Lung Diseases (i.e. restrictive, obstructive, pulmonary hypertension)

Name of Instrument	Short Description	Scoring	Comments/Special Instructions	Copyright Information	Reference(s)	Classification
Six-Minute Walk Test (6MWT) With Borg dyspnea scale	Distance walked in 6 minutes walking as quickly as possible	Use change in absolute 6MW distance Compare to healthy normative values based on age and gender	Review absolute contraindications before beginning: unstable angina or myocardial infarction during the previous month. Relative contraindications: resting heart rate > 120, systolic blood pressure > 180 mm Hg, and a diastolic blood pressure > 100 mm Hg		ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test [published correction appears in Am J Respir Crit Care Med. 2016 May 15;193(10):1185]. *Am J Respir Crit Care Med*. 2002;166(1):111-117. **Normative values in age 20-50 years:** Chetta A, Zanini A, Pisi G, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. *Respir Med*. 2006;100(9):1573-1578. **Normative values in age ≥ 60:** *Steffen et al. Age- and Gender-Related Test Performance in Community-Dwelling Elderly People: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and Gait Speeds. Physical Therapy. 2002* See sickle cell references[i]	**Core**
Heart Rate Recovery (HRR)	Recovery of heart rate 1 minute and 2 minutes after completion of 6MWT	For HHR1, subtract HR at 1 minute after completion of 6MWT from HR immediately after completion of 6MWT. For HRR2. subtract HR 2 minute after 6MWT from			Alvarado AM, Ward KM, Muntz DS, Thompson AA, Rodeghier M, Fernhall B, Liem RI: Heart rate recovery is impaired after maximal exercise testing in children with sickle cell anemia. *J Pediatr.* 2015, 166(2):389-393.e381.	Exploratory

Name of Instrument	Short Description	Scoring	Comments/Special Instructions	Copyright Information	Reference(s)	Classification
		HR immediately after of 6MWT.			Qiu S, Cai X, Sun Z, Li L, Zuegel M, Steinacker JM, Schumann U: Heart Rate Recovery and Risk of Cardiovascular Events and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc.* 2017, 6(5):e005505.	
Pulmonary Function Test (*See PFT Module)* CSSD CRFs						Core
American Thoracic Society Division of Lung Disease questionnaire (ATS-DLD) (forms from SAC study)	Used in asthma and COPD					Supplemental
Medical Outcomes Study SF-36	8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or	See link to SF-36 Manual: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html		Rand		Supplemental

Name of Instrument	Short Description	Scoring	Comments/Special Instructions	Copyright Information	Reference(s)	Classification
	emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.					
PROMIS Item Bank v1.0 Dyspnea Functional Limitations	Assesses the impact of dyspnea on ability to function while performing specific daily activities rated in terms of degree of difficulty while engaging in the activity over the past 7 days	Recommend to use response pattern scoring in HealthMeasures Scoring Service	If using short forms, to use the scoring tables, respondents must indicate that they have done (answered) all 10 items	© 2010-2016PROMIS Health Organization and PROMIS Cooperative Group	Yount SE, Choi SW, Victorson D, et al. Brief, valid measures of dyspnea and related functional limitations in chronic obstructive pulmonary disease (COPD). *Value Health*. 2011;14(2):307-315. doi:10.1016/j.jval.2010.11.009 Yount SE, Atwood C, Donohue J, et al. Responsiveness of PROMIS® to change in chronic obstructive pulmonary disease. *J Patient Rep Outcomes*. 2019;3(1):65. Published 2019 Oct 29. doi:10.1186/s41687-019-0155-9	Supplemental
PROMIS Item Bank v1.0 – Dyspnea Severity	Assesses the severity of dyspnea experienced in response to various	Recommend to use response pattern scoring in HealthMeasures Scoring Service	If using short forms, to use the scoring tables, respondents must indicate that they have done	© 2010-2016PROMIS Health Organization and PROMIS	Yount SE, Choi SW, Victorson D, et al. Brief, valid measures of dyspnea and related functional limitations in chronic obstructive pulmonary disease (COPD). *Value Health*. 2011;14(2):307-315. doi:10.1016/j.jval.2010.11.009	Supplemental

