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Comments on "Tutorial on statistical considerations on subgroup analysis in confirmatory clinical trials"

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Abstract

This paper is the letter to the editor regarding several comments on ‘Tutorial on statistical considerations on subgroup analysis in confirmatory clinical trials.’

Keywords

clinical trial; adaptive design; sample size; expected value

Alosh et al [1] provide a very comprehensive and useful statistical consideration of prospective subgroup design and analysis for clinical trials. The topics discussed in the paper are quite meaningful from the practical perspective, and we read it in detail to digest the content from the paper for our research reference, meanwhile, we find two errors in the paper:

1. Sample size calculation

In section 2, the paper presents the formula ($N = 2[(z_{1-\alpha} + z_{1-\beta})\sigma/\delta]^2$) [1] of sample size calculation per arm (i.e. each treatment group) under an design assumption of balanced 1:1 randomization ratio clinical trial with a treatment effect δ , significance level at α . this equation is correct. However, the sample size is incorrectly calculated by this formula in Section 6.3. For example (The second paragraph in Section 6.3, from Line 5 to Line 7) if one plugs in 1.96 ($z_{1-\alpha} = z_{1-0.025} = 1.96$), 1.2816, ($z_{1-\beta} = z_{1-0.9} = 1.2816$), 1 (standard error, σ) and 0.3 (treatment effect size, δ) into the formula [1], the calculated sample size is 234 patients per arm, rather than 117 patients per arm as the paper stated [1]. Apart from this example, the incorrect calculations appear several times within the rest of the second paragraph of section 6.3. They include:

- 1.1 In Page 1355, the second paragraph of section 6.3, start from Line 10: that “314 patients would ensure a power of 0.8 for the subgroup and this sample size corresponds to a power of 0.96 for the overall population” [1] is stated. The 314 should be the sample size per arm;

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- 1.2 In Page 1355, the second paragraph of section 6.3, start from Line 12: the paper mentioned that “A design would require a sample size of 276 patients for power of 0.90 for the overall population” [1]. The sample size should be referred as “per arm”;
- 1.3 In Page 1356, the third paragraph of section 6.3, start from Line 3 (line count from page 1356): “The overall population is 248 patients and....” [1] was incorrectly specified; 248 patients is the sample size per arm;
- 1.4 In Page 1356, the third paragraph of section 6.3, start from Line 8 (line count from page 1356): it wrote that “the overall population is reduced to 212....” [1]; the 212 patients should be for each arm;
- 1.5 In Page 1356 Table X: the “sample size” values under the tabs of “overall population” and “pre-defined subgroup” [1] is actually the value of sample size per arm;

2. Expected value of test statistic

In the first paragraph of section 2, the paper arrived at the test statistic Z final derivation in terms of proportion of variance reciprocal summation (w_j) and subgroup test statistic (Z_j) [1]. In Line 5 (line count from page 1338) it specified that

$$Z = \hat{\delta}(\sum_{j=1}^S I_j)^{1/2} = \sum_{j=1}^S w_j^{1/2} Z_j, \text{ where } E(Z) = \delta \sum_{j=1}^S w_j^{1/2} \text{ and } Z_j = \hat{\delta}_j I_j^{1/2} [1]. \text{ We tried to re-derive the } E(Z) \text{ final formula, it should be equal to } \delta \sum_{j=1}^S w_j^{1/2} I_j^{1/2} \text{ rather than } \delta \sum_{j=1}^S w_j^{1/2}.$$

These two errors do not greatly detract the readers from following the key ideas, formula derivation, or key statements of paper. The reason we raise them is so that a correction may facilitate the understanding of this paper for future readers and to avoid improper calculations and use of incorrect formulae in the future.

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References

1. Alosh M, Huque MF, Bretz F, D’Agostino RB Sr. Tutorial on statistical considerations on subgroup analysis in confirmatory clinical trials. *Statistics in Medicine*. 2017; 36:1334–1360. [PubMed: 27891631]