

Development and validation of a patient-reported outcome measure of the impact of chronic hand eczema on health-related quality of life: the Hand Eczema Impact Scale (HEIS)

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Supplementary Tables

Table S1. Independent ethics committee (IEC)/institutional review board (IRB) committee and study investigators for the phase 2b trial

IEC/IRB Committee Chair, Name of Committee, and Reference Number	Investigator Site
Denmark	
<p>Chair: Susanne Langer The Regional Committees on Health Research Ethics for Capital Region of Denmark – committee C, The Capital Region of Denmark Center for Kongens Vænge 2 3400 Hillerød / Denmark</p>	<p>Dr. Tove Agner Bispebjerg Hospital, Dermato-Venerologisk Afdeling, Nielsine Nielsens Vej, opg. 9, 1. sal, DK-2400 København NV Denmark</p>
<p>Chair: CEC</p>	<p>Dr. Mette Sommerlund Aarhus Universitetshospital Dermato-Venerologisk Afdeling Palle Juul Jensens Boulevard 99 DK-8200 Aarhus N Denmark</p>
<p>Chair: CEC</p>	<p>Ledende overlæge Claus Zachariae Herlev og Gentofte Hospital Afdeling for Allergi, hud og kønssygdomme Gentofte Hospital Gentofte Hospitalsvej 15, st 2900 Hellerup Denmark</p>
<p>Chair: CEC</p>	<p>Professor Jacob Thyssen Sanos Clinic Herlev Hovedgade 82 2730 Herlev Denmark</p>
<p>Chair: CEC</p>	<p>Afdelingslæge Kristina Ibler Dermatologisk afdeling Roskilde Sygehus Sygehusvej 10, indgang 5 4000 Roskilde Denmark</p>
Germany	
<p>Chair: PD Dr. med. H. Theilen Ethikkommission an der TU Dresden Postanschrift: Fetscherstraße 74 1307 Dresden</p>	<p>Prof. Dr. med. Andrea Bauer (200-0033) Universitätsklinikum Carl Gustav Carus Dresden Klinik und Poliklinik für Dermatologie, Fetscherstr. 74 1109 Dresden</p>
<p>Chair: Prof. Dr. rer. nat. Hans-Joachim Trampisch Ethik-Kommission der Medizinischen Fakultät der Ruhr-Universität Bochum Gesundheitscampus 33 44801 Bochum</p>	<p>PD Dr. med. Heinrich Dickel (201-0041) Ruhr-Universität Bochum Klinik für Dermatologie, Venerologie und Allergologie St. Josef-Hospital Gudrunstr. 56 44791 Bochum</p>
<p>Chair: Prof. Dr. med. Petra Thürmann Ethik-Kommission der Universität Witten/Herdecke, Alfred-Herrhausen-Str. 50 58448 Witten</p>	<p>Prof. Dr. med. Thomas Dirschka (202-0036) CentroDerm Study Center, Heinz-Fangman-Str. 57 42287 Wuppertal</p>
<p>Chair: Prof. Dr. med. Gerlinde Egerer</p>	<p>Dr. med. Nicolas Leitz (203-0995)</p>

Table S1. Independent ethics committee (IEC)/institutional review board (IRB) committee and study investigators for the phase 2b trial

IEC/IRB Committee Chair, Name of Committee, and Reference Number	Investigator Site
Ethik-Kommission bei der Landesärztekammer Baden-Württemberg Liebknechtstr. 33, 70565 Stuttgart	Hautarztpraxis Dres. Leitz und Kollegen, Marienstraße 1 70178 Stuttgart
Chair: Prof. Dr. Wolfgang Eisenmenger/ Prof. Dr. Rudolf M. Huber / Prof. Dr. Clemens Wendtner Ethik-kommission bei der Medizinischen Fakultät der LMU München Pettenkoferstr. 8a D-80336 München	Prof. Dr. med. Franziska Rueff (204-0441) Klinik und Poliklinik für Dermatologie und Allergologie Klinikum der Universität München, Frauenlobstrasse 9-11 D-80337 München
Chair: Prof. Dr. med. Ulrich Brandl Ethik-Kommission der Friedrich-Schiller-Universität Jena Bachstraße 18 07740 Jena	PD Dr. med. Sibylle Schliemann (205-0677) University Hospital Jena Department of Dermatology
Chair: Prof. Dr. med. Gerlinde Egerer Ethik-Kommission bei der Landesärztekammer Baden-Württemberg Liebknechtstr. 33, 70565 Stuttgart	Dr. med. Beate Schwarz (206-1216) Studienzentrum Dr.Beate Schwarz, Bismarckstr. 49 89129 Langenau
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Chair: Prof. Dr. med. Gerhard Hintze (Ethik-Kommission 1), Prof. Dr. med. Diether Ludwig (EthikKommission 2)	Dr. med. Harald Brüning (212-1238) MVZ DermaKiel GmbH, Schönberger Str. 72-74 24148 Kiel

Table S1. Independent ethics committee (IEC)/institutional review board (IRB) committee and study investigators for the phase 2b trial

IEC/IRB Committee Chair, Name of Committee, and Reference Number	Investigator Site
Ethikkommissionen bei der Ärztekammer Schleswig-Holstein Bismarckallee 8-12 23795 Bad Segeberg	
Chair: Prof. Dr. med. Gerlinde Egerer Ethik-Kommission bei der Landesärztekammer Baden-Württemberg Liebnechtstr. 33, 70565 Stuttgart	Prof. Dr. med. Christian Termeer (213-0220) Hautarztpraxis am Löwenmarkt, Prof. Dr. med. Christian Termeer, Rennstraße 2 70499 Stuttgart-Weilimdorf
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	Vivian Shi Banner-University Medical Center Tucson Campus
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Chair: Schuff Kathryn MD, MCR Oregon Health & Science University IRB 3181 S.W. Sam Jackson Park Road Mail Code L106RI Portland, OR 97239-3098	John Hanifin Oregon Health & Science University

Table S2. Summary of concepts reported across sources used for item development

Domain/Concept	Reported in literature/blog review	Reported in concept elicitation interviews with patients/clinicians	Included in the 10-item HEIS instrument
Domain: Sleep			
Sleep quality	✓	✓	✓
Sleep duration	✓	✓	
Domain: Physical functioning			
Infection	✓	✓	
Restricted movement of hands	✓	✓	*
Touching objects		✓	✓
Holding/gripping objects		✓	✓
Physical deformation of the hands	✓		
Domain: Social			
Family relationships	✓	✓	
Lack of understanding	✓		
Relationship with friends		✓	
Sexual/intimate relationships		✓	
Domain: Activities of daily living			
Difficulty washing hair	✓	✓	*
Difficulty dressing	✓	✓	✓
Domestic chores	✓	✓	✓
Avoidance of soaps/chemicals		✓	✓
Domain: Emotional			
Embarrassment/self-consciousness	✓	✓	✓
Frustration/annoyance	✓	✓	
Dislike in appearance of the hands	✓	✓	✓
Sadness/depression	✓	✓	
Fear of public opinion	✓	✓	*
Low self-esteem	✓	✓	*
Inability to cope (coping)	✓		
Loneliness	✓		
Helplessness	✓		
Domain: Work			
Inability to complete work tasks	✓	✓	
Ending employment/chance in career	✓	✓	

Table S2. Summary of concepts reported across sources used for item development

Domain/Concept	Reported in literature/blog review	Reported in concept elicitation interviews with patients/clinicians	Included in the 10-item HEIS instrument
Stigma/lack of understanding in workplace	✓	✓	
Missed days of work	✓	✓	

✓=concept reported in source, ✓=concept included, *=concept indirectly assessed by other items
 HEIS=Hand Eczema Impact Scale

