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THREE PERIOD CROSSOVER PHASED DIAGNOSTIC SCREENING TESTS

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ABSTRACT: *The Three Period Crossover Phased Diagnostic Screening Test is a test design aimed at evaluating consistency of clinical performance of clinicians; this process involves repeated measurements of a clinical search for a disease or medical condition of interest. The repeated nature of the test is to enable calculation of performance errors. This process is phased in such a way that previous trials do not influence the outcome or outcomes of subsequent phase(s). Processes of computing probabilities of various possible sequences of outcomes, positive or negative, for the assessment of clinicians' consistency were developed and presented. Its functionality was demonstrated with an illustrative example. The beauty of the Three Period Crossover Phased Diagnostic Screening Test is that no matter the order the three clinicians carry out the phased diagnostic tests, the probability of positive outcomes by any chosen clinician or the probability of negative outcomes of any chosen clinician can still be calculated accurately.*

KEYWORDS: Phased, Crossover, Three, Diagnostic, Screening, Clinician, Test.

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INTRODUCTION

In controlled comparative diagnostic screening tests and clinical trials, subjects or patients are first matched on characteristics associated with the outcome or event of interest and then randomly assigned the treatments or tests. An extreme example of matching termed "Crossover Design" is where each subject or patient serves as its own control (Zeng et al., 2020; Fleiss, Levin & Paik, 2003). In this type of test, each subject or patient receives each of the two treatments or tests. One half of a random sample of study subjects or patients is randomly selected to be given the two treatments or tests and the other half to be given the two treatments or tests in the reverse order. This study design is more specifically referred to as a "two-period Crossover" study design, because one-half of study subjects or patients are randomly subjected to one of the tests or treatments T_1 say, and the remaining one-half of the subjects or patients are given the other test or treatment T_2 say, at a given time or period (Wellek & Blettner, 2012).

The tests or treatments are at a later time period given in the reverse order with one-half of the subjects or patients given tests or treatments T_1 in the first period now given treatment T_2 and the other one-half of subjects or patients given treatment T_2 at the first period now given treatment T_1 at the second period. Several problems arise, including the problems of time order and carry-over effects, when two period crossover study design is used in clinical trials of drugs to determine their differential potencies, especially when the drugs of interest have long acting and lasting effects on patients or subjects and the time order in which the drugs or treatments are administered has an influence on their effectiveness.

However, in diagnostic screening tests and clinical trials where research interest is not necessarily in effectiveness of drugs or treatments, but in the screening or testing of subjects in a population to determine the possible presence or absence of a condition such as disease in the population, two, three-period and several periods crossover study design time phased diagnostic screening tests are matched without encountering the problem of time order and carry-over effects, especially when there are fairly long-time intervals between successive administration of the tests and the clinicians have comparable qualifications and practical experiences (Dwan, Li, Altman & Elbourne, 2019; Ebutt, 1984; Fletcher, Lewis & Mathews, 1990).

We, in this paper, present and discuss a method for the estimation of probabilities obtainable with the application of phased three period crossover study design in controlled comparative, prospective phased diagnostic screening test to screen subjects in a population for the possible presence or absence of a condition of research interest. Estimates of absolute and conditional probabilities of positive response by subjects or patients to a condition or disease in a population in each of the three phases of diagnostic screening test, as well as test statistics are provided.

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The Proposed Method

Now, suppose three research scientists or clinicians X, Y and Z are interested in conducting diagnostic screening tests to identify subjects with a certain condition such as disease in a population. The screening tests would be conducted in three phases with each study subject serving as its own control and the screening test would be performed by each of the three clinicians at different periods in time. Suppose further and for simplicity, that clinician X is the most qualified, experienced, best equipped and most senior of the three clinicians, followed by clinician Y and then by clinician Z in this order. This would in effect means that in this so-called three period crossover design, where each study subject serves as own control at three different periods in time, clinician Z would first screen each study subject who if test is positive (negative) would be rescreened and retested by clinician Y and then finally by clinician X at the third phase if the subject still tests positive (negative) under clinician Y in the second phase.

