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Phase II Basket Group Sequential Clinical Trial with Binary Responses

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Abstract

The basket trial is a recent development in the design of clinical trial. It tests the same treatment on several different related diseases in a single trial and reduces cost and enhances efficiency. The group sequential trial design is commonly used for phase II trials, in which the trial is monitored in several stages and may terminate before the planned end if significant inefficiency is detected. While most existing basket trials are for continuous data, binary data are commonly used in phase II clinical trials. This article will study group sequential basket trial for binary data. We use frailty model to account for the dependence among the different diseases. Simulation studies are carried out to evaluate the performance of the trial.

Keywords: Basket trial; Binary response; Decision boundary; Group sequential clinical trial; Shared frailty model

Introduction

The basket clinical trial design [1-5] is introduced recently to clinical trials. Different from traditional clinical trials, which examine one treatment for one targeted disease, the basket design examines one treatment on several different (but often related) diseases in a single trial. By this way, it explores much more potential of the treatment and reduces costs and time compared with separate trials on different diseases. Another motivation for this type of design is to examine a common response (such as a biomarker response) across multiple diseases (tumors). The number of patients with a putative biomarker within a single disease is small, which makes it difficult to enroll adequate number of patients in a conventional trial and the basket trial which pools the responses of the same biomarker from all the patients with different diseases makes the trial possible, as the enlarged sample size enables the trial be powered adequately. The rationale for basket trial is that the fundamental classification of disease is the molecular subtypes, not disease types [4-10]. The disadvantage of this trial design is that inactive responses from some disease patients may dilute the pooled signal and trigger failure of the entire trial. Thus, this type of trial has been used primarily for exploratory settings [4,11]. Described several examples of such trials in cancer studies, in which six to ten different indications from the same biomarker entered the same trial. They concluded that in their example, a confirmatory study of 120-350 patients has the potential to result in approval of up to 10 indications. Apparently if patients of each indication enter the trial separately, the evidences will be too weak for approval due to insufficient sample sizes.

The group sequential (or multi-stage) design is commonly used in phase II and III clinical trials to evaluate a new treatment against some existing one(s) [12-21]. In contrast to the non-sequential clinical trial, the group sequential trial allows early stopping of the trial before the planned end, if extreme outcome is detected at some intermediate stage.

Most of the existing basket trials are for continuous endpoints. In practice, binary data are commonly used in clinical trials. Here we study group sequential basket trial for such data. As mentioned, patients with different diseases enter the trial through some common factor(s) (such as a biomarker), thus the underlying diseases are generally not independent. We use frailty model to account for the shared dependence among the different diseases. Simulation studies are carried out to evaluate the performance of the trial.

Method

With basket trial design, patients with several different diseases are on the same trial with the same treatment. The goal is to assess the efficacy of the treatment. In this type of trial, patients with the same genetic mutations are brought into the trial, but it is known from diagnosis that their locations of cancer are different and thus the patients have different types of cancer.

In this study, we concentrate on binary response. Assume there are k stages in the trial, up to stage l, the observed data are (x_i,δ_i) for the ith patient, $i=1,\dots,n_l\,(l=1,\dots,k)$. $x_i=1$ or 0 if the ith patient has positive or negative response to the treatment; δ_i is the disease indicator, $\delta_i=j$ if the ith patient has disease type j, $j=1,\dots,d$. Let $I(\cdot)$ be the indicator function, $n_{lj}=\sum_{i=1}^{n_l} I(\delta_i=j)$ be the cumulative sample size for the jth disease at the end of trial stage l, denote $x_{i|j}=x_i|(\delta_i=j)$, i.e., the ith patient given disease type j, and $\mathbf{S}_l=(S_{l1},\dots,S_{ld})$.

$$S_{lj}=\sum_{i=1}^{n_l} x_{i|j},\,(j=1,\dots,d;\,l=1,\dots,k)$$

We assume $x_{i|j}\sim Bernoulli(p_j)$ for all i, then $S_{lj}\sim Binomial(n_{lj},p_j)$.

