Bayesian Approach for Analysis of Binary Responses in Clinical Trials with Protocol Amendments

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Abstract

In clinical trials, the study protocols are often amended to modify trial procedures and/or statistical methods during the conduct of the clinical trials. Major or significant modification (adaptation) could result in a shift in the target patient population and consequently lead to a totally different trial, which is unable to answer the medical or scientific questions that the trial is intended to answer. The approaches of covariate-adjusted model for continuous and binary responses have been proposed. In this paper, we propose a Bayesian approach for analysis of binary study endpoint when there is a shift in patient population after protocol amendments.
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Abstract

In clinical trials, the study protocols are often amended to modify trial procedures and/or statistical methods during the conduct of the clinical trials. Major or significant modification (adaptation) could result in a shift in the target patient population and consequently lead to a totally different trial, which is unable to answer the medical or scientific questions that the trial is intended to answer. The approaches of covariate-adjusted model for continuous and binary responses have been proposed. In this paper, we propose a Bayesian approach for analysis of binary study endpoint when there is a shift in patient population after protocol amendments.

\textit{Key Words: Target patient population, Population shift, Protocol amendment, Bayesian approach.}

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1. INTRODUCTION

In clinical research, it is not uncommon to modify trial procedures and/or statistical methods through protocol amendments during the conduct of the clinical trials due to various reasons such as the availability of updated safety information and/or new diagnostic/testing procedures, regularly violations of entry criteria, and/or slow recruitment (see e.g., Cleophas et al., 2002; Chow and Liu, 2003). As indicated in Chow and Shao (2005), a major modification or change to the study protocol could result in a shift in target patient population with respect to location or scale (shape) of the distribution. In addition, frequent and significant modifications/changes could lead to a totally different study, which is unable to address the medical/scientific questions or hypotheses that the original study intended to answer. As a result, statistical inference on the treatment effect under investigation obtained based on the data collected from the clinical trials by ignoring the potential shift in target patient population could be biased and hence misleading.

As indicated in Chow and Chang (2006), if the test procedures and/or statistical methods are modified during the trial, then the resulting data may not be from the target population and, thus, standard statistical methods for data analysis have to be modified in order to reflect the possible shift in target patient population. Lösch and Neuhäuser (2008) also pointed out that the difference in the populations before and
after protocol amendments is usually ignored and the data are pooled in the statistical analysis in practice. In these circumstances, the procedure may introduce a significant bias which undermines the testing assumption that the estimates are unbiased and hence the treatment differences should have mean 0 under null hypothesis. As a result, it can decrease the power of the study, and hence the drawn conclusion may not be reliable and misleading.

Chow and Shao (2005) proposed a covariate-adjusted model with continuous study endpoint for obtaining statistical inference of the treatment effect on the original patient population assuming that the shift in target patient population can be linked by some covariates. Follow the ideas of Chow and Shao (2005), statistical inference with binary study endpoint and the corresponding sample size adjustment are proposed in Yang et al. (2010). In practice, however, such covariates may not exist or may not be observed. To overcome this difficulty, alternatively, Chow et al. (2005) proposed using a sensitivity index, as defined in Chow et al. (2002), to measure the impact of population shift. Under the assumption that the shift in location parameter is random and the shift in scale parameter is fixed, conditional and unconditional inference of the treatment effect of the original patient population can be obtained.

As pointed out by Woodcock (2005), Bayesian approaches to clinical trials of great interest in the medical product development because that they offer a way to gain
valid information in a manner that is more parsimonious of time, resources, and investigational subjects than our current method. In recent years, the possible use of Bayesian methods in clinical trials has been studied extensively in the literature. For example, see Brophy and Joseph (1995); Lilford and Braunholtz (1996); Spiegelhalter et al. (2004); and Louis (2005). In this paper, a Bayesian approach for analysis of binary responses in clinical trials with protocol amendments is derived.

In the next section, a Bayesian approach for estimation of parameters of resultant patient population after some modifications are made is proposed. The impact on statistical inference and sample size adjustment following modifications are given in Section 3. The numerical results are presented in Section 4. Section 5 gives a brief concluding remark.