Now, suppose that A and $\underline{A}$ are respectively the events that a randomly selected study subject tests positive and negative when tested by clinician X; B and $\underline{B}$ are respectively the events that a randomly selected subject tests positive and negative when tested by clinician Y; C and $\underline{C}$ are respectively the events that a randomly selected subject tests positive and negative when tested by clinician Z. Also, following the ordering by seniority of the clinicians, suppose that a random sample of size n = n_z subjects or patients of comparable ages, sex and body weight drawn from the population are available for screening and are in fact screened in the first phase of the first period of the three phased three period cross-over screening test by clinician Z.

To estimate the proportion of subjects testing positive under clinician Z we may let

$$U_{iz} = \begin{cases} 1, \ if\ the\ ith\ subject\ screened\ and\ tested\ by \\ clinician\ Z\ at\ the\ first\ phase\ tests\ positive. \\ 0, \ otherwise. \end{cases} \quad \ldots \ (1)$$

for i=1,2, . . .,n_z

let

$$\pi_z^+ = \mathrm{P}(\mathrm{U_{iz}} = 1) \quad \ldots (2)$$

and

$$\mathrm{W_z} = \sum_{i=1}^{n_z} U_{iz} \quad \ldots (3)$$

Now, the mean or expected value and variance of Uiz are respectively

$$\mathrm{E}(\mathrm{U_{iz}}) = \pi_z^+ \ ; \qquad \mathrm{Var}(\mathrm{U_{iz}}) = \pi_z^+(1 - \pi_z^+) \quad \ldots (4)$$

Similarly, the expected value and variance of $\mathrm{W_z}$ are respectively

$$\mathrm{E}(\mathrm{W_z}) = \sum_{i=1}^{n_z} U_{iz} = \mathrm{n_z}.\pi_z^+ \ ; \qquad \mathrm{Var}\ (\mathrm{W_z}) = \sum_{i=1}^{n_z} Var(U_{iz}) = \mathrm{n_z}\,.\pi_z^+(1 - \pi_z^+) \quad \ldots (5)$$

Now π_z^+ is the proportion of subjects or the probability that a randomly selected subject from the study population tests positive to a condition of interest when screened by clinician Z at the first phase of the three phase, three period crossover diagnostic screening test or clinical trials. Its sample estimate is

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$$\hat{P}(C) = \hat{\pi}_z^+ = P_z = \frac{W_z}{n_z} = \frac{F_z^+}{n_z} \quad \ldots (6)$$

where

$F_z^+ = W_z$ is the number of study subjects who test positive when screened by clinician Z in phase 1 of the three phased cross-over screening tests in a clinical trial. In other words, F_z^+ is the number of 1's in the frequency distribution of the n_z values of 0's and 1's in U_{iz}, for i=1,2, . . . , n_z. The sample variance of $\hat{\pi}_z^+$ is (from equation 5)

$$\text{Var}(\hat{\pi}_z^+) = \frac{Var(W_z)}{n_z^2} = \frac{\hat{\pi}_z^+(1-\hat{\pi}_z^+)}{n_z} \quad \ldots (7)$$

A null hypothesis that may be of interest in the first phase of screening tests may be that the proportion of subjects in a study population testing positive to a condition when screened by clinician Z at the first phase is at most some value π_{z_0} , that is, the null hypothesis

$$H_0: \pi_z^+ \leq \pi_{z_0} \text{ versus } H_1: \pi_z^+ > \pi_{z_0} \quad (0 \leq \pi_{z_0} \leq 1) \quad \ldots (8)$$

The null hypothesis of equation 8 is tested using the test statistic

$$\chi^2 = \frac{(W_z - n_z.\pi_{z_0})^2}{Var(W_z)} = \frac{n_z\,(\hat{\pi}_z^+ - \pi_{z_0})^2}{\hat{\pi}_z^+(1-\hat{\pi}_z^+)} \quad \ldots (9)$$

Under the null hypothesis H_o of equation 8 has approximately the Chi-Square distribution with 1 degree of freedom for sufficiently large n_z.

