Estimation of New Drug Product Approval Probabilities in Phased Clinical Trials

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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 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.

Index terms— evaluation committees, product, volunteer, probabilities, phased controlled clinical trials, diagnostic screening tests.

1 I. Introduction

s 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 intervention procedure to adopt in patient treatment and management and often rely on own experience or these of colleagues in actual practice. However, health professionals are increasingly relying on evidence based medical and health practices hinged on a systematic revision evaluation, evaluation, assessment and application of clinical research findings **??**Rising, Bacchetti and Baro,2009; **??**how 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 **??**eske, 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; **??**ipkovic 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 the three period phased clinical trials by three evaluation committees. Onyiora et al **??**2013) proposed and 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 the authors is however most useful if the probabilities a-g are given or already be used in the estimation of the probabilities of possible outcomes including the outcomes or

evenly listed in the authors' Table 2.The method under reference does not however provide a method to use in the a-priori estimate of the probabilities 'a-g' if not already given and are not known, and must be estimated from sample data obtained in relevant count phased clinical test 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: cross-section, prospective or retrospective 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 phased of the clinical trials three samples of the three cooperating approval agencies, three equal samples of size n 2 .

2 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-preen 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) phased controlled clinical trials. The evaluation would be done using controlled crosssectional comparative either prospective or retrospective study in clinical trials conducted in three phases. Now to conduct the clinical trails, 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 samples of 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 n 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. ? ? = ? ? ? = Let**(1)**

x ix P u ? + = = Also define ix x ix x x E u Var u ? ? ? + + + = = ? 1 1 1 1 1 1 n n x ix x x ix x x i i E W E u n Var W Var u n ? ? ? + + + = = = = = = ? ? ? 1 1 ?x x x x W f P n n ? + + = = =**(1)**

The sample estimate of the variance of ?x ? + is from Equation **??**2 1 1 ?( ) (1) ( )x x x x W Var Var n n ? ? ? + + + ? = =

A null hypothesis that may often be of interest could be that the proportion x ? + of subjects responding positive under evaluation committee X is at most some value , xo ? or symbolically:0 1 : : (0 1) x xo x xo xo H versus H ? ? ? ? ? + + ? > ? ?

The null hypothesis H 0 of Equation 8 may be tested using the test statistic( ) ( ) ( ) 2 2 1 1 2 . ( ) ?1 x xo x xo x x x n W n Var W ? ? ? ? ? ? + + + ? ? = = ?

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 ? level of significance if ? + is the proportion on probability that on the average subjects tested, screened or treated by evaluation committee X responds positive. Its sample estimate is where x f + is the number of subjects responding positive under evaluation committee X, that is when tested by evaluation committee X. This x f + is the total number of 1s in the frequency distribution of the n 1 values of 0s and 1s in ix u for i=1,2,?n 1 . where y f + 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 1 , 1, 2,..,? ? = ? ? ? = Let 1 1 1 1 (1)( ) ; ( )**(1) ( ) . ; ( ) . (1)**iy u i n = .

The corresponding sample variance is2 1 1 ?( ) (1) ( ) y y y y Var W Var n n ? ? ? + + + ? = =

A null hypothesis similar to that of Equation **??**7for evaluation committee X may also be stated and tested for evaluation committee approval agency.

Following similar approaches as above, we also develop sample estimate approval probability z ? + for evaluation committee agency Z as1 1 ?z z z z W f p n n ? + + = = =

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

Note that , 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 The expected value and variance of

3 = = =

Where . y x f + 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 x n = ?

The sample variance of . ?y x ? + is from Equation **??**3( ) ( ) ( ). . . . 2 .

4 ?1 ?y x y x y x y x y x x

Var W Var ny n? ? ? + + + ? = =

For the second phase of clinical trials, the null hypothesis that may be of interest concerning evaluation committees approved agencies X 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 0 . , y x ? + that+ + + + + ? < ? ?

The null hypothesis H 0 of Equation 26 may be tested using the test statistic( ) ( ) 0 0**2 2 . . 2 .** . .

5 ( )

?(1)y x x yx x y x yx y x y x y x W n n Var W ? ? ? ? ? ? + + + ? ? = = ?

Which has approximately the chi-square distribution with 1 degree of freedom for sufficiently large yx n .The null hypothesis H 0 is rejected at the ? level of significance if Equation 10 is satisfied otherwise H 0 is accepted.

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

(1) is the number of matched triples of subjects in which the subjects tested in phase three by evaluation committee Y respond positive given that the other two subjects in the matched triples tested by evaluation committee X and Z respectively have also responded positive, which is also really the total number of 1s in z x z x iz x n Z x iz x i iz x z x iz x z x z x Z x zx z x Z x zx z x z x

6 P P >

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 really 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 seniority in assessment, evaluation and approval of now 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 subject 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 present 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(/) AB C which is (/) ( ) ( ).