For phase II clinical trial, often the total number of patients $n=\sum_{l=1}^{k}\sum_{j=1}^{d} n_{lj}$ is small (typically $10<n<100$, $2\le d\le 10$ and $2\le k\le 10$). The hypothetical population means positive response is $\boldsymbol{p}=(p_1,\dots,p_d)'$. We are interested in testing the null hypothesis

$$H_0{:}p\le p_0 \ vs\ H_1{:}p>p_0,$$

where $\boldsymbol{p_0}=(p_{01},\dots,p_{0d})'$ is the given vector of threshold values for the responses to be effective. The diseases themselves are dependent via

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the shared common factor(s), for example, the common biomarker(s) which brought the patients to the trial. Also, the observations of responses S_{lj}'s are dependent. With given marginal distributions, a commonly used method to model dependence among them is to use the copula [22]. For multiple binary outcomes, there are a number of methods using copula, such as the multivariate log it copula model [23]. For binary outcome, a popular copula is the Frank copula [24]. It has been applied in the analysis of familial binary data [25]. Given d marginal distribution functions $F_1(x_1),\ldots,F_d(x_d)$, the Frank copula combines the margins into a joint distribution of the following form

$$F(x) = C_\alpha\left(F_1(x_1),\ldots,F_d(x_d)\right) = -\frac{1}{\alpha}\log\log\left(1+\left(e^{-\alpha}-1\right)\prod_{j=1}^{d}\frac{e^{-\alpha F_j(x_j)-1}}{e^{-\alpha}-1}\right)$$

with the independence model $\lim_{\alpha\to 0}\lim_{\alpha\to 0} C_\alpha(F_1(x_1),\ldots,F_d(x_d)) = \prod_{j=1}^{d} F_j(x_j)$. The dependence between any pairs of (X_i,X_j) can be explained by the relationship between the odds ratio and a function of α [25]. Although the Frank copula (or other copula) gives closed form for the joint distribution and the dependence can be explained, it is not easy to use. For example, we will evaluate the conditional distributions and some quantities *via* simulation and sampling from $C_\alpha(F_1(x_1),\ldots F_d(x_d))$ (or other copula distribution) are not easy, so we propose a simpler model below.

We use shared frailty to model the dependence among the disease responses S_l. With this method, the dependences among the diseases can be characterized in a simple way, without specifying a particular dependence structure on the joint distribution of the diseases. Let C be the shared common factor of the diseases $X_{i|j}$'s and $p_j(C)=P(X_{i|j}=1|C)$ be the conditional probability of disease type j. We assume that conditioning on C, the test statistics for the diseases are independent, i.e.

$$P(S_l|C) = \prod_{j=1}^{d} P(S_{lj}\mid C) = \prod_{j=1}^{d} p_j^{S_{lj}}(C)\left(1-P_j(C)\right)^{n_{lj}-S_{lj}}$$

Thus, the joint law of S_l is given by

$$P(S_l) = \int P(S_l|C=c)P(c)dc = \int\prod_{j=1}^{d} P\left(S_{lj}|C=c\right)P(c)dc$$

In particular, we assume

$P(X_{i|j}=1|C=c)=1-P(X_{i|j}=0|C=c)=\exp(-c\lambda_j)$, $\lambda_j>0,(j=1,\ldots,d)$,

where $C\sim Gamma(\gamma,\gamma)(\gamma\geq 0)$ with density $\frac{\gamma^\gamma}{\tilde{A}(\gamma)}c^{\gamma-1}e^{-\gamma c}$. λ can either be obtained from prior studies, or to be estimated from the current data and λ_j and p_{0j} are related by

$$p_{0j} = \frac{\gamma^\gamma}{\Gamma(\gamma)}\int_0^\infty \exp(-c\lambda_j)c^{\gamma-1}e^{-\gamma c}dc = \frac{\gamma^\gamma}{\left(\gamma+\lambda_j\right)^\gamma},\ (j=1,\ldots,d) \qquad (1)$$

and $\lambda_j = \frac{\gamma}{p_{0j}^{1/\gamma}} - \gamma$.

The covariance between individuals with disease i and $j(1\leq i,j\leq d)$ is

$$Cov(X_i,X_j)=E(X_iX_j)-E(X_i)E(X_j)=E[E(X_iX_j|C)]-p_{0i}p_{0j}$$

$$=\int_0^\infty \frac{\gamma^\gamma}{\Gamma(\gamma)}\exp\left(-c(\lambda_i+\lambda_j)\right)c^{\gamma-1}e^{-\gamma c}dc - p_{0i}p_{0j}$$

$$=\frac{\gamma^\gamma}{(\gamma+\lambda_i+\lambda_j)^\gamma} - \frac{\gamma^\gamma}{\left(\gamma+\lambda_i\right)^\gamma}\frac{\gamma^\gamma}{\left(\gamma+\lambda_j\right)^\gamma} \qquad (2)$$

Then, with $p\left(\lambda_j,c\right)=\exp\left(-c\lambda_j\right)=\exp\left(-c\left(\frac{\gamma}{p_{0j}^{1/\gamma}}-\gamma\right)\right)$

$$P\left(S_l|\gamma\right) = \frac{\gamma^\gamma}{\Gamma(\gamma)}\int_0^\infty\prod_{j=1}^{d} p(\lambda_j,c)^{S_{lj}}\left[1-p\left(\lambda_j,c\right)\right]^{n_{lj}-S_{lj}}c^{\gamma-1}e^{-\gamma c}dc \qquad (3)$$

