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Revised Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

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Matthew Chukwuma Michael [α], Oyeka I. C. A. [σ] & Ajibade Bright [ρ]

Abstract- This paper proposes and presents a method for the estimation of approval probabilities of new drug or product. The proposed method assumes that three evaluation communities are used to assess and evaluate the quality of a new drug or product and that the evaluation is done by the committees in three period phased clinical trials of the drug or product using matched samples of subjects at each phase. Estimates of absolute and conditional approval probabilities by various combination evaluation committees at each phase of clinical trials are provided. Test statistics are also developed testing desired hypothesis at each of the phased clinical trials. The proposed method is illustrated with some sample data. It is shown in terms of estimated probability that it is more difficult for all three evaluation committees to be in complex agreement to approve or not approve a new drug or product than for fewer evaluation committees to grant approval.

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I. Introduction

As observed in Onyiora et al (2013) most health care professionals would want their patients to have the best available clinical care but the problem these professional often have is the inability to clearly identify the optimum drug or interventionist procedure to adopt in patient treatment and management and often rely on own experience or those of colleagues in actual practice. However, health professionals are increasingly relying on evidence based medical and health practices hinged on a systematic review, evaluation, assessment and application of clinical research findings (Rising, Bacchetti and Baro, 2009; Chow and Liu, 2004). In medical practice and health management, erroneous and misguided approval of a new drug or product is often hazardous and costly in human and material resources (Gobburn and Leske, 2009). Following a sequence of clinical trials often conducted in phases by evaluation bodies or committees, approval of a new drug or product for use in a population may be granted if the drug or product satisfies some set of predetermined criteria for use (Haff, 2003). In controlled clinical trials of new drug or product using cross sectional, prospective or retrospective study methods, the trials are usually conducted in phases using usually test animals and subsequently volunteer human subjects (Onyiora et al, 2013; Lipkovic et al, 2008). Approval for use of a new drug product in a population is granted only after the phased clinical trials the proportion of subjects improving with the new drug or product is higher than the proportion improving with the standard drug under all or most of the evaluation committees involved in the phased clinical trials.

Following the phased clinical trial procedures, specifically using three period phased clinical trials by three evaluation committees. Onyiora et al (2013) proposed and

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developed a probability model that would enable the calculation of the proportion or probabilities of approving or not approving new drug or product by none, some or all the evaluation committees.

The probability estimation model developed by the authors is however most useful if the probabilities'*a-g*' are given or already known and hence can readily be used in the estimation of the probabilities of possible outcomes including the outcomes listed in the authors' Table 2.The method under reference does not however provide a method to use in the a-priori estimation of the probabilities '*a-g*' if not already given and are not known, and must be estimated from sample data obtained in relevant phased clinical trials of a new drug or product.

In this paper we propose to develop a more generalized method for the estimation of probabilities of outcomes in phased controlled clinical trials of a drug or product by three evaluation committees. The present method would readily enable one estimate probabilities of approval or non-approval of a new drug or product using sample data obtained in three phased clinical trials by three evaluation committees: in a cross-sectional, prospective or retrospective clinical trials conducted in three phases.

II. Proposed Method

To develop a method for use in estimating probabilities that may help in the assessment and evaluation of a new drug or product for possible approval for use in a population when these probabilities are not a-priori given, we may assume following Onyiorah et al (2013) (that three mutually co-operating evaluation bodies or committees x, y and z co-operating in the sense that they employ the same evaluation criteria used for the drug or product quality assessment or evaluation) in phased controlled clinical trials. The evaluation would be done using controlled cross-sectional comparative either prospective or retrospective study in clinical trials conducted in three phases. Now to conduct the clinical trials, matched random samples of consenting subjects or volunteers matched by age, sex, body weight and other demographic characteristics are to be used. If the study is a retrospective one then the required data would of course be obtained from case history files of the study participants. Suppose in the first phase of the controlled clinical trials each of the evaluation committees tests, screens or administers a new drug or product to a different but comparable sample of such matched samples of subjects of equal sizes, n_1. In the second phase of the clinical trials samples of three equal size n_2 matched pairs of subjects matched on the same demographic characteristics as in the first phase of the trials are used. Pairs of the three co-operating evaluation committees are assigned to test, screen or treat members in one of each of the three paired samples of matched subjects, with one evaluation committee in each pair testing the first members say of each paired sample of subjects and the other member of the paired evaluation committees testing the second members, say of the paired sample of subjects assigned to that evaluating committee.

In the third and last phase of the clinical trials matched triples of size n_3 subjects are used. That is matched triples of sizen_3 samples each of three matched subjects are used. One subject in each matched triple, that is one subject in each of three matched subjects is tested, screened or treated by one of the three evaluation committees.

Now as in Onyiorah et al (2013), suppose A and $\bar{A}$are respectively the events that evaluation committee X approves and does not approve a new drug or product for use; B and $\bar{B}$ are respectively the events that evaluation committee Y approves and does not approve a new drug or product for use; and C and $\bar{C}$ are respectively the events that evaluation committee Z approves and does not approve a new drug or product for use in a population. The resulting set of all possible outcomes, that is the sample space, S, of the experiment; namely, three-phased Clinical trials by three evaluation committees is then,

Notes

$$S = \{ABC, AB\bar{C}, A\bar{B}C, A\bar{B}\bar{C}, \bar{A}BC, \bar{A}B\bar{C}, \bar{A}\bar{B}C, \bar{A}\bar{B}\bar{C},\}$$

To develop a method for the estimation of new drug or product approval probability assuming that three mutually cooperating evaluation committees X, Y and Z are used in clinical trials conducted in three phases to assess the quality of the drug or product for possible approval, we may proceed as follows: For the first phase of the clinical trials, considering drug assessment by evaluation committees X, say, we may let