2. MODEL FORMULATION AND ESTIMATION RESULTS

Consider the case where the study endpoint of a given clinical trial is binary response. In this case, for a given protocol amendment \( i \), the binary responses \( Y_{ij} \), \( j = 1, 2, \ldots, n_i \), are independent and identically distributed in which the sum \( Y_i = \sum_{j=1}^{n_i} Y_{ij} \) has a binomial distribution. Suppose that there are \( k \) protocol amendments. In practice, it is reasonable to assume that there are a set of \( k+1 \) independent binomial variables with possibly different response rates \( p_i \).
\( i = 0, 1, \ldots, k \) before and after protocol amendments. Let \( p_0 \) denote the response rate of the target patient population (i.e., the patient population before any protocol amendments). Our goal is then to estimate the mean response rate when there is a shift in this parameter due to protocol amendments. This problem can be solved in a Bayesian formulation, by treating \( p_i \) as a random variable.

### 2.1 Power-function prior distribution

For Bayesian approach, we need to choose a prior for \( p_i \). In this section, we consider describing \( p_i \) by means of a power-function distribution \( \pi(p) = \theta p^{a-1} \), where \( \theta > 0 \). Given the \( i^{th} \) protocol amendment and the observation \( Y_y = y_y, j = 1, 2, \ldots, n_i \), the likelihood function is

\[
\ell_i = \prod_{j=1}^{n_i} \left[ p_i^{y_j} (1 - p_i)^{1-y_j} \theta p_i^{a-1} \right].
\]

Thus, given \( k \) protocol amendments and independent observations \( y_y, i = 0, 1, \ldots, k \), \( j = 1, 2, \ldots, n_i \), the joint likelihood function is given by

\[
\ell = \prod_{i=0}^{k} \ell_i = \theta^N \prod_{i=0}^{k} \left[ p_i^{y_i + a, (\alpha-1)} (1 - p_i)^{n_i - y_i} \right], \tag{1}
\]

where \( N = \sum_{i=0}^{k} n_i \) and \( y_i = \sum_{j=1}^{n_i} y_j \). The resultant maximum likelihood estimators of \( p_i, i = 0, 1, \ldots, k \), and \( \theta \), which maximize \( \ell \) in (1), can be obtained by solving values \( \hat{p}_i, i = 0, 1, \ldots, k \), and \( \hat{\theta} \) in following equations iteratively:
\[ \hat{p}_i = \frac{y_i + n_i(\hat{\theta} - 1)}{n_i \hat{\theta}}, \quad i = 0, 1, \ldots, k, \text{ and } \hat{\theta} = -\frac{\sum_{i=0}^{N} n_i \ln \hat{p}_i}. \]

Based on the above prior, it can be verified that the mean of random response rate \( p_i \) is \( \mu_p = \theta/(1 + \theta) \). Thus, the maximum likelihood estimator of \( \mu_p \) can be obtained as \( \hat{\mu}_p = \hat{\theta} /(1 + \hat{\theta}) \) by the functional invariance of maximum likelihood estimate (see Casella and Berger, 1990, page 320).

Based on the asymptotic normality of maximum likelihood estimator (under suitable regularity conditions), \( \hat{\theta} \) is normally distributed, \( \sqrt{N}(\hat{\theta} - \theta) \overset{D}{\to} N(0, \theta^2) \). Based on the delta method (Bickel and Doksum, 2001), it follows that \( \sqrt{N}(\hat{\mu}_p - \mu_p) \) is asymptotically normal distributed with mean 0 and variance

\[ V_p = \frac{\theta^2}{(1 + \theta)^2} \]

The derivation is given in Appendix A. Let \( \hat{V}_p = \hat{\theta}^2 /(1 + \hat{\theta})^2 \). It can be shown that \( \hat{\theta} \overset{p}{\to} \theta \) by consistency of maximum likelihood estimator. Thus, it can be shown that \( \sqrt{N}(\hat{\mu}_p - \mu_p) / \sqrt{\hat{V}_p} \) is asymptotically distributed as a standard normal distribution by Slutsky’s Theorem. Consequently, an approximate \( 100(1 - \alpha) \) % confidence interval for \( \mu_p \) is given as \( (\hat{\mu}_p - z_{\alpha/2} \sqrt{\hat{V}_p / N}, \hat{\mu}_p + z_{\alpha/2} \sqrt{\hat{V}_p / N}) \) where \( z_{\alpha/2} \) is the \( 100(1 - \alpha / 2) \) percentile of a standard normal distribution.

### 2.2 Beta prior distribution

In general, the beta distribution is commonly used to model data that are restricted
to the (0, 1) interval, which is indexed by two parameters, $\theta_1$ and $\theta_2$. The beta distribution has been used in certain Bayesian applications as a prior distribution for the binomial parameter, $p_i$ (see, for example, Anscombe, 1961). It should be noted that a number of special cases may be obtained when the values of $\theta_1$ and/or $\theta_2$ are fixed. For example, when $\theta_2 = 1$, the beta distribution reduces to the power-function distribution described above. Beta distribution is often considered in order to display different shapes depending on the parameter values.

