Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Duncan PW, Sullivan KJ, Behrman AL, et al. Body-weight–supported treadmill rehabilitation after stroke. N Engl J Med 2011;364:2026-36.

On-Line Supplement
Consort Diagram

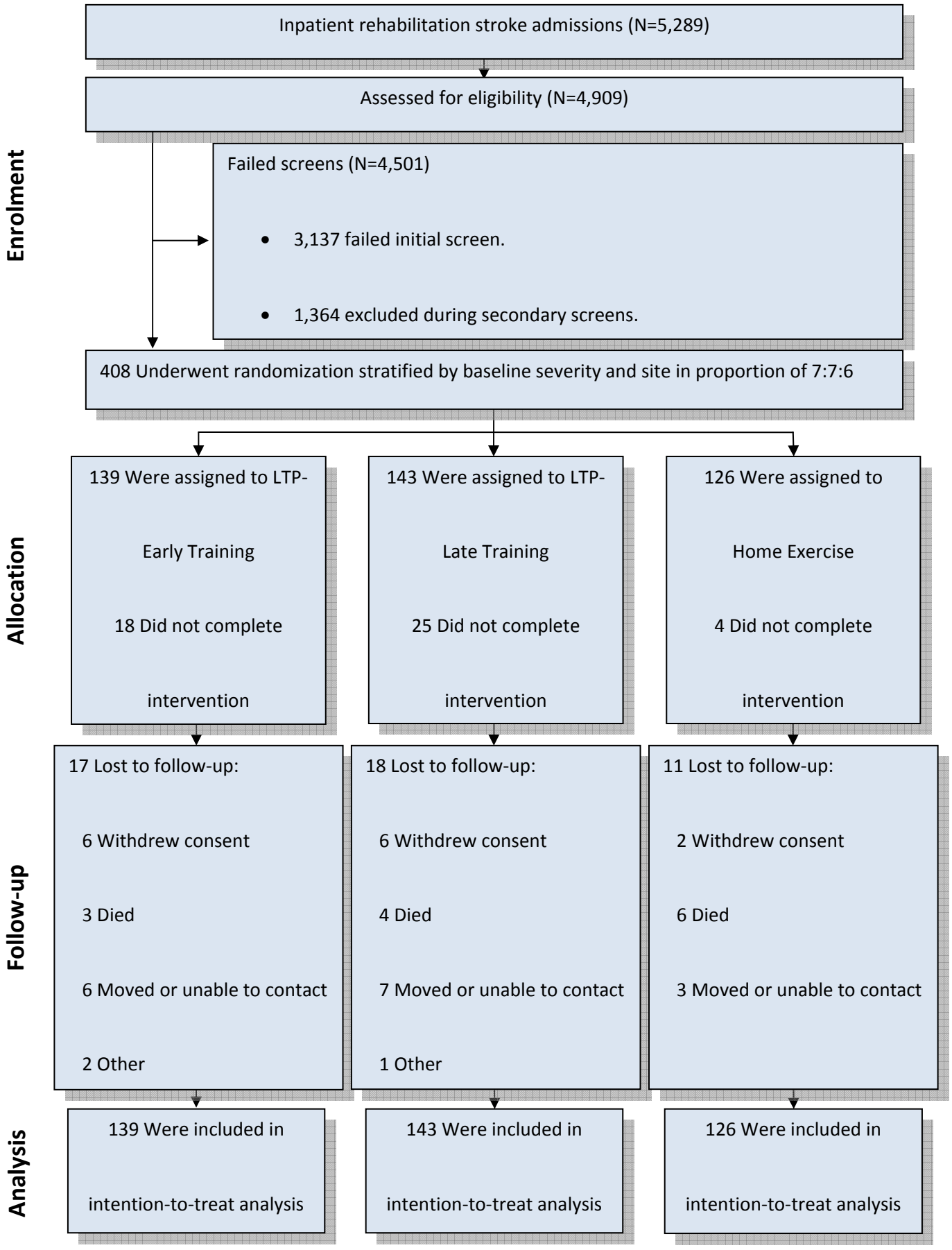
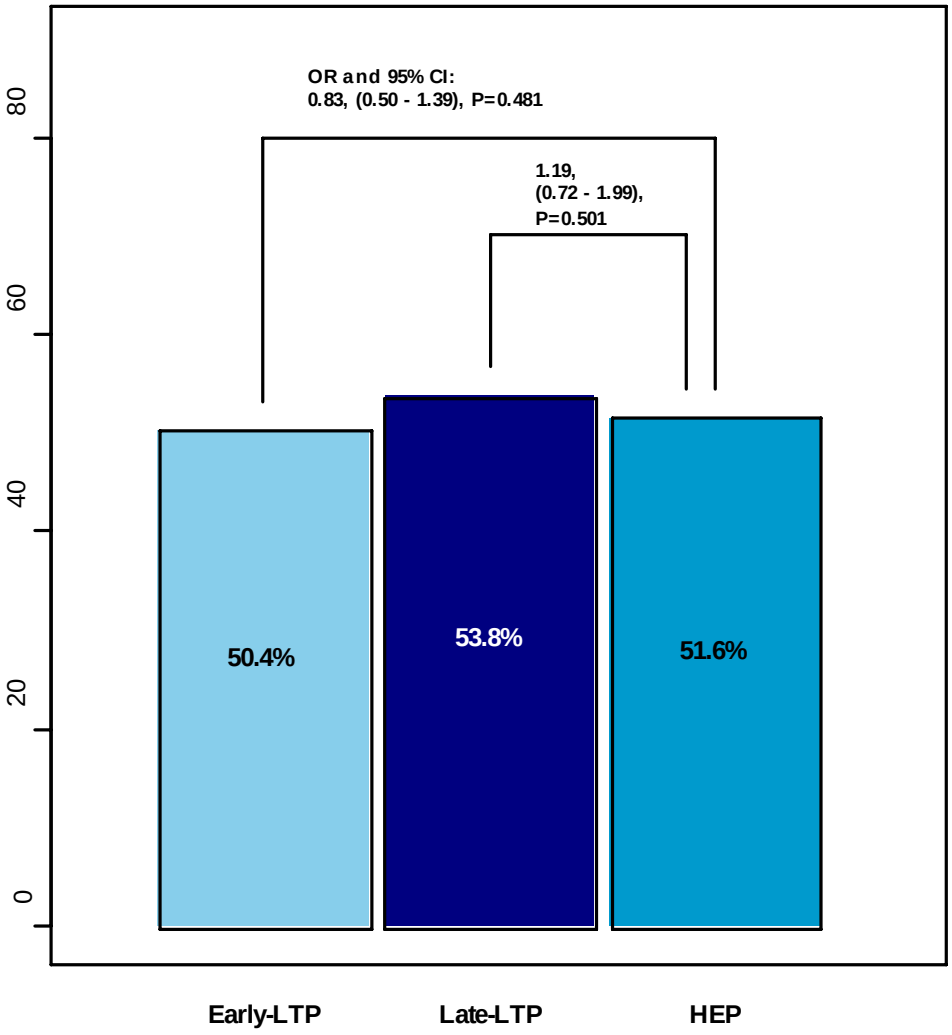


