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**Transcranial Continuous and Pulse Near-Infrared Light in  
Depression: a Placebo-Controlled Study (ELATED-3).**

**Study Sponsor**

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The method and general statistical analytical procedure of study, sequential parallel comparison design, has been described in previously published materials. That being that subjects are allocated to receive either the active treatment or placebo in both phases, or receive placebo within the first phase then receive the active treatment in the second. Therefore, there will be three groups analyzed: Active-Active, Sham-Sham, and Sham-Active. Only those considered non-responders in the first phase are analyzed within the second phase, as it is hypothesized they have a reduced placebo response, or have not found the initial phase of the intervention effective (Fava et al. 2003).

Process of calculation has been described in the Statistical appendix of the reference above. That being:

"Assume that patients will be randomized into three groups, the first two groups will initially receive placebo, those patients that do not respond to placebo will receive placebo (group 1) or drug (group 2). The third group will initially receive drug. The proportions randomized to the three groups will be  $a$ ,  $a$  and  $1 - 2a$ .

Let  $p_1$ ,  $q_1$  be the response rates to the first administration of drug and placebo respectively and let  $p_2$ ,  $q_2$  by the responses to the second treatment. To analyze these data we use a statistic based on  $h = w(p_1 - q_1) + (1 - w)(p_2 - q_2)$ . The weight,  $w$  and the randomization fraction,  $a$  are chosen to maximize the power of the test, based on the alternative hypothesis.

The standard error for  $h$  requires a special formula because some of the same patients who are included in the estimation of  $p_2$ ,  $q_2$  are included in the estimation of  $p_1$ ,  $q_1$ . The delta method was used to compute the standard error of  $h$ ...

Then

$$h = w \left( \frac{n_{3,1}}{n(1 - 2a)} - \frac{(n_{1,3} + n_{2,3})}{2na} \right) + (1 - w) \left( \frac{n_{2,1}}{n_{2,1} + n_{2,2}} - \frac{n_{1,1}}{n_{1,1} + n_{1,2}} \right)$$

where  $n$  is the total number of patients. Let  $D$  be the column vector of derivatives of  $h$  with respect to  $n_{3,1}$ ,  $n_{1,3}$ ,  $n_{2,3}$ ,  $n_{2,1}$ ,  $n_{2,2}$ ,  $n_{1,1}$ ,  $n_{1,2}$ , and let  $V$  be the variance covariance matrix of  $n_{3,1}$ ,  $n_{1,3}$ ,  $n_{2,3}$ ,  $n_{2,1}$ ,  $n_{2,2}$ ,  $n_{1,1}$ ,  $n_{1,2}$ , from the multinomial distribution. Then the standard error of  $h$  is given by  $\sqrt{D}VD$ , which is computed with the observed values of  $p_1$ ,  $p_2$ ,  $q_1$ ,  $q_2$ . The formula below is a simplified calculation of the standard error of  $h$  derived using Mathematica (Wolfram Research).

$$\sqrt{\frac{-2(-1 + 2a)p_2(-1 + w)^2 + 2(-1 + 2a)p_2^2(-1 + w)^2 - 2(-1 + 2a)q_2(-1 + w)^2 + 2(-1 + 2a)q_2^2(-1 + w)^2 + (-1 + q_1)((-1 + q_1)q_1 + 2a(-p_1 + p_1^2 + q_1 - q_1^2))w^2}{2a(-1 + 2a)(-1 + q_1)}}$$

To test the null hypothesis, we use  $z = h/s$ . The values of  $a$  and  $w$  were calculated by substituting the alternative hypothetical values of  $p_1$ ,  $p_2$ ,  $q_1$ ,  $q_2$  and finding the values of  $a$  and  $w$  that maximize  $z$ . The power of the test is then  $\sum(z - 1.96)$ , where  $\sum$  is the cumulative distribution of

the normal distribution. Software for computing  $a$ ,  $w$  and calculating the power of the test is available from the authors. "

### **Primary Analysis**

QIDS: The changes in QIDS scores and the response rates, which was defined as 50% or more drop in QIDS score, are the two main output measures of the current study. All statistical analyses are performed on R software version 3.6.2 (R Core Team, 2019) with SPCDAnalyze package version 0.1.0 (Schoenfeld 2019). The package uses constrained longitudinal data analysis model. The level of statistical significance was set at  $p \leq 0.05$ .

### **Secondary Analysis:**

HAMD: Secondary outcome measure was change in HAM-D scores and response rate defined as 50% or more drop in HAMD score. All statistical analyses performed R software version 3.6.2 (R Core Team, 2019) with SPCDAnalyze package version 0.1.0 (Schoenfeld 2019). The package uses constrained longitudinal data analysis model. The level of statistical significance was set at  $p \leq 0.05$ .