Assume that $p_i$ follows a beta distribution with parameters $\theta_1$ and $\theta_2$. The density of $p_i$ is, for each $i = 0, 1, ..., k$, given by

$$
\pi(p) = \frac{\Gamma(\theta_1 + \theta_2)}{\Gamma(\theta_1)\Gamma(\theta_2)} p^{\theta_1-1}(1 - p)^{\theta_2-1},
$$

where $\theta_1 > 0$, $\theta_2 > 0$ and $\Gamma(\cdot)$ is the gamma function. Given the $i^{th}$ protocol amendment and the observations $y_{ij}$, $j = 1, 2, ..., n_i$, the likelihood function is

$$
\ell_i = \prod_{j=1}^{n_i} \left[ \frac{\Gamma(\theta_1 + \theta_2)}{\Gamma(\theta_1)\Gamma(\theta_2)} p_i^{x_{ij}}(1 - p_i)^{1-x_{ij}} \right].
$$

Thus, given $k$ protocol amendments and independent observations $y_{ij}$, $i = 0, 1, ..., k$, $j = 1, 2, ..., n_i$, the joint likelihood function is given by

$$
\ell = \left[ \frac{\Gamma(\theta_1 + \theta_2)}{\Gamma(\theta_1)\Gamma(\theta_2)} \right]^N \prod_{i=0}^{k} \prod_{j=1}^{n_i} \left[ p_i^{x_{ij}}(1 - p_i)^{1-x_{ij}} \right].
$$

The maximum likelihood equations, $\partial \log \ell / \partial p_i = 0$, $i = 0, 1, ..., k$, $\partial \log \ell / \partial \theta_1 = 0$ and $\partial \log \ell / \partial \theta_2 = 0$ for estimators $\hat{p}_i$, $i = 0, 1, ..., k$, $\hat{\theta}_1$ and $\hat{\theta}_2$, respectively, are
\[
\frac{y_i + n_i(\hat{\theta}_1 - 1)}{\hat{p}_i} = \frac{n_i - y_i + n_i(\hat{\theta}_2 - 1)}{1 - \hat{p}_i}, \quad i = 0, 1,..., k;
\]

\[
\psi(\hat{\theta}_1) - \psi(\hat{\theta}_1 + \hat{\theta}_2) = N^{-1} \sum_{i=0}^{k} n_i \log \hat{p}_i;
\]

\[
\psi(\hat{\theta}_2) - \psi(\hat{\theta}_1 + \hat{\theta}_2) = N^{-1} \sum_{i=0}^{k} n_i \log(1 - \hat{p}_i), \quad (3)
\]

where \( \psi(x) = d \log \Gamma(x)/dx \) denotes the digamma function (see, e.g., Bury, 1999).

From equations (3), it is clear that maximum likelihood estimators cannot be obtained in closed forms and have to be computed numerically with an iterative algorithm.

If \( \hat{\theta}_1 \) and \( \hat{\theta}_2 \) are not too small, the approximation \( \psi(x) \approx \log(x - 1/2) \) can be used. (see, e.g., Johnson et al., 1995). Then approximate values of \( \hat{\theta}_1 \) and \( \hat{\theta}_2 \) can be obtained:

\[
\hat{\theta}_1 \approx \frac{1}{2} \left[ 1 - \prod_{i=0}^{k} \left[ n_i(1 - \hat{p}_i) \right]^{1/N} \right] \sqrt{\left[ 1 - \prod_{i=0}^{k} (n_i\hat{p}_i)^{1/N} - \prod_{i=0}^{k} [n_i(1 - \hat{p}_i)]^{1/N} \right]};
\]

\[
\hat{\theta}_2 \approx \frac{1}{2} \left[ 1 - \prod_{i=0}^{k} (n_i\hat{p}_i)^{1/N} \right] \sqrt{\left[ 1 - \prod_{i=0}^{k} (n_i\hat{p}_i)^{1/N} - \prod_{i=0}^{k} [n_i(1 - \hat{p}_i)]^{1/N} \right]}.
\]

Hence, the estimator of \( p_i \) is

\[
\hat{p}_i = \frac{y_i + n_i(\hat{\theta}_1 - 1)}{n_i(\hat{\theta}_1 + \hat{\theta}_2 - 1)}
\]

Starting from these values, solutions of (3) can be obtained by an iterative process.