Notes

$$u_{ix} = \begin{cases} 1, if\ the\ i^{th}\ subject\ tested, screened\ or\ administered\ a\ new \\ \quad drug\ by\ committee\ X\ responds\ positive. \\ o, therwise \end{cases} \quad (1)$$

for $i = 1, 2, \ldots, n_1$
Let

$$\pi_x^+ = P(u_{ix} = 1) \quad (2)$$

Also define

$$W_x = \sum_{i=1}^{n_1} u_{ix} \quad (3)$$

Now the expected value and variance of u_{ix} are respectively

$$E(u_{ix}) = \pi_x^+; Var(u_{ix}) = \pi_x^+(1 - \pi_x^+) \quad (4)$$

Also, the expected value and variance of W_x are respectively,

$$E(W_x) = \sum_{i=1}^{n_i} E(u_{ix}) = n_1\pi_x^+; Var(W_x) = \sum_{i=1}^{n_1} Var\,(u_{ix}) = n_1.\pi_x^+(1 - \pi_x^+) \quad (5)$$

Now π_x^+ is the proportion or probability that on the average subjects tested, screened or treated by evaluation committee X responds positive. Its sample estimate is

$$\hat{\pi}_x^+ = p_x = \frac{W_x}{n_1} = \frac{f_x^+}{n_1} \quad (6)$$

where f_x^+ is the number of subjects responding positive under evaluation committee X, that is when tested by evaluation committee X. Thus f_x^+ is the total number of 1s in the frequency distribution of thenn_1 values of 0's and 1's in u_{ix} for $i = 1, 2, \ldots, n_1$.
The sample estimate of the variance of $\hat{\pi}_x^+$ is from Equation 5

$$Var(\pi_x^+) = \frac{Var\,(W_x)}{n_1^2} = \frac{\hat{\pi}_x^+(1-\hat{\pi}_x^+)}{n_1} \quad (7)$$

A null hypothesis that may often be of interest could be that the proportion π_x^+ of subjects responding positive under evaluation committee X is at most some value , π_{x0}or symbolically

$$H_0: \pi_x^+ \leq \pi_{x0} \text{Versus}\, H_1: \pi_x^+ > \pi_{x0} (0 \leq \pi_{x0} \leq 1) \quad (8)$$

The null hypothesis H_0 of Equation 8 may be tested using the test statistic

$$\chi^2 = \frac{(W_x - n_1.\pi_{x0})^2}{Var\,(W_x)} = \frac{n_1(\hat{\pi}_x^+ - \pi_{x0})^2}{\hat{\pi}_x^+(1-\hat{\pi}_x^+)} \quad (9)$$

Which under H_0 has approximately the chi-square distribution with 1 degree of freedom for sufficiently large n_1. The null hypothesis H_0 of equation 8 is rejected at α level of significance if

$$\chi^2 \geq \chi^2_{1-\alpha;1} \tag{10}$$

Otherwise H_0 is accepted. To estimate the probability of approval of a new drug or product by evaluation committee Y during the first phase of clinical trials we may let

$$u_{ix} = \begin{cases} 1 \text{ if the subject tested, screened or treated with a new drug product} \\ \quad \text{by evaluation committee or approval agency } Y \text{ responds positive} \\ 0, \text{otherwise} \end{cases} \tag{11}$$

for all $i = 1, 2, \ldots, n_1$.
Let

$$\pi_y^+ = P(u_{iy} = 1) \tag{12}$$

and

$$W_y = \sum_{i=1}^{n_1} u_{iy} \tag{13}$$

now,

$$E(u_{iy}) = \pi_y^+; Var(u_{iy}) = \pi_y^+(1 - \pi_y^+) \tag{14}$$

and

$$E(W_y) = n_1.\pi_y^+; Var(W_y) = n_1.\pi_y^+(1 - \pi_y^+) \tag{15}$$

For evaluation committee or approval agency, Y, $\pi_y^+$is the proportion of subjects responding positive when tested, screened or administered by evaluation committee Y during the first phase of clinical trials. Its sample estimate is

$$\hat{\pi}_y^+ = p_y = \frac{W_y}{n_1} = \frac{f_y^+}{n_1} \tag{16}$$

where f_y^+ is the number of subjects responding positive to evaluation committee Y in the first phase of clinical trials which is the total number of 1s in u_{iy}, $i = 1, 2, \ldots, n_1$. The corresponding sample variance is

$$Var(\hat{\pi}_y^+) = \frac{Var\,(W_y)}{n_1^2} = \frac{\hat{\pi}_y^+(1-\hat{\pi}_y^+)}{n_1} \tag{17}$$

A null hypothesis similar to that of Equation 17 for evaluation committee X may also be stated and tested for evaluation committee approval agency, Y. Following similar approaches as above, we also develop sample estimate of approval probability π_z^+ for evaluation committee agency Z as

$$\hat{\pi}_z^+ = p_z = \frac{W_z}{n_1} = \frac{f_z^+}{n_1} \tag{18}$$

Where f_z^+ is the number of subjects responding positive when tested, screened or administered a new drug or products by evaluation committee or approval agency Z during the first phase of clinical trials. The corresponding sample variance is similarly estimated.

Note that π_x^+, π_y^+ and π_z^+ are respectively the equivalence of A, B and c in Onyiorah et al (2013).

To estimate conditional probabilities of approval of a new drug or product by any pair of evaluation committees X and Y, say, during the second phase of clinical trials, we may first suppose that of the n_2 matched paired samples of subjects used in this phase of trials $n_{y,x}$ and $n_{z,x}$ subjects respond positive to the drug or product when

Notes

tested by evaluation committee Y and Z respectively; and $n_{z,y}$ subjects respond positive under evaluation committees Y when paired with evaluation committee Z.

