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Leveraging Bayesian Posterior Probability for Analyzing Treatment Effects in Clinical Trials: A Statistical Programmer's Guide

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ABSTRACT

In clinical trial analysis, the Bayesian posterior probability, particularly with non-informative priors, emerges as a valuable tool for assessing the true underlying mean improvement between treatment and placebo groups. This method enables the evaluation of whether improvements exceed predefined thresholds, such as 0%, 10%, and 20%, leveraging LS means and estimated standard deviations derived from the Mixed Models for Repeated Measures (MMRM). This approach proves especially beneficial when sample sizes are insufficient for detecting significant differences through traditional MMRM analysis. Utilizing an empirical approach, Bayesian posterior probability is computed using Proc Bglimm, which generates posterior samples to determine the probabilities of improvement. This paper provides comprehensive insights into this methodology. For statistical programmers, it outlines practical strategies for deriving Bayesian posterior probabilities and seamlessly incorporating statistical models in SAS. Additionally, it offers invaluable tips and tricks for conducting thorough data checks to ensure the accuracy and reliability of TLFs.

INTRODUCTION

Statistical analysis is essential in clinical research, allowing researchers to derive accurate conclusions from data collected across various participant groups. In clinical trials, two primary statistical analysis methods are used: the frequentist approach and the Bayesian approach. Most clinical trials employ the frequentist approach, which relies on null hypothesis significance testing. Interest in the Bayesian approach is limited, and it remains largely unexplored area for clinical programmers. This paper seeks to explore the use of Bayesian Posterior Probability in clinical trials and enhance statistical programmers to effectively work with this concept.

CONCEPT OF BAYESIAN POSTERIOR PROBABILITY

Bayesian statistics is grounded in Bayes' theorem, which calculates the probability of an event occurring based on prior knowledge of the conditions related to that event data. Before getting to know about Bayesian statistics, we will see what is Bayes' theorem which is the foundation for Bayesian statistics.

Bayes' theorem (also referred to as Bayes' rule) is a mathematical relationship between the prior probability and the posterior probability conditional on data. In general terms, Bayes' theorem is expressed as follows.

$$P(A/B) = \frac{P(A)P(B/A)}{P(B)}$$

Where A and B are events of interest, and P(A) and P(B) are probabilities of event A and B, respectively. P (A|B) denotes the probability of event A happening on the condition that event B has already happened. Similarly, P(B|A) denotes the probability that the event B happens conditional on information that event A has already happened.

Bayesian analysis leverages this rule to derive posterior probabilities about parameters of interest by integrating prior probabilities with likelihood derived from the data. For instance, consider a scenario where a group of volunteers is tested for a medical condition. Given that there is an error rate associated with the test used, we might be interested in determining whether the medical condition is truly present given the positive result. This can be determined using the Bayes rule,

$$P(Condition/Positive\ Result) = \frac{P(Condition) \times P(Positive\ Result/Condition)}{P(Positive\ Result)}$$

In this method, the prior probability (i.e., probability that the medical condition is truly present) is combined with likelihood (i.e., probability of positive test result when the medical condition is truly present) and the resulting probability is known as posterior probability (or Bayesian posterior probability). The posterior probability represents the updated belief about the parameter of interest, in this example, our belief that medical condition is truly present given a positive test result.

Consider another scenario: a person reports persistent shortness of breath and a persistent cough. Determining the likelihood of chronic obstructive pulmonary disease (COPD) based solely on these symptoms can be challenging. However, the patient's smoking history significantly influences the probability of COPD. The goal here is to determine the probability of COPD given the patient is a smoker, with prior information about the proportion of smokers among those diagnosed with COPD.

$$P(COPD/Smoker) = \frac{P(COPD) \times P(Smoker/COPD)}{P(Smoker)}$$

Priors are fundamental to Bayesian methodology. The prior distribution is essential in Bayesian inference, representing information about an uncertain parameter before data collection begins. Conceptually, the prior outlines the feasible values and the associated uncertainty of these parameters. Priors can vary in informativeness, from non-informative to weakly informative or highly informative. The prior is established before a clinical trial starts. Once data from the trial is collected, Bayes' theorem provides a mathematical method for integrating the prior and the likelihood to derive the posterior distribution. This posterior distribution reflects the probability distribution of the unobserved parameters of primary interest, based on the observed data and prior information. With the posterior distribution in hand, we can perform predictive checking by simulating future data to assess whether the model accurately fits the original data.