Based on the prior, it can be verified that the mean of random response rate \( p_i \) is

\[
\mu_p = \frac{\theta_i}{(\theta_1 + \theta_2)} \quad \text{(see, e.g., Johnson et al., 1995).}
\]

Thus, we can obtain the maximum likelihood estimator of \( \mu_p \) as follows.
\[ \hat{\mu}_p = \frac{\hat{\theta}_1}{(\hat{\theta}_1 + \hat{\theta}_2)}. \]

It is shown by the similar derivation for the case of power-function prior shown above that

\[ \sqrt{N}(\hat{\mu}_p - \mu_p) / \sqrt{\hat{V}_p} \xrightarrow{d} N(0, 1), \quad (4) \]

where \( \hat{V}_p = \hat{\theta}_1 \hat{\theta}_2 (\hat{\theta}_1 + \hat{\theta}_2 - 1)/(\hat{\theta}_1 + \hat{\theta}_2)^4 \) is an estimator of \( V_p \) which is the asymptotic variance of \( \hat{\mu}_p \). The proof of (4.4) is given in the Appendix B.

### 3. SAMPLE SIZE ADJUSTMENT

After some modifications are made, the sample size is necessarily adjusted in order to achieve the desired power for detecting a clinically meaningful difference in response rates. First, sample size calculation for one treatment is considered. To test the hypotheses for testing superiority

\[ H_0 : \mu_p - \mu_0 \leq \delta \quad \text{vs.} \quad H_1 : \mu_p - \mu_0 > \delta, \quad (5) \]

where \( \delta \geq 0 \) is the superiority margin. Under the null hypothesis, the following test statistic

\[ T = \frac{\sqrt{N}(\hat{\mu}_p - \mu_0 - \delta)}{\sqrt{\hat{V}_p}} \]

is asymptotically distributed as a standard normal random variable. Thus, for a given significance level \( \alpha \), the null hypothesis would be rejected if \( T > z_\alpha \).
Mathematically, the power function takes the form

\[ P(T > z_\alpha) = P \left( \frac{\sqrt{N}(\hat{\mu}_p - \mu_p)}{\sqrt{\hat{V}_p}} + \frac{\sqrt{N}(\mu_p - \mu_0 - \delta)}{\sqrt{V_p}} > z_\alpha \right) \]

\[ = P \left( \frac{\sqrt{N}(\hat{\mu}_p - \mu_p)}{\sqrt{\hat{V}_p}} > z_\alpha - \frac{\sqrt{N}(\mu_p - \mu_0 - \delta)}{\sqrt{V_p}} \right) \]  

(6)

Since \( \hat{V}_p \) converges in probability to \( V_p \), the second \( \hat{V}_p \) appears in the right hand side of the above expression (6) can be approximated by \( V_p \) to facilitate the determination of the sample size. To achieve a power of \( 1 - \gamma \), the required sample size satisfies

\[ 1 - \gamma = P \left( \frac{\sqrt{N}(\hat{\mu}_p - \mu_p)}{\sqrt{V_p}} > z_\alpha - \frac{\sqrt{N}(\mu_p - \mu_0 - \delta)}{\sqrt{V_p}} \right) . \]

Under the alternative hypothesis, \( \frac{\sqrt{N}(\hat{\mu}_p - \mu_p) / \sqrt{\hat{V}_p}}{\sqrt{V_p}} \) has a limiting standard normal distribution. Thus, the required sample size satisfies

\[ -z_\alpha + \frac{\sqrt{N}(\mu_p - \mu_0 - \delta)}{\sqrt{V_p}} = z_\gamma . \]

The formula for \( N \) is given as

\[ N = \frac{(z_\alpha + z_\gamma)^2 V_p}{(\mu_p - \mu_0 - \delta)^2} \]  

(7)

To use (7), information regarding \( \theta_1 \) and \( \theta_2 \) are needed, which may be obtained through a pilot study or based on historical data. Instead of considering the adjustment for protocol amendments, an alternative classical method of obtaining sample size,
with the same general setup just presented above, is given by

\[
N_{\text{classic}} = \frac{(z_\alpha + z_\gamma)^2 p_0 (1 - p_0)}{(p_0 - \mu_0 - \delta)^2}.
\]  

(8)

This formula and the proposed method (7) are fundamentally different with respect to the specification of the variance of \( \hat{p}_0 \) under the pooled population.