Name of Instrument	Short Description	Scoring	Comments/Special Instructions	Copyright Information	Reference(s)	Classification
	Specific activities over the past 7 days		(answered) all 10 items	Cooperative Group	Yount SE, Atwood C, Donohue J, et al. Responsiveness of PROMIS® to change in chronic obstructive pulmonary disease. *J Patient Rep Outcomes*. 2019;3(1):65. Published 2019 Oct 29. doi:10.1186/s41687-019-0155-9	
Echocardiogram (*See Echo Module)*	Assess Peak Tricuspid Regurgitant Velocity (TRV) (m/s) and Peak Right Ventricular Systolic Pressure (mmHg) to screen for pulmonary hypertension	TRV ≥ 2.5 m/s associated with an increased risk of mortality	Phenx Instructions		Sachdev V, Kato GJ, Gibbs JS, et al. Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. *Circulation*. 2011;124(13):1452-1460. doi:10.1161/CIRCULATIONAHA.111.032920 Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. *Am J Respir Crit Care Med*. 2012;185(11):1154-1165. doi:10.1164/rccm.201111-2082CI	Core
CT Chest (London group)	CT of chest to be used only if indicated	Assess for abnormal findings				Supplemental
Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP)	Serum biomarker used in screening for pulmonary hypertension	NT-proBNP ≥ 160 pg/ml is abnormal			Machado RF, Anthi A, Steinberg MH, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *JAMA*. 2006;296(3):310-318. doi:10.1001/jama.296.3.310	Supplemental-Highly Recommended

Name of Instrument	Short Description	Scoring	Comments/Special Instructions	Copyright Information	Reference(s)	Classification
					Sachdev V, Kato GJ, Gibbs JS, et al. Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. *Circulation*. 2011;124(13):1452-1460. doi:10.1161/CIRCULATIONAHA.111.032920 Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. *Am J Respir Crit Care Med*. 2012;185(11):1154-1165. doi:10.1164/rccm.201111-2082CI	
Sleep Study *Cohen to obtain*	Assess Nocturnal O2 desaturation Difficulty comparing AHI across institutions (how to define obstructive event) and getting high quality data due to number of hours sleep				Po-Yang Tsou, Christopher M Cielo, Yu-Hsun Wang, Pei-Lun Kuo, Ignacio E Tapia, The Burden of Obstructive Sleep Apnea in Pediatric Sickle Cell Disease: a Kids' Inpatient Database Study, *Sleep*, , zsaa157, https://doi.org/10.1093/sleep/zsaa157	Exploratory (unclear what results mean in SCD yet)

6MWD can be used in stratifying populations, in determining an individual patient's risk, or as an outcome in a clinical trial to determine mean change after an intervention or responder rate (proportion of subjects achieving a clinically meaningful improvement). With a good quality-assurance program, with patients tested by the same technician using identical methodology, and using practice tests, short-term reproducibility of the 6MWD is excellent. It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value or (*2*) a percentage change. Expression as a change in % predicted is discouraged because of significant variation in current prediction equations. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. Recent studies have determined a clinically meaningful response to 6MWD to be approximately 30 meters.

1. **6MWT with Borg** according to American Thoracic Society - PHENX protocol (Core)
   https://www.phenxtoolkit.org/protocols/view/90602
   a. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test [published correction appears in Am J Respir Crit Care Med. 2016 May 15;193(10):1185]. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
   b. **Normative values in age 20-50 years:** Chetta A, Zanini A, Pisi G, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. *Respir Med*. 2006;100(9):1573-1578.
   c. **Normative values in age ≥ 60:** *Steffen et al. Age- and Gender-Related Test Performance in Community-Dwelling Elderly People: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and Gait Speeds. Physical Therapy. 2002*

2. **Heart Rate Recovery** (Exploratory)