The null hypothesis H_o of equation 8 is rejected at the α level of significance if

$$\chi^2 \geq \chi^2_{(1-\alpha;\, 1)} \quad \ldots (10)$$

Otherwise, H_o is accepted.

If per chance, clinicians X and Y are also to conduct the screening tests at the first phase of the clinical trial using respectively n_x and n_y random samples of subjects or patients of comparable demographic characteristics such as age, sex and body weight as the n_z subject or patients used by clinician Z, then the sample estimate of the resulting probabilities of positive response would be respectively

$$\hat{P}(A) = \hat{\pi}_x^+ = p_x = \frac{F_x^+}{n_x} = \frac{W_x}{n_x} \quad \ldots (11)$$

And

$$\hat{P}(B) = \hat{\pi}_y^+ = p_y = \frac{F_y^+}{n_y} = \frac{W_y}{n_y} \quad \ldots (12)$$

Where

$F_x^+ = W_x$ and $F_y^+ = W_y$ have similar definitions as $F_z^+ = W_z$ as given above.

The variance of $\hat{\pi}_x^+$ and $\hat{\pi}_y^+$ are also calculated similar to the variance of $\hat{\pi}_z^+$.

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The corresponding null hypothesis H_o, similar to that of equation 8, are similarly stated and tested for $\hat{\pi}_z^+$ and $\hat{\pi}_y^+$ respectively.

In the second phase of diagnostic screening tests, the only subjects or patients who may be rescreened and retested by clinician Y are only the $n_{y.z} = F_z^+$ subjects who test positive under clinician Z in the first phase of the three phased three period crossover diagnostic screening test or clinical trials.

To obtain sample estimate of the probability that a randomly selected study subject or patient tests positive under clinician Y at the second phase of the diagnostic screening tests out of the $n_{y.z} = F_z^+$ subjects who test positive under clinician Z in the first phase of the three phased three period crossover diagnostic screening tests or clinical trials, we may let

$U_{iy.z} = \{1,$
$if\ the\ ith\ subject\ screened\ and\ tested\ by\ clinician\ \ Y\ at\ the\ second\ phase\ of\ the\ diagnostic\ scree$
$otherwise\ .\ .\ .$ (13)

for i=1,2, . . ., $n_{y.z} = F_z^+$ subjects or patients.

Let

$\hat{\pi}_{y.z}^+ = \mathrm{P}(U_{iy.z} = 1\ )$ . . . (14)

and

$W_{y.z} = \sum_{i=1}^{n_{y.z}} U_{iy.z}$ . . . (15)

Now

$\mathrm{E}\ (U_{iy.z}) = \pi_{y.z}^+$; $\mathrm{Var}\ (U_{iy.z}) = \pi_{y.z}^+(1 - \pi_{y.z}^+\ )$ . . . (16)

Also

$\mathrm{E}\ (W_{y.z}) = n_{y.z}\ .\ \pi_{y.z}^+$; $\mathrm{Var}\ (W_{y.z}) = n_{y.z}\ .\ \pi_{y.z}^+(1 - \pi_{y.z}^+)$ . . . (17)

Now $\pi_{y.z}^+$ is the probability that a randomly selected study subject test positive when tested by clinician Y in the second phase of screening test given that the same subject has earlier also tested positive when tested by clinician Z in the first phase of screening test. Its sample estimate is

$\hat{P}(B/C) = \hat{\pi}_{y.z}^+ = p_{y.z} = \frac{W_{y.z}}{n_{y.z}} = \frac{F_{y.z}^+}{n_{y.z}}$ . . . (18)

where

$F_{y.z}^+ = W_{y.z}$ is the number of subjects testing positive under clinician Y at the second phase of tests given that the same subjects have earlier also tested positive under clinician Z at the first phase of the tests. In other words, $F_{y.z}^+ = W_{y.z}$ is the number of 1's in the frequency distribution of the $n_{y.z}$ values of 0's and 1's in $U_{iy.z}$, i=1,2, . . ., $n_{y.z}$

