



Letter to the Editor

An approach to sample size calculation for research on duration of untreated psychosis



A shorter duration of untreated psychosis (DUP) - the time between the onset of psychosis and initiation of treatment - is a robust predictor of symptom remission, functional recovery, and relapse prevention (Penttila et al., 2014). The World Health Organization and the International Early Psychosis Association recommend that treatment for psychosis begin within 3 months of symptom onset (Bertolote and McGorry, 2005), yet more than two dozen studies worldwide have reported DUP as long as 2 years (Penttila et al., 2014). In response to this, international bodies and funding agencies – including the National Institute of Mental Health – have increasingly created research initiatives to identify factors and strategies aimed at reducing DUP (Oliver et al., 2018).

One challenge to DUP research is adequately estimating sample sizes when DUP is the outcome. Sample size calculation is an important step in study design to ensure that a project is both feasible and sufficiently powered to provide conclusive evidence. Because DUP data are typically highly right-skewed, however, standard sample size formulas that assume a normal distribution may not be suitable (Norman et al., 2005). As a workaround, non-parametric methods could be applied, though these tend to be underpowered and overinflate sample sizes (Randles and Wolfe, 1979). Alternatively, researchers could log transform DUP or dichotomize the data using a cut-off (e.g., 3 months) (Chow et al., 2017) but these approaches may lead to loss of information or of clinical meaningfulness in the data. Studies that are powered to detect differences across the continuous range of DUP could provide additional insights. We propose a recent method for sample size calculation (O'Keeffe et al., 2017), suitable for skewed DUP data, that could be helpful in future DUP study design.

1. Method description

O'Keeffe et al. recently introduced a sample size calculation based on difference in medians (O'Keeffe et al., 2017). Briefly, the formula assumes that the outcome data are right-skewed with a log-normal distribution – typical of DUP data. Taking the standard sample size calculation formula for a two-sample *t*-test with equal group sizes (group 1 and 2), and given that a) the mean of the log-transformed data can be calculated as the natural logarithm of the median on the untransformed scale and b) the variance of the log-transformed data relates to the variance of the untransformed data, the authors show that the number of participants per group (*n*) can be calculated using the formula:

$$n = \frac{\left[\log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_1^2}{m_1^2}}\right) + \log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{\phi_2^2}{m_2^2}}\right) \right] (z_{\alpha/2} + z_{\beta})^2}{(\log(m_1) - \log(m_2))^2}$$

where m_1 and m_2 and ϕ_1 and ϕ_2 are the pre-specified values of the medians and standard deviations of group 1 and 2, respectively; $z_{\alpha/2}$ is the z-score to a desired level of significance $100\alpha\%$ (usually set at 5%); and z_{β} is the z-score to a desired level of study power $100(1 - \beta)\%$ (usually set at 80%). Readers should note that the pre-specified median DUP values should be >0 (e.g., >0 weeks) for the assumption of a log-normal distribution to be valid. The use of time units in weeks or days instead of months or years may therefore be useful in this regard.

To facilitate the implementation of this new method, we have provided an easy-to-use spreadsheet calculator (Supplementary material 1) that readers can use to estimate sample size for their work. This spreadsheet additionally allows for unequal sample sizes using standard methods (Sakpal, 2010), as recommended by O'Keeffe et al. (2017). Further supplementary tables illustrate estimated sample sizes under different scenarios of median DUP when the standard deviation for groups 1 and 2 are equal (Supplementary Table 1) and unequal (Supplementary Table 2).

2. Example

In a fictional randomized controlled trial, researchers want to compare differences in DUP between an intervention group (group 1) and a control group (group 2). Based on previous work, researchers expect that the difference in median DUP between the two groups would be about 4 weeks, with group 1 having a median DUP of 12 weeks (m_1) with a SD of 10 weeks (ϕ_1), and group 2 having a median DUP of 16 weeks (m_2) with a SD of 18 weeks (ϕ_1). Assuming a 5% significance level ($z_{\alpha/2} = 1.96$) and 80% power ($z_{\beta} = 0.84$), the formula suggests a sample size of 89 for each group:

$$n = \frac{\left[\log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{10^2}{12^2}}\right) + \log\left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{18^2}{16^2}}\right) \right] (1.96 + 0.84)^2}{(\log(12) - \log(16))^2} = 89$$

3. Discussion

In sum, the method proposed by O'Keeffe et al. allows researchers to calculate sample sizes using pre-specified values for median DUP's, circumventing the need to categorize or transform the data. The formula is easy to implement and uses information on DUP that is clinically intuitive and meaningful. Given the growing interest in DUP, this approach could assist with ensuring that future studies are appropriately powered to advance DUP knowledge. Although the method is relatively straightforward, identifying pre-specified values to enter in the formula can be challenging. Researchers can derive relevant median DUPs (and standard deviations) from previous studies, preliminary data, or their own service evaluation or clinical knowledge. To further facilitate this process, epidemiological research on the distribution of DUP across different populations, sites, and contexts would also be of great value.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2018.11.012>.

Conflict of interest

The authors report no conflict of interest.

CRedit authorship contribution statement

Geneviève Gariépy: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Sarah V. McIlwaine:** Investigation, Writing - original draft, Writing - review & editing. **Norbert Schmitz:** Methodology, Validation, Visualization, Writing - review & editing. **Jai L. Shah:** Conceptualization, Investigation, Project administration, Writing - original draft, Writing - review & editing.

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