At each stage l, the parameter γ will be estimated by the maximum likelihood estimate $\hat{\gamma}_l$,

$$\hat{\gamma}_l = \arg\max_\gamma P\left(S_l|\gamma\right),\left(l=1,\ldots,k\right).$$

Also, conditioning on $\boldsymbol{S}_k$, the distribution of $\boldsymbol{S}_l$ is

$$P\left(S_l|S_k,\gamma\right) = \frac{P\left(S_k|S_l,\gamma\right)P\left(S_l|\gamma\right)}{P\left(S_k|\gamma\right)}$$

$$=\frac{\int_0^\infty\prod_{j=1}^{d} p(\lambda_j,c)^{S_{kj}-S_{lj}}[1-p(\lambda_j,c)]^{\left(n_{kj}-n_{lj}\right)-\left(S_{kj}-S_{lj}\right)}c^{\gamma-1}e^{-\gamma c}dc\times P\left(S_l|\gamma\right)}{\int_0^\infty\prod_{j=1}^{d} p(\lambda_j,c)^{S_{kj}}[1-p\left(\lambda_j,c\right)]^{n_{kj}-S_{kj}}c^{\gamma-1}e^{-\gamma c}dc},$$

w.ith $P(S_l|\gamma)$ given in (3).

The above method using a shared common factor to describe the dependence relationship among several variables is called *shared frailty model* in statistics [26,27] and has appeared in many applications [28-31]. The choice of Gamma distribution for C is also common and convenient to use.

Without the shared frailty assumption, one must use another method to model the dependence among the multiple binary responses $(S_1,\ldots,S_k)$. One simple joint model for binary responses is the multinomial distribution. However, this distribution is inappropriate for this problem, since for the multinomial distribution, once the values of $(S_1,\ldots,S_{k-1})$ are known, the value of S_k is determined. Apparently, the observations of our problem were not obtained this way. Except for multinomial distribution, there are few options for a joint model which is simple to use. The copula model described in Section 2 is a general way for modeling dependence, but as mentioned before, this model is also complicated to use for our case. In contrast, the frailty model described above is relatively simple to use, without specifying a particular dependence structure on the joint distribution of the diseases.

Testing each single hypothesis

In practice, it is of interest to test the effect of the treatment on each of the disease types, which can be formulated as $H_{0j}:p_j\leq p_{0j}$ vs $H_{1j}:p_j>p_{0j},(j=1,\ldots,d)$.

To test H_{0j} *vs* H_{1j} at the lth interim stage, a simple way is just use the statistic $S_{lj}(j=1,\ldots,d)$. However, that is the classical trial, not the basket trial. In the latter trial, we want to use the information across all the diseases to perform each single hypothesis. To borrow information from all the disease types, let $S_{l,-j}$ be S_l with the jth component removed, we use the conditional statistic $S_{lj}|S_{l,-j}$, which has distribution for

$r=0,1,\ldots,n_{lj}$; $j=1,\ldots,d$; $P\left(S_{lj}=r|S_{l,-j}\right)=\frac{P(S_{l,-j},S_{lj}=r)}{S_{l,-j}}$

$$=\frac{\int_0^\infty\left(\prod_{i\neq j}^{d} p(\lambda_i,c)^{S_{li}}[1-p(\lambda_i,c)]^{n_{li}-S_{li}}\right)p^r(\lambda_j,c)\left(1-p\left(\lambda_j,c\right)\right)^{n_{lj}-r}c^{\gamma-1}e^{-\gamma c}dc}{\int_0^\infty\prod_{i\neq j}^{d} p(\lambda_i,c)^{S_{li}}[1-p\left(\lambda_i,c\right)]^{n_{li}-S_{li}}c^{\gamma-1}e^{-\gamma c}dc}. \qquad (4)$$

Let (a_{lj},b_{lj}) be the decision boundary such that, with α_{lj} be determined in Section 2.2,

$P_{Ho}(S_{lj}\leq a_{lj}|S_{l,-j})\leq\alpha_{lj}$, $P_{Ho}(S_{lj}\geq b_{lj}|S_{l,-j})\leq\alpha_{lj}$.