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

$$\text{Var}\,(\hat{\pi}^{+}_{y.z}) = \frac{Var(W_{y.z}\,)}{n^{2}_{y.z}} = \frac{\hat{\pi}^{+}_{y.z}(1-\hat{\pi}^{+}_{y.z})}{n_{y.z}} \quad \ldots (19)$$

A null hypothesis that may be tested is that the population of subjects who test positive under clinician Y at the second phase of clinical trials, having earlier also tested positive under clinician Z at the first phase of the clinical trials or tests, is at most some value $\pi_{y.z_0}$ $(0 \leq \pi_{y.z_0} \leq 1)$ and is tested using the test statistic

$$\chi^{2} = \frac{(W_{y.z}-n_{y.z}.\pi_{y.z_0})^{2}}{Var(W_{y.z})} = \frac{n_{y.z}\ (\hat{\pi}^{+}_{y.z}-\pi_{y.z_0})^{2}}{\hat{\pi}^{+}_{y.z}(1-\hat{\pi}^{+}_{y.z})} \quad \ldots (20)$$

Which under H_0 has approximately the chi-square distribution with 1 degree of freedom. For sufficiently large $n_{y.z} = F^{+}_{y.z}$.

The null hypothesis is rejected at the α level of significance if equation 10 is satisfied, otherwise H_0 is accepted.

If again, perchance, at the second phase of clinical trials, clinician Y is to rescreen and retest the $n_{y.x} = F^{+}_{x}$ subjects or patients who have earlier tested positive when screened and tested by clinician X at the first phase of clinical trials and also clinician Z is to retest the $n_{y.z} = F^{+}_{y.z}$ subjects or patients who had earlier tested positive when screened and tested by clinician Y at the first phase of clinical trials or tests, then the resulting estimated conditional probabilities are respectively

$$\hat{P}(B/A) = \hat{\pi}^{+}_{y.x} = p_{y.x} = \frac{W_{y.x}}{n_{y.x}} = \frac{F^{+}_{y.x}}{n_{y.x}} \quad \ldots (21)$$

and

$$\hat{P}(C/B) = \hat{\pi}^{+}_{z.y} = p_{z.y} = \frac{W_{z.y}}{n_{z.y}} = \frac{F^{+}_{z.y}}{n_{z.y}} \quad \ldots (22)$$

where

$F^{+}_{y.x} = W_{y.x}$ and $F^{+}_{z.y} = W_{z.y}$ have similar definitions as $F^{+}_{y.z} = W_{y.z}$ above.

The corresponding variances, null hypothesis and test statistics for $\pi^{+}_{y.x}$ and $\pi^{+}_{z.y}$ are similarly calculated and tested as for $\pi^{+}_{z.y}$ above.

Finally, to obtain sample estimates of the proportion of subjects testing positive when screened and tested by clinician X at the third phase of screening tests given that the same subjects or patients have also earlier tested positive when screened and tested by clinicians Y and Z at the second and first phases of the three phased, three period crossover diagnostic screening test or clinical trials respectively, we note that the number of such subjects to be now screened and tested by clinician X are only those $n_{x.yz} = F^{+}_{y.z}$ subjects who have already tested positive under clinicians Y and Z at the second and first phases respectively of the clinical trials.

Thus, to estimate the required proportion of positive response under clinician X at the third phase of the clinical trials, we may le

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$U_{ix.y}$=
$\{1, if\ the\ i^{th}\ subjects\ screened\ and\ tested\ by\ Clinician\ X\ at\ the\ third\ phase\ of\ tests\ , test\ positive$
….23

For i=1, 2, …. , $n_{x.yz} = F^{+}_{y.z}$

Let

$\pi^{+}_{x.yz}$ = P ($U_{ix.yz}$ = 1) . . . 24

and

$W_{x.yz} = \sum_{i=1}^{n_{x.yz}} U_{ix.yz}$ . . . 25

The expected value and variance of $U_{ix.yz}$ are respectively

E($U_{ix.yz}$) = $\pi^{+}_{x.yz}$; Var ($U_{ix.yz}$) = $\pi^{+}_{x.yz}$(1- $\pi^{+}_{x.yz}$) . . . 26

