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# Statistical Remarks Concerning the Odds Ratio and its Interpretation for the Comparison of Two Treatments in a Randomized Clinical Trial *

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**Abstract**

This paper explains why the odds ratio is a valid criterion for the comparison between two treatments in a randomized clinical trial where the outcome for a patient is classified as favorable versus unfavorable. The odds ratio has such validity through its description of the extent to which the odds of favorable versus unfavorable outcome is multiplicatively larger for the patients with one treatment than the patients with the other treatment. For a multi-center clinical trial, a logistic regression model can enable the estimation of the odds ratio to have appropriate statistical adjustment for the potential variation across centers of the probability of favorable response to each treatment, and this model can have a more correct application through conditional logistic regression methods for studies where many centers have small sample sizes (for either favorable or unfavorable outcome).

## 1 Introduction

The purpose of this manuscript is to clarify why the odds ratio is a fully valid criterion for expressing the comparison between two treatments for the probability of a favorable (or unfavorable) outcome in a randomized clinical study. The odds ratio validly describes the extent to which favorable (or unfavorable) outcome is more likely for one of the two treatments than the other by specifically addressing the extent to which the odds of favorable versus unfavorable

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outcome is multiplicatively larger (or smaller) for one of the two treatments than the other. For example, if the probability of favorable outcome for treatment $A$ is 0.60, then the corresponding odds of favorable versus unfavorable outcome for treatment $A$ is $(0.60/0.40) = 1.5$; and this odds expresses favorable outcome as being 1.5 times more likely than the unfavorable outcome for patients with treatment $A$; or relative to the expected number of patients with unfavorable outcome for treatment $A$ in this setting, the odds of 1.5 expresses that the expected number with favorable outcome is 50% larger. Similarly, if the probability of favorable outcome for treatment $B$ is 0.75, then the corresponding odds of favorable versus unfavorable outcome for treatment $B$ is $(0.75/0.25) = 3.0$; and this odds expresses the favorable outcome as being 3.0 times more likely than unfavorable outcome for patients with treatment B.

Since the example has an odds of 1.5 (for favorable versus unfavorable outcome) for treatment $A$ and an odds of 3.0 for treatment $B$, the corresponding odds ratio for the comparison between treatment $B$ and treatment $A$ is $3.0/1.5 = 2.0$; and it expresses the odds of favorable versus unfavorable outcome being twice as large for patients with treatment $B$ as for patients with treatment $A$ (or similarly that such odds is 100% greater for treatment $B$ relative to treatment $A$); see Chapters 2 and 8 of Stokes, Davis, and Koch (2000).

More generally, the odds ratio equals 1.0 if the odds of favorable versus unfavorable outcome is equal for treatment $A$ and treatment $B$ (or correspondingly if the probabilities of favorable outcome are equal for treatment $A$ and treatment $B$); and the odds ratio becomes progressively larger (or smaller) than 1.0 as the odds for favorable versus unfavorable outcome for treatment $B$ becomes progressively larger (or smaller) than such odds for treatment $A$ (and thereby as the difference between the probabilities of favorable outcome for treatment $B$ and treatment $A$ becomes progressively larger (or smaller) than 0). In this way, the odds ratio expresses the extent of larger (or smaller) probability for more favorable outcome for treatment $B$ than treatment $A$ as validly as the difference between the probabilities of favorable outcome for treatment $B$ and treatment $A$; but each of these two criteria for the comparison between treatment $B$ and treatment $A$ has its own interpretation, and that interpretation is not directly applicable to the other. For the previously stated example, the difference between the probabilities of favorable outcome for treatment $B$ and treatment $A$ is 0.75 - 0.60 = 0.15, and the odds ratio is 2.0. Accordingly, each of these criteria reasonably expresses the extent of larger probability for more favorable outcome for treatment $B$ than treatment $A$, but in a different manner from the other. This statement similarly applies to the ratio of the probabilities of favorable outcome for treatment $B$ and treatment $A$ (e.g., $(0.75/0.60) = 1.25$) or correspondingly to the reciprocal of the ratio of the probabilities of unfavorable outcome (e.g., $1/(0.25/0.40) = 1.6$). Moreover, the odds ratio has the attractive property of being the product of the ratio of the probabilities of favorable outcome and the reciprocal of that for unfavorable outcome (e.g., $1.25 \times 1.6 = 2.0$) and so unifies their roles for the comparison between two treatments.

