EmPHasis-10 as a Measure of Health-Related Quality of Life in Pulmonary Arterial Hypertension

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The PHAR Study Group – Please refer to Author Appendix

ONLINE SUPPLEMENT

Pulmonary Hypertension Association Registry:

Beginning September 2015, patients have been consecutively approached for enrollment in the Pulmonary Hypertension Association Registry (PHAR) (S1) at the time of their first visit at a pulmonary hypertension care center (PHCC). Patients are considered active in the registry unless marked by their PHCC's clinical research coordinator as having refused, been lost to follow-up, transferred, received a lung transplant, or died. Data were collected using electronic study tablets. Demographic factors, height, pulmonary arterial hypertension (PAH) etiology, and hemodynamic data were recorded at baseline and lifestyle information, patient-assigned care ratings, weight, six-minute walk distance, World Health Organization (WHO) functional class, medication information, and lab values were recorded at baseline and follow-up PHCC visits.

Data Variables:

Demographic parameters recorded in PHAR include age, sex, race/ethnicity, highest education level, employment status, yearly income, marital status, health insurance information, patient-assigned PHCC quality-of-care rating, history of alcohol use, history of cocaine, crack cocaine, or methamphetamine use, smoking status, participation status in a pulmonary hypertension clinical trial, presence of an advance directive, and United States regional location of the PHCC. Clinical parameters include the emPHasis-10 (e10) score, 12-item Short Form Survey physical component summary and mental component summary scores, body mass index, whether a patient was diagnosed with PAH within six months of entry into PHAR, PAH etiology, WHO functional class, six-

minute walk distance, supplemental oxygen use, PAH therapy use, B-type natriuretic peptide (BNP), N-terminal-pro BNP (NT-pro BNP), creatinine, heart rate, right atrial pressure, mean pulmonary artery pressure, pulmonary artery wedge pressure, left ventricular end-diastolic pressure, cardiac output, pulmonary vascular resistance, stroke volume, pulmonary artery compliance, number of emergency room visits in the last six months or since the last PHCC visit, and number of hospitalizations in the last six months or since the last PHCC visit.

We used each patient's reported income range and number of individuals in household to assign a yearly income level according to the 2018 US Department of Health and Human Services guidelines (S2). PHCC care ratings were assigned by patients on a 0 to 10 scale, where 0 is the worst health care possible and 10 is the best health care possible. History of illicit stimulant use was defined as having ever used cocaine, crack cocaine, or methamphetamine prior to enrollment.

Medications were separated into four classes: prostacyclin analogs, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and soluble guanylate cyclase stimulators. Pulmonary artery wedge pressure and left ventricular end-diastolic pressure data were combined into one variable and, if both values were available, the reported pulmonary artery wedge pressure was used. Values for cardiac output, stroke volume, and pulmonary artery compliance were computed for patients who were missing these values but had the hemodynamic parameters from which they could be derived. The REVEAL Registry Risk Score Calculator (S3) was used to determine the REVEAL risk

stratum for patients with a value available for at least seven of the following ten parameters: PAH etiology, creatinine, age and sex, WHO functional class, systolic blood pressure, heart rate, six-minute walk distance, brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT-pro BNP), right atrial pressure, and pulmonary vascular resistance.

Multiple imputation for missing data:

We identified variables with more than 10% missingness at baseline and used the R package 'mice' (S4) to impute missing data for these variables. The predictive mean matching method was used for continuous variables and the proportional odds model method was used for ordinal variables. Forty imputed data sets were generated, relevant baseline models were re-run using all imputed data sets, and model results were pooled for comparison against our initial model results. We reported on changes to the coefficient, standard error of the coefficient, or R^2 that differed from the initial results by more than 10% and changes to the p-value that affected our conclusions at the 0.05 significance level. We identified income level, six-minute walk distance, heart rate, stroke volume, and pulmonary artery compliance were as having over 10% missingness at baseline and repeated analyses as detailed below.

Income level: We found that 19% of income level values were missing at baseline. After imputing missing data, the R^2 value from the unadjusted model went from 0.03 to 0.04, indicating that income level explained a greater proportion of the variance in e10 score

with the imputed data. Still, the R^2 value remained small and our conclusions were not affected.

Six-minute walk distance: There were considerable amounts of data missing for the six-minute walk distance at baseline (14%). Imputation of missing baseline data had no or negligible effects on all baseline six-minute walk distance model outputs.

Heart rate: We found that 35% of heart rate values were missing at baseline. After imputing missing data, the heart rate parameter in the unadjusted model with heart rate as the independent variable and e10 score as the dependent variable reached statistical significance at a significance level of 0.05 (p=0.032). All other outputs from the unadjusted and adjusted models did not change or changes were negligible.

Stroke volume: We found that 36% of stroke volume values were missing at baseline. After imputing missing data, the R^2 for the adjusted stroke volume model decreased from 0.06 to 0.04. Still, the R^2 value from the initial model was small and our conclusions were not affected by the imputed data.