WHEN TO CHOOSE BAYESIAN POSTERIOR PROBABILITY FOR CLINICAL TRIALS

Posterior predictive distributions are utilized to extend beyond observed data and make forecasts. They can be utilized to estimate the likelihood of trial success or other trial aspects based on interim data. Additionally, they can inform adaptive designs, where treatment arms may be discontinued as planned if they are not expected to succeed, or only a subset of participants may be studied moving forward if certain groups are unlikely to show meaningful treatment effects. Similarly, historical data can create priors for design purposes rather than for analysis, with the prior predictive distribution helping to determine the sample size for future trials.

CASE STUDY ON BAYESIAN POSTERIOR PROBABILITY WITH NON-INFORMATIVE PRIOR

Consider a clinical trial evaluating the efficacy of study treatment compared to placebo in reducing disease-associated pain. The treatment effect is assessed using the Faces Pain Scale-Revised (FPS-R) score. Due to the rarity of the disease, there are very few subjects to study the treatment effect. Bayesian posterior probability proves to be a better choice for analysis in this case. Below is a step-by-step procedure to obtain posterior probability.

The change from baseline to Week 7, Week 13 etc., in FPS-R score is compared between treatment and placebo using MMRM model. The MMRM model includes factors for treatment group (Treatment, Placebo), time (Week 7, 13, 25), and treatment by-time interaction. Random effect for subject is also added. An unstructured covariance structure is used to model the within-subject errors. As previously stated, due to the rarity of the disease there are few subjects in the trial, which makes it difficult to detect a treatment effect. Hence, Bayesian posterior probabilities that the mean improvement due to treatment exceeds 0%, 10% and 20% are also computed.

DATA

Say, we have a final sample dataset as shown below:

AVAL – The average FPS-R score of the Week
BASE – The FPS-R score at Baseline.
CHG - Change from Baseline
FASFL – Full Analysis Set (whether a subject belongs to the population of analysis)

SUBJID	AVISIT	AVAL	BASE	CHG	FASFL	TRTA	AGE
10001	Week 25	8.85714	6.28571	2.57143	Y	Treatment	29
10002	Week 7	3.42857	6.28571	-2.85714	Y	Placebo	22
10002	Week 13	4.57143	6.28571	-1.71429	Y	Placebo	22
10002	Week 25	4	6.28571	-2.28571	Y	Placebo	22
10003	Week 7	3.14286	4.85714	-1.71429	Y	Treatment	50
10003	Week 13	3.71429	4.85714	-1.14286	Y	Treatment	50
10003	Week 25	0.85714	4.85714	-4	Y	Treatment	50
…							

LSMEAN ESTIMATES FROM PROC MIXED

To obtain the LSMEAN and its 95% CI estimates for each week, you can use PROC MIXED. These estimates can also be obtained from PROC GENMOD, provided no random effects need to be modeled.

```
/*MMRM to get the LS mean and estimates*/
ods trace on;
proc mixed maxiter = 1000 maxfunc = 5000 data = input_data;
class TRTA AVISIT SUBJID;
model CHG = TRTA AVISIT TRTA*AVISIT / solution;
```

```
repeated AVISIT/ type=un /*Unstructured covariance matrix*/ subject = SUBJID;
random SUBJID;
lsmeans TRTA*AVISIT/ pdiff cl e;
ods output lsmeans=lsmeans diffs=lsmean_diff(where=(TRTA ne _TRTA and AVISIT eq _AVISIT))
coef=coef convergencestatus=cs;
run;
```