The corresponding expected value and variance of $W_{x.yz}$ are respectively

E($W_{x.yz}$)=$n_{x.yz}$. $\pi^{+}_{x.yz}$; Var ($W_{x.yz}$) = $n_{x.yz}$. $\pi^{+}_{x.yz}$(1 − $\pi^{+}_{x.yz}$) . . . 27

Now, $\pi^{+}_{x.yz}$ is the probability that a randomly selected subject tests positive when screened and tested by Clinician X at the third phase of the screening tests, given that the same subject has also earlier tested positive when tested by Clinicians Y and Z at the second and first phases of screening tests respectively. Its sample estimate is

$$\hat{P}(A/BC) = \hat{\pi}^{+}_{x.yz} = p_{x.yz} = \frac{W_{x.yz}}{n_{x.yz}} = \frac{F^{+}_{x.yz}}{n_{x.yz}} \quad \ldots 28$$

Where = $W_{x.yz}$ is the number of subjects who test positive under Clinician X at the third phase of the screening tests given that these subjects have also tested positive under Clinicians Y and Z at the second and first phases of the three phase, three period diagnostic screening tests or clinical trials. In other words, $F^{+}_{x.yz}$ is the total number of 1's in $U_{ix.yz,}$ for i=1, 2, …, $n_{x.yz}$.

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

Var ($\hat{\pi}^{+}_{x.yz}$) = $\frac{Var(W_{x.yz})}{n^2_{x.yz}} = \frac{\hat{\pi}^{+}_{x.yz}(1-\hat{\pi}^{+}_{x.yz})}{n_{x.yz}}$ . . . 29

To test the null hypothesis, if of research interest, that the proportion of study subjects with a condition of interest in a population, who would test positive when tested by Clinician X at the third phase of the clinical trials is at least some value Θ_0 say ($0 \leq \Theta_0 \leq 1$), we may use the test statistic

$$\chi^2 = \frac{(W_{x.yz} - n_{x.yz}\,\Theta_0)^2}{Var(W_{x.yz})} = \frac{n_{x.yz}\,(\hat{\pi}^{+}_{x.yz} - \Theta_0)^2}{\hat{\pi}^{+}_{x.yz}(1-\hat{\pi}^{+}_{x.yz})}$$

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Which under the null hypothesis, H_0, has approximately the chi-square distribution with 1 degree of freedom for sufficiently large $n_{x.yz}$.

The null hypothesis is rejected at the α level of significance if equation 10 is satisfied otherwise H_0 is accepted.

The probability of positive response by subjects screened at the third phase of clinical trials by Clinician Y given that the same subjects have also responded positive when screened at the second phase by Clinician X and also positive at the first phase of tests by Clinician Z as well is $\pi^{+}_{y.xz}$.

The probability of positive response by subjects screened at the third phase of clinical trials by Clinician Z given that the same subject have also responded positive when screened at the second phase by Clinician Y and also positive at the first phase by Clinician X, are obtained, if required, following similar approaches as above, yielding the estimate $\pi^{+}_{z.xy}$.

$$\hat{P}(B/\text{AC}) = \hat{\pi}^{+}_{y.xz} = p_{y.xz} = \frac{F^{+}_{y.xz}}{n_{y.xz}} = \frac{W_{y.xz}}{n_{y.xz}} \quad \ldots 31$$

$$\hat{P}(C/\text{AB}) = \hat{\pi}^{+}_{z.xy} = p_{z.xy} = \frac{F^{+}_{z.xy}}{n_{z.xy}} = \frac{W_{z.xy}}{n_{z.xy}} \quad \ldots 32$$

