables, but there is no discussion that contrasts the results with related works, so it is suggested that the authors should include a discussion of the results duly compared contrasted with related studies. It should exhibit the unique contribution of this study by comparing with others.

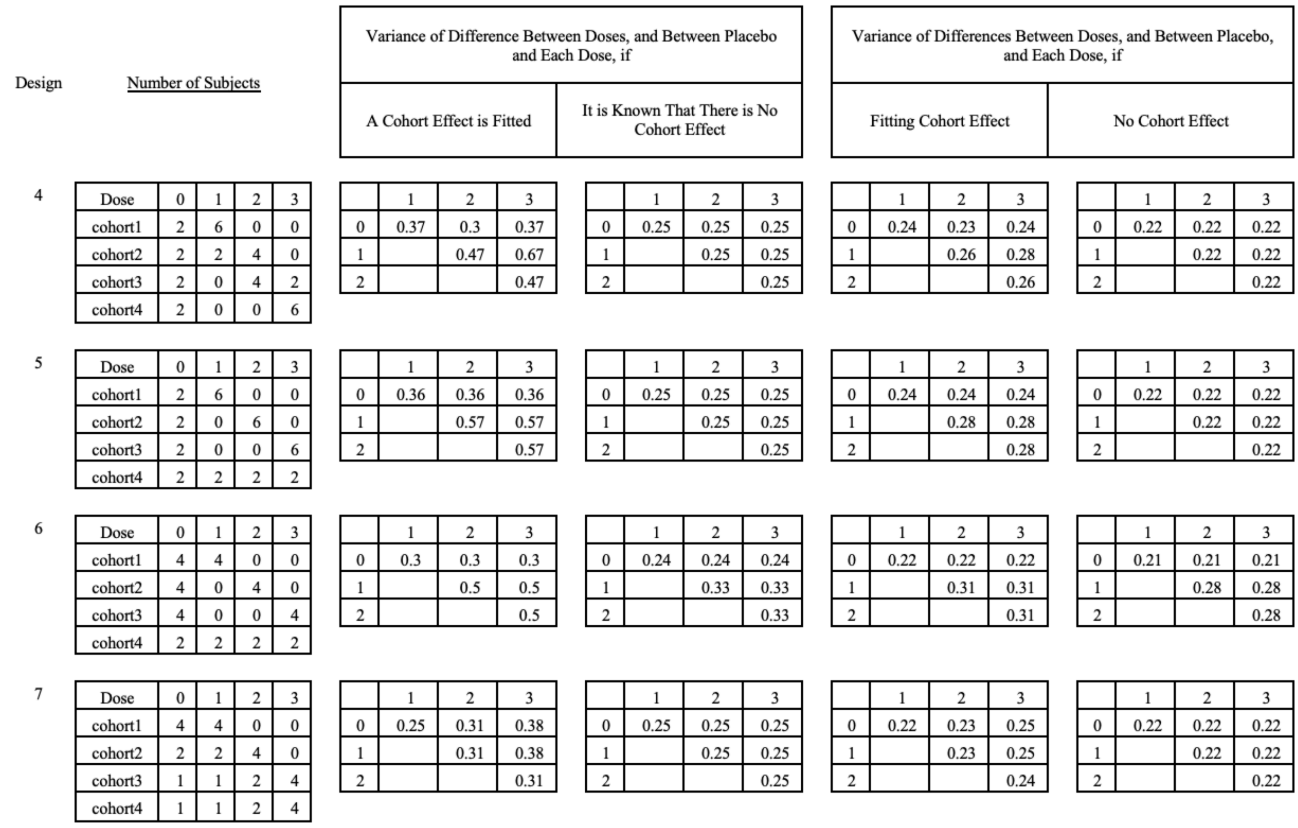
When compared to the other two iteration models for the analysis the Model-I trace plot out of the three iteration models exhibits the best parameter values. The Model-I has converged, and the trace plot moves around the mode of the distribution. While the burn-in iterations are set up, the trace plots are configured to monitor parameters. Numerous posterior estimates are expected to be observed in the model's results. As a result, the posterior patterns will have a large spike, and the estimates may appear erratic on the trace plots as they fluctuate between around 0 and other values. The dataset is used to observe the plots of 15,000 iterations in the form of patterns and corresponding trace plots. As the initial values are set near their posterior modes, convergence occurs relatively quickly, especially if there is no autocorrelation problem.

