Statistical Assessment of Clinical Trials with Discordant Pairs of Observations

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Abstract

In this communication, we propose a way to analyze a parallel group design with 2 treatment groups (Active vs. Placebo) wherein each patient having both patient's and investigator's assessments and the response variable is of the dichotomous type (success or failure). The optimum statistical inference procedure turns out to be one that discards the discordant pairs of data, only the concordant pairs of data are used. The result agrees with one's intuition. This is an interesting contrast to a matched pairs design using Exact McNemar's test wherein only the discordant pairs of data are used in the comparison of the 2 treatments.

Key Words: Discordant Pairs, Exact McNemar's test, Hypergeometric Distributions, Conditional Distribution, Clinical Trials

1. Introduction

In a clinical trial having patient's self-assessment and investigator's assessment of the same symptoms/signs of a disease, the result of patient's assessment may not be totally in agreement with Investigator's assessment. This inconsistency makes the approval of a new drug somewhat difficult. It is felt the discordant pairs of assessment may not be reliable to judge whether the treatment is a success or a failure. Worse it creates white noise which clouds the efficacy or safety evaluations. Instead, the concordant pairs wherein both patient and investigator agree that the treatment is a success or a failure should be used. The situation is similar to "getting a second opinion" in medical practice. When 2nd opinion agrees with the 1st opinion, one would have more confidence on the recommendation.

2. Possible Areas of Applications

In drug clinical trials, whenever 2 separate evaluations on the same patient are made, comparing "agreed" proportions can help to remove uncertainty or contradictory evaluations between patient's assessments and physician's assessments, enabling regulatory authority to make approval decision with confidence on the efficacy or safety of the drug products. This is particularly useful when less objective endpoints are used in the study. For example, analgesics for pain and suffering, allergy medications for seasonal allergic rhinitis symptoms, Psychopharmacological drugs for psychotics, and medicines for neurological impairments such as Parkinson's and Alzheimer's. Recent stride in ovarian cancer treatment centers on requiring 2 physicians independently judge and agree on the extent of a patient's lesion from a laparoscope examination so that the order of treatments to a patient , chemotherapy first or surgery first, may be optimally determined is another example of the usefulness of concordant opinions.

3. Study Design, Notation, and Parameters of Interest

The usual parallel group design remains the same but it does need 2 separate evaluations (2nd opinion) of the same symptoms or signs of a patient. It is essentially the assessment made by 2 or more panelists in a panel evaluation.

3.1 Study Design and Notations

A parallel group design with 2 treatment groups: Active vs. Placebo. Both the patient and the investigator make assessment of the outcome of the treatment, either success (= 1) or failure (= 0).

3.1.1 Active Group (Treatment 1)

		Investigator's Assessment	
		0	1
Patient's Assessment	0	P_{00} (S_{00})	P_{01} (S_{01})
	1	P_{10} (S_{10})	P_{11} (S_{11})
			m

$m = S_{00} + S_{01} + S_{10} + S_{11}$ = sample size for the Active group.

Notation for the Active Group or Treatment 1:

S_{00} (P_{00}) = Number (proportion) of "Agreed" failures. Both patient and Investigator rates the treatment as a "Failure"

S_{11} (P_{11}) = Number (proportion) of "Agreed" Success. Both patient and Investigator rates the treatment as a "Success"

$S_{00} + S_{11}$ = total number of Patients with "Agreed" assessments, both failures and successes.

$S_{11} / (S_{00} + S_{11})$ = Proportion of "Agreed" Success in the sample, Active Group or Treatment 1

$P \equiv P_{11} / (P_{00} + P_{11})$ = Proportion of "Agreed" Success in the population, Active Group or Treatment 1

3.1.2 Placebo Group (Treatment 2)

		Investigator's Assessment	
		0	1
Patient's Assessment	0	P_{00}' (S_{00}')	P_{01}' (S_{01}')
	1	P_{10}' (S_{10}')	P_{11}' (S_{11}')
			m′

$m' = S_{00}' + S_{01}' + S_{10}' + S_{11}'$ = sample size for the Placebo group.

Notation for the Placebo Group or Treatment 2:

S_{00}' (P_{00}') = Number (proportion) of "Agreed" failures. Both patient and Investigator rates the treatment as a "Failure"

S_{11}' (P_{11}') = Number (proportion) of "Agreed" Success. Both patient and Investigator rates the treatment as a "Success"

$S_{00}' + S_{11}'$ = total number of Patients with "Agreed" assessments, both failures and successes.