Pulmonary artery compliance: We found that 37% of pulmonary artery compliance values were missing at baseline. After imputing missing data, the coefficient from the unadjusted model went from -1.0 to -0.6, indicating a weakened correlation between pulmonary artery compliance and e10 score (although this relationship remained statistically insignificant). The coefficient from the adjusted pulmonary artery compliance

model went from -1.1 to -0.8, again suggesting a weakened correlation between pulmonary artery compliance and e10 score. The R^2 value from the adjusted model was also affected by the imputed data and went from 0.04 to 0.03, indicating that the adjusted pulmonary artery compliance model explained less of the variance in the e10 score after missing data were imputed. Still, the R^2 value from the initial model was small and our conclusions were not affected.

Factors Associated with Patient Attrition:

We identified patient demographic and clinical parameters associated with attrition via loss to follow-up and death or lung death (as indicated by lung transplant). We used the Wilcoxon rank-sum test to evaluate relationships between patient status in PHAR (active, lost to follow-up, and died/lung transplant) and continuous parameters and the Fisher's exact test to evaluate relationships between patient status and categorical parameters. Non-parametric tests were used due to small sample sizes in the lost to follow-up and died/lung transplant groups. We assessed differences between the active versus lost to follow-up and active versus died/lung transplant patients separately.

A total of 12 patients (2%) were lost to follow-up and 39 patients (7%) died or received a lung transplant signifying organ death during the data collection period. We found that patients lost to follow-up had significantly higher e10 scores, lower income, and reported higher PHCC care ratings than those who remained active (see table below). The majority of patients lost to follow-up also had marked medical leave/disability as their employment status, reported having a history of illicit stimulant use, were identified

as having drug/toxin-associated PAH, and reported having been hospitalized in the six months prior to their baseline PHCC visit. Further, compared to patients who remained active in PHAR during the study period, we found that deceased and lung transplant patients were significantly older, had higher e10 scores and BNP/NT-pro BNP z-scores, had shorter six-minute walk distances, were more frequently identified as belonging to WHO functional class IV and high-risk REVEAL risk strata, and had a greater proportion of individuals who indicated they were retired, insured through Medicare, had an advance directive, used supplemental oxygen, had visited the emergency room in the six months prior to their baseline PHCC visit, and were seen at a PHCC in the Northeast United States.

	Active	**Lost to follow-up**		**Died/lung transplant**	
Parameters	**(n = 498)**	**(n = 12)**	**p-value**	**(n = 39)**	**p-value**
Demographic					
Age, yr	55.5 (42.5-67.3)	51.6 (44.9-61.4)	0.788	67.5 (58.2-74.3)	<0.001
Sex, female, n (%)	377 (75.7)	7 (58.3)	0.181	25 (64.1)	0.125
Race/ethnicity, n (%)			0.574		0.725
White, non-Hispanic	320 (64.3)	6 (50.0)		28 (71.8)	
Asian/Pacific Islander	32 (6.4)	1 (8.3)		1 (2.6)	
Hispanic	62 (12.4)	2 (16.7)		4 (10.3)	
Black, non-Hispanic	62 (12.4)	3 (25.0)		2 (5.1)	
Native American	7 (1.4)	0 (0.0)		0 (0.0)	
Mixed race	7 (1.4)	0 (0.0)		0 (0.0)	
Highest education level, n (%)			0.273		0.324
Less than high school	44 (8.8)	2 (16.7)		6 (15.4)	
High school/GED	285 (57.2)	8 (66.7)		19 (48.7)	
College or graduate degree	165 (33.1)	2 (16.7)		12 (30.8)	
Employment status, n (%)			0.032		0.012
Unemployed	65 (13.1)	1 (8.3)		3 (7.7)	
Employed	146 (29.3)	0 (0.0)		5 (12.8)	
Medical leave/disability	132 (26.5)	8 (66.7)		9 (23.1)	
Student	8 (1.6)	0 (0.0)		1 (2.6)	