To estimate conditional probabilities of approval of a new drug or product by any pair of evaluation committees $X$and Y say during the second phase of clinical trials, we may let

Notes

$$u_{iy,x} = \begin{cases} 1, \text{if the } i^{th} \text{pair of subjects tested by evaluation committees } X \text{ and } Y \\ \text{during the second phase of trials, the subjects tested by evaluation} \\ \text{committee } Y \text{ responds positive given that the correspo nding subject} \\ \text{in the pair tested by evaluation committee } X \text{ has also responded} \\ \text{positive} \\ 0, \text{otherwise} \end{cases} \quad (19)$$

for $i = 1, 2, \ldots, n_{y.x}$

Let

$$\pi^+_{y.x} = P\left(u_{iy.x} = 1\right) \quad (20)$$

and

$$W_{y.x} = \sum_{i=1}^{n_{y.x}} u_{iy.x} \quad (21)$$

The expected value and variance of $u_{iy.x}$ are respectively

$$E\left(u_{iy.x}\right) = \pi^+_{y.x}; \quad Var\left(u_{iy.x}\right) = \pi^+_{y.x}\left(1 - \pi^+_{y.x}\right) \quad (22)$$

Also the expected value and variance of $W_{y.x}$ are respectively

$$E\left(W_{y.x}\right) = \sum_{i=1}^{n_{y.x}} E\left(u_{iy.x}\right) = n_{y.x}\,\pi^+_{y.x}; \; Var\left(W_{y.x}\right) = \sum_{i=1}^{n_{y.x}} Var\left(u_{iy.x}\right) = n_{y.x}\pi^+_{y.x}\left(1 - \pi^+_{y.x}\right) \quad (23)$$

Now $\pi^+_{y.x}$ is the proportion or probability that on the average in the pairs of subjects tested by evaluation committees X and Y during the second phase of clinical trials subjects tested by evaluation committee Y respond positive given that the corresponding subjects tested by evaluation committee X have also responded positive to the new drug product. Its sample estimate is

$$\hat{\pi}^+_{y.x} = P_{y.x} = \frac{W_{y.x}}{n_{y.x}} = \frac{f^+_{y.x}}{n_{y.x}} \quad (24)$$

Where $f^+_{y.x}$ is the number of pairs of subjects for which subjects tested in the pairs by evaluation committee Y respond positive given that the corresponding subjects in the same pairs treated by evaluation committee X have also responded positive to the drug or product in the second phase of clinical trials. Thus $f^+_{y.x}$is the total number of 1s in the frequency distribution of the $n_{y.x}$ values of 0s and 1s in $u_{iy.x}$ for $i = 1, 2, \ldots, n_{y.x}$.

The sample variance of $\hat{\pi}^+_{y.x}$ is from Equation 23

$$Var\left(\hat{\pi}^+_{y.x}\right) = \frac{Var\left(W_{y.x}\right)}{n^2_{y.x}} = \frac{\hat{\pi}^+_{y.x}\left(1 - \hat{\pi}^+_{y.x}\right)}{n_{y.x}} \quad (25)$$

For the second phase of clinical trials, the null hypothesis that may be of interest concerning evaluation committees or approval agencies Y and Y say may be that the proportion of subjects responding positive when tested by evaluation committee Y given positive response under evaluation committee agency X is at least some value $\pi^+_{y.x_0}$ that is the null hypothesis

$$H_0: \pi_{y.x}^{+} \geq \pi_{y.x_0}^{+} \; versus \; H_1: \pi_{y.x}^{+} < \pi_{y.x_0}^{+}, (0 \leq \pi_{y.x_0}^{+} \leq 1) \quad (26)$$

The null hypothesis H_0 of Equation 26 may be tested using the test statistic

$$\chi^2 = \frac{(W_{y.x} - n_x \pi_{y.x_0})^2}{Var\,(W_{y.x})} = \frac{n_{y.x}(\hat{\pi}_{y.x}^{+} - \pi_{y.x_0}^{+})^2}{\hat{\pi}_{y.x}^{+}(1-\hat{\pi}_{y.x}^{+})} \quad (27)$$

which has approximately the chi-square distribution with 1 degree of freedom for sufficiently large $n_{y.x}$. The null hypothesis H_0 is rejected at the α level of significance if Equation 10 is satisfied otherwise H_0 is accepted.

Notes

To estimate conditional probability of positive response under evaluation committees X and Z we may let

$$u_{iz.x} = \begin{cases} 1, if\ for\ the\ i^{th}\ pair\ of\ subjects\ tested\ by\ evaluation\ committees\ X\ and\ Z \\ in\ the\ second\ phase\ of\ trials, the\ subject\ tested\ by\ evaluation\ committee \\ Z\ responds\ positve\ given\ that\ the\ corresponding\ subject\ tested\ by\ evalu \\ ation\ committee\ X\ has\ also\ responded\ positive \\ 0, otherwise \end{cases}$$

for

$$i = 1, 2, \ldots, n_{z.x} \quad (28)$$

Let

$$\pi_{z.x}^{+} = P(u_{iz.x} = 1) \quad (29)$$

and

$$W_{z.x} = \sum_{i=1}^{n_{z.x}} u_{iz.x} \quad (30)$$

Now,

$$E(u_{iz.x}) = \pi_{z.x}^{+}; Var(u_{iz.x}) = \pi_{z.x}^{+}(1 - \pi_{z.x}^{+}) \quad (31)$$

and

$$E(W_{z.x}) = n_{z.x}.\pi_{z.x}^{+};\; Var(W_{z.x}) = n_{z.x}.\pi_{z.x}^{+}(1 - \pi_{z.x}^{+}) \quad (32)$$

Note that $\pi_{z.x}^{+}$ is the proportion or conditional probability that in the paired samples of subjects tested by evaluation committees X and Z the subjects testedby evaluation committee Z respond positive given that the corresponding subjects tested by evaluation committee X have also responded positive to the new drug or product during the second phase of clinical trials. Its sample estimate is

$$\hat{\pi}_{z.x}^{+} = P_{z.x} = \frac{W_{z.x}}{n_{z.x}} = \frac{f_{z.x}^{+}}{n_{z.x}} \quad (33)$$

Where $f_{z.x}^{+} = W_{z.x}$ is the number of pairs of subjects in which the subjects tested by evaluation committee Z respond positive given that the corresponding subject tested by evaluation committee X have also tested positive. Thus, $f_{z.x}^{+}$ is the total number of 1's in the frequency distribution of the $n_{z.x}$ values of 0's and 1's in $u_{iz.x}$, for $i = 1, 2, \ldots, n_{z.x}$.