$S_{11}' / (S_{00}' + S_{11}')$ = Proportion of "Agreed" Success in the sample, Placebo Group or Treatment 2

$P' \equiv P_{11}' / (P_{00}' + P_{11}')$ = Proportion of "Agreed" Success in the population, Placebo Group or Treatment 2

3.2 Parameters of Interest

The metric of interest is the Proportion of "Agreed" Success. The proportion of "Agreed" Success P of the Active Group will be compared to the proportion of "Agreed" Success P′ of the Placebo group. Specifically, we are interested in comparing P to P′.

3.3 Exact Test to Compare Proportion P to Proportion P′

In one of the authors' NDA defense for certain allergic rhinitis medication, he used chi-squared test with d.f. = 1 to compare P to P′ which is a large sample approximation test.

In the discussion below, we develop a small sample exact test which is analogous to Fisher's exact test to compare the 2 proportions: P vs. P′. However the underlying distribution of Fisher's test is derived from 2 binomial distributions, here the 2 underlying distributions involved are again binomial but of different forms.

Since

$P = P_{11} / (P_{00} + P_{11}) = (P_{11}/ P_{00}) / [\, 1 + (P_{11}/ P_{00})\,]$

$P' = P_{11}' / (P_{00}' + P_{11}') = (P_{11}'/ P_{00}') / [\, 1 + (P_{11}'/ P_{00}')\,]$

Consider the "Odds" θ of the Active Treatment Group based on its Proportion of Agreed Success:

$$\theta = P / (1 - P)$$

Note $\theta = P_{11} / P_{00}$,

And $P = P_{11} / (P_{00} + P_{11}) = \theta / (1 + \theta)$.

Similarly, consider the "Odds" θ′ of the Placebo Treatment Group based on its Proportion of Agreed Success:

$$\theta' = P' / (1 - P')$$

Note $\theta' = P_{11}' / P_{00}'$,
And $P' = P_{11}' / (P_{00}' + P_{11}') = \theta' / (1 + \theta')$.

Thus the odds ratio of P over P′ is

$[P / (1 – P)] / [P' / (1 – P')] = \theta / \theta'$

In conclusion, we have shown that θ / θ' is the odds ratio comparing P to P′ and will serve as the key parameter of interest.

4. Existence of Distributions for Comparing P to P′

4.1 Existence of Distribution which Depends on the Desired Parameter θ

For the Active Group, we have the following sampling distribution which is a 4-component (or 4- category) multinomial distribution:

$P\{ \mathbf{S} = \mathbf{s} \}$

$$= \binom{m}{S_{00}, S_{01}, S_{10}, S_{11}} P_{00}^{S_{00}} P_{01}^{S_{01}} P_{10}^{S_{10}} P_{11}^{S_{11}}$$

(Apply the Divide and Recover operation on the 2 terms involving P_{11} and P_{00}) which may be written as

$$= \binom{m}{S_{00}, S_{01}, S_{10}, S_{11}} (P_{11}/P_{00})^{S_{11}} P_{00}^{S_{00}+S_{11}} P_{01}^{S_{01}} P_{10}^{S_{10}}$$

Since $S_{10} = m - (S_{00} + S_{01} + S_{11})$, we have

$$= P_{10}^{m} \binom{m}{S_{00}, S_{01}, S_{10}, S_{11}} (P_{11}/P_{00})^{S_{11}} (P_{00}/P_{10})^{S_{00}+S_{11}} (P_{01}/P_{10})^{S_{01}}$$

This factored-out form of the multinomial distribution $P\{ \mathbf{S} = \mathbf{s} \}$ is seen to be in a form of the exponential family of distributions. And it assures that, by Lemma 2.7.2 (Lehmann and Romano (2005), p. 48), the conditional distribution:

$$P\{ S_{11} = s_{11} \mid S_{00} + S_{11} = t_1, S_{01} = s_{01} \} \quad (1)$$

depends only on the desired parameter $\theta = P_{11} / P_{00}$ (function of "Agreed" Proportion of Success P for the Active group).

4.2 Existence of Distribution which Depends on the Desired Parameter θ′

Similarly, for the Placebo Group, we have the following multinomial distribution:

P { **S′ = s′** }

$$= \binom{m'}{S_{00}', S_{01}', S_{10}', S_{11}'} P_{00}'^{S_{00}'} P_{01}'^{S_{01}'} P_{10}'^{S_{10}'} P_{11}'^{S_{11}'}$$

which may be written as

$$= P_{10}'^{m'} \binom{m'}{S_{00}', S_{01}', S_{10}', S_{11}'} \left(P_{11}'/P_{00}'\right)^{S_{11}'} \left(P_{00}'/P_{10}'\right)^{S_{00}'+S_{11}'} \left(P_{01}'/P_{10}'\right)^{S_{01}'}$$

This factored-out form of the multinomial distribution is seen again to be in a form of the exponential family of distributions. Again it assures that, by Lemma 2.7.2 (Lehmann and Romano (2005), p. 48), the conditional distribution:

$$P\ \{ S_{11}' = s_{11}' \mid S_{00}' + S_{11}' = t_2,\ S_{01}' = s_{01}' \} \qquad (2)$$

depends only on the desired parameter θ′ = P_{11}' / P_{00}' (function of “Agreed” Proportion of Success P′ for the Placebo group).

