Title page

A randomized controlled trial to assess the safety and tolerability of the nutritional supplement, nicotinamide riboside, in systolic heart failure

Test drug:	Nicotinamide Riboside (NR)
Study purpose:	to assess the safety and tolerability of the nutritional supplement, nicotinamide riboside, in systolic heart failure
Clinical Study phase: I/II	Date: 2/17/2016
Sponsor:	Investigator initiated study funded by the NIH

NR in HF Study: Biostatistical Analysis Plan.

5.a. Statistical Methods. After import into statistical software (R, Stata or SAS), data will be screened for outliers and the validity of any outlier values will be verified and/or any potential errors will be corrected. Changes in outcomes (including serum NR level, $NADH/NAD^+$ ratio, 6MWT, MNQOL score, 3D-Echo, Doppler/TDI) from Week 0 to Week 12 will be compared between the NR and placebo arms using a two-sample t-test, the Mann-Whitney test or the permutation test, as appropriate. Changes in serum NR, $NADH/NAD^+$ levels, 6MWT and MNQOL score outcomes over the multiple visits (0, 2, 4, 6, 8 and 12 Weeks) will be explored visually and by calculating and tabulating mean outcomes for each visit by assigned treatment.

Power calculations. Detectable differences for LVEF are calculated from power calculations for a two-sample t-test (PASS 2008, NCSS, Kaysville, UT), using the initial sample sizes of 20 patients in the NR group, 10 patients in the placebo group, and a dropout rate of 10%, leading to a final expected sample size of 18 and 9 patients in the NR and placebo groups, respectively. Two-sided tests, 0.05 significance level and 80% power are assumed. Based on these parameters we calculate a detectable difference of 1.190 standard deviations for a change in an outcome between the means in the placebo and NR groups. The standard deviation (SD) for the change in LVEF by 3D Echo is based on a study of 50 patients with LV dysfunction due to previous MI (32). The SD for change, measured between baseline and one year follow-up, was 7%, and scatterplots for the LVEF changes measured by MRI or 3D echo suggested that SD values for EF are similar for both modalities. We conservatively assumed that the SD at 12 weeks would not be smaller than that at 52 weeks.

Expected results. Assuming a 7% SD for LVEF change (32), the detectable difference by 3D-TTE for this 30 participant trial is 8.3%. Much larger sample sizes would be required to detect much lesser changes in LVEF. Thus, Study echocardiograms will explore the potential range of effect sizes for NR on LVEF.

	le Sizes (N) to Achieve Power of:	
	85%	**90%**
	74	86
	198	232

Table 1. Sample sizes to detect 5% or 3% differences in LVEF at 80%, 85% or 90% power (1:1 randomization and 2-sided α=0.05). Total sample sizes are shown.