## 2 Relationships for how the odds ratio affects the difference and ratio of probabilities for favorable outcome

With $P_A$ and $P_B$ as the probabilities of favorable outcome for treatment $A$ and treatment $B$, the odds ratio is

$$\begin{aligned} \text{OR} &= \{P_B/(1-P_B)\}/\{P_A/(1-P_A)\} \\ &= \{P_B \times (1-P_A)\}/\{(1-P_B) \times P_A\}. \end{aligned} \quad (1)$$

The general relationships for how the odds ratio and $P_A$ correspond to a particular $P_B$, a particular difference $(P_B - P_A)$, and a particular ratio $(P_B/P_A)$ are specified in (2) - (4).

$$P_B = \{\text{OR} \times P_A\}/\{(\text{OR}-1) \times P_A + 1\}, \quad (2)$$

$$(P_B - P_A) = \{(\text{OR}-1) \times P_A \times (1-P_A)\}/\{(\text{OR}-1) \times P_A + 1\}, \quad (3)$$

$$(P_B/P_A) = \text{OR}/\{(\text{OR}-1) \times P_A + 1\}. \quad (4)$$

The relationships in (2) - (4) are of interest because they express for any $P_A$ what any odds ratio OR implies for the corresponding $P_B$, $(P_B - P_A)$, and $(P_B/P_A)$. More specifically, when OR = 1, (2) - (4) imply $P_B = P_A$, $(P_B - P_A) = 0$ and $(P_B/P_A) = 1$; and as OR increases above 1, they imply that $P_B$ increases above $P_A$, $(P_B - P_A)$ increases above 0, and $(P_B/P_A)$ increases above 1. The patterns for such increases are illustrated in Table 1 for situation with $P_A = 0.6$.

Table 1: Relationships of $P_B$, $(P_B - P_A)$, and $(P_B/P_A)$ to OR when $P_A = 0.6$.

| $P_A$ | OR | $P_B$ | $(P_B - P_A)$ | $(P_B/P_A)$ |
|---|---|---|---|---|
| 0.6 | 1.0 | 0.600 | 0.000 | 1.000 |
| 0.6 | 1.5 | 0.692 | 0.092 | 1.154 |
| 0.6 | 2.0 | 0.750 | 0.150 | 1.250 |
| 0.6 | 2.5 | 0.789 | 0.189 | 1.316 |
| 0.6 | 3.0 | 0.818 | 0.218 | 1.364 |
| 0.6 | 4.0 | 0.857 | 0.257 | 1.429 |
| 0.6 | 5.0 | 0.882 | 0.282 | 1.471 |

The relationships (2) -(4) shed light as well for how variation of $P_A$ influences the implications of a particular OR to $P_B$, $(P_B - P_A)$, and $(P_B/P_A)$. This point is illustrated in Table 2 for a situation with OR =2, and consideration there also includes $(1 - P_A)/(1 - P_B)$.

Table 2: Relationships of $P_B$, $(P_B - P_A)$, $(P_B/P_A)$, and $(1 - P_A)/(1 - P_B)$ to $P_A$ when OR = 2.

| $P_A$ | OR | $P_B$ | $(P_B - P_A)$ | $(P_B/P_A)$ | $(1 - P_A)/(1 - P_B)$ |
|---|---|---|---|---|---|
| 0.01 | 2 | 0.0198 | 0.0098 | 1.980 | 1.010 |
| 0.10 | 2 | 0.1818 | 0.0818 | 1.818 | 1.100 |
| 0.25 | 2 | 0.4000 | 0.1500 | 1.600 | 1.250 |
| 0.50 | 2 | 0.6667 | 0.1667 | 1.333 | 1.500 |
| 0.60 | 2 | 0.7500 | 0.1500 | 1.250 | 1.600 |
| 0.80 | 2 | 0.8889 | 0.0889 | 1.111 | 1.800 |
| 0.90 | 2 | 0.9474 | 0.0474 | 1.053 | 1.900 |
| 0.95 | 2 | 0.9744 | 0.0244 | 1.026 | 1.950 |
| 0.99 | 2 | 0.9950 | 0.0050 | 1.005 | 1.990 |

As is evident in Table 2, an OR of 2 corresponds to relatively small distances between $P_B$ and $P_A$ when $P_B$ and $P_A$ are near 0 or near 1 and to increasingly larger distances as $P_A$ becomes closer to 0.5. Also, the ratios $(P_B/P_A)$ that correspond to OR of 2 decrease from near 2 for $P_A$ near 0, to near 1 for $P_A$ near 1, but their counterparts $(1 - P_A)/(1 - P_B)$ for unfavorable outcome have the opposite pattern of variation by increasing from near 1 for $P_A$ near 0, to near 2 for $P_A$ near 1. Since the odds ratio is the product of $(P_B/P_A)$ and $(1 - P_A)/(1 - P_B)$, it has the attractive property of unifying their roles for the comparison between treatment $B$ and treatment $A$; and in Table 2, such unification is homogeneously provided with an odds ratio of 2.

