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A Stopping Rule in the Clinical Trial on Acute Non-Bloody Diarrhea Using a Bayesian Approach[1]

Aristotle B. Magallanes[2]

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ABSTRACT

The study is an application of the Bayesian method on data monitoring and analysis of clinical trials, where the odds ratio (OR) is a common parameter of interest and the number of subjects with the disease of interest is the primary endpoint. It uses data from a randomized controlled clinical trial on the efficacy and safety of probiotics Ohhira OMX capsules in the treatment of acute non-bloody diarrhea among 3 to 24-month old infants and children. It aims to formulate a stopping rule in a two-drug treatment, where drug A is a combination of OMX plus Oral Rehydration Solution (ORS) and drug B consists of ORS alone. The findings show that there is a strong evidence that log(OR) is less than zero with the associated 0% target prevalence difference of having diarrhea between the two groups on the first day of interim analysis. This provides conclusive evidence of an advantage in favor of drug A over drug B since the predictive probability is greater than the 95% cut-off probability as the stopping rule. Thus, the trial is terminated on the second day and recommended that the use of drug B be stopped and the use of drug A be continued.

Keywords: Randomized controlled clinical trial on diarrhea, Bayesian method, prior and posterior distributions

I. INTRODUCTION

Diarrhea was third of ten leading causes of morbidity in the Philippines in 2004. There were 557,118 cases of acute watery diarrhea reported during the year, which represented a rate of 722.00 per 100,000 populations. In the Control of Diarrheal Diseases (CDD) in the same year, 500,169 cases affected 0 to 59-month old infants and children who were given Oral Rehydration Solution (ORS), which represented 15% of the eligible population (Field Health Service Information System-Department of Health, 2004).

A number of clinical trials on diarrhea showed probiotic consumption to be beneficial in the treatment of many types of diarrhea, including antibiotic associated diarrhea in adults, traveler's diarrhea and diarrhea in young children caused by rotaviruses. Some studies showed that probiotic products, such as *Infloran berna*, were effective in shortening the duration of diarrhea among 2 to 5-year old children and 6 to 24-month old infants and children (Arnaldo and Gatcheco, 2004).

Studies that assessed the relative efficacy of two therapeutic drugs and measured the benefit size and their favorable response were the common bases of clinical trials on diarrhea. They were helpful in determining the significant difference of drug efficacy and in data

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[2] Assistant Professor of the Department of Epidemiology and Biostatistics, College of Public Health, University of the Philippines Manila; email address: abmagallanes@yahoo.com

monitoring in order to secure the patient's well-being. Since data monitoring is helpful in dealing with the ethical, medical and moral issues and the economic and social costs of treatment, there was a need to formulate a stopping rule while the trials were ongoing. Two independent clinicians and an independent statistician did the monitoring of the trials. It was presumed that the clinicians had the expertise and experience to conduct the trials.

The Bayesian method is a technique applied on data monitoring and analysis of clinical trials, where the odds ratio (OR) is the parameter of interest and the number of subjects with diarrhea is the primary endpoint. The method is helpful in the analysis not only of emergency cases but also the immediate results in therapeutic trials (Kpozehouen, Alioum, Anglaret et al., 2005).

The study aims to formulate a stopping rule in a two-drug treatment to acute non-bloody diarrhea among 3 to 24-month old infants and children, where drug A is a combination of probiotics Ohhira OXM plus ORS and drug B consists of ORS only as a conventional treatment. It uses the randomized controlled clinical trials on diarrhea conducted by Arnaldo and Gatcheco in 2004 at the Dr. Jose R. Reyes Memorial Medical Center, Manila. The medical center reported diarrhea as one of four leading causes of morbidity. Diarrhea had the highest number of consultations at the Emergency Department, which accounted for 11.5% of all admissions during the year.