Retired	137 (27.5)	3 (25.0)		21 (53.8)	
Yearly income level, n (%)			0.047		0.91
Below poverty level	85 (17.1)	4 (33.3)		7 (17.9)	
Above poverty, <$75k	194 (39.0)	7 (58.3)		16 (41.0)	
≥$75k	120 (24.1)	0 (0.0)		8 (20.5)	
Marital status, n (%)			0.102		0.058
Single	138 (27.7)	5 (41.7)		6 (15.4)	
Married	254 (51.0)	3 (25.0)		24 (61.5)	
Divorced	68 (13.7)	4 (33.3)		2 (5.1)	
Widowed	31 (6.2)	0 (0.0)		5 (12.8)	
Health insurance, n (%)			0.481		0.003
Uninsured	9 (1.8)	0 (0.0)		0 (0.0)	
Medicare	205 (41.2)	5 (41.7)		28 (71.8)	
Medicaid	51 (10.2)	3 (25.0)		0 (0.0)	
Other government service	46 (9.2)	1 (8.3)		1 (2.6)	
Private insurance	183 (36.7)	3 (25.0)		9 (23.1)	
Pt. PHCC care rating	10 (9-10)	10 (10-10)	0.023	10 (9-10)	0.814
Drinks alcohol, n (%)	178 (35.7)	4 (33.3)	1	8 (20.5)	0.106
History of illicit stimulant use*, n (%)	71 (14.3)	7 (58.3)	0.001	2 (5.1)	0.145
Smoking status, n (%)			0.264		0.586
Non-smoker	272 (54.6)	5 (41.7)		20 (51.3)	
Past	185 (37.1)	5 (41.7)		17 (43.6)	
Current	33 (6.6)	2 (16.7)		1 (2.6)	
Participates in PH clinical trial, n (%)	71 (14.3)	0 (0.0)	0.388	10 (25.6)	0.064
Presence of an advance directive, n (%)	156 (31.3)	7 (58.3)	0.061	19 (48.7)	0.033
United States Region, n (%)			0.168		0.006
Northeast	91 (18.3)	1 (8.3)		16 (41.0)	
Midwest	81 (16.3)	0 (0.0)		2 (5.1)	
South	146 (29.3)	3 (25.0)		11 (28.2)	
West	180 (36.1)	8 (66.7)		10 (25.6)	
Clinical					
EmPHasis-10 score	26 (16-34)	39 (23-46)	0.006	31 (25-40)	0.005
PCS-12 score	34.8 (30.4-38.5)	35.2 (30.8-39.4)	0.955	34.1 (26.9-39.2)	0.674
MCS-12 score	48.3 (41.7-54.8)	48.0 (39.2-53.3)	0.555	49.8 (39.2-56.7)	0.657
BMI, kg/m^2	28.2 (24.1-32.6)	26.6 (23.1-33.1)	0.619	27.7 (22.9-32.7)	0.466
Diagnosed in last 6 mo., n (%)	250 (50.2)	6 (50.0)	1	22 (56.4)	0.508
PAH etiology, n (%)			0.003		0.174
Idiopathic	194 (39.0)	2 (16.7)		21 (53.8)	
Heritable	18 (3.6)	0 (0.0)		0 (0.0)	
Drug/toxin-associated	54 (10.8)	7 (58.3)		1 (2.6)	

CTD-associated	163 (32.7)	1 (8.3)		13 (33.3)	
HIV-associated	9 (1.8)	0 (0.0)		0 (0.0)	
PPHTN-associated	31 (6.2)	1 (8.3)		4 (10.3)	
CHD-associated	29 (5.8)	1 (8.3)		0 (0.0)	
WHO functional class, n (%)			0.43		0.008
I	40 (8.0)	0 (0.0)		3 (7.7)	
II	159 (31.9)	2 (16.7)		4 (10.3)	
III	241 (48.4)	8 (66.7)		19 (48.7)	
IV	28 (5.6)	1 (8.3)		6 (15.4)	
6MWD, m	341.0 (260.0-427.0)	303.9 (259.5-337.5)	0.197	249.0 (185.0-343.0)	0.002
Supplemental oxygen use, n (%)	178 (35.7)	5 (41.7)	0.764	23 (59.0)	0.006
No. PAH medications, n (%)			0.392		0.359
None	74 (14.9)	2 (16.7)		3 (7.7)	
One	151 (30.3)	6 (50.0)		13 (33.3)	
Two	207 (41.6)	2 (16.7)		17 (43.6)	
Three	61 (12.2)	2 (16.7)		6 (15.4)	
PAH medication classes, n (%)					
Prostacyclin analog	144 (28.9)	2 (16.7)	0.523	16 (41.0)	0.145
Endothelin receptor antagonist	257 (51.6)	3 (25.0)	0.082	19 (48.7)	0.741
Phosphodiesterase-5 inhibitor	338 (67.9)	10 (83.3)	0.356	29 (74.4)	0.478
sGC stimulator	11 (2.2)	1 (8.3)	0.252	1 (2.6)	0.601
Laboratory tests					
BNP/NT-pro BNP z-score[†]	-0.3 (-0.5-0.3)	-0.1 (-0.4-0.8)	0.49	0.1 (-0.3-1.2)	0.003
Creatinine, mg/dL	0.9 (0.8-1.1)	1.0 (0.7-1.2)	0.551	1.0 (0.8-1.2)	0.446
Hemodynamics					
Heart rate, bpm	79 (69-90)	80 (73-98)	0.54	76 (69-90)	0.954
Right atrial pressure, mmHg	9 (5-13)	13 (10-17)	0.084	10 (7-15)	0.179
mPAP, mmHg	48 (39-58)	44 (37-54)	0.256	52 (41-60)	0.394
PAWP/LVEDP, mmHg	10 (7-14)	11 (7-13)	0.902	10 (7-13)	0.538
Cardiac output, L/min	3.9 (3.3-5.2)	3.2 (2.1-5.6)	0.189	3.5 (3.0-4.9)	0.094
PVR, dyn*s*cm^{-5}	720 (480-1040)	680 (480-1105)	0.839	876 (640-1178)	0.071
Stroke volume, mL	50.6 (39.5-67.0)	40.0 (12.9-79.7)	0.141	49.5 (31.5-65.3)	0.434
PAC, mL/mmHg	1.1 (0.8-1.6)	1.0 (0.2-1.4)	0.229	1.0 (0.7-1.8)	0.407
REVEAL risk stratum[‡], n (%)			0.886		0.001
Low risk	257 (51.6)	5 (41.7)		11 (28.2)	
Average risk	77 (15.5)	2 (16.7)		3 (7.7)	
Moderate high risk	59 (11.8)	1 (8.3)		7 (17.9)	
High risk	63 (12.7)	2 (16.7)		10 (25.6)	
Very high risk	11 (2.2)	0 (0.0)		4 (10.3)	
Visited ER in last 6 mo., n (%)	268 (53.8)	10 (83.3)	0.074	30 (76.9)	0.007