The sample variance of $\hat{\pi}_{z.x}^{+}$ is

$$Var(\hat{\pi}_{z.x}^{+}) = \frac{Var\,(W_{z.x})}{n_{z.x}^2} = \frac{\hat{\pi}_{z.x}^{+}(1-\hat{\pi}_{z.x}^{+})}{n_{z.x}} \quad (34)$$

If desired, a null hypothesis similar to that of Equation 26 for $\pi_{y.x}^{+}$ may also be tested for $\pi_{z.x}^{+}$. Similar procedure as above are also followed to obtain sample estimate of the conditional probability $\pi_{z.y}^{+}$ of positive approval by evaluation committee Z given positive approval by evaluation committee Y during the second phase of clinical trials. This would yield a sample estimate of the conditional approval probability $\pi_{z.y}^{+}$ of positive approval by evaluation committee Z given positive approval by evaluation committee Y as

$$\hat{\pi}_{z.y}^{+} = P_{z.y} = \frac{W_{z.y}}{n_{z.y}} = \frac{f_{z.y}^{+}}{n_{z.y}} \quad (35)$$

Notes

where $f_{z.y}^{+}$ is the number of pairs of subjects tested by evaluation committees Y and Z in which subjects tested by evaluation committee Z respond positive given that the corresponding subjects tested by evaluation committee Y have also responded positive to the drug or product. The sample variance of $\hat{\pi}_{z.y}^{+}$ is given by

$$Var(\hat{\pi}_{z.y}^{+}) = \frac{Var\,(W_{z.y})}{n_{z.y}^{2}} = \hat{\pi}_{z.y}^{+}\frac{(1-\hat{\pi}_{z.y}^{+})}{n_{z.y}} \quad (36)$$

If of research interest a null hypothesis similar to Equation 26 for $\pi_{y.x}^{+}$ may also be stated and tested for $\pi_{z.y}^{+}$. Note that $\pi_{y.x}^{+}$, $\pi_{z.x}^{+}$ and $\pi_{z.y}^{+}$ are respectively the equivalence of a, c and f in Onyiora et al (2013).

Note also that by the above specifications the sample estimates of marginal and conditional probabilities of positive approval by the three evaluation committees X, Y and Z are respectively

$$P(A) = \hat{\pi}_{x}^{+} = P_x; P(B) = \hat{\pi}_{y}^{+} = P_y; P(C) = \hat{\pi}_{z}^{+} = P_z \quad (37)$$

and

$$P(B/A) = \hat{\pi}_{y.x}^{+} = P_{y.x}; P(C/A) = \hat{\pi}_{z.x}^{+} = P_{z.x}; P(C/B) = \hat{\pi}_{z.y}^{+} = P_{z.y} \quad (38)$$

In practice there may actually be no need to estimate such conditional probabilities of positive approval as the conditional probability of positive approval by evaluation committee X given positive approval by evaluation committee Y, that is $P(A/B)$; conditional probability of positive approval by evaluation committee Y given positive approval by evaluation committee Z, namely $P(B/C)$; etc. This is because by the rule of conditional probability and algebraic manipulations, we have for example that

$$P(A/B) = \frac{P(B/A).P(A)}{P(B)} = \frac{P_{y.x}.P_x}{P_y} \quad (39)$$

Finally, to obtain sample estimates of approval probabilities by three evaluation committees X, Y and Z during the third and last phase of controlled clinical trials, we would proceed as follows:

Suppose each of the n_3 matched triples of subjects that is of each sample of three matched subjects screened or administered a new drug or product by three evaluation committees in the third phase of clinical trials, $n_{z.xy}$ subjects respectively under evaluation committees X and Y in comparison with evaluation committee Z, $n_{y.xz}$ subject respond positive under evaluation committees X and Z in comparison with evaluation committee Y, and $n_{x.yz}$ subjects respond positive under evaluation committees Y and Z in comparison with evaluation committee X.

Now to estimate conditional probability of positive approval by say approval evaluation committee Z given positive approval by evaluation committees X and Y during the third and last phase of clinical trials we may let

$$u_{iz.xy} = \begin{cases} 1, \textit{if for the } i^{th} \textit{ matched sample of three subjects, that is for the } i^{th} \textit{match} \\ \textit{ed tripple of subjects, the subject tested by evaluation committee Z res} \\ \textit{pond pisitive given that the corresponding subjects in the tripple tested} \\ \textit{by evaluation committees X and Y respectively have also tested positive.} \\ 0, \textit{otherwise} \end{cases}$$

for $$i = 1, 2, \ldots, n_{z.xy} \quad (40)$$

Let

$$\pi^+_{z.xy} = P(u_{iz.xy} = 1) \quad (41)$$

and

$$W_{z.xy} = \sum_{i=1}^{n_{z.xy}} u_{iz.xy} \quad (42)$$

Now,

$$E(u_{iz.xy}) = \pi^+_{z.xy}; \; Var(u_{iz.xy}) = \pi^+_{z.xy}(1 - \pi^+_{z.xy}) \quad (43)$$

Also,

$$E(W_{z.xy}) = n_{z.xy}.\pi^+_{z.xy}; \; Var(W_{z.xy}) = n_{z.xy}.\pi^+_{z.xy}(1 - \pi^+_{z.xy}) \quad (44)$$

Here $\pi^+_{z.xy}$ is the proportion or conditional probability that in the third phase of clinical trials for the matched samples of three subjects tested by three evaluation committees, subjects tested by evaluation committee Z respond positive given that the other two subjects in the triple separately tested by evaluation committees X and Y have also responded positive to a new drug or product. Its sample estimate is

$$\hat{\pi}^+_{z.xy} = P_{z.xy} = \frac{W_{z.xy}}{n_{z.xy}} = \frac{f^+_{z.xy}}{n_{z.xy}} \quad (45)$$

where $f^+_{z.xy}$ is the number of matched samples of three subject, that is the number of matched triples of subjects in which subjects in the triple tested by evaluation committee Z respond positive given that the other subjects in the same triple tested respectively by evaluation committees X and Y have also responded positive.

In other words, $f^+_{z.xy}$ is the total number of 1's in the frequency distribution of the $n_{z.xy}$ values 0's and 1's in $u_{iz.xy}$; $i = 1, 2, \ldots, n_{z.xy}$.