II. MATERIALS AND METHODS

2.1. Randomized controlled clinical trial on acute non-bloody diarrhea

Diarrhea is a condition in which a patient has watery stools (also known as loose bowel movement) at least 3 times in 24 hours. It is a symptom of bacterial or viral infection, allergy, food intolerance, food-borne illness and/or extreme excesses of vitamin C and/or magnesium, which may be accompanied by abdominal pain, fever, thirst, and nausea and vomiting Symptomatic treatments involve the use of ORS or consumption of adequate amounts of water, preferably mixed with electrolytes to provide essential salts and some amount of nutrients to replace the loss of friendly bacteria. The quantification of recovery or having no diarrhea is defined as the passage of 2 consecutive formed stools or no stool output for the next 12 hours. When the quantification is met, the patient is considered recovering from diarrhea or is cured.

The randomized controlled clinical trials on diarrhea from Arnaldo and Gatcheco's study had a sample size of 70 patients. The sample size was more than the required number, which was computed at 54 to detect a 95% confidence level, 95% power and 75% expected percentage of not successfully treated using ORS alone against 25% OMX plus ORS. The figures were taken from the pilot study of clinical trials on diarrhea taken at the fourth day of follow-up, the mean duration of the efficacy of both treatment arms.

Probiotics are live microbial food supplements that beneficially affect an individual by improving intestinal microbial balance. They include *Lacto bacillus acidophilus*, which regulate the normal colonic flora by preventing bad bacteria, promoting good digestion, giving proper intestinal peristaltic movement and reinforcing recovery. Ohhira OMX capsule is a new probiotic, organically fermented in paste form and is available in the market. It has

no side effects and toxicity and is hypothesized to shorten the course of diarrhea (Arnaldo et al., 2004). However its safe use among infants in the Philippines has not yet been established.

The trial had a one-shot recruitment of subjects. Randomization was aimed to control the effect of other intervening variables and other sources of biases that may affect the results of the trials. All subjects were given equal opportunity to be included in either treatment. There were 35 patients in each treatment group. Group 1 received drug A, which was a combination of OMX plus ORS, with a dosage of one capsule twice a day for a five-day trial. Group 2 received drug B, which was ORS only. The treatments followed CDD protocol for both fluid therapy and nutrition.

The inclusion criteria were limited to 3 to 24-month old infants and children with acute non-bloody diarrhea in less than three days, with some dehydration or none based on the World Health Organization (WHO) CDD protocol. Upon inclusion, the patient was randomly assigned to either treatment group. The exclusion criteria included bloody diarrhea, severe stool discharge and intake of antimicrobials or anti-diarrheal and special formulas prior to admission.

Prior to the screening, admission and randomization, the parents or guardians of the patients were interviewed with their informed consents. Data relating to each patient's age, sex, weight, height, duration of diarrhea before admission, nutritional status, type of feeding, medical history, presence of fever, vomiting, and other associated manifestations, were recorded during the interview. Data on comprehensive physical examination centering on the type and degree of dehydration based on the WHOCDD protocol and anthropometric measurements like weight, length and quality of bowel sounds of each patient on a day to day basis were also recorded.

The stool specimens were sent to the Medical Technologist for routine stool microscopy. All patients were followed-up until the cessation of diarrhea. After the completion of the examination, the findings from the microscopy and the frequency and consistency of stools were described and noted every day until the patient was discharged.

2.2. The Data Monitoring and Interim Analysis

The Data Monitoring Committee (DMC) of the hospital monitored closely the patient safety and treatment efficacy data while the clinical trial was ongoing. Data monitoring was important in making recommendations whether the trials should be continued or terminated (Souhami, 1994). The DMC was responsible for controlling the running of the trials and performing the interim analysis. The interim analysis refers to the analysis intended to compare the two drugs A and B with respect to their efficacy or safety from the start up to the termination of the trial (Kim, 1998). The DMC also decided when the trials should be stopped for ethical reasons. If one treatment is found to be inferior, the trial should be stopped early. In case of identical effect size in both treatments, termination should also be considered.