4.3 Distribution which Depends on the Desired θ / θ′

So far, we have shown that the conditional distribution (1) from the Active treatment group depends on the desired parameter θ = P_{11} / P_{00}; while the conditional distribution (2) of the Placebo group depends on the desired parameter θ′ = P_{11}' / P_{00}'.

The 2 distributions are independent (different treatment groups). Their joint distribution is their product:

P { **S** = **s**, **S′ = s′** } = P { **S** = **s** } • P { **S′ = s′** }

$$= P_{10}^{m} \binom{m}{S_{00}, S_{01}, S_{10}, S_{11}} \left(P_{11}/P_{00}\right)^{S_{11}} \left(P_{00}/P_{10}\right)^{S_{00}+S_{11}} \left(P_{01}/P_{10}\right)^{S_{01}}$$

$$\bullet\ P_{10}'^{m'} \binom{m'}{S_{00}', S_{01}', S_{10}', S_{11}'} \left(P_{11}'/P_{00}'\right)^{S_{11}'} \left(P_{00}'/P_{10}'\right)^{S_{00}'+S_{11}'} \left(P_{01}'/P_{10}'\right)^{S_{01}'}$$

$$= P_{10}^{m} P_{10}'^{m'} \binom{m'}{S_{00}', S_{01}', S_{10}', S_{11}'} \binom{m}{S_{00}, S_{01}, S_{10}, S_{11}} \left[\left(P_{11}/P_{00}\right)/\left(P_{11}'/P_{00}'\right)\right]^{S_{11}}$$

$$\bullet \left(P_{11}'/P_{00}'\right)^{S_{11}+S_{11}'} \left(P_{00}/P_{10}\right)^{S_{00}+S_{11}} \left(P_{00}'/P_{10}'\right)^{S_{00}'+S_{11}'} \left(P_{01}/P_{10}\right)^{S_{01}} \left(P_{01}'/P_{10}'\right)^{S_{01}'}$$

This factored-out form of the joint distribution is seen again to be in a form of the exponential family of distributions. Again it assures that, by Lemma 2.7.2 (Lehmann and Romano (2005), p. 48), the conditional distribution:

$$P \{ S_{11} = s_{11} \mid S_{11}' + S_{11} = t_3, S_{00} + S_{11} = t_1, S_{00}' + S_{11}' = t_2, S_{01} = s_{01} , S_{01}' = s_{01}' \}$$

depends on the desired parameter $(P_{11} / P_{00}) / (P_{11}' / P_{00}') = \theta / \theta'$ = odds ratio of P over P′ only.

And again by Lehmann's theory for multi-parameter exponential families (p. 119), there exists tests which have the desired property of UMPU that can perform inference on the parameter θ / θ'.

5. Actual Derivation of the 3 Conditional Distributions

Having shown that there exists 3 conditional distributions which depend on the desired parameters θ, θ', and θ / θ', respectively, we now actually derive these distributions. It turns out that the conditional distribution which depends on θ is a Binomial distribution. The conditional distribution which depends on θ' is also a Binomial distribution. These 2 binomials are independent. Hence the conditional distribution which depends on θ / θ' may be derived, and is a hypergeometric distribution.

5.1 Actual Derivation of the Conditional Distribution which Depends on θ

From (1), the conditional distribution by definition is:

$$P \{ S_{11} = s_{11} \mid S_{00} + S_{11} = t_1, S_{01} = s_{01} \}$$
$$= P \{ S_{11} = s_{11}, S_{00} = t_1 - S_{11}, S_{01} = s_{01} \} / P \{ S_{00} + S_{11} = t_1, S_{01} = s_{01} \}$$
$$= P \{ S_{11} = s_{11}, S_{00} = t_1 - S_{11}, S_{01} = s_{01} \} / \Sigma_{\Omega} \ P \{ S_{11} = s_{11}, S_{00} = t_1 - S_{11}, S_{01} = s_{01} \}$$

Where Ω = { All S_{11} such that $S_{00} + S_{11} = t_1$, t_1 being a constant. }