Following a similar procedure in the two-treatment cases, the sample size to achieve a pre-specified power \( 1 - \gamma \) with significance of level \( \alpha \) for each test can be determined. For comparison for two treatments based on beta prior, we have

\[
\sqrt{N}((\hat{\mu}_r - \hat{\mu}_c) - (\mu_r - \mu_c))/\sqrt{\hat{V}_d} \xrightarrow{D} N(0, 1)
\]

where \( N = N_r + N_c \) is the total sample size of the test treatment and the control treatment, \( \hat{\mu}_r \) and \( \hat{\mu}_c \) are the maximum likelihood estimates of the mean response rate for the test treatment \( \mu_r \) and control treatment \( \mu_c \), respectively, and

\[
\hat{V}_d = \frac{1}{w} \left[ \hat{\theta}_r \hat{\theta}_c (\hat{\theta}_r + \hat{\theta}_c - 1)/(\hat{\theta}_r + \hat{\theta}_c)^4 \right] + \frac{1}{1 - w} \left[ \hat{\theta}_c \hat{\theta}_c (\hat{\theta}_c + \hat{\theta}_c - 1)/(\hat{\theta}_c + \hat{\theta}_c)^4 \right],
\]

where \( w = N_r / N_c \).

As indicated by Chow et al. (2007), the problem of testing superiority and non-inferiority can be unified by the following hypotheses:

\[
H_0 : \mu_r - \mu_c \leq \delta \quad \text{vs.} \quad H_1 : \mu_r - \mu_c > \delta
\]  

(9)

where \( \delta \) is the superiority or non-inferiority margin. When \( \delta > 0 \), the rejection of the null hypothesis indicates the superiority of the test treatment over the control.
When \( \delta < 0 \), the rejection of the null hypothesis indicates the non-inferiority of the test treatment against the control. Under the null hypothesis, the test statistic

\[
T = \frac{\sqrt{N}(\hat{\mu}_p - \hat{\mu}_c - \delta)}{\sqrt{V_d}}
\]

approximately follows a standard normal distribution. Thus, we reject the null hypothesis at the \( \alpha \) level of significance if \( T > z_\alpha \).

The required sample size for testing hypotheses in (10) satisfies the following equation,

\[
-z_\alpha + \frac{\sqrt{N}(\mu_p - \mu_c - \delta)}{\sqrt{V_d}} = z_\gamma,
\]

were

\[
V_d = \frac{1}{w}\left[\theta_1 \theta_2 (\theta_1 + \theta_2 - 1)/(\theta_1 + \theta_2)^4 + \frac{1}{1-w}\left[\theta_1 \theta_2 \theta_1 (\theta_1 + \theta_2 - 1)/(\theta_1 + \theta_2)^4\right]\right].
\]

The total sample size is given as

\[
N = \frac{(z_\alpha + z_\gamma)^2 V_d}{(\mu_p - \mu_c - \delta)^2}.
\]

For testing equivalence, the following hypotheses are considered:

\[
H_0 : |\mu_p - \mu_c| \geq \delta \quad \text{vs.} \quad H_1 : |\mu_p - \mu_c| < \delta
\]

where \( \delta \) is the equivalence limit. Thus the null hypothesis is rejected at a significance level \( \alpha \) and the test treatment is concluded to be equivalent to the control if
\[
\frac{\sqrt{N} (\hat{\mu}_p - \hat{\mu}_{pc} - \delta)}{\sqrt{\hat{V}_d}} < -z_\alpha \quad \text{and} \quad \frac{\sqrt{N} (\hat{\mu}_p - \hat{\mu}_{pc} + \delta)}{\sqrt{\hat{V}_d}} > z_\alpha.
\]

Similarly, for testing equivalence (12), the total sample size obtained as

\[
N = \frac{(z_\alpha + z_{\alpha/2})^2 V_d}{(\delta - |\mu_p - \mu_{pc}|)^2}
\]

4. NUMERICAL STUDIES

In this section, the small-sample performance of the proposed method compared with the standard (average) method is assessed through simulations. To compare the different estimators, we investigate the properties of the estimators in terms of the bias and mean square error (MSE).