The corresponding sample variance of $\hat{\pi}^+_{z.xy}$ from Equation 44

$$Var(\hat{\pi}^+_{z.xy}) = \frac{Var(W_{z.xy})}{n^2_{z.xy}} = \frac{\hat{\pi}^+_{z.xy}(1-\hat{\pi}^+_{z.xy})}{n_{z.xy}} \quad (46)$$

Although hypothesis testing may not be as important as the need to determine whether most or all the evaluation committees are able to grant positive approval to a new drug or product for use in a population after a series of phased controlled clinical trials, one may nevertheless wish to test any desired null hypothesis. For example, one may wish to test the null hypothesis that the probability of positive approval of a new drug or product by a given evaluation committee, Z say, assuming that positive approval has been granted by evaluation committees X and Y say, is not more than some value, $\pi_{z.xy0}$. That is, the null hypothesis;

$$H_0: \pi^+_{z.xy} \leq \pi_{z.xy0} \; versus \; H_1: \pi^+_{z.xy} > \pi_{z.xy0} (0 \leq \pi_{z.xy0} \leq 1)$$

which is tested using the test statistic

Notes

$$\chi^2 = \frac{(W_{z.xy} - n_{z.xy}.\pi_{z.xy\,0})^2}{Var(W_{z.xy})} = n_{z.xy} \frac{(\hat{\pi}^+_{z.xy} - \pi_{z.xy\,0})^2}{\hat{\pi}^+_{z.xy}(1-\hat{\pi}^+_{z.xy})} \quad (48)$$

The null hypothesis of Equation 47 is rejected at the α −level of significance if Equation 10 is satisfied; otherwise the null hypothesis is accepted. Note that $\pi^+_{z.xy}$ is the equivalence of g in Onyiora et al (2013).

Notes

To obtain a sample estimate of the probability of positive response under evaluation committee Y given positive approval by evaluation committees X and Z we may define

$$u_{iy.xz} = \begin{cases} 1, \textit{if for the } i^{th} \textit{ matched sample of three subjects of the } i^{th} \textit{ matched tripple of subjects tested by three evaluation committees } X, Y \textit{ and } Z, \textit{the subjects tested by evaluation committee } Y \textit{ responds positive given that the other two subjects in the matched tripple tested respectively by evaluation committees } X \textit{ and } Z \textit{ also responded positve to a new drug or product at the third phase of trials.} \\ 0, \textit{otherwise.} \end{cases}$$

For $$i = 1, 2, \ldots, n_{y.xz} \quad (49)$$

Let

$$\pi^+_{y.xz} = P(u_{iy.xz} = 1) \quad (50)$$

and

$$W_{y.xz} = \sum_{i=1}^{n_{y.xz}} u_{iy.xz} \quad (51)$$

Now,

$$E(u_{iy.xz}) = \pi^+_{y.xz}; Var(u_{iy.xz}) = \pi^+_{y.xz}(1 - \pi^+_{y.xz}) \quad (52)$$

and

$$E(W_{y.xz}) = n_{y.xz}.\pi^+_{y.xz}; Var(W_{y.xz}) = n_{y.xz}.\pi^+_{y.xz}(1 - \pi^+_{y.xz}) \quad (53)$$

Note that $\pi^+_{y.xz}$ is the proportion or conditional probability that for the matched samples of three subjects, that is for the matched triples of subjects tested by three evaluation committees, subjects tested by evaluation committee Y respond positive given that the corresponding two subjects separately tested by evaluation committees X and Z respectively also respond positive to the drug or product during the third phase of clinical trials. Its sample estimate is

$$\hat{\pi}^+_{y.xz} = P_{y.xz} = \frac{W_{y.xz}}{n_{y.xz}} = \frac{f^+_{y.xz}}{n_{y.xz}} \quad (54)$$

where $f^+_{y.xz}$ is the number of matched triples of subjects in which the subjects tested by evaluation committee Y respond positive given that the other two subjects in the matched triples tested by evaluation committees X and Z respectively have also responded positive, which is also really the total number of 1's in $u_{iy.xz}, i = 1, 2, \ldots, n_{y.xz}$. The sample estimate of the variance of $\hat{\pi}^+_{y.xz}$ is

$$Var(\hat{\pi}^+_{y.xz}) = \frac{Var(W_{y.xz})}{n^2_{y.xz}} = \frac{\hat{\pi}^+_{y.xz}(1-\hat{\pi}^+_{y.xz})}{n_{y.xz}} \quad (55)$$

Again if of research interest a null hypothesis similar to that of Equation 47 may be stated and similarly tested for $\hat{\pi}^+_{y.xz}$. Similar procedures as above would enable us to also obtain sample estimate of the conditional probability $\hat{\pi}^+_{y.xz}$, the proportion or conditional probability that during the third phase of clinical trials by evaluation committees X, Y and Z for subjects in the matched triples of subjects tested by these committees, the subjects tested by evaluation committee X respond positive given that corresponding subjects in the matched triples tested by evaluation committees Y and Z respectively also respond positive. This conditional probability is estimated as

$$\hat{\pi}^{+}_{x.yz} = P_{x.yz} = \frac{W_{x.yz}}{n_{x.yz}} = \frac{f^{+}_{x.yz}}{n_{x.yz}} \quad (56)$$

where $W_{x.yz} = f^{+}_{x.yz}$ is the number of matched triples of subjects; that is, matched samples of three subjects in which subjects tested by evaluation committee X respond positive given that the other two subjects in the matched triples tested by evaluation committees Y and Z respectively also tested positive to the new drug or product in the third phase of controlled clinical trials. The sample estimate of the variance of $\hat{\pi}^{+}_{y.xz}$ is similarly obtained as

$$Var(\hat{\pi}^{+}_{y.xz}) = \frac{Var\,(W_{x.yz})}{n^{2}_{x.yz}} = \frac{\hat{\pi}^{+}_{y.xz}(1-\hat{\pi}^{+}_{y.xz})}{n_{x.yz}} \quad (57)$$

Again if research interest a null hypothesis similar to that of Equation 47 may also be stated and similarly tested for $\pi^{+}_{x.yz}$. Note again that by the specifications adopted above conditional probabilities $P(C/AB), P(B/AC)$ and $P(A/BC)$ namely; $\pi^{+}_{z.xy}, \pi^{+}_{y.xz}$ and $\pi^{+}_{x.yz}$ are estimated as respectively

$$\hat{\pi}^{+}_{z.xy} = P_{z.xy};\ \hat{\pi}^{+}_{y.xz} = P_{y.xz};\ \hat{\pi}^{+}_{x.yz} = P_{x.yz} \quad (58)$$

Other conditional probabilities may be similarly estimated as desired.