With these results one would be able to estimate the probabilities of other possible events or outcomes. For instance, one may wish to estimate the probability that a randomly selected subject tests negative when tested by Clinician Y at the second phase of screening tests given that that subject has earlier tested positive when screened by Clinician Z at the first phase of the screening tests. This is the probability of the event $\underline{B}/C$, which is estimated as

$$\hat{P}(\underline{B}/C) = 1 - \hat{P}(B/C) = 1 - p_{y.z} \quad \ldots 33$$

Similarly, the probability that a randomly selected subject tests positive under Clinicians Y and Z at the first and second phases of the clinical trials respectively but test negative under Clinician X in the third phase of the trials is the probability of the event $\underline{A}BC$, which is

$$\hat{P}(\underline{A}BC) = \hat{P}(\underline{A}/BC)\,.\,\hat{P}(BC) = (1 - \hat{P}(A/BC).\,\hat{P}(B/C).\,\hat{P}(C)$$

or

$$\hat{P}(\underline{A}BC) = (1-p_{x.yz}).\hat{p}_{y.z}.p_z \quad . \quad . \quad . \quad 34$$

The probabilities of other possible events or outcomes are similarly estimated. The results are shown in table 1, which reflect the assumed seniority rankings of Clinicians.

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Table 1: Sample Estimates of Probabilities of Outcomes in Three Period Crossover Design in Phased Diagnostic Screening Tests

S/N	OUTCOME (EVENT)	PROBABILITY OF OCCURRENCE
1	C	p_z
2	B/C	$p_{y.z}$
3	$\underline{B}$/C	1-$p_{y.z}$
4	BC	$p_{y.z}.p_z$
5	$\underline{B}$C	(1-$p_{y.z}$).p_z
6	A/BC	$p_{x.yz}$
7	$\underline{A}$/BC	1-$p_{x.yz}$
8	AB/C	$p_{x.yz}.p_{y.z}$
9	$\underline{A}$B/C	(1-$p_{x.yz}$)$p_{y.z}$
10	$\underline{A}BC$	(1-$p_{x.yz}$).$p_{y.z}$. p_z
11	ABC	$p_{x.yz}.p_{y.z}.p_z$

Note that in a three period crossover design type diagnostic screening tests conducted in three phases, where interest is mostly only in positive responses, other probabilities can also be estimated. For example, the probability that a randomly selected subject tests positive in the second phase given that the same subject has earlier tested negative in the first phase of screening tests can be estimated with the probabilities obtained above as

$$\text{P (B/}\underline{A}) = \frac{P(\underline{A}B)}{P(A)} = \frac{P(\underline{A}B).P(B)}{P(\underline{A})} = \frac{(1-P(A\backslash B).P(B)}{1-P(A)}$$

or

$$\hat{P}(\text{B/}\underline{C}) = \frac{\left(1-\hat{p}\left(\frac{C}{B}\right)\right)\hat{p}\,(B)}{1-\hat{p}(C)} = \frac{(1-p_{z.y}).p_y}{1-p_z}$$

Similarly, in the third phase of the screening tests the probabilities of the events or outcomes in which a randomly selected subject has earlier tested positive in the first two phases or the two earlier phases of screening tests may be used to estimate other probabilities. In other words, in phase three period crossover diagnostic screening tests where research interest by a subsequent clinician is to rescreen and retest subjects who respond positive to test by a clinician in an immediately preceding screening test, the probability of an outcome in a subsequent test conditional on a negative response or outcome in a previous screening test by a clinician colleague can be estimated indirectly using available or estimated probabilities of positive response.

However, the more senior clinicians or research scientists involved in the phased screening tests may still, if necessary, in order of seniority for example, rescreen, that is retest, mostly not only subjects who test positive under their more junior clinician colleagues, but also subjects who test negative. For example, research interest may be in clinician Y in the second phase of screening test, rescreening and retesting subjects who test negative under clinician Z in the first phase of the tests while in the third phase of screening tests; clinician X may choose

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to retest and confirm the response of subjects who in the process test negative when tested by clinician Y in the second phase of the tests.

Note however that if ab initio, research interest is in subjects who respond negative and hence in the probabilities of negative response in the three phased three period crossover screening tests or clinical trials, then only the $n_z - F_z^+$ subjects who respond negatively when screened and tested by clinician Z during the first phase of the trials would need to be rescreened and retested by clinician Y during the second phase of trials.