Least Squares Means

Effect	TRTA	AVISITn	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TRTA*AVISITn	Placebo	7	-1.8286	0.7588	11	-2.41	0.0346	0.05	-3.4986	-0.1585
TRTA*AVISITn	Placebo	13	-1.5429	0.8881	11	-1.74	0.1102	0.05	-3.4975	0.4118
TRTA*AVISITn	Placebo	25	-1.9141	1.1400	11	-1.68	0.1213	0.05	-4.4231	0.5950
TRTA*AVISITn	Treatment	7	-0.7366	0.6168	11	-1.19	0.2575	0.05	-2.0941	0.6209
TRTA*AVISITn	Treatment	13	-0.9552	0.7114	11	-1.34	0.2064	0.05	-2.5211	0.6106
TRTA*AVISITn	Treatment	25	-1.9229	0.8735	11	-2.20	0.0500	0.05	-3.8454	-0.00038

OBTAINING POSTERIOR DISTRIBUTION USING BGLIMM

PROC BGLIMM uses syntax similar to that of PROC MIXED. The major difference in BGLIMM is the availability of COEFFPRIOR, COVPRIOR options to specify the prior distribution. The choice of prior should be specified and justified in the study protocol/analysis plan as appropriate. For the sake of ease, non-informative priors are used in this example.

```
/*BGLIMM to get the Bayesian posterior distribution*/
proc bglimm data = input_data nmc=11000 seed=8654286 outpost=pr_out;
  class TRTA AVISIT SUBJID;
  model CHG = TRTA AVISIT TRTA*AVISIT/ coeffprior=constant;
  repeated AVISIT/ type=un subject=SUBJID;
  random SUBJID;

  /*Estimating LSMEANs for Treatment group and Placebo group at respective visits*/
  estimate 'Treatment_at_Week_7' intercept 1 TRTA 1 0 AVISIT 1 0 0 TRTA*AVISIT 1 0 0 0 0 0;

  estimate 'pb_at_Week_7' intercept 1 TRTA 0 1 AVISIT 1 0 0 TRTA*AVISIT 0 0 0 1 0 0;

  estimate 'Treatment_at_Week_13' intercept 1 TRTA 1 0 AVISIT 0 1 0 TRTA*AVISIT 0 1 0 0 0 0;

  estimate 'pb_at_Week_13' intercept 1 TRTA 0 1 AVISIT 0 1 0 TRTA*AVISIT 0 0 0 0 1 0;

  estimate 'Treatment_at_Week_25' intercept 1 TRTA 1 0 AVISIT 0 0 1 TRTA*AVISIT 0 0 1 0 0 0;

  estimate 'pb_at_Week_25' intercept 1 TRTA 0 1 AVISIT 0 0 1 TRTA*AVISIT 0 0 0 0 0 1;
run;
```

Priors for Fixed Effects

Parameter	Prior
Intercept	Constant
TRTA Placebo	Constant
AVISITn 7	Constant
AVISITn 13	Constant
TRTA Placebo*AVISITn 7	Constant
TRTA Placebo*AVISITn 13	Constant

COEFFPRIOR=CONSTANT provided in the above SAS code instructs the procedure to use non-informative flat prior

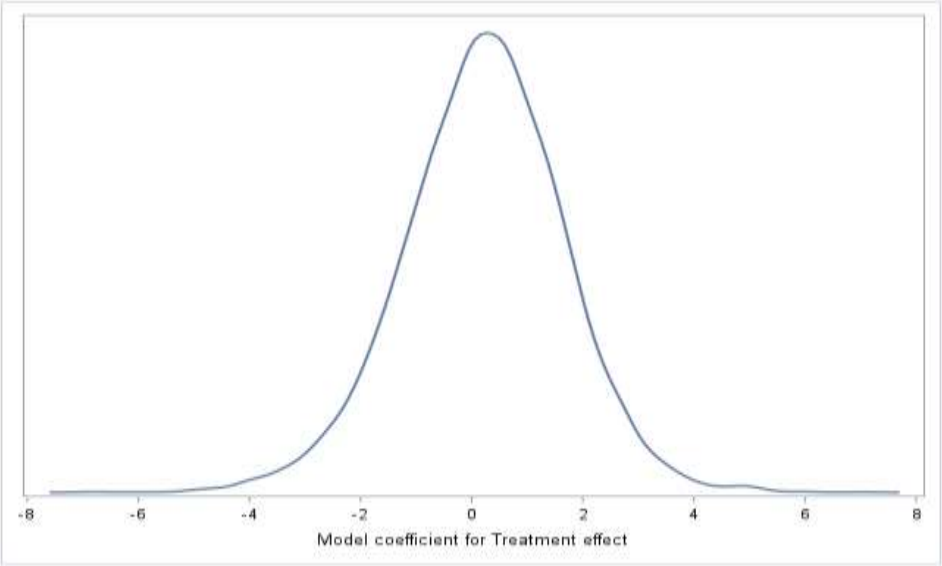
for fixed effect coefficients in estimating the posterior distribution. This is the default prior for fixed effect coefficients in the BGLIMM procedure and it assigns equal likelihood for all possible values of the coefficients. Normal distributions with very high variance, for ex: COEFFPRIOR=NOMRAL(VAR=1e4), are also considered non-informative priors for these coefficients.