Hospitalized in last 6 mo., n (%)	249 (50.0)	10 (83.3)	0.037	25 (64.1)	0.099

Values are expressed as median (interquartile range). The p-values correspond to comparisons between active versus lost to follow-up participants and active versus dead/lung transplant participants.
*Stimulants include cocaine, crack cocaine, and methamphetamine
†Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)
‡Determined using the REVEAL Registry Risk Score Calculator (S3)
Pt. = patient; PHCC = pulmonary hypertension care center; PH = pulmonary hypertension; PCS-12 = SF-12 physical component summary; MCS-12 = SF-12 mental component summary; BMI = body mass index; PAH = pulmonary arterial hypertension; CTD = connective tissue disease; PPHTN = portopulmonary hypertension; CHD = congenital heart disease; WHO = World Health Organization; 6MWD = six-minute walk distance; sGC = soluble guanylate cyclase; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; mPAP = mean pulmonary artery pressure; PAWP/LVEDP = pulmonary artery wedge pressure or left ventricular end-diastolic pressure; PVR = pulmonary vascular resistance; PAC = pulmonary artery compliance; ER = emergency room.

Incident Patient Subgroup Analyses:

We sought to evaluate what effect restricting our study cohort to those who were marked as incident at baseline would have on our longitudinal analyses, where incident patients were defined as those who had been diagnosed with PAH within the six months prior to their baseline PHCC visit. To do this, we re-ran all longitudinal models using only data from incident patients and identified changes to the within-subject coefficients, standard errors of the coefficients, or R^2 that differed from the initial results by more than 10% and changes to p-values that affected our conclusions at the 0.05 significance level.

We found that the within-subject coefficients for smoking status (0.7; 95% CI, -2.5-3.8), body mass index (0.0; 95% CI, -0.3-0.4), REVEAL risk stratum (0.6; 95% CI, -1.1-2.2), supplemental oxygen use (0.5; 95% CI, -2.3-3.3), phosphodiesterase-5 inhibitor use (1.0; 95% CI, -1.9-3.9), and creatinine (0.1; 95% CI, -4.2-4.3) moved closer to zero,

meaning that the correlations between within-subjects changes in these parameters and the e10 score were weaker among incident patients. Conversely, the within-subject coefficients for alcohol consumption (-1.7; 95% CI, -4.3-0.8), prostacyclin analog use (2.2; 95% CI, -1.2-5.5), endothelin receptor antagonist use (-0.1; 95% CI, -2.7-2.6), soluble guanylate cyclase stimulator use (-6.5; 95% CI, -12.3--0.7), and BNP/NT-pro BNP z-score (2.8; 95% CI, 1.0-4.5) moved further from zero, meaning that the correlations between within-subjects changes in these parameters and the e10 score were stronger among incident patients. The standard errors of the within-subject coefficients from all models increased and this likely resulted from the small number of patients in the incident subgroup (n = 285) compared to the complete patient cohort (n = 565).

The marginal R^2 values for the WHO functional class (R^2, 0.17), REVEAL risk stratum (R^2, 0.10), supplemental oxygen use (R^2, 0.13), number of PAH medications (R^2, 0.11), prostacyclin analog use (R^2, 0.12), and endothelin receptor antagonist use (R^2, 0.12) models all decreased, indicating that the variance in the e10 score explained by each fixed effects model decreased among incident patients. We also found that the within-subject effect of the number of emergency room visits in the last six months/since last visit on the e10 score was no longer statistically significant (p=0.079) among the incident patient subgroup, while the within-subject effect of soluble guanylate cyclase stimulator use on the e10 score reached statistical significance (p=0.030) among the incident patient subgroup.

Through analyzing the relationships between within-subjects changes in patient characteristics and e10 score among the incident patient subgroup, we found that changes in PAH medication use appeared to have stronger relationships with the e10 score in incident patients as compared to a mixed cohort of both incident and prevalent patients. This might have been related to the large proportion of incident patients who were treatment naive at baseline (82%, compared to 14% in the whole study cohort). The number of incident patients on soluble guanylate cyclase stimulators also did not exceed ten across all PHCC visits.

SF-12 Relationship

We used Pearson correlation coefficients to evaluate relationships between the e10 score and the 12-item Short Form Survey (SF-12) (S4) physical component summary (PCS-12) and mental component summary (MCS-12) scores at baseline given that the SF-12 has been studied extensively as a measure of HRQoL in non-PAH cardiac and respiratory diseases. The mean e10 score in our study cohort (25.4 ± 12.2) aligned with the center of the 0 to 50-point range of possible scores. The mean PCS-12 (34.2 ± 6.7) and MCS-12 (48.1 ± 8.8) scores were lower than the United States population average of 50. Further, the entire e10 score range was represented in our study cohort (score range, 0 to 50; cohort range, 0 to 50) while the PCS-12 (score range, 0 to 100; cohort range, 15 to 56) and MCS-12 (score range, 0 to 100; cohort range, 20 to 80) score ranges were not.