If stringencies in terms of high approval probability is a desired and preferred criterion for new drug or product approval, then in the third phase of clinical trials the outcome or event C/AB, say is more desirable and preferable to eventB/AC, say if and only if$P(C/A) > P(B/A)$. This is because if event $C/AB$is more preferable to event B/AC, then

$$P(C/AB) = \frac{P(ABC)}{P(AB)} > \frac{P(ABC)}{P(AC)} = P(B/AC)$$

So that

$$\frac{1}{P(AB)} = \frac{1}{P(A).P(B/A)} > \frac{1}{P(A).P(C/A)} = \frac{1}{P(AC)}$$

Hence

$$P(C/A) > P(B/A)$$

On the other hand if $P(C/A) > P(B/A)$ then clearly $P(C/AB) > P(B/AC)$.

Stated in terms of sample estimates of probabilities, this would mean that in the third phase of three phased controlled clinical trials of a new drug or product by these evaluation committees $X, Y$and$Z$. $P_{z.xy} > P_{y.xz}$ if and only if in the second phase of clinical trials $P_{z.x} > P_{y.x}$.

Other conditional probabilities may be similarly estimated as desired.

Now we have so far presented the probability estimation procedures generally under the assumption that all three evaluation committees are equally competent in experience or otherwise to assess and evaluate new drug or product. In reality however some evaluation committees may be better qualified, experienced, with higher expertise, better equipped etc., than others and hence may play supervisory roles and be able to obtain more reliable results. Hence we may but without loss of generality assume that three evaluation committees used here can be ordered in terms of experience and

Notes

Notes

seniority in assessment, evaluation and approval of new drugs or products ranked from the most senior down to the least senior. Thus we may again but without loss of generality assume that evaluation committee X is the most senior followed by evaluation committees Y and Z in this order. This would in effect mean that any drug or product approved by evaluation committee Z would be subjected to further approvals by evaluation committee Y and finally by evaluation committee X. Under these assumptions the probabilities already estimated above would be sufficient to estimate the required overall approval probability after the third and last phase of controlled clinical trials.

Never the-less, the proposed probability estimation model would enable the estimation of the probabilities of all events that can possibly be obtained in the event space of all conceivable outcomes in phased controlled clinical trials. For example the probability that say evaluation committees X and Y do not approve a new drug or product given that evaluation committee Z approves, is the probability of the event $(\bar{A}\bar{B}/C)$ which is

$$P(\bar{A}\bar{B}/C) = \frac{P(C) - P(A).P(C/A) - P(B).P(C/B) + P(C/AB).P(B/A).P(A)}{P(C)}$$

or In terms of estimated probabilities,

$$P(\bar{A}\bar{B}/C) = P_z - P_x.P_{z.x} - P_y P_{z.y} + P_{z.xy}.P_{y.x}.P_x$$

However for the purpose of this paper, if interest is only in the estimation of the probabilities of the events in table 1 of Onyira et al (2013) which we obtained using the marginal and conditional probabilities already estimated above, namely

$$P(A) = a = P_x; P(B) = b = P_y; P(C) = c = P_z \quad (59)$$

and

$$P(B/A) = d = P_{y.x}; P(C/A) = e = P_{z.x}; P(C/B) = f = P_{z.y}; P(C/AB) = g = P_{z.xy} \quad (60)$$

With these results the probability that all the three evaluation committees X, Y and Z approved a new drug or product is the probability of the event$S_3 = (ABC)$ which is estimated using sample values obtained above as

$$P(ABC) = P(C/AB).P(B/A).P(A) = P_{z.xy};\ P_{y.x};\ P_x \quad (61)$$

If at least two evaluation committees must approve a new drug or product before use, then the corresponding events set is $S_2 = (ABC, AB\bar{C}, \bar{A}BC)$ whose probability is easily shown to be

$$P(S_2) = P_x.P_{y.x} + P_x.P_{z.x} + P_y.P_{z.y} - 2P_{z.xy}.P_{y.x}.P_x \quad (62)$$

If there is a supervising evaluation committee such as evaluation committee X who must approve in addition to at least one other evaluation committee before a new drug or product is considered approved for use, then the required events set is $S_x = (ABC, AB\bar{C}, A\bar{B}C)$ whose sample estimate is

$$P(S_x) = P_x.P_{y.x} + P_x.P_{z.x} - P_{z.xy}.P_{yx}.P_x \quad (63)$$

The probability that evaluation committees Y and Z approve a drug or product but evaluation committee X does not approve it is the probability $S_{yz} = (\bar{A}BC)$which is estimated as

$$P(S_{yz}) = P(\bar{A}.BC) = (1 - P(A/BC)).P(BC) = P(C/B).P(B) - P(ABC)$$

which when expressed in terms of sample probabilities becomes

$$P(S_{yz}) = P_y.P_{zy} - P_{z.xy}.P_{y.x}.P_x \tag{64}$$

The probability that none of the evaluation committees approves the drug or product for use is the probability of the event $S_0 = (\bar{A}\bar{B}\bar{C})$ which is

$$P(S_0) = P(\bar{A}\bar{B}\bar{C}) = 1 - \big(P(A) + P(B) + P(C) - P(B/A).P(A) - P(C/A).P(A) - P(C/B).P(B) + P(ABC)\big)$$

Which when evaluated in terms of sampled estimates becomes

$$P(S_0) = 1 - \big(P_x + P_y + P_z - P_x.P_{y.x} - P_x.P_{z.x} - P_y.P_{z.y} + P_{z.xy}.P_{y.x}P_x\big) \tag{65}$$

Other probabilities are similarly estimated. The results are shown in Table 1

Table 1: Sample Estimates of New Drug or Product Approval Probabilities by three Evaluation in Phased Clinical Trials