Note that the boundaries (a_{lj},b_{lj})'s depend on the $S_{l,-j}$'s, so the decision at each stage is data dependent, such data dependent procedure is favored from the Bayesian point of view. If $S_{lj}\leq a_{lj}$, H_{0j} is accepted; if $S_{lj}\geq b_{lj}$, H_{0j} is rejected. For given value of $(S_{lj},S_{l,-j})$, the boundaries$(a_{lj},b_{lj})(j=1,\ldots,d;l=1,\ldots,k)$ can be computed using (4) and (3).

If H_{0j} is either accepted or rejected at stage l, then data on the jth disease will be removed and the trial moves on based on the remaining data. If $S_{lj} \in (a_{lj}, b_{lj})$, the trialon disease j is continued to the next stage.

However, the conditional distribution (4) is not easy to evaluate. Below we use approximate method. Note that approximately $T_{lj} = \frac{S_{lj}}{\sqrt{n_{lj}}} \sim N\left(u_{0j}, w_{jj}\right)$ with, $u_{0j} = \sqrt{n_{lj}}\, p_{0j}, w_{jj} = Var\left(X_j\right) = p_{0j}\left(1-p_{0j}\right)$. Let $T_l = (T_{l1}, \ldots, T_{ld})'$. Similarly, $T_l \sim (u_0, \Omega)$, with $\Omega = (w_{ij})_{d*d}$ and $w_{ij} = Cov(X_i, X_j)$ given in (2). Let $T_{l,-j}$ be T_l with the jth component removed. Let Ω_{-j} be the $(d-1)*(d-1)$ matrix of Ω with jth row and jth column removed, w_{-j} be the jth row of Ω and with w_{jj} removed, $u_{0,-j}$ be $u_0$with the jth component removed. Then approximately $T_{lj} | T_{l,-j} \sim N(u_{l,j}, w_{l,j})$, where. $u_{l,j} = u_{0j} + w_{-j}\Omega_{-j}^{-1}\left(T_{l,-j} - u_{0,-j}\right)$, $w_{l,j} = w_{jj} - w_{-j}\Omega_{-j}^{-1}w_{-j}$ With α_{lj}'s given in Section 2, the boundaries (a_{lj}, b_{lj})'s for the T_{lj}'s are given by

$$a_{lj} = u_{l,j} + \sqrt{w_{l,j}}\,\Phi^{-1}(\alpha_{lj}), b_{lj} = u_{l,j} + \sqrt{w_{l,j}}\,\Phi^{-1}\left(1-\alpha_{lj}\right) \qquad (5)$$

In comparison, for independent trial (non-basket trial), $T_{lj} \sim N(u_{0j}, w_{l,jj})$. Its boundaries are computed similarly as

$$\tilde{a}_{lj} = u_{0j} + \sqrt{w_{l,jj}}\,\Phi^{-1}(\alpha_{lj}), \tilde{b}_{lj} = u_{0j} + \sqrt{w_{l,jj}}\,\Phi^{-1}(1-\alpha_{lj}) \qquad (6)$$

Family-wise type I error

For group sequential clinical trial, the family-wise type I error is an important issue. It requires, for given significance levelα,

$$P_{H0}(\text{Reject}H_0) \le \alpha$$

Let $\alpha(\cdot)$ be a non-decreasing function on [0,1] with $\alpha(0)=0$ and $\alpha(1)=\alpha$, in the case of two-tests and two-stages, [32] proposed boundary (c_1, c_2) in their case by

$P_{H_0}\left(T_1 > c_1\right) = \alpha(\frac{n_1}{n})$ and $P_{H0}(T_1 > c_1) + P_{H0}(T_1 \le c_1, T_2 > c_2) = \alpha(1) = \alpha$.

Let $n = \sum_{l=1}^{k} n_l$. In our case, we set $\alpha_{lj} = \frac{n_{lj}}{n}\alpha_0$, with α_0 determined below.

In our case, we define rejection of H_0 in the strict sense as: at least one rejection of the tests at any of the stages. We only consider the case of $k=2$ stages. The case $k>2$ is similar. In this case the family-wise type I error is

$P_{Ho}(\text{Reject}H_0) = P_{Ho}$(at least one rejection at stage I)$+P_{Ho}$(no rejection at stage I and trial continue, at least one rejection at stage II)

Note that

P_{Ho}(at least one rejection at stage I)$=1-P_{Ho}$(no rejection at stage I)

$$= 1 - \int_0^\infty \prod_{j=1}^{d} P_{H_0}\left(S_{1j} \le b_{1j} | c\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= 1 - \int_0^\infty \prod_{j=1}^{d} E\left(P_{H_0}\left(S_{1j} \le b_{1j} | S_{1,-j}, c\right)\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= 1 - \int_0^\infty \prod_{j=1}^{d} \left(1 - \frac{n_{1j}\alpha_0}{n}\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= 1 - \prod_{j=1}^{d} \left(1 - \frac{n_{1j}\alpha_0}{n}\right)$$