Suppose that the protocol is amended twice during the conduct of the trial \((k = 2)\). In the \(i\)th amendment, \(i = 0, 1, 2\), we generate \(n_i\) binary responses \(y_{ij}\), \(j = 1, 2, ..., n_i\), with parameter \(p_i\), determined by a power-function prior distribution with parameter \(\theta_i\). In this simulation, three values of \(\theta_i\) are studied to represent different trends of response rates between protocol amendments, namely 1/2, 1, and 3. The corresponding means of random variables \(p_i\) (i.e. \(\mu_p\)) are 0.33, 0.5, and 0.75, respectively, and the corresponding variance of \(p_i\) (i.e. \(V_p\)) are 0.090, 0.083, and 0.038. The three density functions are presented in Figure 1.

For illustrative purposes, the simulations are performed to compare the accuracy of
the proposed estimate $\hat{\mu}_p$ for parameter $\mu_p$ based on different variances of prior distributions. Estimates of accuracy associated with a given sample size $(n_0, n_1, n_2)$ and model configurations are then computed through Monte Carlo simulation based on 1000 replicate data sets. One thousand estimates are computed, and deviations and squared deviations of the estimate from true value are averaged to obtain (estimated) bias and MSE.

The results of the simulation studies are presented in Table 1. From Table 1 it is shown that, in general, the absolute (estimated) bias and MSE of $\hat{\mu}_p$ in the case of large variances are larger than those in the case of small variances. For the three parameter settings, the (estimated) bias and MSE of $\hat{\mu}_p$ decrease as the total sample size increase.

As indicated earlier, in fact, it is of interested to examine the response rate in the original patient population after protocol amendments are made. To compare the
proposed estimate ($\hat{p}_0$) and classical estimate ($\bar{p} = \sum_{i=0}^k \sum_{j=1}^{i_0} y_{ij} / \sum_{i=0}^k n_i$), the small-sample size performance of the two estimators is assessed. We investigate the properties of the estimators in terms of the bias and mean square error (MSE) at the fixed values of $p_0$, $p_1$, and $p_2$. For each generated data set, the deviation and squared deviation of the estimator from the drawn value $p_0$ are obtained. Those deviations and squared deviations are averaged to obtain (estimated) bias and (estimated) MSE.

The results are presented in Table 2(a)-(c). In general, the absolute (estimated) bias and MSE of $\hat{p}_0$ are smaller than those of $\bar{p}$ in the three settings of variance of prior distribution. The absolute (estimated) bias and MSE of $\hat{\mu}_p$ in the case of large variances are larger than those in the case of small variances. For the three cases of variance, the (estimated) bias and MSE of $\hat{p}_0$ decrease as the total sample size increase. However, those of $\bar{p}$ is larger as the total sample size increase.

When there is a shift in response rate of the patient population, it is obvious that the bias and MSE of the proposed method tend to be smaller than those of the classical method. Especially, the classical method displays considerable bias and MSE for large total sample size. Thus, the simulation study indicates that the propose method is superior when a substantial difference in response rate due to protocol amendments.
Table 1  Simulation results for bias and MSE of $\hat{\mu}_p$ based on Bayesian method with different prior parameters

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<th>$n_2$</th>
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<th>$\theta = 1$ ($V_p = 0.083$)</th>
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5. CONCLUDING REMARKS

In clinical research and development, it is not uncommon to issue protocol amendments during the conduct of a clinical trial. As a result, statistical inference on the treatment under investigation obtained based on the data collected before and after protocol amendments ignoring the potential shift in target patient population could be biased and hence misleading. In this paper we propose a Bayesian method to inference the mean response rate and the sample size adjustment for protocol amendments, assuming the actual patient population after modifications is random.

The proposed method is introduced to modify the estimation and the determinations of power and sample size by linking response rate for each amendment by a prior beta distribution. Using computer simulations, if we use the classical method ignoring the shift in population, it shows an increase in estimate bias in the targeted response rate. It is shown that the proposed method performed well as the response rate has been shifted due to protocol amendment. Further research on the issue for protocol amendments is needed to eliminate any bias caused by the modifications.

The goals of this dissertation are to examine the impact of protocol amendments for the clinical trials with binary responses. The corresponding statistical inferences and sample size adjustments are obtained. The results can be easily extended to general discrete variable (categorical data). In clinical trials, in addition to continuous variable and binary (discrete) response, time-to-event data is often considered especially in cancer trials. As indicated by Keogh et al. (2004), it is not uncommon to modify or
adjust the trial procedure of an on-going trial with time-to event data. In this case, the assessment of impact of protocol amendments on statistical inference and the corresponding sample size adjustment have to be developed.

In this paper we only focus on the case where the shift parameters are random. In practice, sample sizes (before and after a protocol amendment) and the number of protocol amendments are also random variables. By taking these into consideration in our statistical model, it will complicate the procedure for obtained estimates of parameters.