The simulation results that were obtained by generating the design for the clinical trial when compared with the frequentist approach shows the cohort effects priors were minimal in the Bayesian setting. 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 to simulate samples from posterior distributions of relevant parameters.

The table layout considers doses 1, 2 and 3. These could be the doses 0.1, 0.5 and 2.0 in the TeGenero study, and the placebo is denoted as 0.The following analysis assumes that outcomes are continuous variables whose variances do not change with dose. The table displays three possible designs with escalating doses. The third and fourth columns of the table give the variances of the estimates of the differences between doses, and between each dose and placebo. Each design uses 24 human subjects, eight in each of three cohorts, each cohort being treated and observed before the next starts. In the variance tables, the variance of the estimator of the difference between doses i and j is considered per observation.

The subjects in the cohort are equally split between dose and the placebo. If cohort effects are fitted, design 2 gives lower variances than design 1 for all simple contrasts. If there is no cohort effect, and this is known in advance so that the data can be analyzed appropriately, then some contrasts have a bigger variance with design 2 than with design 1.Design 3 is from a new class of designs. The principle is that half of the subjects in cohort have dose, the remainder being split between placebo and doses in the same proportions as in the cohort. If cohort effects are fitted then design 3 gives lower variances than design 1 for all simple contrasts; compared with design 2 it gives lower variances for all but one of the simple contrasts, where it is slightly bigger. If there is no cohort effect, design 3 is intermediate between design 1 and 2. If cohort effects are expected then design 3 is a better choice than design 1 or design 2. Design 4 is based on a crossover design currently used by pharmaceutical companies. The placebo can be inserted into the rising sequence of three doses in any one of four positions. In the crossover design, each of these four sequences is allocated to two subjects.

From the above discussed approach of the Bayesian design analysis, the hierarchical modeling for the posterior distributions of the design matrices for the doses of the trial are predicted. The comparative study for the above design is done between the Cohorts and the doses. The data is also analyzed without fitting the cohort effects, then the average value of all the pair wise variances is minimum when all the overall replications is equal[(5)].



Design	Number of Subjects	Variance of Difference Between Doses, and Between Placebo and Each Dose, if: A Cohort Effect is Fitted	Variance of Difference Between Doses, and Between Placebo and Each Dose, if: It is Known That There is No Cohort Effect	Variance of Differences Between Doses, and Between Placebo, and Each Dose, if: Fitting Cohort Effect	Variance of Differences Between Doses, and Between Placebo, and Each Dose, if: No Cohort Effect
4	Dose 0 1 2 3 cohort1 2 6 0 0 cohort2 2 2 4 0 cohort3 2 0 4 2 cohort4 2 0 0 6	0 0.37 0.3 0.37 1 0.47 0.67 2 0.47	0 0.25 0.25 0.25 1 0.25 0.25 2 0.25	0 0.24 0.23 0.24 1 0.26 0.28 2 0.26	0 0.22 0.22 0.22 1 0.22 0.22 2 0.22
5	Dose 0 1 2 3 cohort1 2 6 0 0 cohort2 2 0 6 0 cohort3 2 0 0 6 cohort4 2 2 2 2	0 0.36 0.36 0.36 1 0.57 0.57 2 0.57	0 0.25 0.25 0.25 1 0.25 0.25 2 0.25	0 0.24 0.24 0.24 1 0.28 0.28 2 0.28	0 0.22 0.22 0.22 1 0.22 0.22 2 0.22
6	Dose 0 1 2 3 cohort1 4 4 0 0 cohort2 4 0 4 0 cohort3 4 0 0 4 cohort4 2 2 2 2	0 0.3 0.3 0.3 1 0.5 0.5 2 0.5	0 0.24 0.24 0.24 1 0.33 0.33 2 0.33	0 0.22 0.22 0.22 1 0.31 0.31 2 0.31	0 0.21 0.21 0.21 1 0.28 0.28 2 0.28
7	Dose 0 1 2 3 cohort1 4 4 0 0 cohort2 2 2 4 0 cohort3 1 1 2 4 cohort4 1 1 2 4	0 0.25 0.31 0.38 1 0.31 0.38 2 0.31	0 0.25 0.25 0.25 1 0.25 0.25 2 0.25	0 0.22 0.23 0.25 1 0.23 0.25 2 0.24	0 0.22 0.22 0.22 1 0.22 0.22 2 0.22

Fig 1. Comparative Study Data

3.1 Bayesian Sensitivity Analysis of the Model Parameters

A sensitivity analysis examines the degree to which results are impacted by modifications to methodologies, models, values of unmeasured variables, or assumptions in order to assess the robustness of trial findings. The sensitivity analysis ensures that unusual observations do not exert an undue influence on inferences [6].