The daily interim analysis was carried out starting on the second day of trial until the fourth day. If deemed necessary, additional interim analysis was permitted. The odds ratio is the parameter of interest used in order to determine the measure of association between the

drug type and its efficacy. The calculation of the estimate of the data-based natural logarithm of odds ratio denoted by $\log(OR_d)$ are compared such that

$$OR_d = \left(\frac{p_1}{1-p_1}\right) \Big/ \left(\frac{p_2}{1-p_2}\right)$$

where p_1 and p_2 represent the prevalence estimates of those subjects having diarrhea in Groups 1 and 2, respectively. The odds ratio is a ratio of the odds of those subjects having diarrhea under drug A to the odds of those under drug B. The odds of drug A, the new intervention, should be in the numerator (Spiegelhalter, Abrams, and Myles, 2004). If OR is less than 1, drug A is more effective than drug B. The probability of having diarrhea in both treatments approaches to zero as the follow-up is about to end. In which case, the odds ratio closely approximates the risk ratio (RR), where:

$$RR = \frac{p_1}{p_2}.$$

The risk ratio is the likelihood of those having diarrhea under drug A relative to those under drug B. It represents how many more times diarrhea is likely to occur in drug A as compared to drug B (Sahai and Khurshid, 1996).

The interim analysis and the statistical analysis were done in every follow-up in order to assess the available information from the trials. It determines whether there is sufficiently convincing accruing evidence from the data at hand for the DMC to consider terminating the trials. The stopping guidelines for the trials at each interim analysis are obtained directly from the posterior distribution. In Bayesian theorem, the posterior distribution is a revised posterior belief of log(OR) having a prior belief which is then modified according to the observed data.

The trials were designed to test a null hypothesis, H_0, of no treatment difference against an alternative hypothesis, H_a, that the treatment difference is at least $(odds_2\text{-}odds_1)$, where $odds_1$ and $odds_2$ are odds in Groups 1 and 2, respectively. It was assumed that the probabilities of having diarrhea in both groups approaches to zero as the follow-ups of the trials were about to end. This is to say that the H_a is at least the difference of the prevalence of having diarrhea in both treatments. In terms of odds ratios, this is equivalent to carrying out a trial to have:

$$H_0: \log(OR) = 0 \qquad \text{against} \qquad H_a: \log(OR) = \log(OR_a),$$

where $\log(OR_a) \neq 0$. The $\log(OR_a)$ closely approximates $\log(RR_a)$, where :

$$RR_a = \frac{\log(p_1)}{\log(p_2)}.$$

Based on the pilot clinical study, the prevalence of having diarrhea after the fourth day of treatment under drug A was 25% while drug B is hypothesized at 75%. Therefore, the 50% prevalence difference between drug A and drug B is the so-called highest target prevalence difference that drug B attained as compared to drug A at each clinical trial day.

2.3. Bayesian Method

Bayesian statistical conclusions about log(OR), denoted by Θ, are made in terms of probability statements. The probability statements of Θ conditional on the observed value of data at hand y, simply written as $p(\Theta|y)$, are known to be posterior distributions. In Bayes' Rule, this can be expressed as

$$p(\Theta|y) \propto p(\Theta)\, p(y|\Theta),$$

where Θ is a hypothesis concerning a parameter of the potential effect size, $p(\Theta)$ equals the pre-study opinion known as the prior distribution about the treatment effect size and which also represents the clinicians' opinions, and $p(y|\Theta)$ equals the likelihood of obtaining the observed data given the effect size, and $p(\Theta|y)$ is the revised opinion known as the posterior probability about the treatment effect size given the observed results, where

$$p(y) = \int p(\Theta)p(y|\Theta)d\Theta$$

(Gelman, Carlin, Stern, and Rubin, 1995).