7 (/) ( ). (/) (/). (/). ( ) ( ) P AB C P C P A P C A P B P C B P C AB P B A P A P C

= ? ? + = = = = = = = = = = = = = = = =

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 whose probability is easily shown to be 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 (, ,)

x

8 S ABC ABC ABC = whose sample estimate is

The probability that evaluation committees Y and Z approve a drug or product evaluation committee X does not approve it is the probability of the event, The probability that none of the evaluation committees approves

a drug or product for use is the probability of the event 0 ( ) 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 herb product each on patients in only one of the three matched samples.S ABC = which is ( )**0 ( ) ( ) 1 ( ) ( ) ( ) (**

9 /). ( ) (/). ( ) (/). ( ) ( ) P S P ABC P A P B P C P B A P A P C A P A P C B P B P ABC

= = ? + + ? ? ? + Which when

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 43 administering the dosage to the remaining patient in the pair.

In the third phase of 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 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 Table 2

10 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 i n 40 40 40 l f + 23( ) x f + 22( ) y f +**22**X Y X Z Y Z 1 N N R N N N 2 R R N R R R 3 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

Volume XVI Issue V Version I 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 . k j n .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 12 N N R 13 R R 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 20 N N R 21 N R N 22 N R N 23 R R R 24 N R R 25 N R R . k lj n .

11 8( )

x yz n .

12 5( )

13 4( )

x yz f + . 4( ) y xz f + . 4( ) z xy f +

= = = = = = = = = = = =

From Table **??** = = = = = = = = = = = = = = = Finally from= = = = = = = =

These probability estimates are now used with Table **??** to obtain sample estimates of some possible outcomes in three phased controlled clinical trials of a product, namely anti-malaria herb product.

The estimates are presented in Table 5. committees Y and Z approved the drug with equal probability of 0.550.

In the second phase of clinical trials (Table **??** 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 (.0575)(0.333) (0.575)(0.556) (0.530(0.688) 3(0.127) 0.889 0.381 0.508,+ + ? = = =

which is relatively more liberal. 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.

14 III. 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 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 [1]

H 0 : ? . y x ? 0 y x . versus H 1 : ? . y x ? 0 y x . , (0 ?

Figure 1:

Estimation of New Drug Product Approval Probabi

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 committee X,Y and Z. V if and only if in the second phase of clinical y.xz =

The sample estimate of the variance of V ar(? + ?y xz . ? + is y.xz) = z ?

Again if of research interest a null hypothesis z
similar to that of Equation 26 may be stated and similarly tested for y xz ? + . ?x yz ? + is similarly obtai

ar(? + x.yz) = ??

Again if of research interest a null hypothesis

similar to that of Equation 26 may also be stated and

OR
In terms of estimated probabilities,
. x z x . P AB C P P P (/) z =? ? . y + . z xy y x x . . .
z y P P P etc .
P
( ) P A ; ( ) a P P B x ; ( ) c c P
b P
P C
y
And
(/) P B A . y x d P P C A e P P C B . ; (/) ; (/) z x . z y f P P C AB ;
(/

Figure 3:

(P (S 2 Year 2016 D D D D) F 39 40 41
42
S yz = (ABC which is estimated as
( ) yz P S (. .) (1 (/ P A B C P A BC P BC P C B P B P ABC)). ( ) (/).
which when expressed in terms of sample probabilities becomes

[Note: P (ABC) = P (C/AB).P (B/A).P (A) = P z.xy ; P y.x ; P x Volume XVI Issue V Version I]

Figure 4:

11

(

Figure 5: Table 1 Table 1 :

Year 2016
Volume XVI Issue V Version I
D D D D) F
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Figure 6: .

2

Figure 7: Table 2 :

Year 2016
D D D D) F
(

Figure 8:

. ?k lj ? + . x yz ?) . y xz ? +) . z xy
+ 0.500(0.800(+ 0.667
f x f y 22 and z 22; so that 23; 0.575( );
+ + f + x x P a ? +
?0.550( ); y y P b and ? + ? z z P 0.550( ). c
+

Figure 9:

n . y x 12; n . 18, and n . z 16
z y
x
Also
f . y x 4; f . z x + 10; f . z 11.
+ y +
Hence
. ??0.333( ); . y x y x P d ? + ? . z x . z 0.556(?
+ x P); e and

Figure 10:

4

we have that

. z xy = = . 6 z xy n and f +

Hence

. ?0.667( ). . z xy z xy P g ? + = = =

Note also from Table 4 that

n . n . 8; f . y f . x 4 so . ?5, . . 0.800; y xz y x
y x xz yz that
xz yz + +

Figure 11: Table 4

5

S/No	Event	Estimated Approval Probability
1	ABC	0.127
2	ABC	0.064
3	ABC	0.193
4	ABC	0.191
5	ABC	0.251
6	ABC	0.108
7	ABC	0.021
8	ABC	0.079
9	S 2 (at least two evaluation committee)	0.635
10	one other) S X (evaluation committee and at least	0.384
11	one other) S Y (evaluation committee and at least	0.442
12	one other) S Z (evaluation committee and at least	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

Figure 12: Table 5 :

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