Similarly,

P_{Ho}(no rejection at stage I and trial continue, at least one rejection at stage II)

$= P_{Ho}(S_{lj} \le b_{lj}$, all j, at least one $S_{lj} > a_{1j}; S_{2j} > b_{2j}$ for at least one $j)$

$= P_{Ho}(S_{lj} \le b_{lj}$, all j; $S_{2j} > b_{2j}$ for at least one $j)$

$-P_{Ho}(S_{lj} \le b_{lj}, S_{lj} \le a_{lj}$ all j, $S_{2j} > b_{2j}$ for at least one $j)$

$= P_{Ho}(S_{lj} \le b_{lj}$, all j; $S_{2j} > b_{2j}$ for at least one $j)$

$-P_{Ho}(S_{1j} \le a_{1j}$ all j; $S_{2j} > b_{2j}$ for at least one $j)$

$= P_{Ho}(S_{lj} \le b_{lj}$, all $j) - P_{Ho}(S_{lj} \le b_{lj}$, all j; $S_{2j} \le b_{2j}$all$j)$

$-P_{Ho}(S_{lj} \le a_{lj}$, all $j) + P_{Ho}(S_{lj} \le a_{lj}$, all j; $S_{2j} \le b_{2j}$all$j)$

$$= \prod_{j=1}^{d}\left(1 - \frac{n_{1j}\alpha_0}{n}\right) - \prod_{j=1}^{d}\left(1 - \frac{n_{1j}\alpha_0}{n}\right)\prod_{j=1}^{d}\left(1 - \frac{n_{2j}\alpha_0}{n}\right)$$

$$-\prod_{j=1}^{d}\frac{n_{1j}\alpha_0}{n} + \prod_{j=1}^{d}\frac{n_{1j}\alpha_0}{n}\prod_{j=1}^{d}\left(1 - \frac{n_{2j}\alpha_0}{n}\right).$$

In the above we assumed $P_{H_0}\left(S_{1j} \le a_{1j}\right) = P_{H_0}\left(S_{1j} > b_{1j}\right) = \frac{n_{1j}}{n}\alpha_0$ and used conditioning to evaluate the probabilities, for example,

$P_{Ho}(S_{lj} \le b_{lj}$, all j; $S_{2j} \le b_{2j}$all$j)$

$$= \int_0^\infty \prod_{j=1}^{d} P_{H_0}\left(S_{1j} \le b_{1j} | c\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc \int_0^\infty \prod_{j=1}^{d} P_{H_0}\left(S_{2j} \le b_{2j} | c\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= \int_0^\infty \prod_{j=1}^{d} E\left(P_{H_0}\left(S_{1j} \le b_{1j} | S_{1,-j}, c\right)\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$\times \int_0^\infty \prod_{j=1}^{d} E\left(P_{H_0}\left(S_{2j} \le b_{2j} | S_{2,-j}, c\right)\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= \int_0^\infty \prod_{j=1}^{d} \left(1 - \frac{n_{1j}\alpha_0}{n}\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc \int_0^\infty \prod_{j=1}^{d} \left(1 - \frac{n_{2j}\alpha_0}{n}\right) \frac{\gamma^\gamma}{\tilde{A}(\gamma)} c^{\gamma-1} \exp\exp\left(-\gamma c\right) dc$$

$$= \prod_{j=1}^{d}\left(1 - \frac{n_{1j}\alpha_0}{n}\right)\prod_{j=1}^{d}\left(1 - \frac{n_{2j}\alpha_0}{n}\right)$$

Collecting terms, the family-wise type I error for the two-stage case is

$$\alpha = 1 - \prod_{j=1}^{d}\frac{n_{1j}\alpha_0}{n} + \prod_{j=1}^{d}\frac{n_{1j}\alpha_0}{n}\prod_{j=1}^{d}\left(1 - \frac{n_{2j}\alpha_0}{n}\right) - \prod_{j=1}^{d}\left(1 - \frac{n_{1j}\alpha_0}{n}\right)\prod_{j=1}^{d}\left(1 - \frac{n_{2j}\alpha_0}{n}\right)$$

For given α (typically $\alpha=0.05$), we solve α_0 from the above equation, then get $\alpha_{lj} = \frac{n_{lj}}{n}\alpha_0$ and then based on these a_{lj}'s, to compute the boundaries (a_{lj}, b_{lj})'s via simulation.

Simulation Study

Our simulation study has two parts: evaluating the performance of the basket trial under the model assumption of Section 2 and comparing it with the classical trial; investigating the sensitivity of the distributional assumption of the shared frailty C. They are described below.