Although the relationships in (2) - (4) and their illustration in Table 2 imply that the interpretation of the odds ratio should account for the corresponding $P_A$ and $P_B$ that produced it, they do not constitute any limitation of the odds ratio as a criterion for the comparison between treatment $B$ and treatment $A$. In this regard, as shown in Table 2, an odds ratio of 2.0 is always interpretable (as doubling the odds of favorable versus unfavorable outcome) regardless of the magnitude of $P_A$.

A limitation of the difference $(P_B - P_A)$ between probabilities of favorable response as a criterion for the comparison between two treatments is that the range for its potential values fundamentally depends on the value of $P_A$; for example if $P_A = 0.60$, then the potential range for $(P_B - P_A)$ is from -0.60 for $P_B = 0.0$, to 0.40 for $P_B = 1.0$, whereas if $P_A = 0.20$, the potential range for $(P_B - P_A)$ is from -0.20 for $P_B = 0.0$, to 0.80 for $P_B = 1.0$. This limitation applies as well to the ratio $(P_B/P_A)$ since its potential range when $P_A = 0.6$ is from 0 for $P_B = 0.0$, to 1.667 for $P_B = 1.0$, whereas when $P_A = 0.2$, its potential range is from 0 for $P_B = 0.0$, to 5.0 when $P_B = 1.0$. Accordingly, the odds ratio is often preferable to the difference (or ratio) between probabilities of favorable outcome because its potential value can be any positive number for the ratio of the odds (regardless of the value of $P_A$, although its interpretation

needs to account for $P_A$ because of the relationships (2) - (4)). Moreover, the odds ratio can homogeneously express the extent of larger (or smaller) odds for favorable outcome for treatment $B$ relative to treatment $A$ in situations where the probability of favorable outcome for treatment $A$ (and also that for treatment $B$) can vary throughout the 0 to 1 range (in a manner like that shown in Table 2) with accordance to background characteristics or centers for patients.

# 3 Interpretation for the odds ratio in a multi-center clinical trial

The previously stated point concerning situations with variation in the probability of favorable outcome is very important; and it can be illustrated by considering a multi-center randomized clinical trial with $q$ centers indexed by $h = 1, 2, \ldots, q$. Let $P_{Ah}$ denote the probability of favorable outcome for treatment $A$ for patients from center $h$, and let $C_h = P_{Ah}/(1 - P_{Ah})$ denote the corresponding odds for favorable versus unfavorable outcome. As $P_{Ah}$ varies from 0.01 (for a center where favorable outcome has very low probability) to 0.99 (for a center where favorable outcome has very high probability), the corresponding odds $C_h$ varies extensively from $(1/99) = 0.01$ to $(99/1) = 99$ with even odds of 1.0 intermediately applying to $P_{Ah} = 0.50$ (for centers where favorable and unfavorable outcome are equally likely). With OR as the homogeneous (or common) ratio of the odds for favorable versus unfavorable outcome for treatment $B$ to that for treatment $A$ for each of the respective centers, the odds for favorable versus unfavorable outcome for treatment $B$ at the $h$th center is

$$P_{Bh}/(1 - P_{Bh}) = \text{OR} \times C_h = \text{OR} \times P_{Ah}/(1 - P_{Ah}). \tag{5}$$

