# The Minimal Important Difference in the Six Minute Walk Test for Patients with Pulmonary Arterial Hypertension

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## Online Data Supplement

## Methods

The SF-36 is a generic instrument used to assess health-related quality of life (HRQOL).[1] The SF-36 consists of 8 domains: physical functioning, role limitations-physical, bodily pain, general health, vitality, social functioning, role limitations-emotional and mental health. The domains can be compiled into summary scores for the physical and mental components; the physical component summary score (PCS) and mental component summary score (MCS). The SF-36 scores range from 0-100, with higher scores indicating better HRQOL. Summary scores are scaled to a mean of 50 and standard deviation of 10 in the general US population. The SF-36 has been validated and demonstrated responsiveness to change in a variety of patient groups and is commonly used in PAH clinical trials.[2;3] Because the PCS has been shown to be the most responsive parameter of the SF-36 to change in patients with chronic lung disease, the PCS was selected as the anchor for anchor-based analyses, as discussed below.[4]

*Estimation of the Minimally Important Difference*

Both anchor-based and distributional methods for determining the MID were used. The anchor-based methods for determination of the MID employ measures for which a MID has been established (the anchor) to estimate the MID for another metric. Further, the anchor must have a relatively strong linear relationship with the metric of interest.[5] Regression of change in each of the eight domains of the SF-36 and the summary scores against the change in the 6MWD demonstrated that the PCS had the strongest linear relationship with the 6MWD. Prior studies of the relative responsiveness of HRQOL measures in a number of chronic disease have defined the MID as 5 units.[6]

After confirming the assumptions of linearity were met, the numerical value of the MID for the 6MWD was determined for PCS MID of 5 units using the linear regression of change in PCS against change in 6MWD.

The distributional methods employed are: 1) effect size (ES), 2) standardized response mean (SRM), 3) standard error of the measurement (SEM), and 4) ½ times the standard deviation of the baseline measure (½ SD). ES is defined as the average of the difference between end of treatment and baseline scores divided by the standard deviation of the baseline scores.[7] While ES is often used as a reference for assessing the magnitude of change in health status, there is no consensus regarding a meaningful ES in for the 6MWT in PAH. Therefore, we selected previously described threshold of 0.5, corresponding to a moderate ES for the 6MWD.[8] There is some debate regarding which is the best way to calculate the effect size, so it was calculated in 2 ways. The first method, which is the standard definition of effect size, uses the standard deviation of the measure at baseline. The second method, which is called the SRM, uses the standard deviation of the change of the measure. The SRM is attractive because it takes into account the covariance between the baseline and end of study measures.[9] The SEM was calculated by multiplying the standard deviation of the baseline measurement by the square root of the difference of 1 minus the intra-class coefficient of the measure.[10] Additionally, we used another distributional method, ½ SD, which simply involves multiplying the standard deviation of the baseline measurement by ½.[11]

In addition, we performed sensitivity analyses, stratifying the cohort by treatment status (treatment-naïve versus background therapy) and in a separate analysis, stratifying the

cohort by disease type (idiopathic pulmonary arterial hypertension versus collagen vascular disease-associated pulmonary arterial hypertension).

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