Published in final edited form as:

Stat Med. 2014 October 15; 33(23): 4139–4140. doi:10.1002/sim.6202.

Biomarker evaluation in randomized trials: addressing different research questions

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Eng [1] discussed four designs for randomized trials to evaluate the use of a single biomarker to target treatments. Design 1(marker interaction) tests for the marker and then separately randomizes participants with each level of the marker to treatment *A* or treatment *B*. Design 2 (marker-based strategy) randomizes participants to MB (marker-based) strategy or treatment *B*, where MB strategy is treatment *A* if the marker is positive and treatment *B* otherwise. Design 3 (modified marker-based strategy) randomizes participants to MB strategy or further randomization to treatment *A* or treatment *B*. Design 4 (reverse marker-based strategy) randomizes participants to MB strategy or RM (reverse marker) strategy, where RM strategy is treatment *B* if the marker is positive and treatment *A* otherwise. Eng noted that “it is of primary importance that the study designer is clear on what quantity best represents the research question: interaction, the marker strategy, or the subgroup treatment effect.” With the goal of “testing the interaction between a marker and its intended treatment,” Eng demonstrated the advantages of Design 4.

However, for addressing research questions involving marker strategy and subgroup treatment effect, designs other than Design 4 are more appropriate. Let *Y* denote binary response, *T=A, B* denote treatment, and *M=M+, M−* denote the outcomes of a binary marker. The four basic quantities in Designs 1, 2, 3, and 4 are $\text{pr}(Y | \text{MB strategy})$, $\text{pr}(Y | \text{RM strategy})$, $\text{pr}(Y | \text{treatment } A)$, and $\text{pr}(Y | \text{treatment } B)$. Also let $\pi = \text{pr}(M=M+)$, $\theta_i = \text{pr}(Y | T=i)$, $\theta_{ij} = \text{pr}(Y | T=i, M=j)$, and

$$\text{pr}(Y | \text{MB strategy}) \equiv \Phi_I = \pi \theta_{A(M+)} + (1 - \pi) \theta_{B(M-)},$$

$$\text{pr}(Y | \text{RM strategy}) \equiv \Phi_4 = \pi \theta_{B(M+)} + (1 - \pi) \theta_{A(M-)}.$$

Noting that $\theta_i = \pi \theta_{i(M+)} + (1 - \pi) \theta_{i(M-)}$ and extending previous analyses [2, 3], research questions related to marker strategy versus treatment involve estimating

$$\text{pr}(Y | \text{MB strategy}) - \text{pr}(Y | \text{treatment } B) = \Phi_I - \theta_B = \pi(\theta_{A(M+)} - \theta_{B(M+)}), \quad (1)$$

$$\text{pr}(Y | \text{MB strategy}) - \text{pr}(Y | \text{treatment } A) = \Phi_I - \theta_A = (1 - \pi)(\theta_{B(M-)} - \theta_{A(M-)}), \quad (2)$$

$$\text{pr}(Y | \text{RM strategy}) - \text{pr}(Y | \text{treatment } B) = \Phi_4 - \theta_B = (1 - \pi)(\theta_{A(M-)} - \theta_{B(M-)}), \quad (3)$$

$$\text{pr}(Y|\text{RMstrategy}) - \text{pr}(Y|\text{treatment } A) = \Phi_4 - \theta_A = \pi(\theta_{B(M+)} - \theta_{A(M+)}). \quad (4)$$

Research questions related to subgroup treatment effect involve estimating

$$\text{pr}(Y|\text{treatment } A, M+) - \text{pr}(Y|\text{treatment } B, M+) = \theta_{A(M+)} - \theta_{B(M+)}, \quad (5)$$

$$\text{pr}(Y|\text{treatment } A, M-) - \text{pr}(Y|\text{treatment } B, M-) = \theta_{A(M-)} - \theta_{B(M-)}. \quad (6)$$

Because equations (1)–(4) are proportional to either equation (5) or (6), research questions involving subgroup treatment effect address research questions involving marker strategy. Thus for addressing research questions involving subgroup treatment effect or marker strategy, investigators need only implement designs which estimate subgroup treatment effects. Also it is desirable if these designs also estimate overall treatment effect. Three designs satisfying these desiderata are Design 1 and two designs called here Design 5 and Design 6. Design 5 randomizes participants to treatments *A* or *B* and then ascertains the biomarker in all participants [4]. Design 6 (biomarker-nested-case-control) randomizes participants to treatments *A* or *B* and then ascertains the biomarker in a random sample of stored specimens stratified by response and treatment, followed by an analysis adjusted for this sampling [3, 5] – an appealing approach when biomarker ascertainment in stored specimens is expensive or there is concern about the irreplaceable usage of stored specimens.

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