Simulation set up

The simulation can be carried out for any given $(k, d, n_1, \ldots, n_k)$. Here we only describe it for $k=2, d=5, (n_1, n_2)=(200,100)$ with various choices of parameters. Set $p_0=(p_0, \ldots, p_0)$, for $p_0=0.4, 0.5, 0.6$, respectively. We want to test $H_0: p \le p_0$ vs $H_1: p > p_0$. Set $\gamma=1$ and 0.5, respectively and $q=(0.2, 0.2, 0.2, 0.2, 0.2)$.

To sample the data, for $i=1, \ldots, M$ (typically $M \ge 10{,}000$), do the following:

(1) Sample $(n_{11}, \ldots, n_{15}) \sim Multinomial(n_1, q), (n_{21}, \ldots, n_{25}) \sim$

Table 1: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(20, 36)[16]	(9, 28)[19]	42	46	0.00471
	2	(20, 36)[16]	(8, 26)[18]	27	42	0.00430
	3	(18, 33)[15]	(7, 24)[17]	33	39	0.00400
	4	(16, 31)[15]	(5, 21)[16]	22	33	0.00338
	5	(18, 34)[16]	(7, 25)[18]	34	40	0.00409
2	1	(30, 48)[18]	(17, 38)[21]	55	68	0.00696
	2	(25, 42)[17]	(12, 31)[19]	34	53	0.00542
	3	(24, 41)[17]	(13, 32) [19]	50	56	0.00573
	4	(28, 45)[17]	(13, 32)[19]	26	56	0.00573
	5	(30, 49)[19]	(16, 37)[21]	49	67	0.00685

Table 2: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(7,24)[17]	(14,33)[19]	2	47	0.00481
	2	(0,15)[15]	(8,25)[17]	13	33	0.00338
	3	(4,21)[17]	(14,32)[18]	18	46	0.00471
	4	(5,21)[16]	(12,30)[18]	1	42	0.00430
	5	(2,16)[14]	(8,24)[16]	0	32	0.00327
2	1	(14,33)[19]	(22,42)[20]	4	64	0.00655
	2	(9,28)[19]	(20,40)[20]	30	60	0.00614
	3	(12,31)[19]	(22,42)[20]	19	64	0.00655
	4	(14,33)[19]	(21,42)[21]	1	63	0.00645
	5	(7,25)[18]	(15,34)[19]	9	49	0.00501

Table 3: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(6,22) [16]	(13,30)[17]	8	36	0.00368
	2	(6,21) [15]	(12,29)[17]	0	34	0.00348
	3	(9,26) [17]	(17,35)[18]	7	43	0.00440
	4	(9,26)[17]	(18,36)[18]	18	45	0.00460
	5	(8,24)[16]	(16,34)[18]	15	42	0.00430
2	1	(20,39)[19]	(27,47)[20]	24	61	0.00624
	2	(19,37)[18]	(24,44)[20]	17	57	0.00583
	3	(20,39)[19]	(26,46)[20]	21	60	0.00614
	4	(20,39)[19]	(27,47)[20]	28	62	0.00634
	5	(19,38)[19]	(26,46)[20]	26	60	0.00614

Multinomial (n_2,q).

(2) Given the n_{lj}'s, sample $C \sim Gamma(\gamma,\gamma)$, then given this c sample S_l from (1), for l=1,2. i.e., given $C=c$, for fixed l, the S_{lj}'s are independent $Binomial(n_{lj},p_j(c))$.

(3) Compute the α_{lj}'s as in Section 2.2 and find the (a_{lj},b_{lj})'s given in Section 2.1.

(4) Test the H_{0j}'s at stage l=1,2, using $S_l=(S_{l1},\ldots,S_{ld})$ and the (a_{lj},b_{lj})'s.

(5) Set v_i=1 is H_0 is rejected, otherwise v_i=0. Then the simulated family-wise type I error rate is

$$\hat{\alpha} = \frac{1}{M}\sum_{i=1}^{M} v_i.$$

Table 4: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(26,42)[16]	(19,37)[18]	47	47	0.00481
	2	(23,39)[16]	(15,33)[18]	29	40	0.00409
	3	(21,35)[14]	(12,29)[17]	19	34	0.00348
	4	(25,41)[16]	(18,36)[18]	42	45	0.00460
	5	(18,33)[15]	(12,29)[17]	34	34	0.00348
2	1	(36,55)[19]	(27,47)[20]	49	62	0.00634
	2	(40,59)[19]	(31,52)[21]	58	69	0.00706
	3	(29,46)[17]	(20,38)[18]	29	48	0.00491
	4	(38,57)[19]	(30,51)[21]	61	67	0.00685
	5	(30,48)[18]	(23,42)[19]	52	54	0.00552