Table S3. Demographic and clinical characteristics of interview participants

Description		Number of interview participants (N=20)
Gender, n (%)	Female	14 (70.0%)
	Male	6 (30.0%)
Age	Mean (range)	46.6 (18-69)
Ethnicity, n (%)	Hispanic or Latino	3 (15.0%)
	Non-Hispanic or Latino	17 (85.0%)
Race, n (%)	White/Caucasian	13 (65.0%)
	Black/African American	5 (25.0%)
	Asian or Pacific Islander	1 (5.0%)
	Indian	1 (5.0%)
Work status, n (%)	Working full or part time	16 (80.0%)
	Retired	2 (10.0%)
	Full time homemaker	1 (5.0%)
	Unemployed	1 (5.0%)
Occupation, n (%)	Office/administration work	6 (30.0%)
	Unspecified	5 (25.0%)
	Physician	1 (5.0%)
	Waitress	1 (5.0%)
	Cleaner	1 (5.0%)
	Eye technician	1 (5.0%)
	Horse groomer	1 (5.0%)
	Nurse	1 (5.0%)
	Sales	1 (5.0%)
	Housekeeper	1 (5.0%)
	Chef	1 (5.0%)
Highest level of education, n (%)	Some high school	3 (15.0%)
	Completed high school	5 (25.0%)
	Some years of college	3 (15.0%)
	Undergraduate or bachelor's degree	8 (40.0%)
	Graduate degree	1 (5.0%)
Clinician reported hand eczema subtype, n (%)	Atopic hand eczema	9 (45.0%)
	Allergic contact dermatitis	6 (30.0%)
	Irritant contact dermatitis	5 (25.0%)
Physician Global Assessment of Disease Severity (PGA), n (%)	Mild	5 (25.0%)
	Moderate	9 (45.0%)
	Severe	6 (30.0%)
Patient Global Assessment of Disease Severity (PaGA), n (%)	Mild	5 (25.0%)
	Moderate	7 (35.0%)

Table S3. Demographic and clinical characteristics of interview participants

Description		Number of interview participants (N=20)
	Severe	7 (35.0%)
	Missing	1 (5.0%)
Time since diagnosis of hand eczema, n (%)		
	<1 year	1 (5.0%)
	1-4 years	3 (15.0%)
	5-10 years	9 (45.0%)
	11-15 years	2 (10.0%)
	>15 years	5 (25.0%)

Table S4. Polychoric correlations between HEIS items at Week 4 (N=242)

HEIS Items	1	2	3	4	5	6	7	8
Item 1: Quality of sleep	-							
Item 2: Ability to use products*	0.72	-						
Item 3: Felt embarrassed**	0.62	0.54	-					
Item 4: Dislike appearance**	0.69	0.58	0.88	-				
Item 5: Hard to do housework*	0.68	0.88	0.53	0.61	-			
Item 6: Hard to hold objects*	0.76	0.71	0.55	0.62	0.75	-		
Item 7: Hard to wash yourself*	0.73	0.79	0.51	0.55	0.81	0.77	-	
Item 8: Feel frustrated	0.71	0.62	0.85	0.85	0.63	0.64	0.62	-
Item 9: Hard to work	0.78	0.65	0.55	0.57	0.69	0.76	0.69	0.61

Note. * Items share the hypothesized HEIS PDAL domain. ** Items share the hypothesized Emb HEIS domain.

Correlations are colour coordinated in accordance with the following colour coding:

<0.40

0.40 ≤ x < 0.50
0.50 ≤ x < 0.60
0.60 ≤ x < 0.70
0.70 ≤ x < 0.80
≥0.80

Table S5. Factor loadings for the HEIS (Model A & Model B solutions) at Week 4 in the psychometric analysis population

HEIS Items	Model A – Unidimensional	Model B - Bifactor	
	Factor 1	General	PDAL
Item 1: Quality of sleep	0.837	0.888	
Item 2: Ability to use products	0.880	0.719	0.567
Item 3: Felt embarrassed	0.874	0.811	
Item 4: Dislike appearance	0.889	0.842	
Item 5: Hard to do housework	0.896	0.722	0.620
Item 6: Hard to hold objects	0.835	0.800	0.296
Item 7: Hard to wash yourself	0.839	0.744	0.451
Item 8: Feel frustrated	0.886	0.949	
Item 9: Hard to work	0.796	0.849	

HEIS=Hand Eczema Impact Scale

Table S6. Internal consistency reliability: Cronbach's alpha for the HEIS scores and alpha with each item deleted at Week 4

HEIS Items	HEIS score (N=240)	HEIS PDAL score (N=240)	HEIS Emb score (N=240)
Cronbach's alpha (total)	0.93	0.90	0.89
Alpha coefficient with each item deleted:			
Item 1: Quality of sleep	0.92		
Item 2: Ability to use products	0.92	0.82	
Item 3: Felt embarrassed	0.93		-
Item 4: Dislike appearance	0.93		-
Item 5: Hard to do housework	0.92	0.82	
Item 6: Hard to hold objects	0.93		
Item 7: Hard to wash yourself	0.93	0.90	
Item 8: Feel frustrated	0.92		
Item 9: Hard to work	0.93		

Emb=Embarrassment with appearance of the hands; HEIS=Hand Eczema Impact Scale; PDAL=Proximal Daily Activity Limitations

Table S7. Test-retest reliability analysis of the HEIS single item scores

Anchor	Timepoint	n	Cohen's Kappa (95% CI)
HEIS Item 1: Quality of sleep			
PaGA	Week 12-16	116	0.78 (0.70, 0.86)
	Week 14-16	129	0.83 (0.75, 0.91)
IGA-CHE	Week 12-16	111	0.65 (0.53, 0.78)
	Week 14-16	132	0.81 (0.73, 0.90)
HEIS Item 8: Feel frustrated			
PaGA	Week 12-16	116	0.84 (0.78, 0.89)
	Week 14-16	129	0.86 (0.80, 0.92)
IGA-CHE	Week 12-16	111	0.78 (0.71, 0.86)
	Week 14-16	132	0.82 (0.75, 0.89)
QOLHEQ (emotions domain)	Week 12-16	149	0.85 (0.80, 0.90)
HEIS Item 9: Hard to work			
PaGA	Week 12-16	116	0.79 (0.71, 0.88)
	Week 14-16	129	0.90 (0.85, 0.95)
IGA-CHE	Week 12-16	111	0.71 (0.59, 0.84)
	Week 14-16	132	0.79 (0.68, 0.89)
QOLHEQ (limitations in functioning domain)	Week 12-16	163	0.82 (0.74, 0.90)

CI=Confidence Interval; IGA-CHE=Investigator Global Assessment of Chronic Hand Eczema; PaGA=Patient Global Assessment; QOLHEQ=Quality of Life in Hand Eczema Questionnaire

Table S8. Known-groups validity analysis of the HEIS PDAL score at Week 6 or Week 8

Grouping Variable	n	Mean HEIS score (SD)	Between groups effect size	Linear trends p-value	Pairwise tests p-value
Week 6: QOLHEQ total score					
< median score	103	0.61 (0.71)		N/A	
≥ median score	111	1.76 (1.06)	-1.27		<0.0001
Week 6: QOLHEQ (Item 6: Itch)					
< median score	68	0.73 (0.89)		N/A	
≥ median score	146	1.42 (1.09)	-0.67		<0.0001
Week 8: PaGA					
0-1 (clear or almost clear)	44	0.41 (0.52)		<0.0001	
2 (mild)	100	0.99 (0.84)	-0.77		<0.0001
3-4 (moderate or severe)	74	1.99 (1.16)	-1.62		<0.0001
Week 8: IGA-CHE					
0-1 (clear or almost clear)	49	0.65 (0.82)		<0.0001	
2 (mild)	99	1.12 (0.87)	-0.55		<0.0001
3-4 (moderate or severe)	70	1.73 (1.29)	-0.96		<0.0001
Week 8: DLQI total score					
< median score	96	0.51 (0.62)		N/A	
≥ median score	121	1.77 (1.06)	-1.41		<0.0001
Week 8: DLQI (Item 1: Itchy, painful, stinging)					
< median score	25	0.47 (0.59)		N/A	

Table S8. Known-groups validity analysis of the HEIS PDAL score at Week 6 or Week 8

Grouping Variable	n	Mean HEIS score (SD)	Between groups effect size	Linear trends p-value	Pairwise tests p-value
≥ median score	192	1.31 (1.10)	-0.80		<0.0001

DLQI=Dermatology Life Quality Index; HEIS=Hand Eczema Impact Scale; IGA-CHE=Investigator Global Assessment of Chronic Hand Eczema; PaGA=Patient Global Assessment; PDAL=Proximal Daily Activity Limitations; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation

Table S9. Known-groups validity analysis of the HEIS Emb score at Week 6 or Week 8