We found that the correlations between baseline e10 and PCS-12 (Pearson correlation [r], -0.16; 95% confidence interval [CI], -0.24--0.07; $p < 0.001$) and baseline e10 and MCS-12 (r, -0.20; 95% CI,-0.28--0.12; $p < 0.001$) were both statistically significant. Still, the correlations were poor despite statistical significance and there was a greater degree of variability in the e10 score within our study cohort (25.4 ± 12.2) compared to the raw PCS-12 (34.2 ± 6.7) and MCS-12 (48.1 ± 8.8) scores.

Table S1. Patient demographic and clinical characteristics across baseline and follow-up PHCC visits

Parameters	Baseline (n = 565)	Follow-up 1 (n = 388)	Follow-up 2 (n = 214)	Follow-up 3 (n = 107)	Follow-up 4 (n = 47)
EmPHasis-10 score	25.4 ± 12.2	22.1 ± 12.3	21.1 ± 12.1	19.8 ± 11.9	23.9 ± 11.7
Pt. PHCC care rating*	10 (9-10)	10 (9-10)	10 (9-10)	10 (9-10)	10 (9-10)
Drinks alcohol, n (%)	197 (34.9)	119 (30.7)	65 (30.4)	29 (27.1)	14 (29.8)
Smoking status, n (%)					
Non-smoker	303 (53.6)	203 (52.3)	112 (52.3)	58 (54.2)	28 (59.6)
Past	217 (38.4)	127 (32.7)	78 (36.4)	40 (37.4)	13 (27.7)
Current	36 (6.4)	15 (3.9)	6 (2.8)	3 (2.8)	2 (4.3)
BMI, kg/m^2	29.1 ± 7.3	29.0 ± 7.1	29.3 ± 6.9	29.3 ± 7.0	28.7 ± 6.9
WHO functional class, n (%)					
I	43 (7.6)	30 (7.7)	22 (10.3)	12 (11.2)	5 (10.6)
II	172 (30.4)	150 (38.7)	88 (41.1)	49 (45.8)	17 (36.2)
III	276 (48.8)	136 (35.1)	66 (30.8)	28 (26.2)	18 (38.3)
IV	36 (6.4)	15 (3.9)	6 (2.8)	1 (0.9)	2 (4.3)
6MWD, m	335.4 ± 123.2	360.8 ± 128.9	373.1 ± 123.3	377.4 ± 127.9	347.1 ± 141.2
Supplemental oxygen use, n (%)	214 (37.9)	163 (42.0)	109 (50.9)	53 (49.5)	27 (57.4)
No. PAH medications, n (%)					
None	81 (14.3)	14 (3.6)	6 (2.8)	3 (2.8)	2 (4.3)
One	176 (31.2)	93 (24.0)	47 (22.0)	25 (23.4)	11 (23.4)
Two	231 (40.9)	183 (47.2)	113 (52.8)	58 (54.2)	21 (44.7)
Three	72 (12.7)	63 (16.2)	36 (16.8)	14 (13.1)	9 (19.1)
PAH medication classes, n (%)					
Prostacyclin analog	166 (29.4)	131 (33.8)	85 (39.7)	44 (41.1)	24 (51.1)
Endothelin receptor antagonist	288 (51.0)	227 (58.5)	129 (60.3)	60 (56.1)	22 (46.8)
Phosphodiesterase-5 inhibitor	389 (68.8)	268 (69.1)	154 (72.0)	76 (71.0)	33 (70.2)
sGC stimulator	13 (2.3)	25 (6.4)	15 (7.0)	5 (4.7)	2 (4.3)
Laboratory tests*					
BNP/NT-pro BNP z-score†	-0.3 (-0.5-0.3)	-0.4 (-0.5--0.1)	-0.5 (-0.5--0.2)	-0.4 (-0.5--0.3)	-0.4 (-0.5-0.0)
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.0)	0.9 (0.7-1.0)
REVEAL risk stratum‡, n (%)					
Low risk	281 (49.7)	210 (54.1)	123 (57.5)	69 (64.5)	29 (61.7)
Average risk	84 (14.9)	56 (14.4)	24 (11.2)	12 (11.2)	5 (10.6)
Moderate high risk	69 (12.2)	42 (10.8)	25 (11.7)	6 (5.6)	4 (8.5)
High risk	78 (13.8)	47 (12.1)	25 (11.7)	12 (11.2)	4 (8.5)
Very high risk	15 (2.7)	10 (2.6)	8 (3.7)	3 (2.8)	2 (4.3)
No. ER visits*‖	1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
No. nights hospitalized*‖	1 (0-10)	0 (0-0)	0 (0-2)	0 (0-2)	0 (0-3)

Values are expressed as mean ± SD.
*Values are expressed as median (interquartile range)
†Parameter reflects scaled values centered around a 246 pg/mL mean BNP (SD, 386 pg/mL) and 1437 pg/mL mean NT-pro BNP (SD, 3292 pg/mL)

‡Determined using the REVEAL Registry Risk Score Calculator (S3)
‖Over the last six months or since the patient's last PHCC visit
Pt. = patient; PHCC = pulmonary hypertension care center; BMI = body mass index; WHO = World Health Organization; 6MWD = six-minute walk distance; PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase; BNP/NT-pro BNP = brain natriuretic peptide or N-terminal pro B-type natriuretic peptide; ER = emergency room.