Table 5: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(0,16)[16]	(9,27)[18]	17	36	0.00368
	2	(5,21)[16]	(12,30)[18]	2	42	0.00430
	3	(7,24)[17]	(14,32)[18]	0	46	0.00471
	4	(2,17)[15]	(10,27)[17]	12	37	0.00379
	5	(4,19)[15]	(11,28)[17]	4	39	0.00399
2	1	(6,24)[18]	(17,37)[20]	33	54	0.00552
	2	(17,36)[19]	(23,45)[22]	3	68	0.00696
	3	(13,32)[19]	(22,43)[21]	17	65	0.00665
	4	(9,27)[18]	(18,38)[20]	17	56	0.00573
	5	(12,30)[18]	(18,39)[21]	4	57	0.00583

Table 6: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(5,23)[18]	(10,28)[18]	5	47	0.00481
	2	(1,17)[16]	(7,25)[18]	24	40	0.00409
	3	(2,17)[15]	(5,22)[17]	0	34	0.00348
	4	(5,22)[17]	(9,27)[18]	1	45	0.00460
	5	(2,17)[15]	(5,22)[17]	2	34	0.00348
2	1	(5,18)[13]	(15,35)[20]	5	62	0.00634
	2	(3,17)[14]	(17,38)[21]	24	69	0.00706
	3	(1,14)[13]	(10,28)[18]	2	48	0.00491
	4	(7,21)[14]	(16,37)[21]	1	67	0.00685
	5	(1,14)[13]	(12,31)[19]	10	54	0.00552

Results

Below we show the simulation results for six different choices of parameters compute the decision boundaries of the basket trial for each disease at each stage and compare the corresponding boundaries with the independent classical trials. We assume the statistics S_{lj}'s are used to test the H_{0j}'s in the basket trial. The results are shown in Tables 1-6, in which (a_{lj},b_{lj}) is the decision boundary for the basket trial at stage l for disease j, $(\tilde{a}_{lj},\tilde{b}_{lj})$ is that for the classical trial. In square

Table 7: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(15,33)[18]	(21,39)[18]	3	50	0.00512
	2	(10,27)[17]	(17,35)[18]	13	43	0.00440
	3	(6,22)[16]	(15,32)[17]	24	39	0.00399
	4	(6,21)[15]	(12,29)[17]	10	34	0.00348
	5	(6,21)[15]	(12,29)[17]	8	34	0.00348
2	1	(27,47)[20]	(35,56)[21]	8	76	0.00778
	2	(16,34)[18]	(25,45)[20]	24	59	0.00604
	3	(14,33)[19]	(25,45)[20]	30	58	0.00593
	4	(16,34)[18]	(24,44)[20]	15	57	0.00583
	5	(12,30)[18]	(21,39)[18]	16	50	0.00512

Table 8: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(12,29)[17]	(21,39)[18]	9	50	0.00512
	2	(9,25)[16]	(17,35)[18]	7	43	0.00440
	3	(4,19)[15]	(15,32)[17]	24	39	0.00399
	4	(5,20)[15]	(12,29)[17]	4	34	0.00348
	5	(5,19)[14]	(12,29)[17]	7	34	0.00348
2	1	(26,46)[20]	(35,56)[21]	18	76	0.00778
	2	(17,35)[18]	(25,45)[20]	18	59	0.00604
	3	(14,33)[19]	(25,45)[20]	32	58	0.00593
	4	(17,36)[19]	(24,44)[20]	7	57	0.00583
	5	(12,30)[18]	(21,39)[18]	18	50	0.00512

Table 9: Summary of simulation results.

Stage	Disease	(a_{lj},b_{lj})	$(\tilde{a}_{lj},\tilde{b}_{lj})$	s_{lj}	n_{lj}	α_{lj}
1	1	(9,25)[16]	(21,39)[18]	11	50	0.00512
	2	(5,20)[15]	(17,35)[18]	15	43	0.00440
	3	(5,20)[15]	(15,32)[17]	3	39	0.00399
	4	(2,17)[15]	(12,29)[17]	4	34	0.00348
	5	(3,17)[14]	(12,29)[17]	3	34	0.00348
2	1	(24,44)[20]	(35,56)[21]	29	76	0.00778
	2	(16,34)[18]	(25,45)[20]	20	59	0.00604
	3	(17,35)[18]	(25,45)[20]	9	58	0.00593
	4	(15,33)[18]	(24,44)[20]	22	57	0.00583
	5	(12,30)[18]	(21,39)[18]	12	50	0.00512

bracket $[b_{lj}-a_{lj}]$ is the length of the interval (a_{lj},b_{lj}), similarly for $[\tilde{b}_{lj}-\tilde{a}_{lj}]$. The shorter the interval length is, the more accurate the decision will be. We see from the following tables that the interval lengths of the basket trial are uniformly shorter than those of the classical trial, due to the use of cross information from all the diseases.