Grouping Variable	n	Mean HEIS score (SD)	Between groups effect size	Linear trends p-value	Pairwise tests p-value
Week 6: QOLHEQ total score					
< median score	103	0.64 (0.74)		N/A	
≥ median score	111	1.85 (1.206)	-1.19		<0.0001
Week 6: QOLHEQ (Item 6: Itch)					
< median score	68	0.67 (0.89)		N/A	
≥ median score	146	1.54 (1.19)	-0.79		<0.0001
Week 8: PaGA					
0-1 (clear or almost clear)	44	0.28 (0.38)		<0.0001	
2 (mild)	100	0.93 (0.80)	-0.93		<0.0001
3-4 (moderate or severe)	74	2.33 (1.11)	-2.24		<0.0001
Week 8: IGA-CHE					
0-1 (clear or almost clear)	49	0.50 (0.70)		<0.0001	
2 (mild)	99	1.16 (1.03)	-0.70		<0.0001
3-4 (moderate or severe)	70	1.99 (1.22)	-1.43		<0.0001
Week 8: DLQI total score					
< median score	96	0.46 (0.54)		N/A	
≥ median score	121	1.92 (1.14)	-1.59		<0.0001
Week 8: DLQI (Item 1: Itchy, painful, stinging)					
< median score	25	0.18 (0.32)		N/A	
≥ median score	192	1.42 (1.17)	-1.12		<0.0001

DLQI=Dermatology Life Quality Index; Emb=Embarrassment with appearance of the hands; HEIS=Hand Eczema Impact Scale; IGA-CHE=Investigator Global Assessment of Chronic Hand Eczema; PaGA=Patient Global Assessment; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation

Table S10. Ability of the HEIS PDAL score to detect change between Baseline and Week 16

Grouping Variable	n	Mean change score (SD)	Median change score (Min-Max)	Within groups effect size	Between groups effect size	Between groups p-value
PaGA						
≥1 point improvement	134	-1.42 (0.97)	-1.33 (-3.7 - 0.7)	-1.44		
Change score=0	57	-0.22 (0.92)	-0.33 (-1.7 - 2.0)	-0.18	-1.12	
≥1 point worsening	13	0.38 (0.78)	0.33 (-0.7 - 2.3)	0.39	-0.50	<.001
PGI-C						
'A little better' + 'Much better'	100	-1.35 (1.03)	-1.33 (-3.3 - 2.3)	-1.36		
'No change'	20	0.12 (0.81)	0.00 (-1.7 - 2.0)	0.09	-1.40	
'A little worse' + 'Much worse'	6	0.39 (1.06)	0.17 (-0.7 - 1.7)	0.32	-0.21	<.001
QOLHEQ (Limitations in functioning domain)						
≥0.5 SD improvement	116	-1.55 (0.91)	-1.67 (-3.7 - 0.7)	-1.66		
<0.5 SD change	75	-0.34 (0.79)	-0.33 (-2.3 - 1.7)	-0.29	-1.17	
≥0.5 SD worsening	13	0.56 (1.40)	0.33 (-2.7 - 2.3)	0.67	-0.80	<.001

HEIS=Hand Eczema Impact Scale; PaGA=Patient Global Assessment; PDAL=Proximal Daily Activity Limitations; PGI-C=Patient Global Impression of Change; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation

Table S11. Ability of the HEIS Emb score to detect change between Baseline and Week 16

Grouping Variable	n	Mean change score (SD)	Median change score (Min-Max)	Within groups effect size	Between groups effect size	Between groups p-value
PaGA						
≥1 point improvement	134	-1.76 (1.12)	-2.00 (-4.0 - 2.0)	-1.65		
Change score=0	57	-0.46 (0.83)	-0.50 (-2.0 - 1.0)	-0.41	-1.19	
≥1 point worsening	13	0.35 (1.01)	0.50 (-1.5 - 2.0)	0.34	-0.73	<.001
PGI-C						
'A little better' + 'Much better'	100	-1.72 (1.12)	-2.00 (-4.0 - 2.0)	-1.61		
'No change'	20	-0.18 (1.00)	0.00 (-2.0 - 1.5)	-0.16	-1.44	
'A little worse' + 'Much worse'	6	-0.25 (0.76)	-0.25 (-1.0 - 1.0)	-0.25	0.07	<.001
DLQI (Item 2: Embarrassment)						
≥1 grade improvement	114	-2.00 (1.04)	-2.00 (-4.0 - 2.0)	-2.32		
Change score=0	73	-0.51 (0.72)	-0.50 (-2.0 - 1.0)	-0.43	-1.50	
≥1 grade worsening	17	0.35 (0.92)	0.50 (-1.5 - 2.0)	0.33	-0.75	<.001
QOLHEQ (emotions domain)						
≥0.5 SD improvement	116	-1.86 (1.11)	-2.00 (-4.0 - 1.0)	-1.79		
<0.5 SD change	74	-0.62 (0.95)	-0.50 (-3.5 - 2.0)	-0.53	-1.13	
≥0.5 SD worsening	14	0.21 (0.98)	0.50 (-2.5 - 1.5)	0.18	-0.71	<.001

DLQI=Dermatology Life Quality Index; Emb=Embarrassment with appearance of the hands; HEIS=Hand Eczema Impact Scale; PaGA=Patient Global Assessment; PGI-C=Patient Global Impression of Change; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation

Supplementary Figures

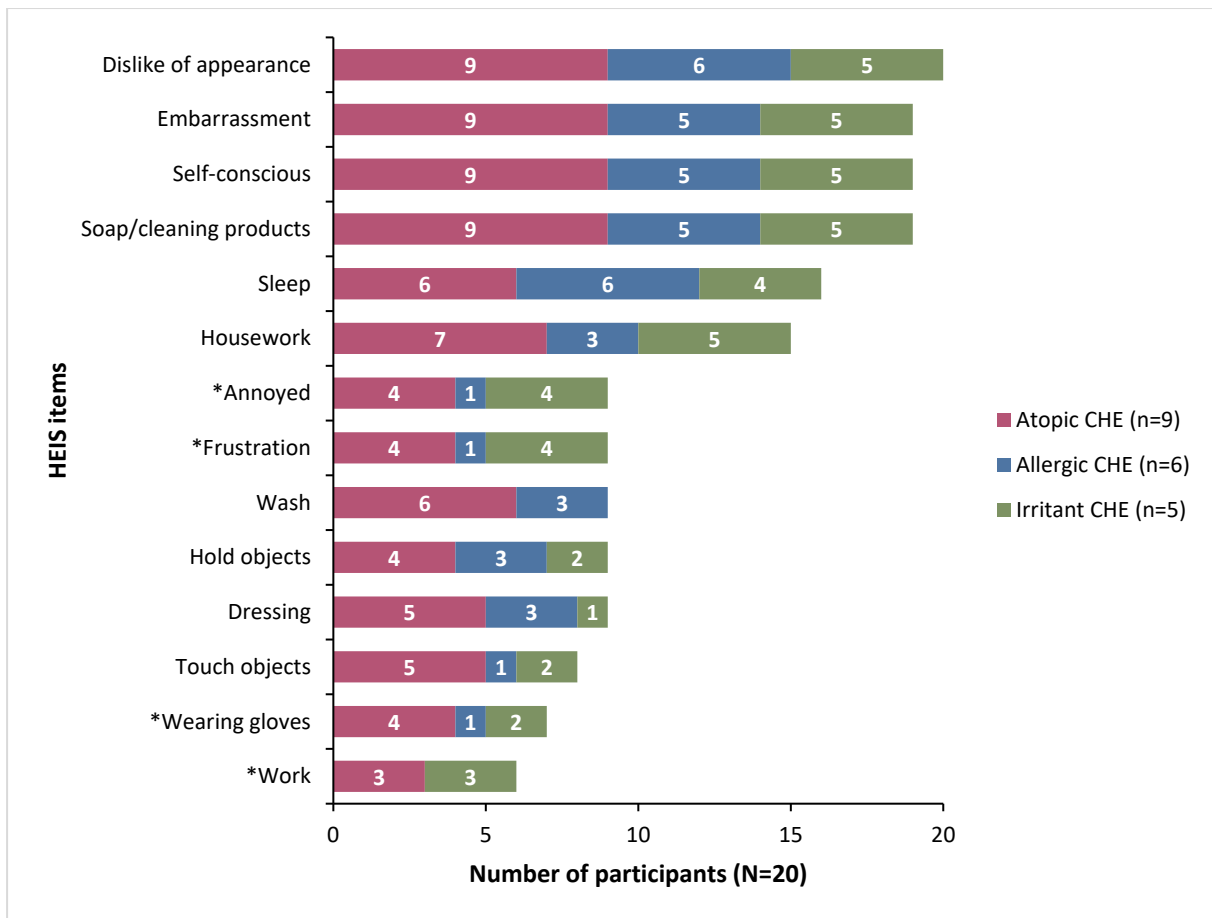


Figure S1. Overall relevance of HEIS items by CHE subtype

* Items only debriefed in round 2 interviews (n=10)