One can make use of the NORMAL option with small variances or even provide the mean and covariance of the prior via an input dataset to include informative priors in the model.

Priors for Scale and Covariance Parameters	
Parameter	Prior
Residual Cov	Inverse Wishart (DF=6, Scale=6)

Similarly, the priors for covariance matrices can be provided using COVPRIOR options in the RANDOM and REPEATED statements which by default assumes inverse Wishart and inverse Gamma distributions for UN and UN (1), VC and TEOP covariance structures. One can vary the scale/shape parameters like COVPRIOR=IG (3, 0.5) based on the information at hand about the prior distribution of covariance structure.

Figure: Density plots for posterior distribution of model coefficient for treatment effect.



Since the posterior distribution is generated using Markov chain Monte Carlo (MCMC) method, it is critical to inspect the integrity of the posterior sample. This involves exploring trace, autocorrelation and density plots and is beyond the scope of this paper.

LSMEAN ESTIMATES FROM PROC BLGIMM

LS-means from the fitted model can be used to explore the mean improvement due to treatment. Unlike PROC MIXED or any other procedures available in SAS for generalized linear models, PROC BGLIMM syntax does not include LSMEANS statement. Hence, we have to rely on the ESTIMATE statement, as noted in the example SAS code above, to obtain the required estimates.

The mean improvement due to treatment, which is the reduction of the Pain Score in this case, is calculated from the LS-mean estimates utilizing the posterior samples generated by the BGLIMM procedure.

```
/*Calculating mean improvement*/
data nmc;
  set pr_out;
  n = _n_ - 1000;
  if n>=1; *discarding first 1000 samples;

  mean_imp_1 = (Treatment_at_Week_7 - pb_at_Week_7)*100/pb_at_Week_7;
  mean_imp_2 = (Treatment_at_Week_13 - pb_at_Week_13)*100/pb_at_Week_13;
  mean_imp_3 = (Treatment_at_Week_25 - pb_at_Week_25)*100/pb_at_Week_25;
```

```
  array mean_ mean_imp_1 mean_imp_2 mean_imp_3;
  array dup dup_imp_1 dup_imp_2 dup_imp_3;

  array treatment_ treatment_at_Week_7 treatment_at_Week_13 treatment_at_Week_25;
  array pb_ pb_at_Week_7 pb_at_Week_13 pb_at_Week_25;

  do over mean;
    if treatment_ lt 0 and pb_ lt 0 then dup = mean;
    else if treatment_ lt 0 and pb_ gt 0 then dup = -1*mean;
    else if treatment_ gt 0 and pb_ lt 0 then dup = -10; *Since this will always be less than 0%
improvement hard coding this as -10;
    else if treatment_ gt 0 and pb_ gt 0 then dup = -1*mean_; *Since negative changes are
prefered directions are changed;

  /*Week 7*/
  ind1_0 = ifn(dup_imp_1 > 0,1,0);
  ind1_10 = ifn(dup_imp_1 > 10,1,0);
  ind1_20 = ifn(dup_imp_1 > 20,1,0);

  /*Week 13*/
  ind2_0 = ifn(dup_imp_2 > 0,1,0);
  ind2_10 = ifn(dup_imp_2 > 10,1,0);
  ind2_20 = ifn(dup_imp_2 > 20,1,0);

  /*Week 25*/
  ind3_0 = ifn(dup_imp_3 > 0,1,0);
  ind3_10 = ifn(dup_imp_3 > 10,1,0);
  ind3_20 = ifn(dup_imp_3 > 20,1,0);
run;
```