The convergence pattern of the prediction values is done for 15,000 iterations with the data in the Bayesian setting. After the model has converged, samples from the conditional distributions are used to summarize the posterior distribution of parameters of interest.

Prior set up: Model 1

$\alpha \sim$ N (2,1)

$\nu \sim$ N (0,1)

presc.y ~ γ (.01,.01)

presc.cohort ~ γ (.01,.01)

Table 1. Results of Model I

	Node	Mean	Sd	MC error	2.50%	Median	97.50%	Start	Sample
Result: Model 1	α	3.092	0.104	0.0012	2.894	3.093	3.287	1	15000
	ν	0.0860	0.381	0.0067	0.8154	-0.088	0.6728	1	15000
	presc.cohort	8.095	7.704	0.1036	0.5869	5.767	29.06	1	15000
	presc.y	1.231	0.327	0.0030	0.6838	1.203	1.95	1	15000
	var.cohort	202.3	2388	202.7	0.0344	0.173	1.707	1	15000
	var.y	196.9	2279	196.8	0.513	0.831	1.463	1	15000

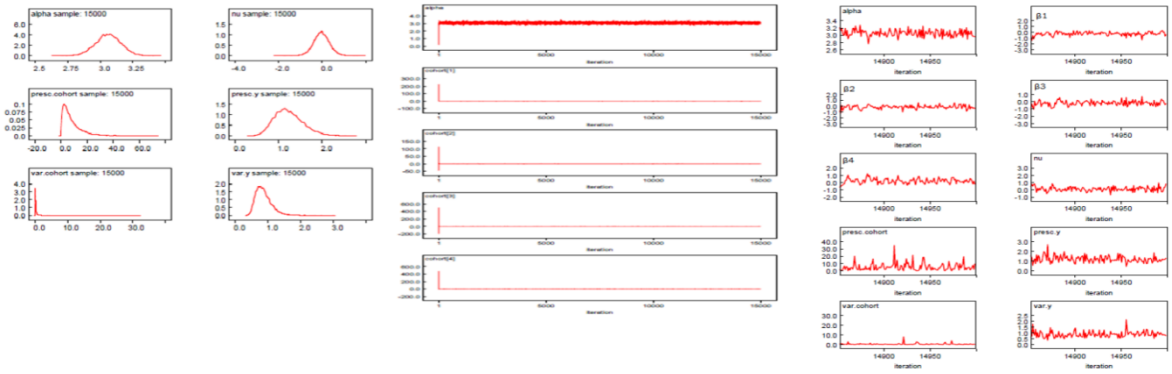


Fig 2. Bayesian Plots

Prior set up: Model II

α~ N (3,2)

ν~ N (1,2)

presc.y ~ γ (.01,.03)

presc.cohort ~ γ (.1, .2)

Table 2. Results of Model II

	Node	Mean	Sd	MC error	2.50%	Median	97.50%	Start	Sample
Results: Model-II	α	3.05	0.0987	0.0010	2.86	3.058	3.24	1	15000
	ν	0.22	0.4074	0.0096	0.50	0.1941	1.11	1	15000
	presc.cohort	4.49	4.113	0.0635	0.31	3.303	15.4	1	15000
	presc.y	1.21	0.3272	0.003	0.67	1.191	1.93	1	15000
	var.cohort	404	47750	405.3	0.06	0.3028	3.14	1	15000
	var.y	392	45450	393	0.51	0.8395	1.44	1	15000

