Statistical Design and Power

Singing and Cardiovascular Health in Older Adults PRO: 35864

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Difference between groups	Power (alpha 0.05)	N	N plus 25% dropout
0.010	0.90	114	143
	0.80	86	108
0.015	***0.90***	***52***	***65***
	0.80	40	50
0.020	0.90	30	38
	0.80	23	29

Brachial artery FMD. FMD is expressed as the change in post-stimulus diameter as a percentage of the baseline diameter (FMD%). Our primary outcome is percent brachial flow-mediated dilation (FMD%). We employ a cross-over design since the most powerful test will compare the same subjects against themselves (i.e., avoiding many potential inherent subject differences). In a scenario with no anticipated differences, FMD correlations were observed to be 0.8 at 12 weeks (95% CI: 0.72, 0.87). Therefore, assuming an auto-regressive structure, we assume the correlation would be 0.64 at 26 weeks and 0.41 at 52 weeks. For a 25% relative difference (2% absolute difference) in FMD with 90% power and alpha 0.05, we would need just 30 subjects (comparing singing interventions to sham/control). But, to compare the singing interventions to each other, using a delta of 0.015, we will need 52 subjects for 90% power and alpha 0.05. To have 52 evaluable subjects (assuming a 25% dropout rate), we will enroll 65 subjects. Please refer to the sample size table (shown above). We will be powered for all primary (FMD) and secondary outcomes (PAT and HRV). All outcome variables over 3 visits will be compared using analysis of variance (ANOVA) with repeated measures. The exposure variable is the singing (or sham) interventions.

PAT measurements. *EndoPAT* is the FDA-cleared non-invasive test and device that provides an index of endothelial function in two forms: reactive hyperemia index (RHI) and LnRHI. The RHI is the post-to-pre-occlusion PAT signal ratio in the occluded side, normalized to the control side and further corrected for baseline vascular tone. Normal values for RHI are >1.67. In our small, pilot study, the average baseline RHI for 23 subjects was 1.93±0.13 (range: 0.93 to 3.62). There was a trend toward improvement to 2.06±0.15 – though we were underpowered for statistical significance. The LnRHI provides a better double-sided distribution than RHI that is closer to normal distribution. It offers better separation between disease states. The PAT ratio is the natural logarithm of the ratio of the post-deflation to baseline pulse amplitude in the hyperemic finger divided by the same ratio in the contralateral (control) finger. This ratio is based on the 90- to 120-second post-deflation interval, which had the strongest correlation to cardiovascular risk factors in the Framingham Heart Study cohort. We saw a significant improvement in the PAT ratio in our 23 subjects. We aim to confirm this finding with this study proposal, which is appropriately powered for both RHI and the PAT ratio.

We were unable to locate the reliable figures for within subject correlation measures of either the RHI or the PAT ratio in order to compute their power in a cross-over design. Fortunately, due to the size of the changes anticipated, sample size calculations for simple comparisons yield values similar to those planned. For example, given a change of 0.08 with 0.1 standard deviation in RHI, a sample size of 52 would yield a power of 81% with alpha 0.05. Therefore, in a cross-over design, we would be able to detect a change of 0.08 with power greater than 81% or we would be able to detect changes less than 0.08 with power equal to 81%. Similar remarks can be made for the PAT ratio.

HRV measurements. The normal-to-normal (NN) intervals include all intervals between adjacent ECG QRS complexes resulting from sinus node depolarizations. Standard measures of HRV (time domain analysis) include the standard deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the natural log (ln)RMSSD and HRV score.

For RMSSD, we also do not have reliable correlation numbers. However, for a simple comparison with a change of 15 and a standard deviation of 22.5 (based on our preliminary data), we would arrive at 65% power with a sample size of 52. Therefore, in a cross-over design, we would obtain more power and/or be able to detect smaller differences.