Figure 2: Functional Outcome by Group*



Sensitivity Analyses Results

Results similar to the primary analyses were obtained in sensitivity analyses. In this appendix, we present the details of sensitivity analyses procedures and corresponding results.

What are the sensitivity analyses?

For subjects who could not complete the one-year evaluation, we planned to impute their outcome based on the last available assessment value, with the exception that, for those who did not complete the 12 month assessment due to a related adverse event, the dichotomous outcome would be imputed as failure in the logistic regression and the improvement in gait speed as the minimum of zero and the change from the baseline and last assessment. Because no subject was lost as a result of a related adverse event, the exception did not apply and our planned imputation procedure for the intent-to-treat analyses is the last-observation-carried-forward (LOCF) method.

In addition, we performed sensitivity analyses by comparing results from the intent-to-treat analyses described above with the subgroup of subjects with one-year follow-up data, as well as those obtained using different imputation procedures, including: (1) missing one-year outcome predicted by subject gait speed trajectory; (2) missing one-year outcome predicted by

subject gait speed trajectory, plus baseline demographic and clinical factors, and (3) missing one-year outcome predicted by a model that takes into account subject dropout bias. For this last model, we evaluated subject dropout bias through the following four steps: (1) determine demographic and clinical variables that characterize differences between those who completed the 12 month assessment and those that did not, which included education, time since stroke to randomization, Upper extremity motor score, baseline walking speed and berg balance; (2) develop a model predicting outcomes for the “completers” using the significant independent variables from previous step; (3) use the resulting model to predict outcomes for the non-completers; and (4) redo the primary analyses for the full dataset.