The uninformative, skeptical and enthusiastic priors are the three prior distributions considered. The distributions may be based on previous beliefs, related studies and the distribution of the data at hand. The uninformative prior pertains to lack of clinical opinion or previous knowledge about the trial with respect to the treatment differences. That is, there is an absence of information about the prior knowledge or background of the trial. The uninformative prior tends to be approximated classical frequentist approach. It is assumed that the priors are approximated by a normal distribution with zero mean which corresponds to the null hypothesis of no difference between the two treatments and with an infinite variance 4/0. Thus, the uninformative prior distribution is expressed as

$$\text{uninformative } \Theta \sim N(0,4/0)$$

(Spiegelhalter, Abrams et al., 2004).

The skeptical prior distribution attempts to formulate that treatments are likely to be equal. This is specified by considering that there is only a small probability, say γ, that the H_a: $\log(OR) = \log(OR_a)$ is likely to be true. Setting $\gamma = 0.05$, the skeptical standard deviation, σ_{skep}, equates $\log(OR_a)/1.6445$. The skeptical prior is adapted, which is represented by a normal distribution with zero mean and variance σ^2_{skep}. It is assumed that the data set has the variance of the $\log(OR_d)$ approximately $4/N_p$ where N_p is the total number of patients suffering from diarrhea. Hence, $N_p = 4/\sigma^2_{skep}$ giving the skeptical prior to be

$$\text{skeptical } \Theta \sim N(0,4/N_p)$$

(Spiegelhalter, Abrams et al., 2004).

Finally, the enthusiastic prior puts a bound that the treatment difference has greater than zero effect size which is likely to be $(odds_2 - odds_1)$. This is considering an effect size

equivalent to the alternative hypothesis. Therefore, it is assumed that enthusiastic prior has mean $\log(OR_a)$ and variance $4/N_p$, and expressed as

$$\text{enthusiastic } \Theta \sim N(\log(OR_a), 4/N_p).$$

Both skeptical and enthusiastic priors have implications on the termination of a trial.

In data likelihood, the $\log(OR_d)$ is assumed to be normally distributed. This has mean $\log(OR_d)$ and variance $4/N_d$, where $N_d = O_1+O_2$, O_1 and O_2 are the number of patients suffering from diarrhea in Groups 1 and 2, respectively. Hence, the data likelihood can be expressed as

$$\text{data } y|\Theta \sim N(\log(OR_d), 4/N_d).$$

The derived posterior distributions can be expressed as the following distributions of revised beliefs (Fayers, Ashby and Parmar, 1997):

$$\text{uninformative } \Theta|y \sim N(\log(OR_d), 4/N_d),$$

with the same distribution as the data likelihood;

$$\text{skeptical } \Theta|y \sim N\left(\frac{N_d \log(OR_d)}{N_p + N_d}, \frac{4}{N_p + N_d}\right); \text{ and}$$

$$\text{enthusiastic } \Theta|y \sim N\left(\frac{N_d \log(OR_d) + N_p \log(OR_a)}{N_p + N_d}, \frac{4}{N_p + N_d}\right).$$

To evaluate the predictive probability of the respective revised posterior beliefs associated with the magnitude of the target prevalence difference, δ, for each of the corresponding prior distributions and the given data at each clinical trial day, we define:

$$\log(OR_\delta) = \log\left[\frac{\log(p_1)}{\log(p_1 + \delta)}\right]$$

(Fayers et al., 1997). The predictive probability of $\log(OR_\delta)$ is less than zero, $[\log(OR_\delta)<0]$, at day t of trial, where t = 2, 3, 4, can be computed at a given prevalence difference - 0%, 25%, and 50%. The 0% represents that drug A is likely better than drug B; 25% means that drug A is less likely better that drug B; and 50% means that there is unlikely to be any treatment difference. The prevalence difference provides conclusive evidence of an advantage in favor of drug A over drug B, if the predictive probability of $\log(OR_\delta)$ is less than zero with an associated δ at day t is at least equal to 0.95 (Kpozehouen et al., 2005). Therefore, the trial is terminated at day t if the predictive probability is at least equal to 0.95. This is an indication that drug A is more effective than drug B.