**APPENDIX**

**Appendix A. Asymptotic distribution of $\hat{\mu}_p$**

Based on the joint likelihood function (1), the log-likelihood function can be written as

$$l = \sum_{i=0}^{k} \sum_{j=1}^{n} \left[ (y_{ij} + \theta - 1) \ln p_i + (1 - y_{ij}) \ln (1 - p_i) \ln \theta \right],$$

The maximum likelihood estimators $\hat{\theta}$ and $\hat{p}_i$, $i = 0, 1, \ldots, k$, are obtained by the maximum likelihood equations, $\partial l / \partial \theta = 0$ and $\partial l / \partial p_i = 0$, $i = 0, 1, \ldots, k$, respectively, where

$$\frac{\partial l}{\partial \theta} = \sum_{i=0}^{k} \sum_{j=1}^{n} \left[ 1 / \theta + \ln p_i \right]$$
\[
\frac{\partial l}{\partial p_i} = \sum_{j=1}^{n_i} \left( \frac{y_{ij} + \theta - 1}{p_i} - \frac{1 - y_{ij}}{1 - p_i} \right), \quad i = 0, 1, \ldots, k.
\]

In the case, however, the joint asymptotic distribution of \((\hat{\theta}, \hat{p_i}, i = 0, 1, \ldots, k)\) cannot be derived by using the property of asymptotic normality of maximum likelihood estimate because the expectation of \(\partial l / \partial p_i\) may not zero.

In this dissertation, the following property is used to derive the asymptotic distribution of \(\hat{\theta}\):

\[
E\left( \frac{\partial l}{\partial \theta} \right) = \sum_{i=0}^{k} \sum_{j=1}^{n_i} \left[ \frac{1}{\theta} + E(\ln p_i) \right] = 0.
\]

Let \(l'(\theta) = \partial l / \partial \theta\). The asymptotic distribution of \(\hat{\theta}\) needs to be derived by expanding \(l'(\hat{\theta})\) about the true parameter value \(\theta\). (see Lehmann and Casella, 1999).

A sum of Taylor expansions leads to the result that

\[
l'(\hat{\theta}) = l'(\theta) + (\hat{\theta} - \theta) l''(\theta) + 1/2 (\hat{\theta} - \theta)^2 l'''(\theta'),
\]

where

\[
l''(\theta) = \frac{\partial^2 l}{\partial \theta^2} = \sum_{i=0}^{k} \sum_{j=1}^{n_i} \left[ -\frac{1}{\theta^2} \right] = -\frac{N}{\theta^2},
\]

and

\[
l'''(\theta^*) = \left. \frac{\partial^3 l}{\partial \theta^3} \right|_{\theta = \theta^*} = -\frac{2N}{(\theta^*)^3}.
\]

and \(\theta^*\) lies between \(\theta\) and \(\hat{\theta}\). The left side of (A.1) is zero, so that (A.1) can be rewritten as
\[
\sqrt{N}(\hat{\theta} - \theta) = \frac{1}{\sqrt{N}} \frac{l'(\theta)}{l''(\theta)} - \frac{1}{N} l''(\theta) - \frac{1}{2N} (\hat{\theta} - \theta) l'''(\theta^*)
\]  
(A.2)

If \( l'_{ij} \) denote the first derivative of the log likelihood based on the \( j \)th sample after the \( i \)th amendment, thus the first derivative of the log likelihood based on all \( N \) observations can be written as

\[
l'(\theta) = \sum_{i=0}^{k} \sum_{j=1}^{n_i} l'_{ij}.
\]

The expectation of these random variables is 0, their variance is

\[
- E(l''_{ij}) = \frac{1}{\theta^2}.
\]

When all the \( n_i \) tend to infinity, we have

\[
\frac{1}{\sqrt{n_i}} \sum_{j=1}^{n_i} l'_{ij} \xrightarrow{d} N(0, 1/\theta^2)
\]

by the central limit theorem for i.i.d. random variables. Suppose that \( n_i / N \to r_i \), the result follows that

\[
\frac{1}{\sqrt{N}} \sum_{j=1}^{n_i} l'_{ij} \xrightarrow{d} N(0, r_i / \theta^2),
\]

and hence, as \( n_i \to \infty (i = 0, 1, \cdots, k) \) and \( k \) is finite and fixed,

\[
\frac{1}{\sqrt{N}} l'(\theta) = \frac{1}{\sqrt{N}} \sum_{i=0}^{k} \sum_{j=1}^{n_i} l'_{ij} \xrightarrow{d} N(0, 1/\theta^2),
\]  
(A.3)

because that \( \sum_{i=0}^{k} r_i = 1 \).