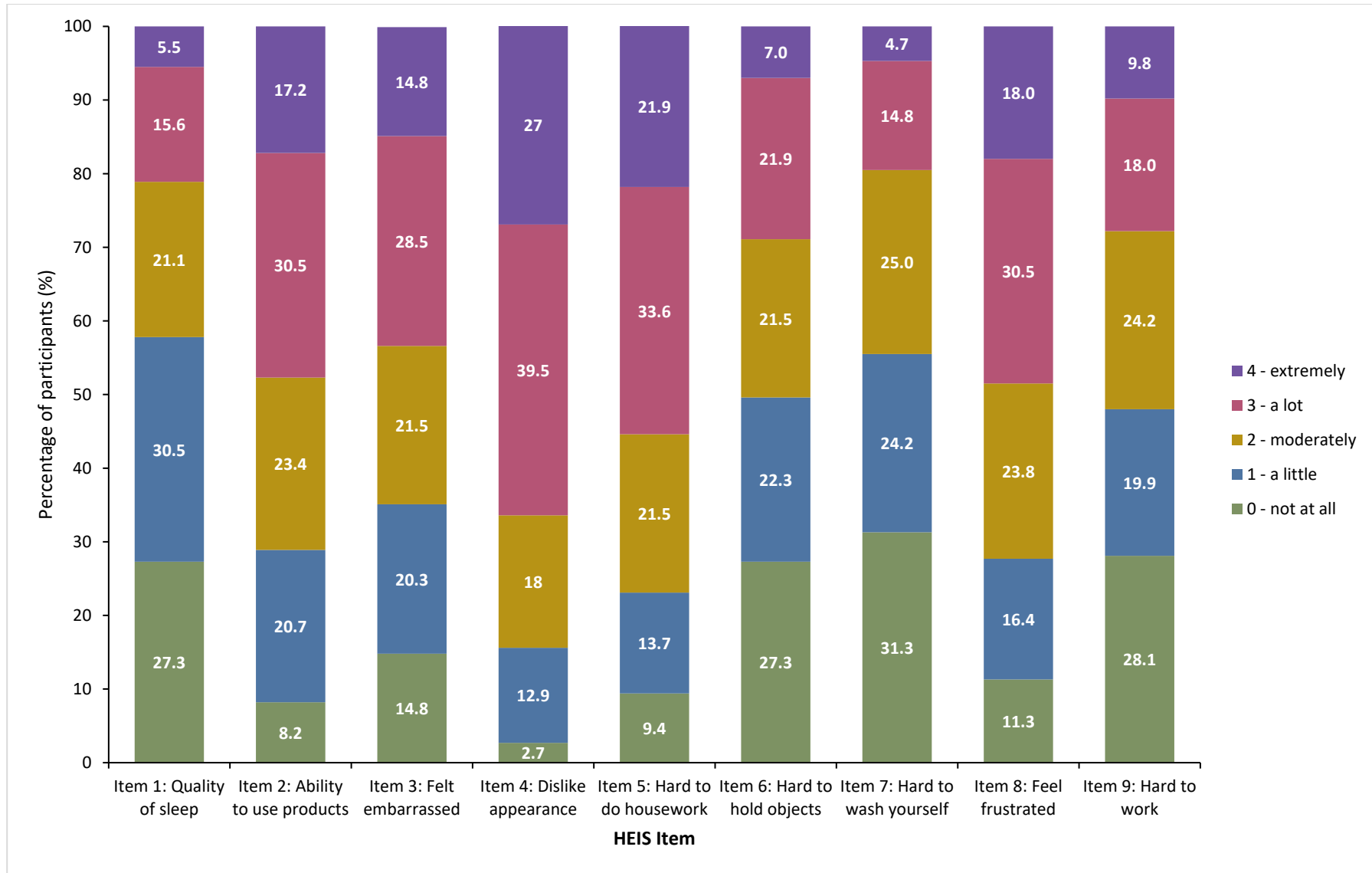


Figure S2. Item response distributions for HEIS at Baseline

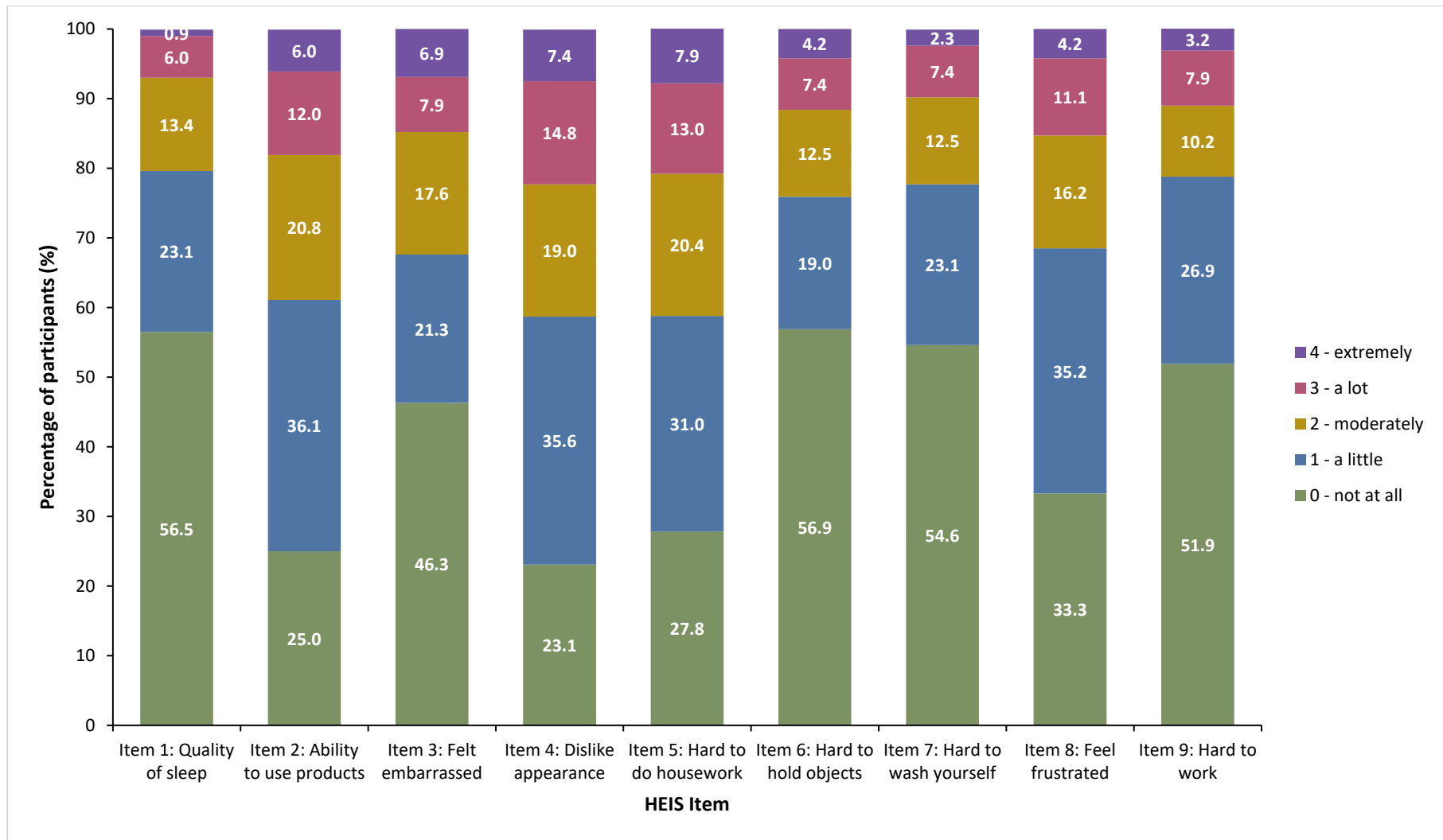