III. RESULTS

The number of patients observed with acute non-bloody diarrheal diseases in a 6-day trial in Groups 1 and 2 is shown in Figure 1. Both treatment groups had 34 (97.14%) patients with diarrhea on the first day. In the succeeding days, the number of patients suffering from diarrhea in group 1 starts decreasing faster compared to that in group 2. In addition, the difference of the proportion of patients suffering from diarrhea in both treatment groups becomes larger as the follow-up of the trial is about to end. The distribution of patients with diarrhea responding to drugs per day is presented in Table 1. On the sixth day of observation, there was only one (2.86%) patient suffering from diarrhea in group 1 while 16 (45.71%) patients remained uncured in group 2. The assumption of a large sample size in the data set was satisfied. Applying Central Limit Theorem, the data set is asymptotically normal in distribution (Casella and Berger, 2002).

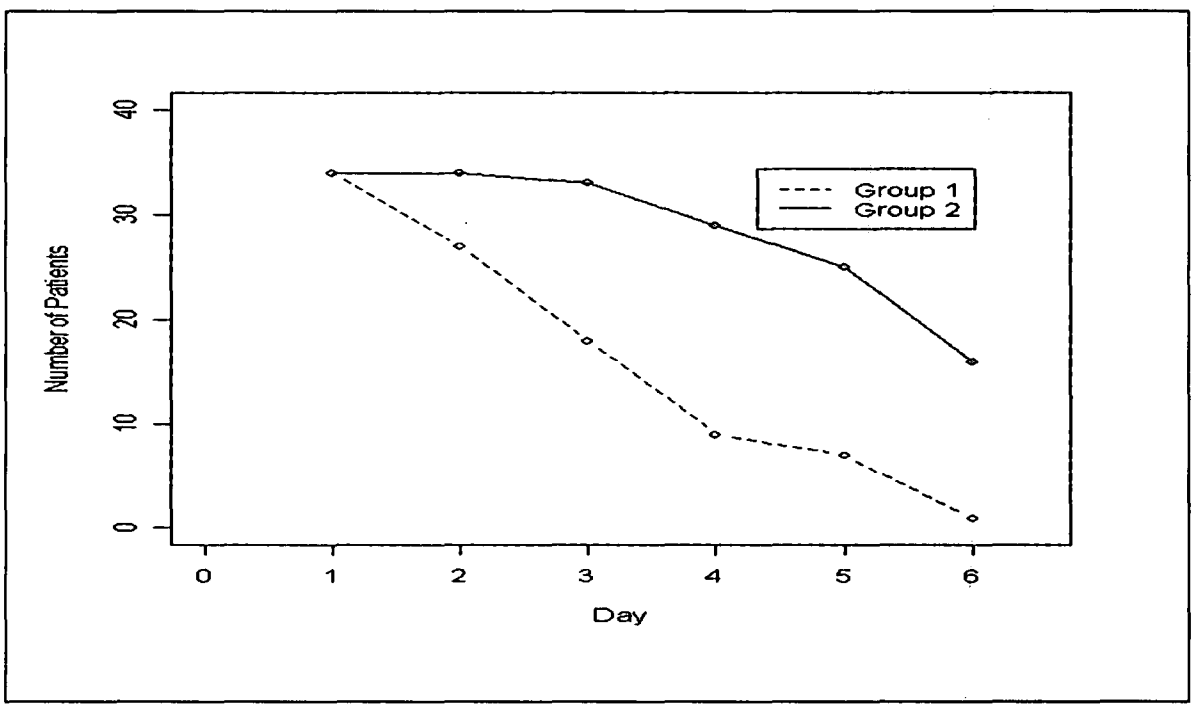

Figure 1. Number of Patients per Group with Diarrhea per Day

The results of the computations of estimated OR and the 95% confidence interval of OR at a given day of follow-up are presented in Table 2. On the first day, the estimated OR is 1.00 and the 95% confidence interval of OR is [0.01, 80.78]. This means that there is no significant association between the drug type and its efficacy (p-value = 1.000). In the succeeding days, there were significant associations and significant differences observed on drug's efficacy (p-value < 0.05). Hence, there is conclusive evidence that drug A is more effective than drug B starting on the second day of trial. In fact, the estimated ORs are less than 1 with the wider 95% confidence interval of OR [0.00,0.84] on day two, which indicates that there is a lower risk of having diarrhea with drug A compared to drug B. This implies that there is a benefit effect in drug A starting on the second day (Sahai et al., 1996). Therefore, the utilization of drug A is said to be favorable.