(Now $m = S_{00} + S_{01} + S_{10} + S_{11}$. Hence $S_{10} = m - t_1 - S_{01}$ is also a constant since t_1 and s_{01} are constants). Hence

$$= P \{ S_{11} = s_{11}, S_{00} = t_1 - S_{11}, S_{01} = s_{01}, S_{10} = m - t_1 - S_{01} \}$$
$$/ \Sigma_{\Omega} \ P \{ S_{11} = s_{11}, S_{00} = t_1 - S_{11}, S_{01} = s_{01}, S_{10} = m - t_1 - S_{01} \}$$

$$= \binom{m}{t_1 - S_{11}, S_{01}, m - t_1 - S_{01}, S_{11}} P_{10}^{m} \left(P_{11}/P_{00}\right)^{S_{11}} \left(P_{00}/P_{10}\right)^{t_1} \left(P_{01}/P_{10}\right)^{S_{01}}$$
$$\Big/ \sum_{\Omega} \binom{m}{t_1 - S_{11}, S_{01}, m - t_1 - S_{01}, S_{11}} P_{10}^{m} \left(P_{11}/P_{00}\right)^{S_{11}} \left(P_{00}/P_{10}\right)^{t_1} \left(P_{01}/P_{10}\right)^{S_{01}}$$

Where Ω = { All S_{11} such that $S_{00} + S_{11} = t_1$, t_1 being a constant }

Cancelling out the two common terms which appear in both numerator and denominator not affected by the summation operation above, we have (recalling that $\theta = P_{11} / P_{00}$)

$$= \binom{m}{t_1 - s_{11}, s_{01}, m - t_1 - s_{01}, s_{11}} \theta^{s_{11}} \left(P_{01}/P_{10}\right)^{s_{01}} \Bigg/ \sum_{\Omega} \binom{m}{t_1 - s_{11}, s_{01}, m - t_1 - s_{01}, s_{11}} \theta^{s_{11}} \left(P_{01}/P_{10}\right)^{s_{01}}$$

The combinatorial term in the numerator and the denominator may be simplified. From (4) of Footnote 1 below, we have

$$= \binom{m}{t_1}\binom{t_1}{s_{11}}\binom{t_2}{s_{01}} \theta^{s_{11}} \left(P_{01}/P_{10}\right)^{s_{01}} \Bigg/ \sum_{\Omega} \binom{m}{t_1}\binom{t_1}{s_{11}}\binom{t_2}{s_{01}} \theta^{s_{11}} \left(P_{01}/P_{10}\right)^{s_{01}}$$

$$= \binom{t_1}{s_{11}} \theta^{s_{11}} \Bigg/ \sum_{\Omega} \binom{t_1}{s_{11}} \theta^{s_{11}} \qquad (3)$$

But the set Ω = { All S_{11} such that $S_{00} + S_{11} = t_1$, t_1 being a constant }
= { $(S_{00}, S_{11}) = (0, t_1), (1, t_1\text{-}1), \ldots, (t_1, 0)$ }

Hence the denominator can be written as

$$\sum_{\Omega} \binom{t_1}{s_{11}} \theta^{s_{11}} = \sum_{s_{11}=0}^{t_1} \binom{t_1}{s_{11}} \theta^{s_{11}} = (1+\theta)^{t_1}$$

The last equation can be established by recognizing the form of Newton's Binomial formula. Hence (3) becomes

$$= \binom{t_1}{s_{11}} \theta^{s_{11}} \Big/ (1+\theta)^{t_1}$$

Noting that $S_{00} + S_{11} = t_1$ and $1 - \theta / (1 + \theta) = 1 / (1 + \theta)$, we have

$$= \binom{t_1}{s_{11}} \left(\theta/(1+\theta)\right)^{s_{11}} \left(1/(1+\theta)\right)^{t_1 - s_{11}}$$

Which is recognized to be a binomial distribution with sample size t_1, and probability parameter $\theta / (1 + \theta)$. Thus the conditional r.v.:

$X = P\{ S_{11} = s_{11} \mid S_{00} + S_{11} = t_1, S_{01} = s_{01} \}$ is

$X \sim \text{Bin}\ (n = t_1,\ P = \theta / (1 + \theta))$

Footnote 1. Simplification of the combinatorial term by some algebraic operations:

$$\binom{m}{t_1 - s_{11}, s_{01}, m - t_1 - s_{01}, s_{11}}$$
$$= m! / [(t_1 - s_{11})!(s_{01})!(m - t_1 - s_{01})!(s_{11})!]$$