Figure S3. Item response distributions for HEIS at Week 8

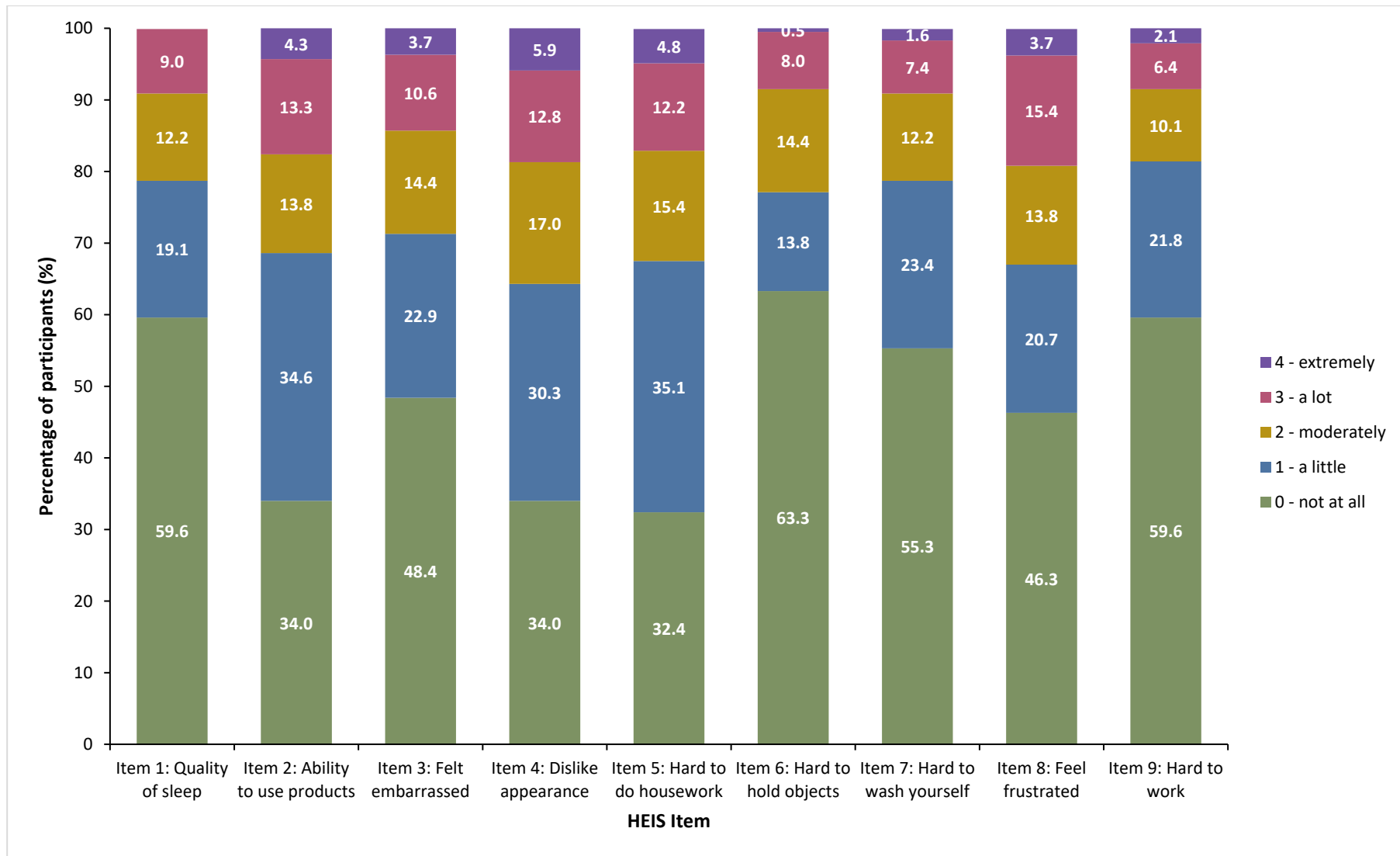
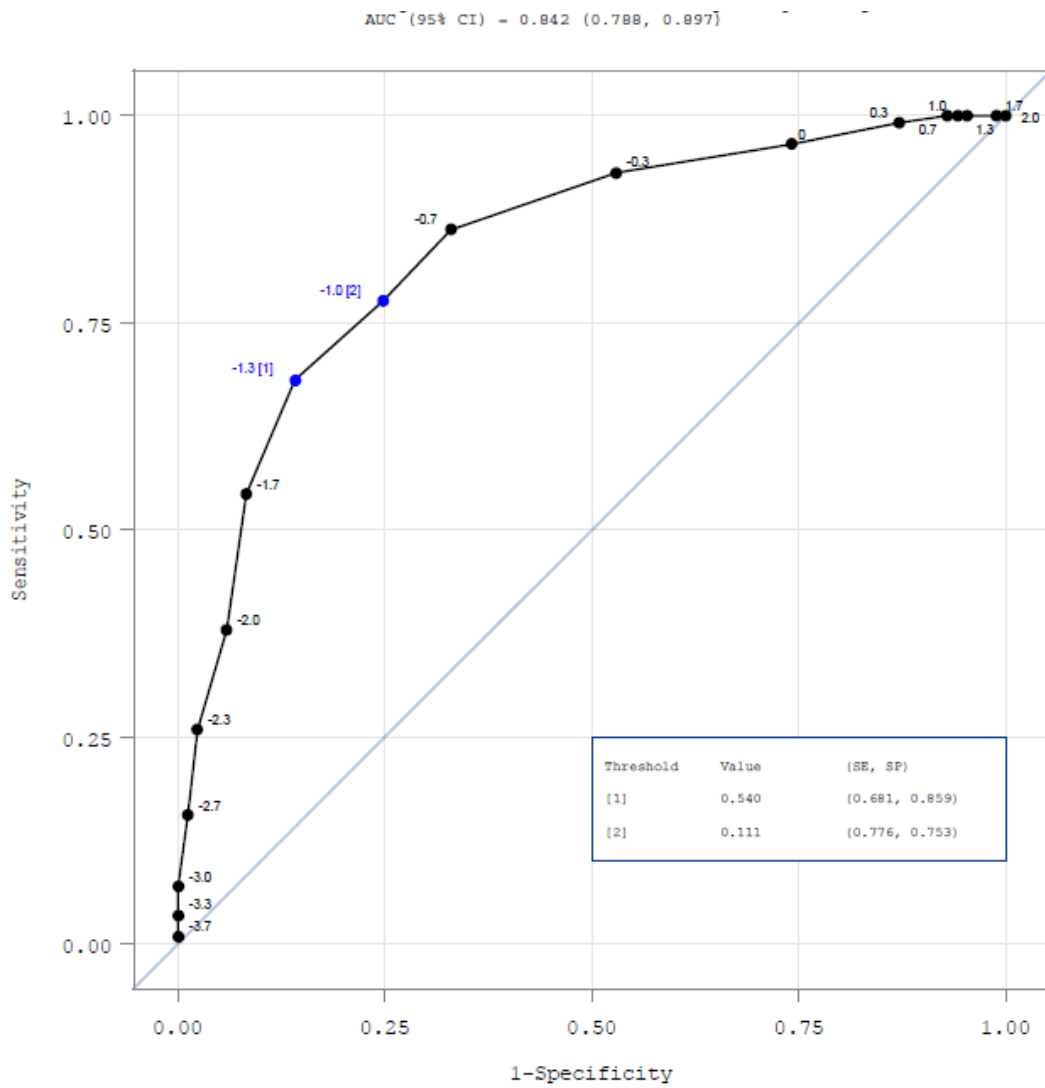
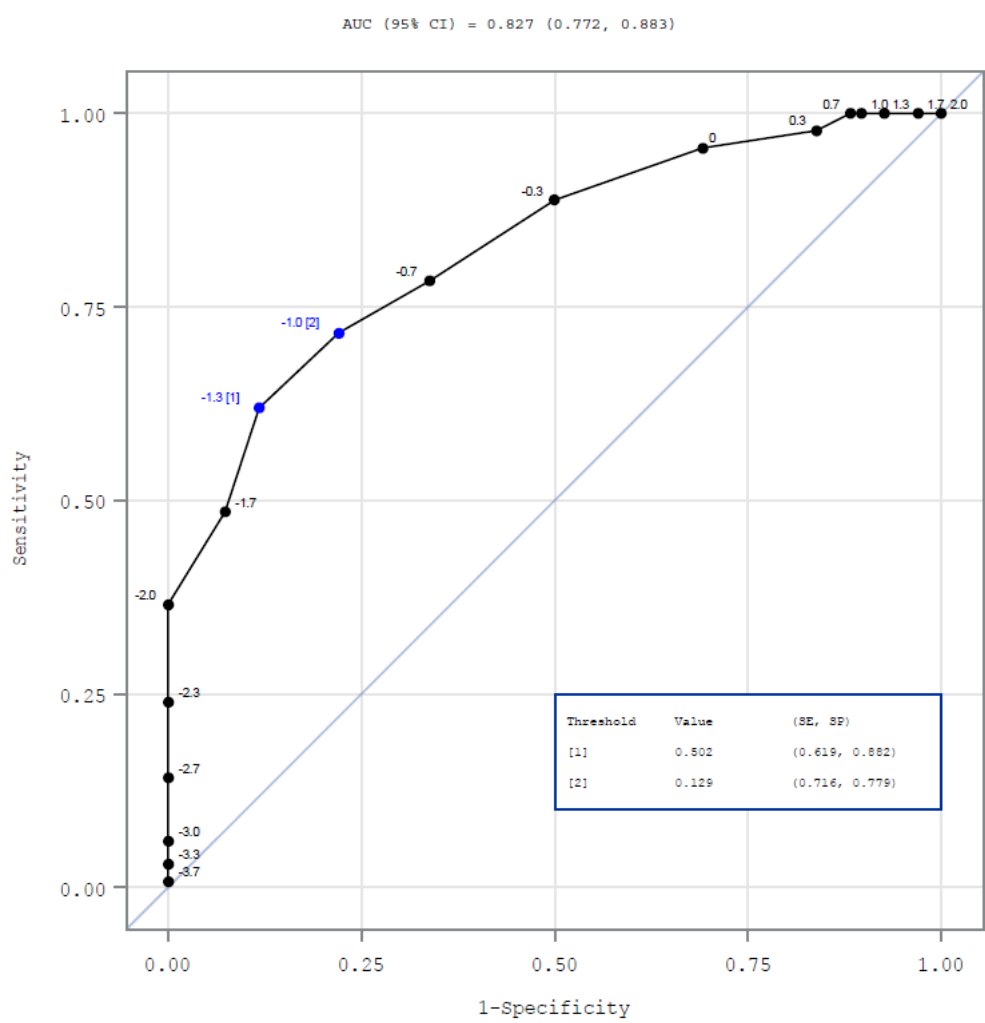