Table 1. The Distribution of Patients Responding to Drugs A and B per Day

DAY	RESPONSE	DRUG			
		A		B	
		Frequency	Percent	Frequency	Percent
1	With Diarrhea	34	97.14	34	97.14
	Without Diarrhea	1	2.86	1	2.86
	Total	**35**	**100.00**	**35**	**100.00**
2	With Diarrhea	27	77.14	34	97.14
	Without Diarrhea	8	22.86	1	2.86
	Total	**35**	**100.00**	**35**	**100.00**
3	With Diarrhea	18	51.43	33	94.29
	Without Diarrhea	17	48.57	2	5.71
	Total	**35**	**100.00**	**35**	**100.00**
4	With Diarrhea	9	25.71	29	82.86
	Without Diarrhea	26	74.29	6	17.14
	Total	**35**	**100.00**	**35**	**100.00**
5	With Diarrhea	7	20.00	25	71.43
	Without Diarrhea	28	80.00	10	28.57
	Total	**35**	**100.00**	**35**	**100.00**
6	With Diarrhea	1	2.86	16	45.71
	Without Diarrhea	34	97.14	19	54.29
	Total	**35**	**100.00**	**35**	**100.00**

Table 2. The Estimated OR and the 95% Confidence Interval of OR per Day

DAY	ESTIMATED OR	95% CONFIDENCE INTERVAL OF OR	p-VALUE
1	1.00	[0.01, 80.78][a]	1.000[a]
2	0.10	[0.00, 0.84][a]	0.028[a]
3	0.06	[0.01, 0.33][a]	0.000[c]
4	0.10	[0.02, 0.26][b]	0.000[c]
5	0.10	[0.03, 0.34][b]	0.000[c]
6	0.03	[0.00, 0.29][a]	0.000[c]

[a] Fisher's Exact
[b] Cornfield
[c] Chi-square/z-normal

The estimated ORs and estimated log(OR)s were used for the derivation of the posterior distributions with respect to their prior distributions. The uninformative, skeptical and enthusiastic prior distributions were computed and derived with the following distributions: N(0,4/0), N(0,4/24) and N(0.683,4/24), respectively. Table 3 summarizes the derived posterior distributions of the respective priors in three simulated interim analyses.

Table 3. The Derived Posterior Distributions per Day of Interim Analysis

POSTERIOR DISTRIBUTIONS	DAY OF INTERIM ANALYSIS		
	First	Second	Third
Uninformative	N(-0.100,0.066)	N(-0.263,0.078)	N(-0.508,0.105)
Skeptical	N(-0.072,0.047)	N(-0.179,0.053)	N(-0.322,0.067)
Enthusiastic	N(0.121,0.047)	N(0.040,0.053)	N(-0.071,0.067)

Figure 2 shows the posterior densities of log(OR) in three simulated interim analyses using R software. The normal curves of the densities start to shift consistently to the left starting on the first day of interim analysis with means (variances) -0.100 (0.066), -0.072 (0.047), and 0.121 (0.047) of uninformative, skeptical and enthusiastic posteriors, respectively. The means are leaving far apart from the hypothesized value of zero in the null hypothesis. This implies the superiority of drug A over drug B. Furthermore, the left shift of the densities represents the modification in the prior belief and therefore indicates the increased effect of drug A compared to drug B.

The curves on the first day of interim analysis are approximately close to each other. The curves start parting and moving in the same direction to the left on the second day of interim analysis. All throughout the interim analyses, the skeptical posterior curves are between the curves of the other two posteriors.