Table S2. Associations between patient clinical parameters and emPHasis-10 score at baseline

	Unadjusted			Adjusted*		
Parameters	**Coefficient [95% CI]**	**R^2**	**p-value**	**Coefficient [95% CI]**	**R^2**	**p-value**
Supplemental oxygen use	5.6 [3.5, 7.6]	0.05	<0.001	3.4 [1.4, 5.4]	0.23	0.001
No. PAH medications (per medication)	-0.6 [-1.7, 0.6]	0	0.321	-0.2 [-1.3, 0.8]	0.21	0.652
PAH medication classes†						
Prostacyclin analog	1.3 [-0.9, 3.6]	0	0.243	0.9 [-1.3, 3.0]	0.21	0.425
Endothelin receptor antagonist	-1.2 [-3.3, 0.8]	0	0.23	-1.1 [-3.1, 0.8]	0.21	0.251
Phosphodiesterase-5 inhibitor	-2.1 [-4.3, 0.1]	0	0.063	-0.2 [-2.3, 2.0]	0.21	0.893
sGC stimulator	1.4 [-5.6, 8.3]	0	0.705	-0.8 [-7.3, 5.7]	0.21	0.805

*Adjusted for age, sex, body mass index, and WHO functional class
†All PAH medication classes also included in adjusted models
PAH = pulmonary arterial hypertension; sGC = soluble guanylate cyclase; WHO = World Health Organization.

Table S3. Associations between within-patient changes and emPHasis-10 score

Parameters	Coefficient [95% CI]	R^2	p-value
Supplemental oxygen use	1.6 [-0.5, 3.6]	0.15	0.133
No. PAH medications (per medication)	0.2 [-1.0, 1.3]	0.13	0.747
PAH medication classes, n (%)			
Prostacyclin analog	0.9 [-1.4, 3.3]	0.14	0.445
Endothelin receptor antagonist	0.0 [-2.0, 1.9]	0.14	0.989
Phosphodiesterase-5 inhibitor	1.7 [-0.7, 4.1]	0.14	0.161
sGC stimulator	-2.1 [-6.3, 2.1]	0.13	0.332

Coefficients and p-values correspond to the within-subject effects in each model. Marginal R^2 values are given and represent the variance in emPHasis-10 explained by each fixed effects model.

PAH = pulmonary artery hypertension; sGC = soluble guanylate cyclase.