Figure S4. Item response distributions for HEIS at Week 16



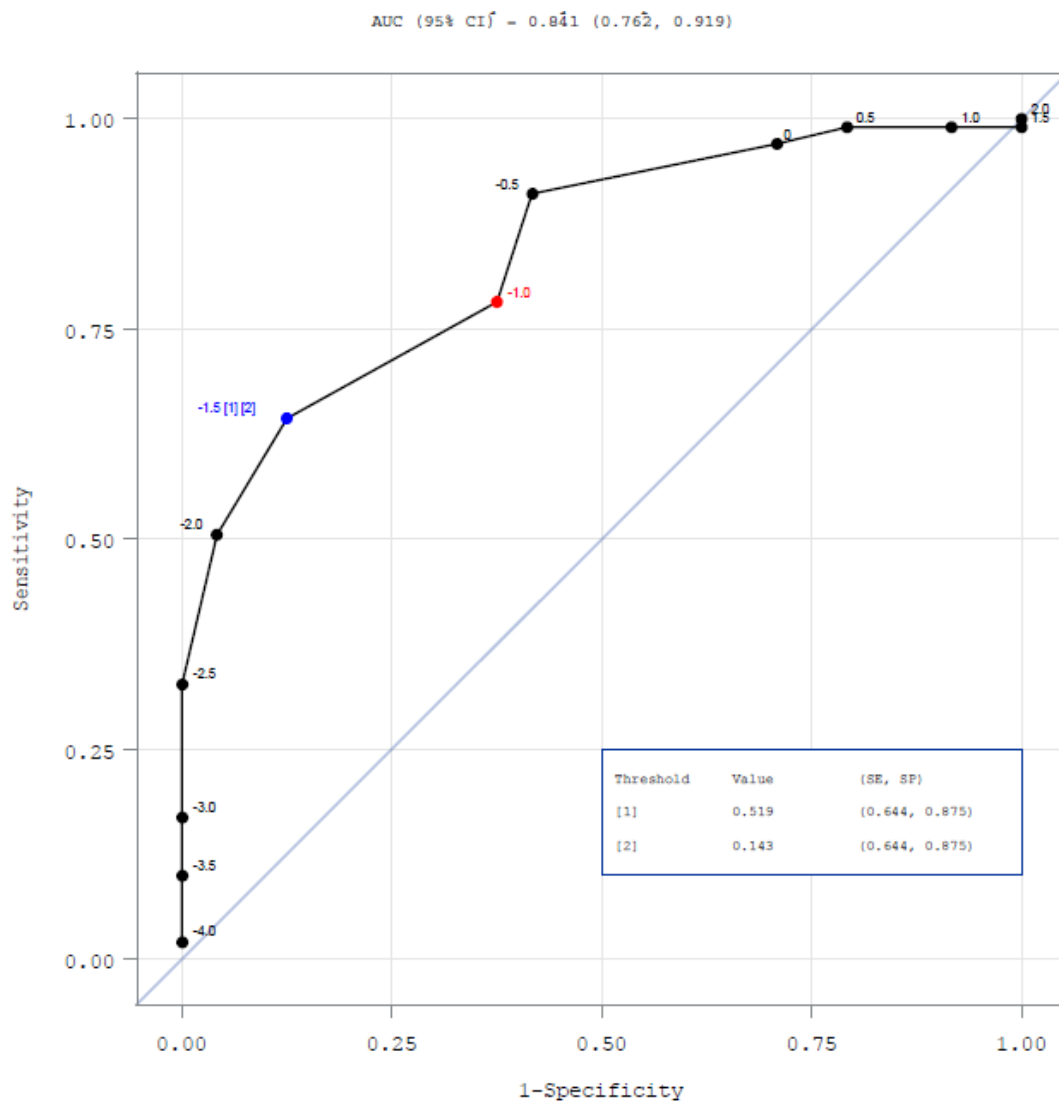
AUC=Area Under the Curve; CI=Confidence Interval; SE=Sensitivity; SP=Specificity

Figure S5. ROC analyses of change from Baseline in HEIS PDAL score predicting QOLHEQ (limitations in functioning domain) Baseline to Week 16 responder status



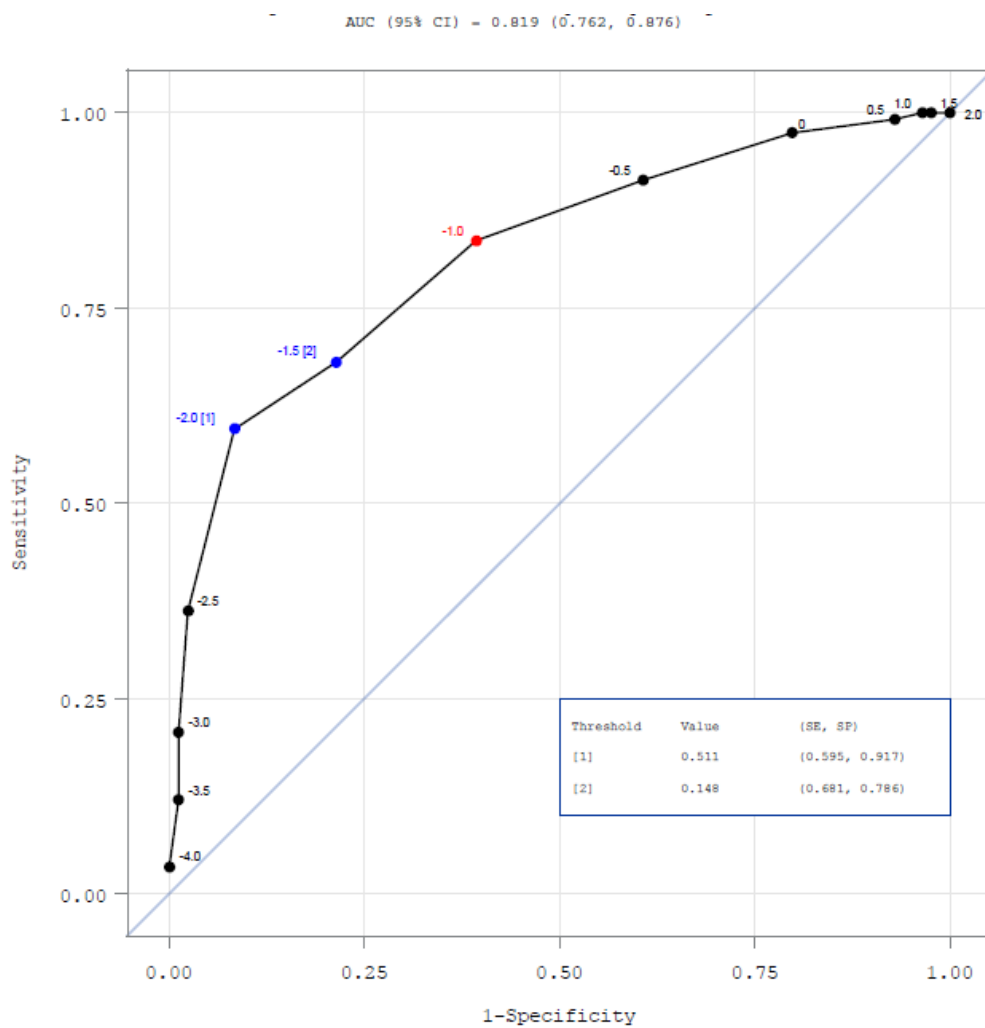
AUC=Area Under the Curve; CI=Confidence Interval; SE=Sensitivity; SP=Specificity