The previously stated relationships imply

$$P_{Ah} = C_h/(C_h + 1) = P(C_h), \tag{6}$$

$$P_{Bh} = \text{OR} \times C_h/(\text{OR} \times C_h + 1) = P(\text{OR} \times C_h), \tag{7}$$

with $P(C)$ expressing the functional relationship of the probability of favorable outcome to the applicable odds $C$ (e.g., $C_h$ for treatment $A$ in center $h$ or $(\text{OR} \times C_h)$ for treatment $B$ in center $h$). Thus, the odds ratio OR expresses the effect of treatment $B$ relative to treatment $A$ as equivalent to an increase (or decrease) in the probability of favorable outcome for treatment $A$ through the multiplicative modification of the background influence of a center from $C_h$ to $(\text{OR} \times C_h)$; i.e., patients with treatment $B$ at center $h$ have the same probability of favorable outcome as those with treatment $A$ at center $h'$ with better (or poorer) odds $C_{h'} = (\text{OR} \times C_h)$ for favorable versus unfavorable outcome for treatment $A$; i.e., $P_{Ah'} = C_{h'}/(C_{h'} + 1) = (\text{OR} \times C_h)/(\text{OR} \times C_h + 1) = P_{Bh}$.

# 4 Interpretation of the odds ratio as a measure of relative potency

More generally, $C$ can be an odds that expresses the prognosis of a patient for favorable versus unfavorable outcome with treatment $A$ in accordance with demographic factors, previous medical history, baseline characteristics, and the center for treatment; and $C$ can vary between 0 and infinity as $P_A = P(C) = C/(C+1)$ varies between 0 and 1. The odds ratio OR for the effect of treatment $B$ relative to treatment $A$ is interpretable as equivalent to the multiplicative modification of $C$ to OR $\times$ $C$ for the influence of prognosis on the probability of favorable outcome for patients with treatment $A$; i.e., patients with treatment $B$ and prognosis $C$ (for the odds of favorable versus unfavorable outcome) have the same probability of favorable outcome (i.e., OR $\times$ $C/(\text{OR} \times C + 1)$) as those with treatment $A$ and better (or poorer) prognosis OR $\times$ $C$ (for the odds of favorable versus unfavorable outcome); see Koch (1999).

The previously stated considerations additionally enable the interpretation of the odds ratio as a measure of the "relative potency" for treatment $B$ versus treatment $A$, in the spirit of bioassay. More specifically, since prognosis $C$ for treatment $A$ and prognosis $(C/\text{OR})$ for treatment $B$ correspond to equal probabilities of favorable outcome for treatment $A$ and treatment $B$ for any $C$, the odds ratio is interpretable as the "multiplicative dilution" of $C$ that corresponds to treatment $B$ having a probability of favorable outcome that equals its counterpart for treatment $A$ at $C$. By representing such "multiplicative dilution" for the effect of treatment $B$ relative to treatment $A$, the odds ratio is interpretable as a "relative potency" of treatment $B$ relative to treatment $A$; see Koch (1999) and Chapters 8 and 11 of Stokes, Davis, and Koch (2000).

# 5 Odds ratios as measures of the effects of treatments and other explanatory variables in the logistic regression model

Although the role of the prognosis $C$ (for the odds of favorable versus unfavorable outcome) has had general discussion in Section 4, it can be given a specific structure to account for the roles of demographic factors, medical history, centers, and baseline variables. A well known structure for this purpose is the logistic regression model. An expression for this model is

$$C = C(X_1, X_2, \ldots, X_t) = M_0 \times M_1^{X_1} \times M_2^{X_2} \times \ldots \times M_t^{X_t}$$

where $X_1, X_2, \ldots, X_t$ are the values of $t$ explanatory variables, the $M_1, M_2, \ldots, M_t > 0$ are corresponding odds ratios per unit change in the $\{X_k\}$, and $M_0$ is the reference value of $C$ when $X_1 = X_2 = \ldots = X_t = 0$ (i.e., $C(0, 0, \ldots, 0) = M_0$). Logistic regression models are widely used to evaluate how treatments and other

explanatory variables are statistically related to the probability of favorable outcome (for a dichotomous variable that can be favorable or unfavorable). In this model, all of the parameters for expressing the influence of the corresponding explanatory variables (including those for the relative effects of two or more treatments) are odds ratios (per unit change). The role of odds ratios in this model is valid and useful for all of the reasons given in the preceding discussion; see Chapter 8 of Stokes, Davis, and Koch (2000).

As noted previously, variation of the probability of favorable outcome according to such factors as treatments, centers, and background characteristics for patients can be appropriately described by a logistic regression model. Through such a model, valid statistical adjustment for a factor such as centers is provided for the estimate of the odds ratio pertaining to the effects of treatments, and this center-adjusted odds ratio is interpretable (in settings where it is homogeneous relative to centers) as the ratio of the odds for favorable versus unfavorable outcome for treatment $B$ relative to that for treatment $A$ for patients at the same center (regardless of which center is involved).