Table S4. Minimal important difference in emPHasis-10 for PAH patients

(A) Across total cohort and by treatment status at baseline

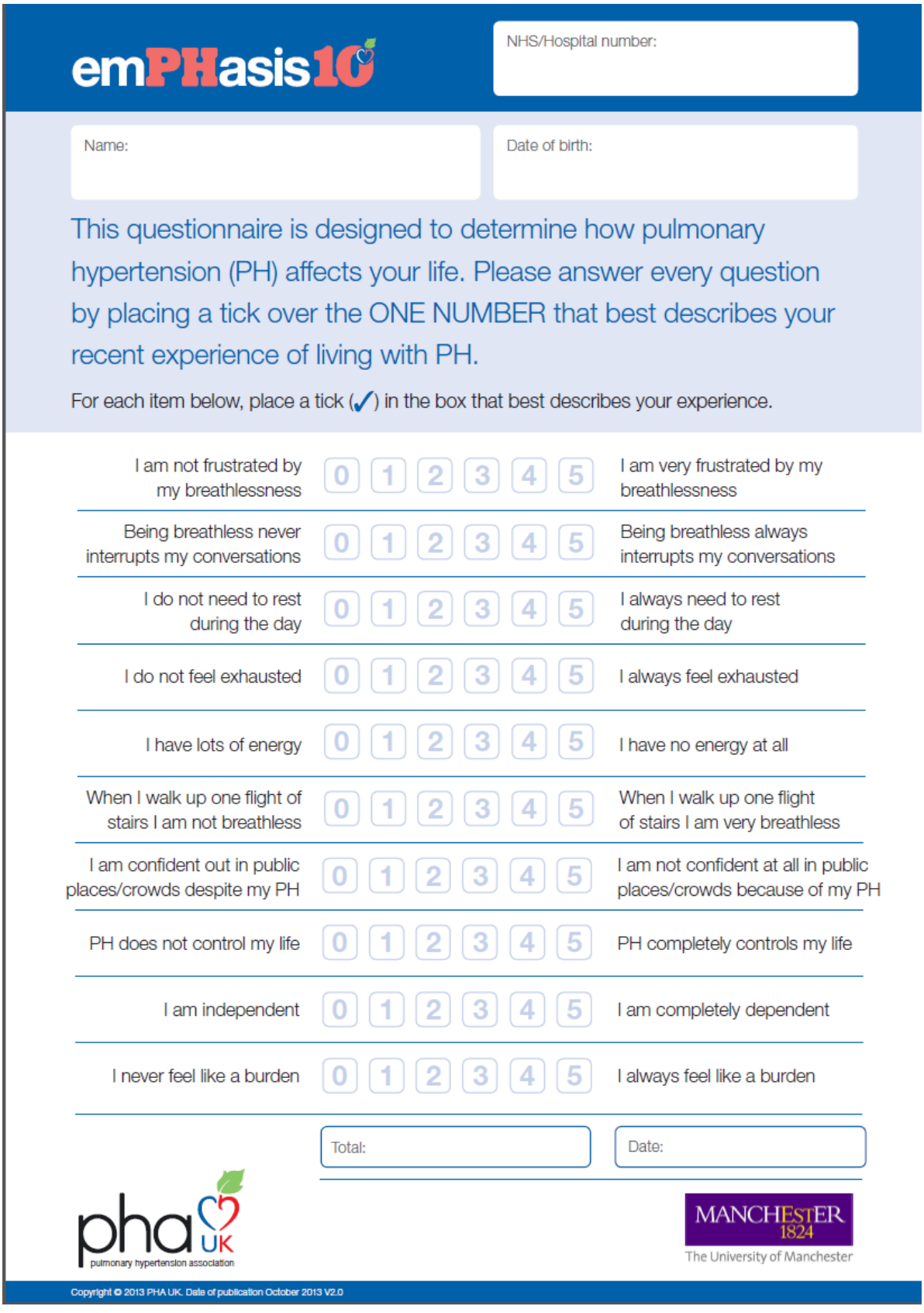
			Approach			
Patient group	**Baseline e10**	**e10**	**SEM**	**RCI**	**0.5 SD**	**ES**
All, (n=340)	25.4 ± 12.2	-2.3 ± 10.0	-5.3	-7.6	-5	-6.1
Incident, (n=180)	25.7 ± 12.1	-3.3 ± 10.1	-5.3	-7.5	-5.1	-6.1
Treatment naive, (n=49)	26.1 ± 12.3	-4.0 ± 11.4	-5.4	-7.7	-5.7	-6.2

(B) Across total and by PAH etiology

			Approach			
Patient group	**Baseline e10**	**e10**	**SEM**	**RCI**	**0.5**	**ES**
All, (n=340)	25.4 ± 12.2	-2.3 ± 10.0	-5.3	-7.6	-5	-6.1
Idiopathic PAH, (n=138)	24.2 ± 12.5	-2.4 ± 8.8	-5.5	-7.8	-4.4	-6.3
CTD-associated PAH, (n=119)	27.1 ± 11.0	-2.9 ± 9.8	-4.8	-6.8	-4.9	-5.5
D&T-associated PAH, (n=30)	29.0 ± 14.3	-3.0 ± 13.1	-6.3	-8.9	-6.6	-7.2

Baseline and change values are expressed as mean ± SD. Incident patients were those diagnosed within six months of their baseline visit and treatment naive patients were those on zero medications at their baseline visit. e10 = emPHasis-10; SEM = standard error of measurement; RCI = reliable change index; 0.5SD = 0.5 standard deviation; ES = effect size; CTD = Connective Tissue Disease, D&T = Drugs and Toxin.

Figure S1



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

MANCHESTER 1824 The University of Manchester

Figure S2 – Histogram of emPHasis-10 scores at baseline.

