Supplemental Methods

Data from the TAC-HFT[24] and POSEIDON[25] trials were collected in a similar fashion in a central electronic data system. Both trials were conducted under an Investigational New Drug Application from the US Food and Drug Administration. All patients provided written informed consent on the University of Miami Institutional Review Board-approved protocols. Eligible patients included those with ischemic cardiomyopathy with LV dysfunction secondary to chronic MI, as documented by confirmed coronary artery disease with corresponding areas of myocardial akinesis, dyskinesis, or severe hypokinesis. Additional eligibility criteria included being 21 to 90 years old as well as having LV ejection fraction of less than 50% within 6 months before screening, without being collected during or recently after an ischemic event.

Patients who received autologous MSCs in either trial underwent bone marrow aspiration from the iliac crest and cells were prepared in culture from the marrow aspirate. Allogeneic MSCs were derived from healthy donor bone marrow aspirates[1, 26]. In both trials, cells were delivered by TESI during retrograde left heart catheterization using the Biocardia Helical Infusion Catheter[27]. They were injected into 10 LV sites to target territories bordering chronically infarcted myocardium. Study assessments in both trials were conducted monthly for 6 months and at 12 months post-TESI, however, we used data only from the baseline, 6 month and 12 month post-TESI time points to compare age groups using a repeated measures model. Cardiac imaging was performed using cardiac CT (at baseline and 13-months) for the POSEIDON[25] trial and a mixture of cardiac MRI (baseline, 3, 6 and 12-months) and cardiac CT (baseline and 12-months) for the TAC-HFT[24] trial. For this reason, only baseline and 12/13-month (1-year) time points were used for cardiac imaging parameter analyses. These parameters were

analyzed using a percent change from baseline to account for differences in CT and MRI measurement scales.

Cardiac imagining parameters were measured using CMR software (Qmass, Medis, Raleigh, NC). Endocardial and epicardial contours were drawn at end-systole, end-diastole, or both depending on the specific parameter being measured. The software then analyzed the corresponding 2D images, using the contours as guides, to calculate the appropriate values. The software then analyzed these images, using the contours as guides, to calculate the appropriate values.

All ICM patients who received hMSCs from these trials were pooled together from both trials and dichotomized into two age groups, <60 yrs. and ≥60 yrs. The associations between age and both clinical and imaging parameters were assessed. Previous studies examining the effect of aging on MSCs have used cutoff ages ranging from 59-66 years to describe aged patients[12, 16, 28]. As a result, and to allow for a closely similar sample size in each group, we chose 60 years old to be the cutoff age in our study. The functional capacity and quality of life parameters included the 6 Minute Walking Distance (6MWD) test and Minnesota Living With Heart Failure Questionnaire (MLHFQ) total score, respectively. Cardiac imaging parameters included absolute scar size, scar size as a percentage of LV mass, ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV), and sphericity index[1, 25, 29, 30].

Supplemental Statistical Methods

Baseline characteristics are presented in Table 1. For continuous variables, mean (SD) as well as minimum, first quartile, median, third quartile, and maximum are presented. A two-sided t-test at alpha=0.05 was used to compare continuous variables between age groups, assuming equal or unequal variances, as appropriate. No

continuous variables at baseline had a significant departure from normality. Absolute (n) and relative (%) frequencies are presented for categorical variables and compared between age groups using Fisher exact tests.

To compare age groups with respect to 6MWD and MLHFQ, we used separate repeated measures models for each endpoint to account for measurements taken at baseline, 6 and 12-months. The models were adjusted for baseline measurements, age group, time, and age by time interaction. We assumed the covariance matrix to be compound symmetric. To compare within group changes from baseline in these endpoints, we used separate repeated measures models assuming a compound symmetric covariance structure for each age group. In order to provide a more robust analysis in determining whether or not there is an association between age at transplant and 6MWD or MLFHQ score, we used a repeated measures model treating age as a continuous covariate, while adjusting for baseline score and time effects.

Cardiac imaging parameters were compared between age groups using percent change from baseline to one year to account for differences in scales between CT and MRI. Parameters were then compared between age groups using two-sided t-tests at alpha=0.05 where the distribution did not show a significant departure from normality. For parameters that did show a significant departure from normality, a non-parametric Wilcoxon-Mann-Whitney test was used. Within age group analyses of cardiac imaging parameters were done using one-sample t-tests and two-sided alpha=0.05, or with a non-parametric sign test, as appropriate. For a further rigorous approach, a linear regression model treating age as a continuous variable was used to examine the relationship between cardiac structure/function and age at transplant. Analyses were conducted using the SAS system version 9.3 (Cary, NC).