POSTERIOR PROBABILITIES OF MEAN IMPROVEMENT

The posterior probability of our parameters of interests, which is mean improvement >0%, >10% and >20%, is obtained from the posterior distribution as the proportion of samples that has mean improvement over 0%, 10% and 20% respectively.

```
/*Posterior probabilities for Mean improvement over 0%, 10% and 20%*/
proc freq data = nmc;
  /*Week 7*/
  table ind1_0 / out = week7_0 binomial(cl=exact level='1'); *to get the proportion (which is
same as the posterior probability) of cases where improvement > 0%;
  tables ind1_10 / out = week7_10 binomial(cl=exact level='1'); *to get the proportion of cases
where improvement > 10%;
  tables ind1_20 / out = week7_20 binomial(cl=exact level='1'); *to get the proportion of cases
where improvement > 20%;

  /*Week 13*/
  table ind2_0 / out = week13_0 binomial(cl=exact level='1');
  tables ind2_10 / out = week13_10 binomial(cl=exact level='1');
  tables ind2_20 / out = week13_20 binomial(cl=exact level='1');

  /*Week 25*/
  table ind3_0 / out = week25_0 binomial(cl=exact level='1');
  tables ind3_10 / out = week25_10 binomial(cl=exact level='1');
  tables ind3_20 / out = week25_20 binomial(cl=exact level='1');
run;

data post_prob(rename=(PERCENT = Posterior));
  set visit: indsname=complete_name;
  visit = scan(complete_name,2,'.');
  indic = coalesce(ind1_0, ind1_10, ind1_20, ind2_0, ind2_10, ind2_20, ind3_0, ind3_10, ind3_20);
run;
```

The posterior distribution, and so the resulting posterior probability and estimates, is influenced by the prior distribution in case of small samples. The influence can be expected to be relatively small when there is a large sample at the hand.

RESULT

Table

MMRM for Change from baseline in Mean Pain Intensity Measured by FPS-R

Visit	Parameter Statistic	Treatment (N=XX)	Placebo (N=XX)	Treatment Difference (N=XX)
Week 7	Change from Baseline			
	n	7	5	
	Mean	-1.082	-1.829	0.747
	LS Means (95% CI)	-0.7366 (-2.094, 0.6209)	-1.8286 (-3.4986, -0.1585)	-1.0920 (-3.2442, 1.0602)
	Posterior probability[1]			
	>0%			0.0939
	>10%			0.0936
	>20%			0.0935
Week x	...			

Note: Change from Baseline = Result at Visit X − Result at Baseline.

MMRM Model: Change from Baseline = Baseline + Treatment + Visit + Treatment*Visit + Baseline*Visit + Age.

[1] Bayesian posterior probability that the TRUE mean improvement is >0%, >10% and >20%. Non-informative priors are assumed for the model coefficients and the posterior distribution is generated using MCMC method.

INTERPRETATION

- We assumed a non-informative prior for the model coefficients which means the probability that the true mean treatment is >0% (or >10%, or >20%) is equally like (i.e., 50-50 chance). The posterior probability for mean improvements >0%, >10% and >20% are 0.0939, 0.0936, and 0.0935 respectively, indicating that the chances for mean improvement to be >0% have notably worsened.
- Unlike hypothesis testing, where we reject or accept a hypothesis at a given significance level, Bayesian analysis continuously updates our belief (expressed as prior distribution) about the model parameter.
- For confirmatory trials, to draw conclude based on posterior probabilities, we should predefine a threshold (e.g., 0.9, 0.95). The treatment effect is confirmed if this threshold is exceeded.