(1) p_0=0.4, γ=1, $\hat{\gamma}_1=1.2, \hat{\gamma}_2=1.2$.

We see that the results from the basket trial are more reasonable. For example, at stage 1, for disease 2, a total response of 27 out of 42 patients is significant for independent trial. But in view of information across all the diseases, it is not significant enough to reject H_{02} at the first stage. Similarly for disease 4 at stage I and disease 2 at stage II.

(2) p_0=0.5, γ=1, $\hat{\gamma}_1=1.1, \hat{\gamma}_2=1.8$.

There are some differences between the basket and classical trial decisions. For example, at stage 2, for disease 3, a total response of 19 out of 64 patients is small enough to accept H_{03}. But in view of information across all the diseases, it is not small enough to accept H_{03} at the second stage. Similarly for disease 5 at second stage. Only for disease 2 at stage 2, a total response of 30 out of 60 patients is significant for basket trial, however is not significant for independent trial.

(3) p_0=0.6, γ=1, $\hat{\gamma}_1=1.3, \hat{\gamma}_2=1.4$.

At stage 1, for disease 1, a total response of 8 out of 36 patients is small enough to accept H_{01} and early stop the trial for independent trial. But in view of information across all the diseases, it is not small enough to accept H_{01} at the first stage. Similarly for disease 1 at stage II, disease 4 and 5 at stage I, disease 3 and 5 at stage II.

(4) p_0=0.6, γ=0.5, $\hat{\gamma}_1=1.1, \hat{\gamma}_2=1.6$.

At stage II, for disease 1, a total response of 49 out of 62 patients is significant for independent trial. But in view of information across all the diseases, it is not significant enough or eject H_{01} at the second stage. Similarly for disease 2 at stage II.

(5) p_0=0.5, γ=0.5, $\hat{\gamma}_1=1.1, \hat{\gamma}_2=1.3$.

We see that at stage I, for disease 1, a total response of 17 out of 36 patients is significant enough to reject H_{01} for basket trial. But for independent trial, it is not significant enough to reject H_{01} at the first stage. Similarly for disease 1 at stage II. However, for disease 4 in stage II, a total response of 17 out of 56 patients is small enough to accept H_{04} for independent trial; it is not small enough for basket trial.

(6) p_0=0.4, γ=0.5, $\hat{\gamma}_1=1.7, \hat{\gamma}_2=0.1$.

We see that at stage I, for disease 2, a total response of 24 out of 40 patients is significant enough to reject H_{02} for basket trial. But for independent trial, it is not significant enough to reject H_{02} at the first stage. Similarly for disease 2 at stage II. However, for disease 3 in stage II, a total response of 2 out of 48 patients is small enough to accept H_{03} for independent trial; it is not small enough for basket trial. Similarly for disease 5 at stage II.

Sensitivity analysis on the distribution of *C*

In our frailty model in Section 2, the shared frailty *C* is assumed as *Gamma(γ,γ)* distribution, which is a common practice in many statistical applications. Here we want to investigate how sensitive the results are to this assumption. Below we simulate three cases. In the first two cases, *C* is not from a *Gamma(γ,γ)* distribution, but we still treat it as *Gamma(γ,γ)* in the analysis. In the third case, *C* is from *Gamma(γ,γ)* distribution. The results are compared and shown in (Tables 7-9).

(1) The data are generated with $C \sim N(1.1)$. We still use the method and treat *C* as Gamma distribution p_0=0.6.

(2) The data are generated with $C \sim Uniform(1-\frac{\sqrt{12}}{2}, 1+\frac{\sqrt{12}}{2})$. We still use the method and treat *C* as Gamma distribution p_0=0.6.

(3) The data are generated based on $C \sim Gamma(1,1)$. p_0=0.6.

From our simulation studies, the results are not very sensitive to the assumption of the shared frailty *C*. However, the *Gamma(γ,γ)* distribution assumption makes the computation much easier.

Conclusion

A frame work for basket trial with binary outcome is proposed and investigated, in which the joint distribution of the different diseases is modeled *via* shared frailty. Simulation study is conducted to evaluate the performance of the method. By borrowing information across all the related diseases, the results from the basket trial are more reasonable than those from the classical in dependent trial.

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