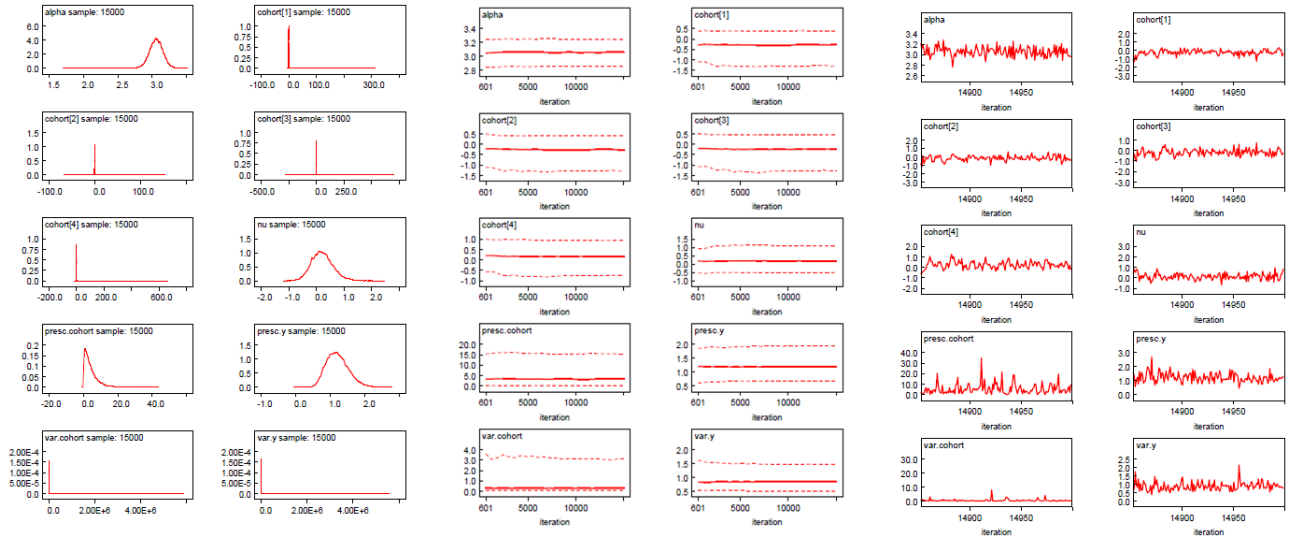


Fig 3. Bayesian Plots

Prior set up: Model III
α~ N (1,2)
ν~ N (0,1)
presc.y ~ γ (.1,.02)
presc.cohort ~ γ (.2,.1)

Table 3. Results of Model III

	Node	Mean	Sd	MC error	2.50%	Median	97.50%	Start	Sample
Results: Model-III	alpha	3.062	0.09842	0.000	2.866	3.062	3.252	15001	15000
	nu	-0.0269	0.3818	0.006	0.7725	0.03247	0.739	15001	15000
	presc.cohort	8.323	7.75	0.102	0.5886	5.987	29.07	15001	15000
	presc.y	1.23	0.3274	0.003	0.6806	1.197	1.945	15001	15000
	var.cohort	0.3402	0.8152	0.011	0.0344	0.167	1.701	15001	15000
	var.y	0.8749	0.2489	0.002	0.5142	0.8357	1.469	15001	15000