Figure S6. ROC analyses of change from Baseline in HEIS PDAL score predicting PaGA Baseline to Week 16 responder status



AUC=Area Under the Curve; CI=Confidence Interval; SE=Sensitivity; SP=Specificity

Figure S7. ROC analyses of change from Baseline in HEIS Emb score predicting PGI-C Baseline to Week 16 responder status



AUC=Area Under the Curve; CI=Confidence Interval; SE=Sensitivity; SP=Specificity

Figure S8. ROC analyses of change from Baseline in HEIS Emb score predicting QOLHEQ (emotions domain) Baseline to Week 16 responder status

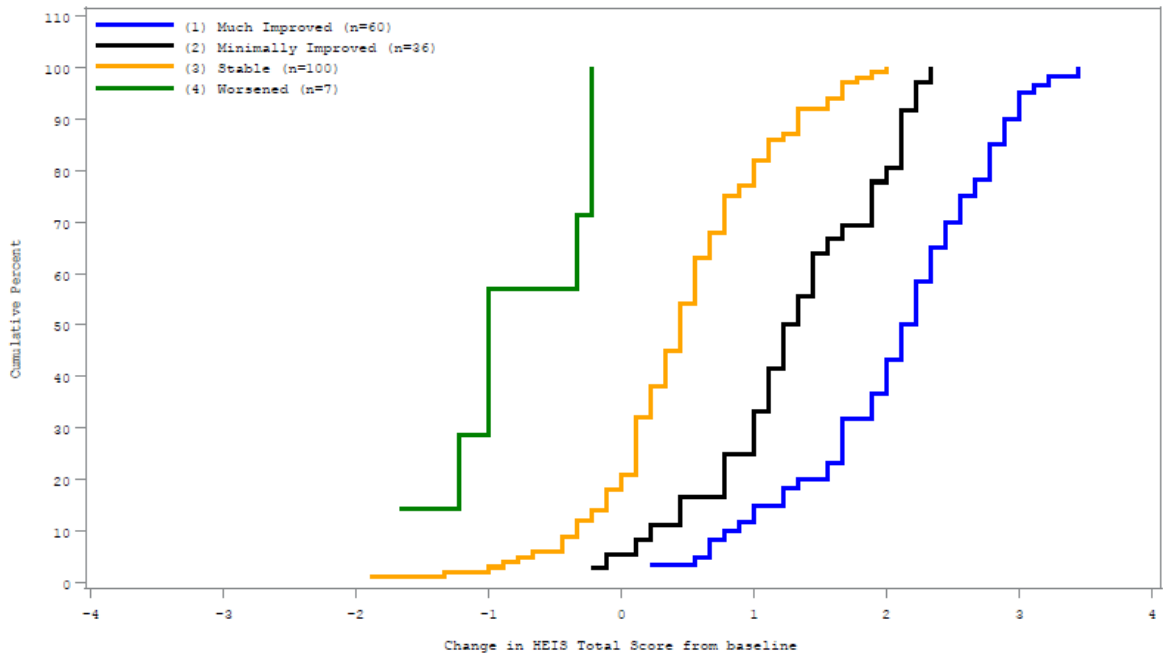


Figure S9. Empirical cumulative frequency distribution function for change in HEIS score by DLQI (total score) from Baseline to Week 16

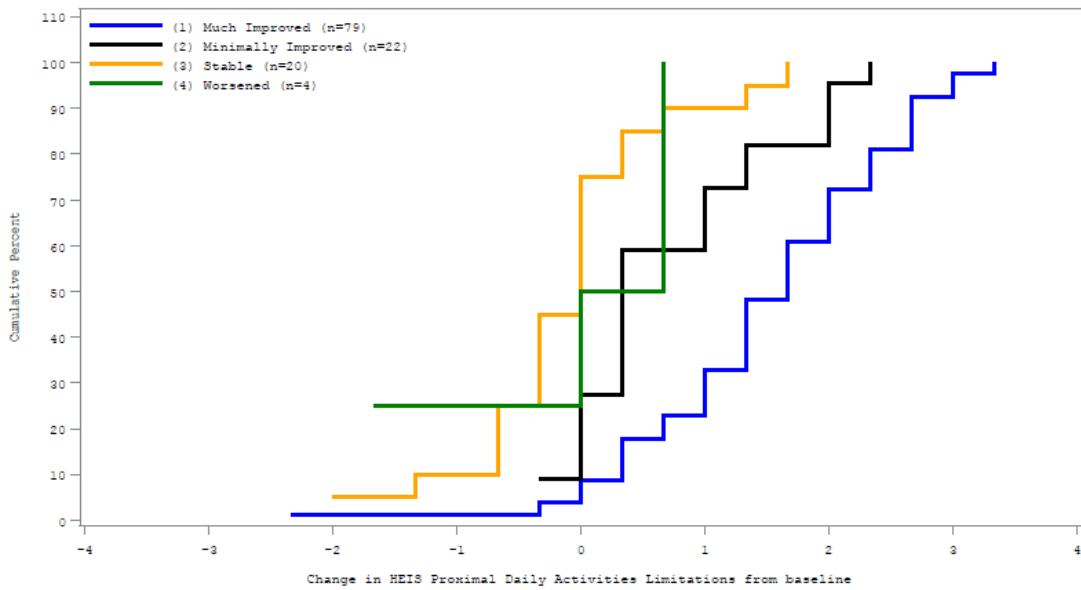


Figure S10. Empirical cumulative frequency distribution function for change in HEIS PDAL score by PGI-C from Baseline to Week 16