KEY ADVANTAGES OF BAYESIAN ANALYSIS

- Bayesian analysis makes use of the prior information in analysis and thereby providing a scientifically sound approach for incorporating prior information in decision making.
- Provide reliable estimates even for small samples with the aid of informative priors.
- Bayesian methods are found to offer more flexibility in designing adaptive trials.
- Bayesian methods also allow for great flexibility in dealing with missing data.

CHALLENGES

- Priors are central to Bayesian analysis, but selecting a universally accepted prior is difficult due to the subjective nature of the prior beliefs. Converting subjective prior beliefs into a mathematically defined prior demands significant skill. Without careful consideration, misleading results can occur. Historical data and expert opinions are common methods for determining the prior distribution. However, expert opinions can be influenced by personal biases and may lack consensus. Similarly, when using historical data, it's crucial to consider its relevance to the current trial, as well as its potential biases and quality.
- The extend of pre-planning the primary analysis contributes to the confidence in the results. For a trial using Bayesian analysis, it is crucial to finalize decisions on the choice of prior information and the method of combining trial data with this prior information during the planning stage. Due to the limited guidelines available for Bayesian approaches, frequent consultations with regulatory authorities may be necessary to finalize the analysis.
- Bayesian methods require extensive mathematical modeling, especially regarding the probability distributions selected to reflect prior information and the relationships between multiple sources of prior information. Additionally,

the techniques used in Bayesian analysis are computationally intense, making the role of computerized systems crucial. The complexity of the techniques also introduces a greater possibility of error.

- May often have to resort to approximations due to high dimensional parameter spaces which could result in different results. It's recommended to use well-established methods like MCMC to provide more reliable approximations.

TIPS AND TRICKS

While it is extremely difficult to verify the correctness of results generated through the BGLIMM procedure, following tips may prove useful during QC and/or review:

- As it is stated previously, this approach involves generation of random samples using MCMC procedure. Establishing fixed seed numbers, determining number of iterations, etc., will ensure reproducibility of the results.
- Other standard precautions should be taken during the execution of GLM models such as using numeric variables (e.g., AVISITN) instead of character variables as needed, specifying the reference levels for class variables (e.g., TRTA(ref="Placebo")), and confirming or agreeing upon the covariance structure or the order in which covariance structures are used in the model in case of convergence issues.
- Though it is not feasible to ensure exact correctness, incorrect results can be identified with information on prior and likelihood from the data. For example, in case of using non-informative priors, Bayesian results generally align with the results obtained from frequentist approach. It is nearly unlikely to have a discrepancy between the results in this case. On the other hand, when informative priors are used the Bayesian results should either heavily resemble the prior distribution if the likelihood from the data agrees with the prior information or the results should lie between the prior and likelihood if the likelihood is different from the prior. This is subject to how strongly the prior is defined. Weakly informative priors will have relative less impact and the posterior results will resemble the likelihood.
- Other models that can be used for Bayesian analysis:
    - PROC MCMC - commonly used.
    - PROC GENMOD (with the BAYES statement) - Bayesian analysis for GLMs.
    - PROC PHREG (with the BAYES statement) - Survival analysis.
    - PROC FMM (with the BAYES statement) - Bayesian analysis of finite mixture models.

GUIDELINES

While Bayesian analysis is increasingly used, there are limited regulatory guidelines specifically for its application in clinical trials. Here are a few references that might be helpful:

- FDA Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials (2010)
- FDA Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics (2019)

CONCLUSION

In light of the limited exploration of Bayesian posterior probability in clinical analysis, our objective was to elucidate its core principles and demonstrate its application in clinical trial evaluations. We applied Bayesian posterior probability in a case study to provide practical insights and analyzed the outcomes comprehensively. Additionally, we outlined best practices and strategies for implementing Bayesian analysis, along with potential challenges that may arise.

REFERENCES

- https://documentation.sas.com/doc/en/statcdc/14.2/statug/statug_introbayes_sect015.htm
- https://users.metu.edu.tr/ozancan/BayesLectureNotes.pdf
- https://online.stat.psu.edu/stat509/lesson/9/9.4
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10117244/#CR13

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