Let $t_2 = S_{01} + S_{10} = m - t_1$, which is a constant. Add $(t_1)!$ and $(t_2)!$ to both the numerator and the denominator, the above can be simplified to

$$= \binom{m}{t_1}\binom{t_1}{s_{11}}\binom{t_2}{s_{01}} \qquad (4)$$

By recognizing $t_1 + t_2 = S_{00} + S_{11} + S_{01} + S_{10} = m$

5.2 Actual Derivation of the Conditional Distribution which Depends on θ′

For the Placebo group, from (2), the conditional distribution which depends on the desired parameter P′ is:

$P\{ S_{11}' = s_{11}' \mid S_{00}' + S_{11}' = t_2, S_{01}' = s_{01}' \}$

Following the same way we derived the conditional distribution for the Active group in section 5.1, it can be shown that the above is

$$= \binom{t_1'}{s_{11}'} \left(\theta'/(1+\theta')\right)^{s_{11}'} \left(1/(1+\theta')\right)^{t_2 - s_{11}'}$$

i.e., the conditional r.v. is Binomial, or

$X' = P\{ S_{11}' = s_{11}' \mid S_{00}' + S_{11}' = t_2, S_{01}' = s_{01}' \}$ is

$X' \sim \text{Bin}\ (n = t_2,\ P' = \theta' / (1 + \theta'))$

5.3. Actual Derivation of the Conditional Distribution which Depends on θ/θ′

Section 5.1 shows that

$X \sim \text{Bin}\ (n = t_1,\ P = \theta / (1 + \theta))$

Section 5.2 shows that

$X' \sim \text{Bin}\ (n = t_2,\ P' = \theta' / (1 + \theta'))$

Since X (from the Active group) and X′ (from the placebo group) are independent Binomial random variables, by Fisher's Exact Test, the conditional random variable $Y \equiv \{X = x \mid X + X' = k\}$ has a non-central hypergeometric distribution with the parameter of Odds of P over odds of P', or $[P/(1-P)] / [P'/(1-P')]$, which is θ / θ'.

Thus we have found the conditional distribution of

$Y \equiv \{X = x \mid X + X' = k\}$

Which depends on the desired parameter (θ / θ') and is the desired final result.

6. Power and Sample Size Determination

In order to plan for a study, we need to estimate sample size required. Recall the (non–central) hypergeometric distribution we just derived depends on the desired parameter

$$\theta / \theta' = (P_{11} / P_{00}) / (P_{11}' / P_{00}')$$

Hwang and Lee (2009) pointed out the difficulty encountered in a matched paired design when trying to estimate sample size based on the multinomial parameters similar to P_{ij}'s here. They provided the transformation of the P_{ij}'s to the familiar marginal (binomial) parameters P_1, P_2, and the correlation ρ (rho) between X_1 and X_2. Thus

Lemma 1.1 $\quad P_{11} = (P_1)(P_2) + \rho\,[P_1(1-P_1)\,P_2(1-P_2)]^{0.5}$

Hence P_{11} is determined if P_1, P_2 and ρ are known. The same holds for P_{00} below.

Lemma 1.4 $\quad P_{00} = (1-P_1)(1-P_2) + \rho\sqrt{P1(1-P1)P2(1-P2)}$

Similar transformation may be made for the multinomial parameters P_{11}' and P_{00}' in P_{11}'/P_{00}' to binomial parameters P_1', P_2', and the correlation ρ′ between X_1' and X_2'.

With the transformation, one can then for any correlation estimated or assigned to ρ and ρ′ and parameter values of interest under various alternative hypothesis assigned to P_1, P_2, and P_1', P_2', determine the value of the desired parameter $(P_{11}/P_{00}) / (P_{11}'/P_{00}')$, which in turn specifies the conditional distribution in Section 5.3 completely (the non-central hypergeometric distribution) and then compute the conditional power for a specified type one error alpha α, and (conditional) critical region $C(t_1, t_2, t_3)$ subject to :

$$S_{11}' + S_{11} = t_3, S_{00} + S_{11} = t_1, S_{00}' + S_{11}' = t_2$$

One may then compute the unconditional power, and hence sample size by "integrating out" the 3 conditioning r.v.'s:

$$S_{11}' + S_{11} = t_3, S_{00} + S_{11} = t_1, S_{00}' + S_{11}' = t_2$$

Note the conditioning r.v.'s $S_{01} = s_{01}$, $S_{01}' = s_{01}'$ need not be considered since the conditional distribution does not depend on them. i.e. They serve as "location indicators only.

So effectively the power will be dependent on the value of the correlation, as in the exact McNemar test case.

References

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