Sensitivity Analyses Results

The drop-out (defined as not completing 12-months assessment) rates are: 12.2%, 12.6% and 8.7% for Early-LTP, Late-LTP, and HEP, respectively. These rates are less than we anticipated (15%) on the basis of reported literature and our prior clinical trial experience, and are a testimony to the tightness of study protocol execution. The participants who did not complete 12-mo assessment were significantly different from subjects who did in the following baseline characteristics: they tended to be less educated, have a longer time from stroke to randomization, and have lower scores in upper extremity motor function, walking speed, and

Berg balance. However, the baseline characteristics were similar across the three groups for those who completed 12-mo assessment; and there was no significant difference across the three groups among those who did not complete 12-mo assessment.

We believe our main result that LTP is not superior to HEP is true despite the drop outs. First, the proportion of subjects who successfully improved functional level of walking among those who did not complete 12-mo assessment was 26.1%, significantly lower than that of subjects who completed 12-mo assessment (55.2%). Since the complete case only analysis excluded more participants who were less likely to improve functional level of walking from the LTP training groups than HEP, it could provide an overestimate of the LTP benefits. However, based on this analysis, we could not obtain superiority of LTP over HEP. Second, the other pre-specified sensitivity analyses yielded adjusted odds-ratios ranging from 0.83 to 0.88 for early-LTP vs. HEP, and 1.09 to 1.10 for late-LTP vs. HEP (see Table 1 below). Third, even if we impute the missing 12-mo outcomes in the LTP groups by the corresponding improvement rates of completers and impute all HEP group missing outcomes as failures (which results improvement proportions of 53.2%, 59.4% and 48.4% for Early-LTP, Late-LTP and HEP, respectively), we still could not obtain superiority of LTP over HEP. The odds ratio and 95% confidence intervals based on this imputation were 1.21 (0.75 - 1.97, p=0.43) for Early-LTP

versus HEP and 1.56 (0.96 – 2.53, p=0.07) for Late-LTP versus HEP; while the Wald test of the joint null hypothesis had a p-value of 0.19. Table 2 below provided summary statistics for the complete cases only.

Table 1. Sensitivity analysis results from logistic regression for 12-moths outcome

Models	Comparion	OR Estimate	95% Wald Confidence Limits		P-Value
Intent-to-treat	Early-LTP vs. HEP	0.831	0.497	1.391	0.481
	Late-LTP vs. HEP	1.192	0.715	1.985	0.501
Complete Case Only	Early-LTP vs. HEP	0.859	0.496	1.488	0.587
	Late-LTP vs. HEP	1.404	0.81	2.434	0.227
Trajectory Only	Early-LTP vs. HEP	0.828	0.496	1.382	0.47
	Late-LTP vs. HEP	1.099	0.661	1.827	0.716
Traj + Demo + Clinical	Early-LTP vs. HEP	0.881	0.524	1.48	0.631
	Late-LTP vs. HEP	1.088	0.651	1.817	0.748
Traj + Sign Demo and Clinical	Early-LTP vs. HEP	0.848	0.507	1.419	0.530
	Late-LTP vs. HEP	1.088	0.653	1.812	0.746

Table 2. Summary of 12-month Primary Outcomes by Group and Severity based on only Those Who Completed 12-mo Assessment

Assignment Group	Severity	Proportion of Success	Walking Speed Change from 2-mo to 12-mo Post-Stroke	
			Mean	SD
Early-LTP	Moderate (N=57)	57.89 (N=33)	0.27	0.20
	Severe (N=65)	49.23 (N=32)	0.23	0.20
	Total (N=122)	53.28 (N=65)	0.25	0.20
Late-LTP	Moderate (N=62)	59.68 (N=37)	0.24	0.25
	Severe (N=63)	58.73 (N=37)	0.27	0.19
	Total (N=125)	59.20 (N=74)	0.26	0.22
HEP	Moderate (N=59)	49.15 (N=29)	0.25	0.2
	Severe (N=56)	57.14 (N=32)	0.27	0.24
	Total (N=115)	53.04 (N=61)	0.26	0.22
Total	Moderate (N=178)	55.62 (N=99)	0.25	0.22
	Severe (N=184)	54.89 (N=101)	0.026	0.21
	Total (N=362)	55.25 (N=200)	0.25	0.21

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