Next, since \( n_i / N \to r_i \) and for fixed \( i (i = 0, 1, \cdots, k) \), \( -\frac{1}{n_i} \sum_{j=1}^{n_i} l''_{ij} \) tends in probability to \( 1/\theta^2 \) by the weak law of large numbers. Then it is seen that
\[- \frac{1}{N} l^*(\theta) = \sum_{i=0}^{k} \frac{n_i}{N} \left( \frac{1}{n_i} \sum_{j=1}^{n_i} l_i^j \right) \overset{p}{\rightarrow} 1/\theta^2 . \] 

(A.4)

Finally, it follows from \((\hat{\theta} - \theta) \overset{p}{\rightarrow} 0\) and \(\frac{1}{N} l^*(\theta^*)\) is bounded in probability, that

\[ \frac{1}{N} (\hat{\theta} - \theta) l^*(\theta^*) \overset{p}{\rightarrow} 0 . \]

(A.5)

By (A.2), it follows from (A.3), (A.4) and (A.5) that

\[ \sqrt{N}(\hat{\theta} - \theta) \overset{d}{\rightarrow} N(0, \theta^2) \]

as \(n_i \rightarrow \infty\ (i = 0, 1, \ldots, k)\) and \(k\) is finite and fixed.

Hence, the asymptotic distribution of \(\hat{\mu}_p\) can be derived. Let \(g(\theta) = \theta/(1 + \theta)\).

Then we have \(g'(\theta) = 1/(1 + \theta)^2\). Based on Delta method, it can be shown that

\[ \sqrt{N}(g(\hat{\theta}) - g(\theta)) \overset{d}{\rightarrow} N(0, \theta^2 [g'(\theta)]^2) \]

i.e.

\[ \sqrt{N}(\hat{\mu}_p - \mu_p) \overset{d}{\rightarrow} N(0, \theta^2 / (1 + \theta^2)) . \]

Appendix B. Derivation of formula (4)

Based on the maximum likelihood equations (3), the asymptotic covariance matrix of \(\sqrt{N}\hat{\theta}_1\) and \(\sqrt{N}\hat{\theta}_2\) is

\[ V_{\theta} = \left[ \psi'(\theta_1) \psi'(\theta_2) - \psi'(\theta_1 + \theta_2) [\psi'(\theta_1) + \psi'(\theta_2)] \right]^{-1} \]

\[ \times \left[ \begin{array}{cc}
\psi'(\theta_2) - \psi'(\theta_1 + \theta_2) & \psi'(\theta_1 + \theta_2) \\
\psi'(\theta_1 + \theta_2) & \psi'(\theta_1) - \psi'(\theta_1 + \theta_2)
\end{array} \right] . \]
Introducing approximations for $\psi'(\cdot)$ we have, for large values of $\theta_1$ and $\theta_2$,

$$V_0 \approx \begin{bmatrix}
\theta_1(2\theta_1 - 1) & (2\theta_1 - 1)(2\theta_2 - 1)/2 \\
(2\theta_1 - 1)(2\theta_2 - 1)/2 & \theta_2(2\theta_2 - 1)
\end{bmatrix}.$$ 

Based on the consistency of maximum likelihood estimate, by the delta method and Slutsky's Theorem (Bickel and Doksum, 1997), it follows that $\sqrt{N}(\hat{\mu}_p - \mu_p)$ is asymptotically normal distributed with mean 0 and variance

$$V_p = \theta_1 \theta_2 (\theta_1 + \theta_2 - 1)/(\theta_1 + \theta_2)^4.$$ 

Let $\hat{V}_p = \hat{\theta}_1 \hat{\theta}_2 (\hat{\theta}_1 + \hat{\theta}_2 - 1)/(\hat{\theta}_1 + \hat{\theta}_2)^4$, it is known that $\hat{\theta}_1 \xrightarrow{p} \theta_1$ and $\hat{\theta}_2 \xrightarrow{p} \theta_2$ by consistency of maximum likelihood estimate under certain regularity conditions. Thus, it can be shown that $\sqrt{N}(\hat{\mu}_p - \mu_p)/\sqrt{\hat{V}_p}$ is asymptotically distributed as a standard normal distribution by Slutsky’s Theorem.

**REFERENCES**