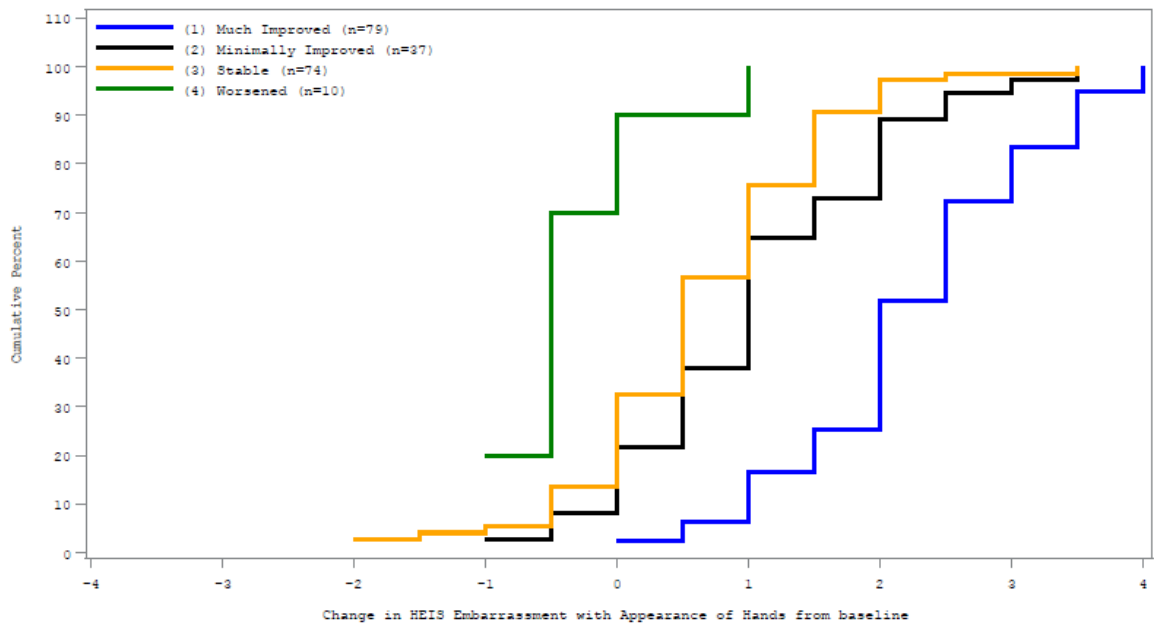
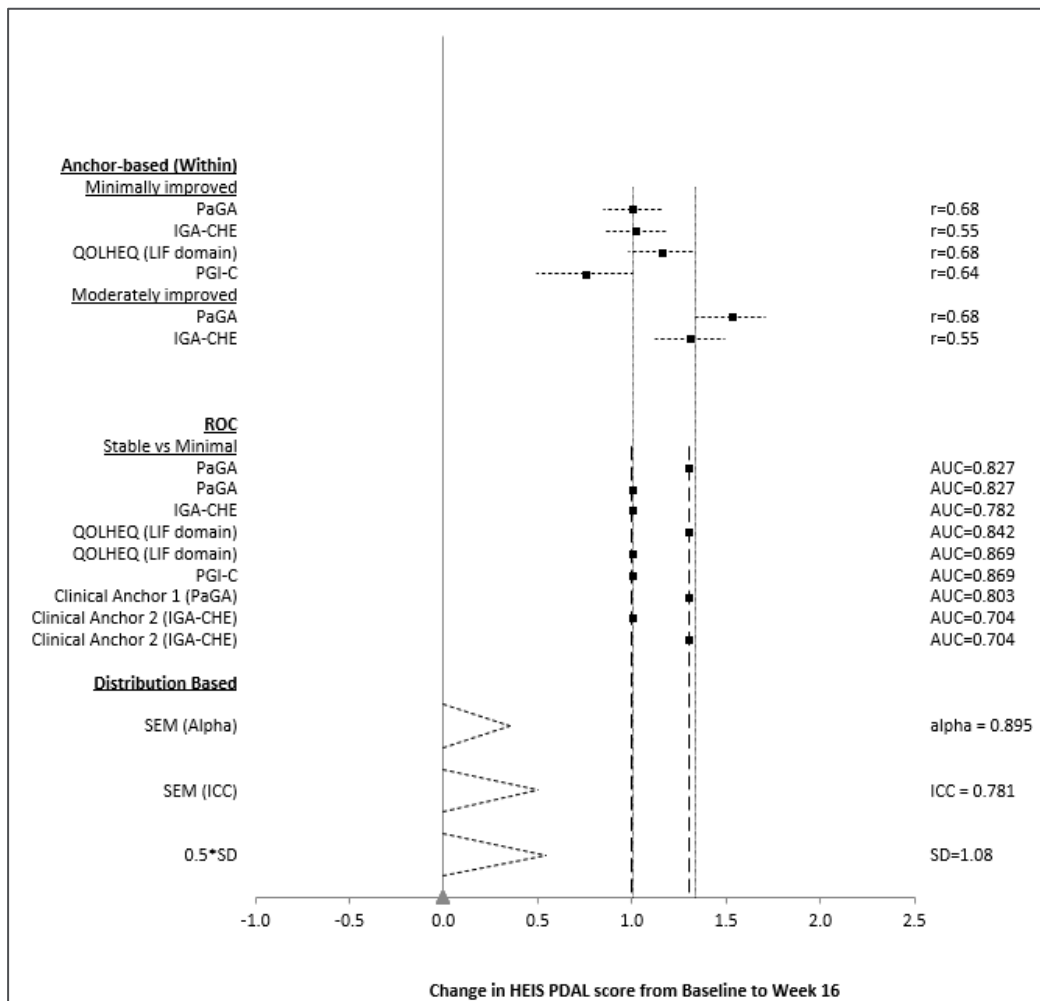
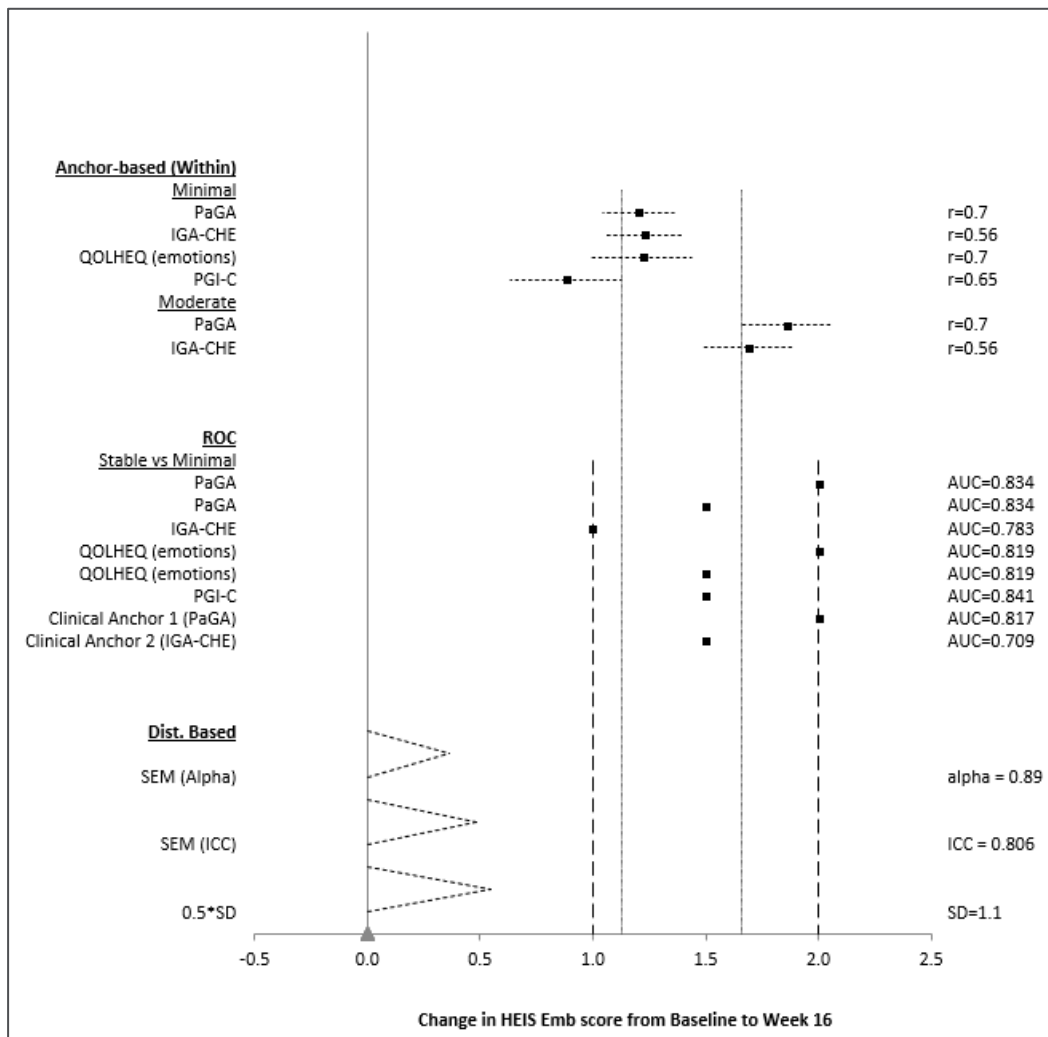


Figure S11. Empirical cumulative frequency distribution function for change in HEIS Emb score by QOLHEQ (emotions domain) from Baseline to Week 16



ICC=Intraclass Correlation Coefficients; IGA-CHE=Investigator Global Assessment of Chronic Hand Eczema; LIF=Limitations in Functioning; PaGA=Patient Global Assessment of Disease Severity; PGI-C=Patient Global Impression of Change; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation; SEM=Standard Error of Measurement

Figure S12. Forest plot showing estimated responder definitions for the HEIS PDAL score



ICC=Intraclass Correlation Coefficients; IGA-CHE=Investigator Global Assessment of Chronic Hand Eczema; PaGA=Patient Global Assessment of Disease Severity; PGI-C=Patient Global Impression of Change; QOLHEQ=Quality of Life in Hand Eczema Questionnaire; SD=Standard Deviation; SEM=Standard Error of Measurement

Figure S13. Forest plot showing estimated responder definitions for the HEIS Emb score