Rejoinder to Commentary: When Mapping Treatment Effects from Disease-Specific to Generic Scales, Ordinary Least Squares Regression Underestimates the Benefits of Treatment

To the Editor—In our article, "Mapping from disease-specific to generic health-related quality of life scales: a common factor model" [1], we propose a method for mapping mean treatment effects reported in trials on one scale into mean treatment effects on another scale. Our approach is based on a structural equation model that, in its simplest form, partitions the variances of responses to all scales into two components. One component is that part of the test that responds to treatment, and the other component is the remaining variance. We show that the true mapping coefficient is the signed square root of the ratio of the variances of the first component. We also point out that the ordinary least squares (OLS) regression coefficient will invariably underestimate the true mapping, because of the measurement error inherent in the test instruments.

One of the motivations of our approach, which is not mentioned by Palta, is that mappings between mean treatment effects should be both invertible and transitive. In other words, suppose we have estimated a mapping $\delta_{Y \rightarrow Q}$ from disease-specific instrument $Y$ to generic scale $Q$, then when we observe an estimated treatment effect $\delta_Y$ in a trial, we would predict an effect $\hat{\delta}_Q = \delta_{Y \rightarrow Q} \delta_Y$ on the generic scale $Q$. Note that $\hat{\delta}_Y$ is usually an unbiased and consistent estimate for the true treatment effect. On the other hand, by the same token, if we observe $\hat{\delta}_Q$ (also unbiased and consistent) in a trial, we would predict $\hat{\delta}_Y = \delta_{Q \rightarrow Y} \hat{\delta}_Q$ on scale $Y$. In other words, $\hat{\delta}_{Q \rightarrow Y} = 1/\delta_{Q \rightarrow Y}$. We show that mappings defined our way have this property. They must also be transitive, which means that a mapping from $X$ to $Z$ must be the product of a mapping from $X$ to $Y$ and a mapping from $Y$ to $Z$.

In her commentary on our article, Palta [2] takes issue with our approach on two grounds. First, she claims that the mean treatment effect is still “prone to measurement error,” and therefore that the “correct conversion is [still] the true mapping multiplied by the reliability of the DSM.” She goes on to assert that the correct mapping coefficient to map from $X$ to $Y$, for either an individual score or an estimated mean score, is the OLS regression, which is the “true” mapping that would be obtained if there were no measurement error in $X$, multiplied by the reliability of $X$. In our notation, her proposed mapping coefficient is $\beta_{Y \rightarrow X} = \beta_{X \rightarrow Y} \rho_X$.

It is easy to see that this will end in a contradiction. The mean treatment effects on scales $X$ and $Y$ have variances that depend on sample size, n, in each arm, the variance of the true scores $\sigma_X^2$, and its reliability:

$$\text{Var}(\hat{\delta}_X) = \frac{2\sigma_X^2}{n} = 2\sigma_X^2 \rho_X$$

Under Palta’s proposed mapping, $\delta_Y = \beta_{Y \rightarrow X} \delta_X = \beta_{X \rightarrow Y} \rho_X \delta_X$, we would then obtain

$$\text{Var}(\hat{\delta}_Y) = (\beta_{Y \rightarrow X})^2 \text{Var}(\hat{\delta}_X) = (\beta_{X \rightarrow Y})^2 \frac{2\sigma_X^2}{n} = 2\sigma_X^2$$

This gives us that $\beta_{Y \rightarrow X} = \sigma_X^2 / \sigma_Y^2 \rho_X^2 \rho_Y$. But by parity of argument, we can also obtain that $\beta_{X \rightarrow Y} = \sigma_Y^2 / \sigma_X^2 \rho_Y^2 \rho_X$.

Given that $\beta_{X \rightarrow Y} = 1/\beta_{Y \rightarrow X}$, we end up with

$$\frac{\sigma_X^2}{\sigma_Y^2 \rho_Y^2 \rho_X} = \frac{\sigma_Y^2 \rho_X^2}{\sigma_X^2} \text{ or } \frac{\sigma_X^2}{\sigma_Y^2 \rho_Y^2 \rho_X} = \frac{\sigma_X^2 \rho_Y^2}{\sigma_Y^2}$$

which is true only when both reliabilities are 1 (clearly $\sigma_X^2, \sigma_Y^2$ are not equal to zero).

The same argument can be made in a less technical and perhaps more intuitive way. Imagine a trial of infinite size in which the treatment effect is examined on three test instruments $X$, $Y$, and $Z$. The true mappings are—by definition—the ratios of the treatment effects $\delta_X, \delta_Y, \delta_Z$ on each scale. These ratios obviously do have, and must have, the properties of transitivity and invertibility. If we imagine, instead, a trial of finite size, the ratios of the estimates must still represent estimates of the mappings, which are still transitive and invertible.

But the OLS mappings proposed by Palta, even if they were all estimated from a single (and infinite sized) cohort study, can never have these properties and must always underestimate the correct mappings. Indeed, with her method, if one mapped from $X$ to $Y$, then back to $X$, one would not end up where one started. Similarly, one could map from $X$ to $Y$, and then from $Y$ to $Z$, but this would end up with a different estimate than mapping from $X$ to $Z$, even if one had used data from a single cohort study with observations on all three instruments.

The second criticism is that the assumptions made by the common factor model may not necessarily be correct for every test, and Palta gives an example where this appears to be the case. We would accept entirely that the common factor model—at least as we have presented it—may be inadequate for some data sets. This is noted in Lu and Brazier [1] where possible extensions are suggested. This, however, does not change the fundamental point that when observations are made under measurement error, mappings between mean treatment effects based on OLS regression are incorrect and invariably underestimate the correct mapping. As a result, estimates of the quality of life gain due to treatment based on such methods are invariably underestimates.

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REFERENCES