S/No	Event	Approval Probability
1	ABC	$P_{z.xy}.P_{y.x}P_x$
2	$AB\bar{C}$	$P_x.P_{y.x} - P_{z.xy}.P_{y.x}.P_x$
3	$A\bar{B}C$	$P_x.P_{z.x} - P_{z.xy}P_{y.x}.P_x$
4	$A\bar{B}\bar{C}$	$P_x - P_x.P_{z.x} - P_xP_{y.x} + P_{z.xy}P_{y.x}.P_x$
5	$\bar{A}BC$	$P_y.P_{z.y} - P_{z.xy}.P_{yx}P_x$
6	$\bar{A}B\bar{C}$	$P_y - P_y.P_{z.y} - P_x.P_{y.x} + P_{z.xy}.P_{y.x}.P_x$
7	$\bar{A}\bar{B}C$	$P_z - P_x.P_{z.y} - P_y.P_{z.y} + P_{z.xy}.P_{y.x}.P_{y.x}$
8	$\bar{A}\bar{B}\bar{C}$	$1 - \big(P_x + P_y + P_x.P_{yx} - P_x.P_{zx} - P_y.P_{z.y} + P_{z.xy}.P_{y.x}.P_x\big)$
9	S_2(at least two Evaluation; committees)	$P_x.P_{y.x} + P_x.P_{z.x} + P_y.P_{z.y} - 2P_{z.xy}.P_{y.x}.P_x$
10	S_x(Evaluation Committee X; and at least one other)	$P_x.P_{y.x} + P_x.P_{z.x} - P_{z.xy}.P_{y.x}.P_x$
11	S_y(Evaluation Committee Y and at least one other)	$P_x.P_{y.x} + P_y.P_{z.y} - P_{z.xy}.P_{y.x}.P_x$
12	S_z(Evaluation Committee Z and at least one other)	$P_y.P_{z.y} + P_x.P_{z.x} - P_{z.xy}.P_{y.x}.P_x$

III. Illustrative Example

Teams of research scientists in the Department of Pharmacology of three Universities X, Y and Z were interested in conducting phased controlled prospective clinical trials on a certain herb product believed by a local population to be effective in the treatment of malaria. In the first phase of clinical trials the three research teams collected three random samples each of size 40 of volunteer malaria patients matched on age, gender and body mass index(BMI),and each research team or committee team administered appropriately determined dosages of the malaria herb product each on patients in only one of the three matched samples.

In the second phase of clinical trials three matched pairs of patients each of size 30 were used. The three research teams were also then paired. Each pair of the research team administered dosages of the herb product to one paired sample of patients with one research team administering the dosage to say the first patient in each pair and the other research team administering the dosage to the remaining patient in the pair.

Notes

Notes

In the third phase of the clinical trials, 25 samples of matched triples of patients, that is 25 samples each of three matched patients were used. The three research teams each administered dosages of the malaria herb product to only one patient in each of the 25 matched triples of patients. At the end of each phase of the clinical trials the research scientists assesses the malaria patients as either recovered (R) or not recovered (N) obtaining the results shown in tables 2 – 4.

Table 2: Patient Response in Phase One Clinical Trials of Anti-Malaria Herb Product by Three Research Teams

S/No	Team 1 (Sample 1)	Team 2 (Sample 2)	Team 3 (Sample 3)
	X	Y	Z
1	R	N	R
2	R	R	N
3	R	N	N
4	N	R	R
5	R	R	R
6	R	N	R
7	N	R	N
8	N	N	N
9	N	N	R
10	N	R	R
11	N	N	N
12	R	N	R
13	N	R	R
14	R	R	R
15	N	N	R
16	R	N	N
17	R	R	N
18	R	R	R
19	N	R	R
20	R	N	R
21	N	N	N
22	R	R	R
23	N	R	N
24	R	R	R
25	N	R	N
26	R	N	R
27	R	R	R
28	R	R	N
29	R	R	N
30	R	R	N
31	N	R	R
32	R	N	R
33	N	R	N
34	R	R	N
35	N	R	R
36	N	N	N
37	N	N	R
38	R	N	N
39	R	N	R
40	R	N	N
n_i	40	40	40
f_i^+	$23(f_x^+)$	$22(f_y^+)$	22
$\hat{\pi}_i^+$	$0.575(\hat{\pi}_x^+)$	0.55	0.55

Table 3: Patient Response in Phase Two Clinical Trials of Malaria Herb Product by Three Research Teams

	Matched Pair Team 1		Matched Pair Team 2		Matched Pair Team 3	
	X	Y	X	Z	Y	Z
1	N	N	R	N	N	N
2	R	R	N	R	R	R
3	R	R	R	R	N	R
4	N	R	R	N	R	R
5	N	R	N	R	R	R
6	R	N	R	R	N	R
7	N	R	N	R	R	N
8	N	N	N	N	R	R
9	R	N	R	R	R	R
10	N	N	R	N	N	N
11	N	N	R	R	N	R
12	R	N	N	R	N	N
13	R	N	N	N	R	N
14	R	R	R	R	N	N
15	N	R	N	R	N	N
16	N	N	R	N	R	R
17	R	N	R	R	R	R
18	N	N	R	R	R	N
19	N	R	N	N	N	N
20	N	N	N	N	N	N
21	N	R	R	N	N	N
22	R	N	R	N	N	R
23	N	N	R	R	R	N
24	R	R	R	N	R	R
25	N	R	N	N	N	R
26	N	R	N	R	N	R
27	N	R	N	N	R	N
28	R	N	R	N	R	R
29	N	N	R	R	R	R
30	R	N	R	R	R	R
$n_{K.J}$	$12(n_{y.x})$		$18(n_{x.z})$		$16(n_{y.z})$	
$f^{+}_{k.j}$	$4(f^{+}_{y.x})$		$10(f^{+}_{x.z})$		$11(f^{+}_{y.z})$	
$\hat{\pi}^{+}_{k\ i}$	$0333(\hat{\pi}^{+}_{y.x})$		$0.556(\hat{\pi}^{+}_{x.x})$		$0.688(\hat{\pi}^{+}_{y.z})$	

Notes

Table 4: Patient Response in Phase Three Clinical Trials of Anti-Malaria Herb Product by Three Research Teams