Similarly, only those subjects or patients who respond negative under clinician Y during the second phase and also respond negative under clinician Z during the first phase of the clinical trials would need to be rescreened and retested by clinician X during the third and last phase of the trials, assuming the seniority ranking of clinicians is still upheld.

If, however there is no inbuilt ranking of clinicians in the process of three phase three period crossover diagnostic screening tests or clinical trials, then all possible combinations of the outcomes or events A, B and C and their complements are admissible.

Perhaps, of greater importance however, in the three period, three phase diagnostic screening tests and clinical trials, is the need to resolve and reconcile in phase three test any inconsistencies that may have arisen in phases one and two when patients or subjects test positive (negative) in phase one only to end up testing negative (positive) in phase two of the diagnostic screening tests or clinical trials.

To do this, the clinician or research scientist identifies, rescreens and retests in phase three all those subjects or patients who test positive (negative) in phase one but test negative (positive) in phase two of the tests. Following these tests, all other procedures remain unchanged. Further analysis may then continue as usual without any new problems.

Illustrative Example

Three research scientists or clinicians X, Y and Z are interested in determining the existence or otherwise of a certain disease in a population using three period crossover phased diagnostic screening tests in which each study subject serves as its own control in each period. A random sample of size $n=n_z= 50$ subjects are drawn from the population to be first screened by clinician Z to determine the possible presence of the disease in each sampled subject. Subjects who test positive to the disease under clinician Z are rescreened by clinician Y in the second phase of screening tests while subjects who are still found to have the disease at this phase are further rescreened and retested by clinician X in the third phase of screening tests.

The test results after the three phases of screening tests are presented in Table 2. Here 1 indicates positive response and 0 indicates negative response by subjects.

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Table 2: Test results by clinicians in three phase, three period crossover diagnostic screening tests for a disease.

S/N	CLINICIAN Z RESPONSE	CLINICIAN Y RESPONSE	CLINICIAN X RESPONSE
1	1	1	1
2	1	1	0
3	1	1	0
4	0	-	-
5	1	0	-
6	1	1	1
7	1	0	-
8	0	-	-
9	0	-	-
10	1	0	-
11	0	-	-
12	1	1	1
13	0	-	-
14	0	-	-
15	0	-	-
16	0	-	-
17	1	1	0
18	1	1	1
19	1	1	0
20	0	-	-
21	1	0	-
22	1	1	0
23	0	-	-
24	0	-	-
25	1	0	-
26	1	0	-
27	0	-	-
28	1	1	1
29	1	0	-
30	1	1	1
31	1	1	1
32	1	0	-
33	1	1	1
34	1	1	1
35	1	0	-
36	0	-	-
37	1	1	0
38	1	0	-
39	1	1	0
40	1	1	1
41	0	-	-

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42	1	1	0
43	1	1	0
44	1	0	-
45	0	-	-
46	1	0	-
47	0	-	-
48	1	1	1
49	1	0	-
50	1	1	1
	F_z^+ = **34**	$F_{Y.Z}^+$ = **21**	$F_{X.YZ}^+$ = **12**

We use the data of Table 2 to illustrate estimation of probabilities of positive response in diagnostic screening tests conducted in three period crossover tests by three clinicians. To estimate the probability of positive response to a disease when clinician Z conducts the screening test first in phase one of three phased, three period crossover screening tests we apply equation 1 to responses by subjects under clinician Z of Table 2 to obtain

$F_z^+ = 34$

$\hat{\pi}_z^+ = p_z = \frac{34}{50} = 0.680$

The estimated variance of $\hat{\pi}_z^+$, from equation 7 is

Var $(\hat{\pi}_z^+) = \frac{(0.680)(0.320)}{50} = \frac{0.218}{50} = 0.004$

Also from Table 2, the estimated probability of positive response to the disease by subjects when tested by clinician Y in the second phase of screening tests given that the same subjects have responded positive to the disease when tested by clinician Z in the first phase of screening tests are as follows

$$F_{Y.Z}^+ = 21$$

Hence, from equation 16, the sample estimate of the proportion of positive responses under clinician Y in the second phase, among subjects who responded positive under clinician Z in the first phase of screening tests is