When a factor such as centers involves a large number of subgroups (and thereby produces a large number of explanatory variables in a logistic regression model) and the sample size per subgroup (or center) is small for either the favorable outcome or the unfavorable outcome (or both), the usual (unconditional) logistic regression method for estimating the odds ratio for comparing the effects of treatment $B$ relative to treatment $A$ may not be applicable (nor provide statistically valid estimates). This issue can be addressed by performing such estimation with conditional logistic regression methods. In this way, the centers are managed as strata which have appropriate adjustment rather than as explanatory variables, and the estimate of the odds ratio for the effects of treatment $B$ relative to treatment $A$ has good statistical properties. Nevertheless, an important point is that the results from the usual (unconditional) logistic regression methods can still serve a useful role when there is robustness to difficulties from centers with small sample sizes (or a large number of explanatory variables) in the form of the similarity of those results to their counterparts from other methods such as conditional logistic regression methods for which the difficulties do not apply; see Chapter 10 of Stokes, Davis, and Koch (2000).

## 6 Confidence intervals for the description of sampling variability

Since a randomized clinical trial only includes a sample of patients in the potential target population for the comparison between two treatments, the estimation of a criterion such as the odds ratio needs to account for sampling variability (i.e., the potential variation of an estimate from one sample to another). The usual method for addressing sampling variability is a confidence

interval, and typically use is made of a two-sided confidence interval that has 0.95 probability for containing the true value of the criterion for a comparison (across hypothetical repeated selections of patients for inclusion in the study or hypothetical repetitions of the study). For such a 0.95 confidence interval, both the lower and upper limits are of similar interest from the perspective of conservatively expressing a sufficiently wide range so as to be highly likely to contain the true value of the criterion (e.g., odds ratio) for the comparison between two treatments. At the same time, the actual estimate itself as well as the range corresponding to a two-sided 0.67 confidence interval (which has half the length of a two-sided 0.95 confidence interval for a linear estimate such as the difference between the probabilities of favorable outcome for treatment $B$ and treatment $A$) can be helpful as more "central" estimates for the true criterion; in this regard, the 0.67 confidence interval for the odds ratio has 2 to 1 odds for containing the true odds ratio; see Chapters 2 and 8 of Stokes, Davis, and Koch (2000).

Although the previous general points concerning confidence intervals are of interest, some specific examples can further clarify how confidence intervals can support the reliability of criteria for the comparison between treatment $B$ and treatment $A$ relative to sampling variability. One setting of interest for potential examples has both $P_A$ and $P_B$ between 0.20 and 0.80 and has sample sizes of at least 300 patients for each treatment. For this setting the lower and upper limits of the 0.67 confidence interval for the difference between the probabilities of favorable outcome for treatment $B$ and treatment $A$ are within 0.04 of the estimate for this difference, and the corresponding 0.95 confidence limits are within 0.08; and so both express relatively good reliability. For the odds ratio for the comparison between treatment $B$ and treatment $A$, the lower and upper limits of the 0.67 confidence interval are respectively within 80% to 125% of the estimated odds ratio and their counterparts for the 0.95 confidence interval are respectively within 67% to 150%, and so they also support relatively good reliability.

# 7 Summary

The odds ratio is a valid criterion for expressing the comparison between two treatments in a randomized clinical trial where the outcome for a patient is classified as favorable versus unfavorable. This criterion describes the extent to which the odds of favorable versus unfavorable outcome is multiplicatively larger for the patients with one treatment than the patients with the other treatment; and in this way, the odds ratio addresses how much larger the probability of favorable outcome is for one treatment than the other as reasonably as the corresponding difference of probabilities; but each of these criteria for expressing the comparison between two treatments has its own interpretation, and that interpretation is not directly applicable to the other. For a multi-center clinical trial, a logistic regression model can enable the estimation of the odds ratio to

have appropriate statistical adjustment for the potential variation across centers of the probability of favorable response to each treatment. Although studies where many centers have small sample sizes (for either favorable or unfavorable outcome) can more correctly have such adjustment applied with conditional logistic regression methods, the usual unconditional logistic regression methods often provide similar results which can be viewed as robust in this sense. For the estimate of the odds ratio, a two-sided 0.95 confidence interval conservatively describes the full range in which the corresponding true odds ratio is likely to lie, and both the ends of this range and its center are of comparable interest for interpreting the relative effects of the two treatments.

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