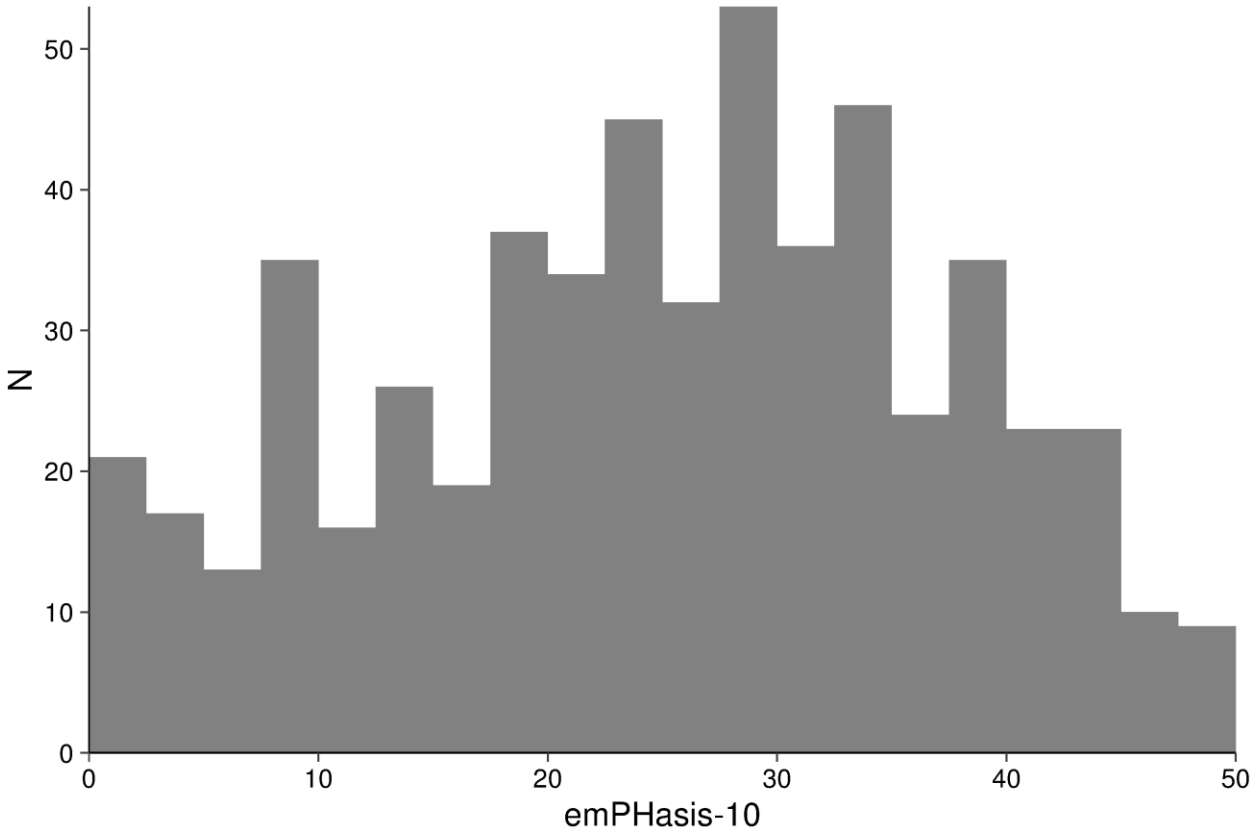
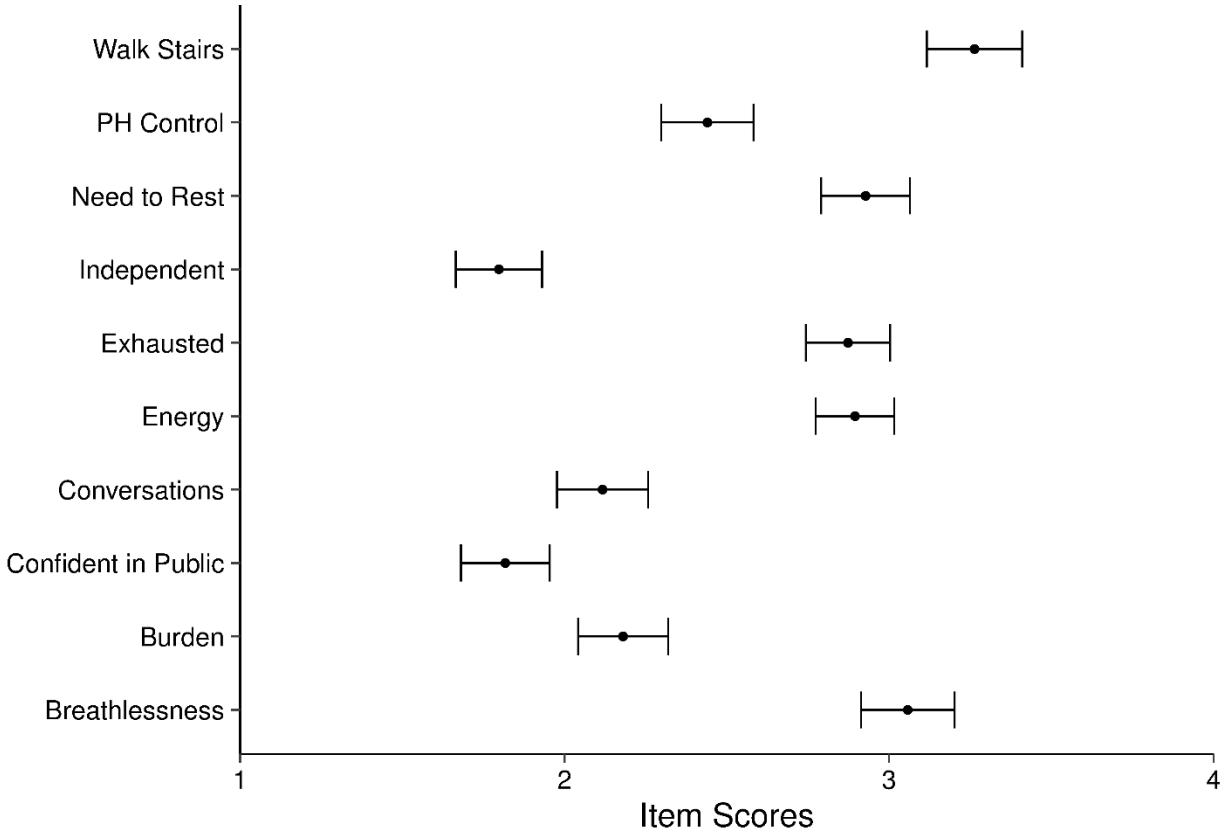


Figure S3 – Mean and 95% CI of emPHasis-10 item scores at baseline.



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