Table 4 reports the predictive probability of $\log(OR_d)$ is less than zero of the respective posterior distributions associated with 0%, 25% and 50% target prevalence difference between drugs A and B at a given day of interim analysis. On the 1st day of interim analysis, the probabilities associated with 0%, 25% and 50% prevalence difference in uninformative posterior are 0.999, 0.941, and 0.651, respectively; the skeptical posterior has 1.000, 0.957, and 0.630 probabilities, respectively; and the enthusiastic posterior has 0.995, 0.797, and 0.288 probabilities, respectively. The rest of the predictive probabilities associated with the prevalence difference up to the third interim analysis are also reflected in the table.

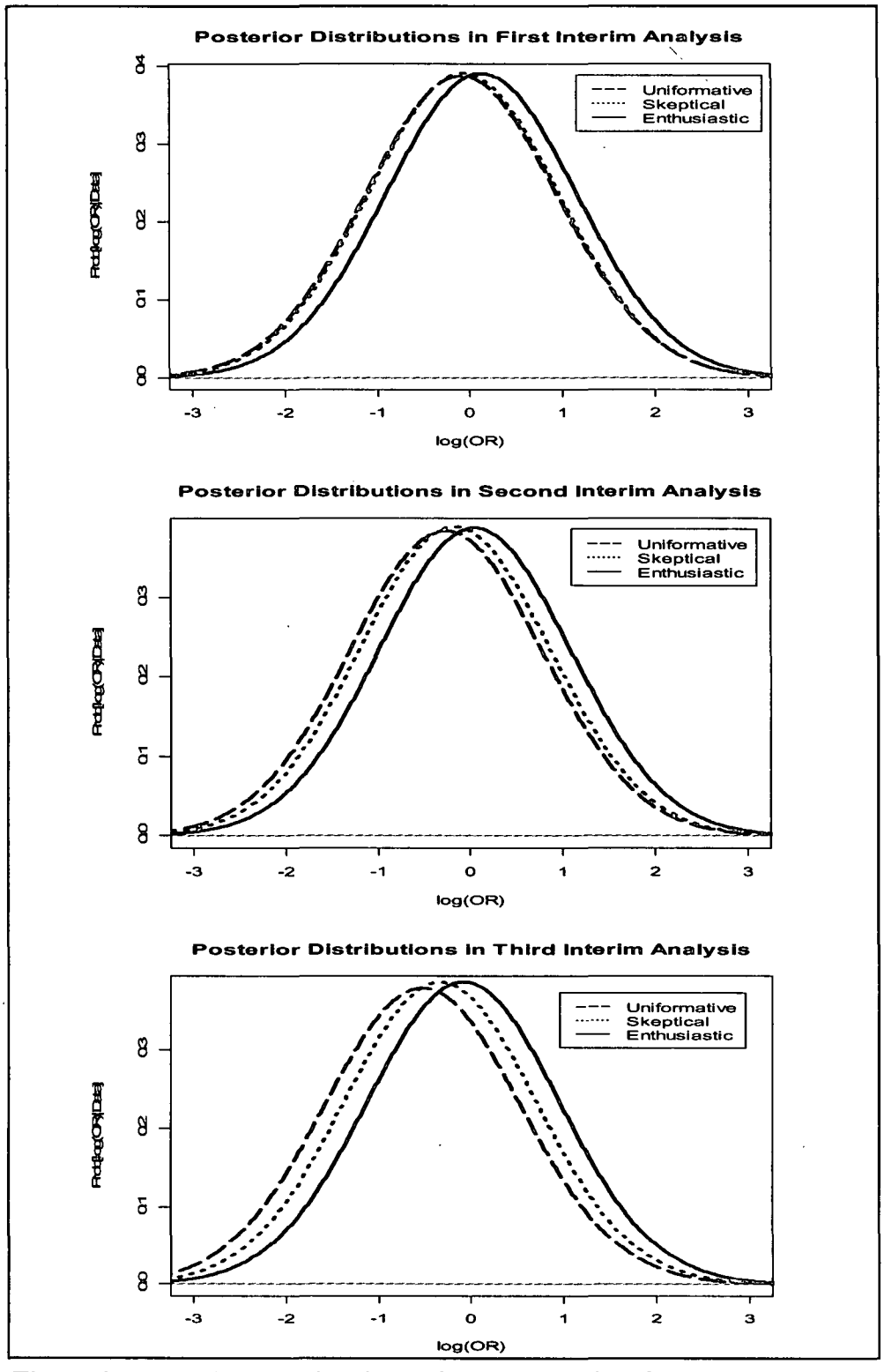

Figure 2. Posterior Distributions of Uninformative, Skeptical and Enthusiastic Priors in Three Simulated Interim Analyses

Table 4. The Predictive Probability of [log(OR_δ)<0] Associated with the Target Prevalence Difference δ with Respect to Prior Distributions per Interim Analysis

DAY		TARGET PREVALENCE DIFFERENCE	log (OR_δ)	PREDICTIVE PROBABILITY		
Clinical Trial	Interim Analysis	δ		Uninformative	Skeptical	Enthusiastic
2	1	0.00	0.683	0.999	1.000	0.995
		0.25	0.301	0.941	0.957	0.797
		0.50	0.000	0.651	0.630	0.288
3	2	0.00	0.683	1.000	1.000	0.997
		0.25	0.301	0.978	0.981	0.872
		0.50	0.000	0.827	0.782	0.431
4	3	0.00	0.683	1.000	1.000	0.998
		0.25	0.301	0.994	0.992	0.925
		0.50	0.000	0.942	0.893	0.608

IV. DISCUSSION

Arnaldo and Gatcheco's study in 2004 showed that the majority of the patients were treated with drugs A and B approximately on the third and fifth days of trial, respectively. However, in this study the Bayesian technique may give a result on when to recommend for the termination of the trial. This technique provides a flexible and philosophically acceptable approach that leads to a consistency between estimation, hypothesis testing and stopping rules (Freedman, Spiegelhalter, and Parmar, 1994).