Matched Triple	Research Team X	Research Team Y	Research Team Z
1	N	R	N
2	R	N	N
3	R	R	N
4	N	R	R
5	N	N	R
6	R	R	R
7	N	N	N
8	N	R	N
9	R	R	R
10	N	N	N
11	N	N	N
14	R	N	N
15	N	N	N
16	R	R	R
17	N	N	R
18	R	N	R
19	R	N	N

Notes

20	N	N	R
21	N	R	N
22	N	R	N
23	R	R	R
24	N	R	R
25	N	R	R
$n_{k.lj}$	$8(n_{x.yz})$	$5(n_{y.xz})$	$6(n_{z.xy})$
$f_{k.lj}^{+}$	$4(f_{x.yz}^{+})$	$4(f_{y.xz}^{+})$	$4(f_{z.xy}^{+})$
$\hat{\pi}_{k.lj}^{+}$	$0.500(\hat{\pi}_{x.yz}^{+})$	$0.800(\hat{\pi}_{y.xz}^{+})$	$0.667(\hat{\pi}_{z.xy}^{+})$

We here use the sample data of Table 2-4 to illustrate the present probability estimation method. Thus applying the methods to the data we have as shown at the bottom of Table 2 with $n = n_1 = 40$, that

$$f_x^+ = 23;\ f_y^+ = 22\ and\ f_z^+ = 22;\ so\ that\ \hat{\pi}_x^+ = P_x = 0.575\ (= a)$$

$$\hat{\pi}_y^+ = P_y = 0.550(= b);\ and\ \hat{\pi}_z^+ = P_z = 0.550\ (= c)$$

From Table 3 we have that

$$n_{y.x} = 12;\ n_{z.x} = 18\ and\ n_{z.y} = 16$$

Also,

$$f_{y.x}^+ = 4;\ f_{z.x}^+ = 10\ and\ f_{z.y}^+ = 11$$

Hence,

$$\hat{\pi}_{y.x}^+ = P_{y.x} = 0.333\ (= d);\ \hat{\pi}_{z.x}^+ = P_{z.x} = 0.556\ (= e);\ and \hat{\pi}_{z.y}^+ = P_{z.y} = 0.688\ (= f).$$

Finally from Table 4 we have that

$$n_{z.xy} = 6\ and\ f_{z.y}^+ = 4$$

Hence,

$$\hat{\pi}_{z.xy}^+ = P_{z.xy} = 0.667\ (= g)$$

Note also from Table 4 that

$$n_{y.xz} = 5, n_{x.yz} = 8;\ f_{y.xz}^+ = f_{x.yz}^+ = 4\ so\ that\ \hat{\pi}_{y.xz}^+ = P_{y.xz} = 0.800;\ and\ \hat{\pi}_{x.yz}^+ = P_{x.yz} = 0.500$$

These probability estimates are now used with Table 2 to obtain sample estimates of some of possibilities of outcomes in three phased controlled clinical trials of a product, namely anti-malaria herb product. The estimates are presented in Table 5.

Table 5: Sample Estimates of Probabilities of the events of Table 1 for anti-malaria herb product

S/No	Event	Estimated Approval Probability
1	ABC	0.127
2	$AB\bar{C}$	0.064
3	$A\bar{B}C$	0.193
4	ABC	0.191
5	ABC	0.251
6	$\bar{A}B\bar{C}$	0.108
7	$\bar{A}\bar{B}C$	0.021
8	$\bar{A}\bar{B}\bar{C}$	0.079
9	S_2 (at least two evaluation committees)	0.635
10	S_x (evaluation committee and at least one other)	0.384
11	S_v(evaluation committee and at least one other)	0.442
12	S_z (evaluation committee and at least one other)	0.571

It is seen from Table 2 that in the first phase of controlled clinical trials, evaluation committee X approved the anti-malaria herb product with an estimated probability of 0.575 while evaluation committees$Y$ and Z approved the drug with equal probability of 0.550.

In the second phase of clinical trials (Table 3 given that evaluation committee X has approved the drug, evaluation committees Y and Z are found to approve the drug with estimated probabilities of 0.333 and 0.556 respectively while if evaluation committee Y has already approved the drug, then evaluation committee Z would be expected to approve the drug with probability 0.688.

In the third phase of clinical trials (Table 4) it is seen that if evaluation committees X and Y have already approved the drug, then evaluation committee Z would approve the drug with an estimated probability of 0.667 while evaluation committee Y would approve with estimated probability of 0.800 if evaluation committees X and Z have already granted the approval. From Table 5, it is seen that if all three evaluation committees are required to grant approval before a new drug or product (anti-malaria herb product) can be approved for use in a population then the estimated probability of such an approval being granted is only 12.7 percent, which is relatively more stringent compared with when only two evaluation committees are required to grant approval with an estimated probability of which is relatively more liberal.

$$(0.575)(0.333) + (0.575)(0.556) + (0.530)(0.688) - 3(0.127) = 0.889 - 0.381 = 0.508$$

Note from Table 5 that at the end of the third phase of clinical trials if the drug must be approved by at least one evaluation committee as the supervisory committee, then evaluation committee X is seen to be the most stringent with an estimated overall probability of approval of only 38.4 percent while evaluation committee Z is the most liberal with an estimated overall probability of approval of as high as 57.1 percent. It is found that just as the probability of three evaluation committees completely agreeing approve drug after the third phase of clinical trials is rather small at 0.127, the probability of three committees being in complete agreement not to approve the drug is even much smaller with an estimated value of only 7.9 percent.

IV. Summary and Conclusion

We have in this paper developed and presented statistical method that would enable the estimation of probabilities of approving and not approving a new drug or

Notes

product for possible use in a population under the assumption that three evaluation committees are used to assess and evaluate the drug or product in clinical trials conducted in three phases. At each phase of clinical trials evaluation committees used matched samples of subjects for drug or product quality evaluation or assessment.

Test statistics were developed for testing any desired hypothesis about approval probabilities each phase of clinical trials. The proposed method was illustrated with some sample data and the results show that the probabilities of three evaluation committees being in complete agreement to approve and not approve a new drug or product are likely to be much smaller than the probabilities that only some of the three evaluation committees approve the drug or product.

Notes

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