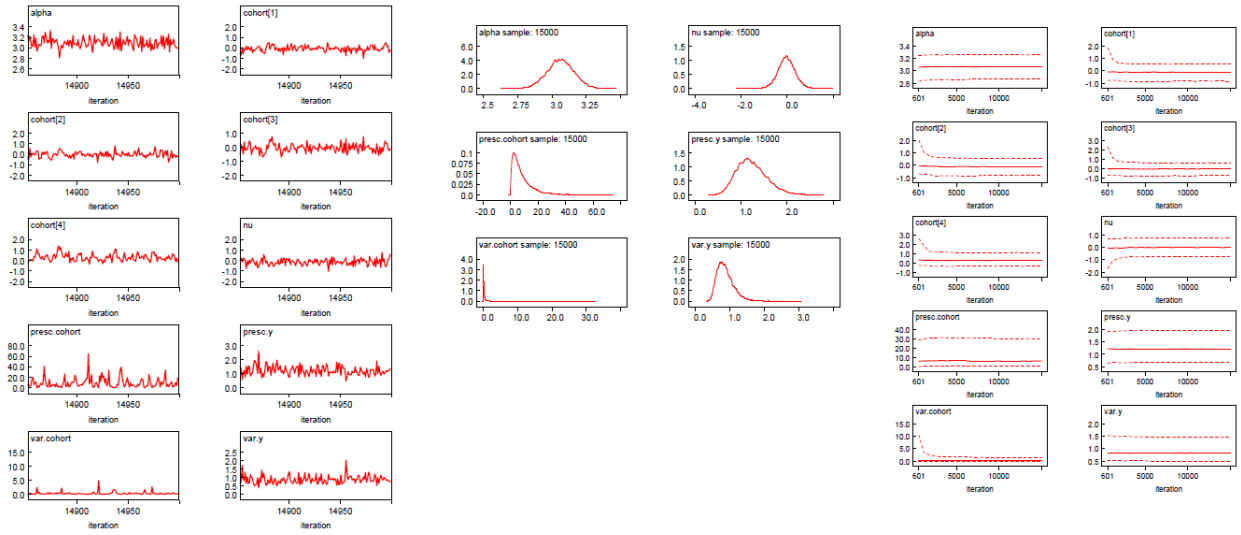


Fig 4. Bayesian Plots

4 Conclusion

Phase I studies are progressively consolidating phase II expansions to exhibit viability and, starting the drug advancement phase in oncology. This led to specialists with clear cut systems of activity and targets, and subsequently with potential adequacy that can be uncovered quickly through a creatively planned stage I parameter which will be enlisting many patients.

When compared to the other two iteration models for the analysis, the Model-I trace plot out of the three iteration models exhibits the best parameter values. The Model-I has converged, and the trace plot moves around the mode of the distribution. While the burn-in iterations are set up, the trace plots are configured to monitor parameters. Numerous posterior estimates are expected to be observed in the model's results. As a result, the posterior patterns will have a large spike, and the estimates may appear erratic on the trace plots as they fluctuate between around 0 and other values. The dataset is used to observe the plots of 15,000 iterations in the form of patterns and corresponding trace plots. As the initial values are set near their posterior modes, convergence occurs relatively quickly, especially if there is no autocorrelation problem.

In all the plots, the Markov Chains each represent a different dataset. The Model-I Bayesian plot describes the Bayesian Convergence Patterns for the data set. The variance is found to be stable after the iterations.

Bayesian methodology conditions on the information and adjusts to the probability rule. Subsequently, frequentist derivation is legitimate just when the specified clinical preliminary plan is followed. The frequentist parameters are not accurate in the clinical setting with the design parameters as it does not loop the dosing effects. Bayesian methodology is adapted on the information, so it can in any case keep up with the likelihood model that is accurately determined.

The proposed method allowed for identifying a set of important regression parameters, estimating survival probabilities, and constructing credible intervals of the survival probabilities. We evaluated operating characteristics of the proposed method via simulation studies. Finally, we apply our new comprehensive method to analyze the motivating breast cancer data from the Surveillance, Epidemiology, and End Results Program, and estimate the five-year survival probabilities for women included in the Surveillance Study.

References

1) Brush J, Lee M, Sherbino J, Taylor-Fishwick JC, Norman G. Effect of Teaching Bayesian Methods Using Learning by Concept vs Learning by Example on Medical Students' Ability to Estimate Probability of a Diagnosis: A Randomized Clinical Trial. 2019. Available from: https://doi.org/10.1001/jamanetworkopen.2019.18023.
2) Lin J, Lin J. Incorporating propensity scores for evidence synthesis under bayesian framework: review and recommendations for clinical studies. *Journal of Biopharmaceutical Statistics*. 2022;32(1):53–74. Available from: https://doi.org/10.1080/10543406.2021.1882481.
3) Halpern SD, Chowdhury M, Bayes B, Cooney E, Hitsman BL, Schnoll RA, et al. The Effectiveness and Ethics of Incentives for Research Participation: Two Embedded Randomized Recruitment Trials. *SSRN Electronic Journal*. 2021;181(11):1479–1488. Available from: https://doi.org/10.1001/jamainternmed.2021.5450.
4) Adler N. Research network on socioeconomic status and health. . Available from: https://www.macfound.org/networks/research-network-on-socioeconomic-status-health.DOI.
5) Barton-Hulsey A, Sterling A. Grammatical judgement and production in male 685 participants. *Clinical Linguistics and Phonetics*. 2020;34(12). Available from: https://doi.org/10.1080/02699206.2020.1719208.
6) Brydges CR, Gaeta L. An Analysis of Nonsignificant Results in Audiology Using Bayes Factors. *Journal of Speech, Language, and Hearing Research*. 2019;62(12):4544–4553. Available from: https://doi.org/10.1044/2019_JSLHR-H-19-0182.