The conclusion drawn in the test for the association between the drug type and its efficacy showed that there is a need for stopping the trials on the second day. In addition, the OR is less than 1 on that day which indicates that OMX plus ORS is more effective than the ORS alone as the conventional medication. Thus, stopping the trials on the second day is apparently clear. The study of Huang, Bousvaros, Lee et al. in 2002 concluded that bacterial probiotic therapy shortens the duration of acute diarrheal illness in children by approximately one day.

Three interim Bayesian analytical simulations of the clinical trial data on assessing the efficacy of OMX plus ORS in treating acute non-bloody diarrhea were applied. Other community of prior distributions which was not considered in the discussion of this study includes clinical priors representing expert opinion, evidence-based priors, reference priors (Spiegelhalter, 2004) and meta-analysis priors. Considering the predictive probabilities on the first day of interim analysis shown in Table 4, the predictive probability of [log(OR_δ)<0] with associated 0% prevalence difference in all prior distributions is higher than the 95% cut-off probability. This is an indication for stopping the trial. Thus, there is a strong evidence that [log(OR_δ)<0] with the associated 0% prevalence difference against a modest evidence of δ = 25% and slim evidence of δ = 50%. This pointed out that on the first day of interim analysis there is sufficient evidence to conclude that drug A is likely better than drug B. On the second day of interim analysis, the same conclusion is drawn except that there is a strong evidence on the associated δ = 25% in both uninformative and skeptical with 0.978 and 0.981 probabilities, respectively. But the probabilities with δ = 0% is greater than with that of

$\delta = 25\%$. Moreover, the conclusions drawn on the third day of interim analysis are similar to that of the second day of interim analysis. Therefore, on the second day of trial, DMC should recommend that the trial be stopped because the results show conclusively that drug A is likely better than drug B. It is also recommended that the medication using drug B be stopped and that drug A be continued as the better treatment.

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