$\hat{p}(B/C) = \hat{\pi}_{Y.Z}^+ = p_{Y.Z} = \frac{21}{34} = 0.618$

Similarly, the number of subjects responding positive under clinician X in the third phase among the $n_{Y.Z} = 21$ subjects who respond positive under clinician Y in the second phase and who also respond positive under clinician Z in the first phase of screening tests is (from Table 2)

$$F_{X.YZ}^+ = 12$$

Hence, from equation 24, the sample estimate of the proportion of subjects who respond positive under clinician X in the third phase among the $n_{X.YZ} = 21$ subjects who respond positive to clinicians Y and Z in the second and first phases of screening tests respectively is

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$\hat{\pi}^{+}_{X.YZ}$ = $p_{X.YZ} = \frac{12}{21} = 0.571$

With these estimates one may estimate the probabilities of outcomes in phased clinical trials. For example, the probability that clinicians Y and Z are in agreement in their assessment of positive responses by subjects in the first two phases of screening tests, is the probability of the event BC which is estimated as

$\hat{P}(BC) = \hat{P}(B/C).\ \hat{P}(C) = p_{Y.Z}\ .\ p_z = (0.618)\ (0.680) = 0.420$

The probability that the three clinicians are in complete agreement in their assessment of positive response by subjects at the end of the three phased, three period cross-over screening tests is the probability of the event ABC which is estimated as

$\hat{P}(ABC) = \hat{P}(A/BC).\ \hat{P}(B/C).\ \hat{P}(C) = p_{X.Y..Z}\ .p_{Y.Z}\ .p_z = (0.571)(0.618)(0.680) = 0.240$

Other probabilities of the events in Table 1 are similarly estimated.

These probability estimates as well as the estimated probability of the events of table 1 are shown in table 3.

Table 3: Sample Estimates of Probabilities in Table 1 for the Data of Table 2

S/N	Outcome (Event) Based on Positive Response	Estimated Probabilities
1	C	0.680
2	B/C	0.618
3	$\underline{B}/C$	0.382
4	BC	0.420
5	$\underline{BC}$	0.260
6	A/BC	0.571
7	$\underline{A}/BC$	0.429
8	AB/C	0.353
9	$\underline{AB}/C$	0.265
10	$\underline{ABC}$	0.180
11	ABC	0.240

Note that if we multiply each estimated probability by N, the population at risk, we obtain the expected number of people who are affected or test positive in the population, in each case.

If subjects are to be declared as testing positive only if they test positive in the first two phases, that is under clinician Y and Z, no matter their test results in the third phase under clinician X, then the estimated probability of such an event is

$\hat{P}(ABC) + \hat{P}(\underline{A}BC) = \hat{P}(A/BC).\ \hat{P}(BC) + (1 - \hat{P}\ (A/BC).\hat{P}(BC)$

Which is given as

$P_{X.YZ}\ .\ p_{Y.Z}\ .\ p_z + (1-p_{X.YZ}).\ p_{Y.Z}\ .\ p_Z = 0.240 + 0.180 = 0.420$

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If a subject must be declared as testing positive only if the subject tests positive under clinician X and at least positive under one other clinician in the three phase three period crossover screening test, then the corresponding estimated probability is easily shown to be

$\hat{P}(\text{ABC}) + \hat{P}(\text{AB}\underline{C}) + \hat{P}(\text{A}\underline{B}\text{C}) = 0.240 + 0.080 + 0.160 = 0.480$

Similarly, if only subjects who test positive under clinician X and Y are to be considered as truly testing positive, then the estimated probability is

$\hat{P}(\text{ABC}) + \hat{P}(\text{AB}\underline{C}) = 0.240 + 0.080 = 0.320$

Other desired probabilities of positive response by subjects to the condition of interest may be similarly estimated.

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