1. Heart rate immediately after the 6-minute walk (measure right after subject stops walking) (bpm):
2. Oxygen saturation immediately after the 6-minute walk (measure right after subject stops walking) (%):
3. Heart rate 1 minute after 6-minute walk (bpm):
4. Oxygen saturation 1 minute after the 6-minute walk (%):
5. Heart rate recovery at 1 minute (HHR1) (bpm)
a. Calculation Equation: [sixmw_hr_immediate]-[sixmw_hr_1min]
6. Heart rate 2 minutes after 6-minute walk:
7. Oxygen saturation 2 minutes after the 6-minute walk:
8. Heart rate recovery at 2 minute (HHR2)
a. Calculation Equation: [sixmw_hr_immediate]-[sixmw_hr_2min]

a. Alvarado AM, Ward KM, Muntz DS, Thompson AA, Rodeghier M, Fernhall B, Liem RI: Heart rate recovery is impaired after maximal exercise testing in children with sickle cell anemia. *J Pediatr.* 2015, 166(2):389-393.e381.
b. Qiu S, Cai X, Sun Z, Li L, Zuegel M, Steinacker JM, Schumann U: Heart Rate Recovery and Risk of Cardiovascular Events and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc.* 2017, 6(5):e005505.

3. **Pulmonary Function Test** (Core). *See PFT Module*

4. American Thoracic Society Division of Lung Disease questionnaire (ATS-DLD) (Supplemental)
5. (forms from SAC study)

6. Medical Outcomes Study SF-36 (Supplemental)

7. **PROMIS Item Bank v1.0** Dyspnea Functional Limitations (Supplemental)

    a. 10-item Fixed Length short for or Computer Adaptive Test/Item Bank

8. **PROMIS Item Bank v1.0** – Dyspnea Severity (Supplemental)

    a. 10-item Fixed Length short for or Computer Adaptive Test/Item Bank
    http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Dyspnea_Scoring_Manual.pdf

    Yount SE, Choi SW, Victorson D, et al. Brief, valid measures of dyspnea and related functional limitations in chronic obstructive pulmonary disease (COPD). *Value Health*. 2011;14(2):307-315. doi:10.1016/j.jval.2010.11.009

    Yount SE, Atwood C, Donohue J, et al. Responsiveness of PROMIS® to change in chronic obstructive pulmonary disease. *J Patient Rep Outcomes*. 2019;3(1):65. Published 2019 Oct 29. doi:10.1186/s41687-019-0155-9

9. **Echocardiogram** - assess Peak Tricuspid Regurgitant Jet Velocity (m/s) and Peak Right Ventricular Systolic Pressure (mmHg) (Core). *See Echo Module*

10. **CT Chest** if indicated – Phenx (Supplemental)

https://www.phenxtoolkit.org/protocols/view/90402?origin=search

Has the subject's identity been confirmed?
Has the subject removed all metallic devices from the chest area?
Has the subject been informed of the importance of compliance with the breathing instructions?
Was at least one rehearsal of the end-inspiratory breath-hold performed?

Were scans reconstructed using the edge enhancing and smooth algorithms?
Were contiguous end-expiratory CT images obtained?
Was the subject allowed to breathe and relax for at least 15 seconds while preparing to take a CT scan of the lungs?
Was the scan taken during one breath-hold at full-inspiration
Was the subject allowed to breathe and relax for at least 15 seconds while preparing to take a CT scan of the lungs?
Was the scan taken during one breath-hold at expiration as quickly as possible?

London group publications on CT chest correlation with lung function. Small sample. Send CRFs

11. **Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP)** (Supplemental-Highly Recommemded)

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[i]Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med.* 2007;175(12):1272-1279.

Brousse V, Pondarre C, Arnaud C, et al. One-Fifth of Children with Sickle Cell Anemia Show Exercise-Induced Hemoglobin Desaturation: Rate of Perceived Exertion and Role of Blood Rheology. *J Clin Med.* 2020;9(1).

Campbell A, Minniti CP, Nouraie M, et al. Prospective evaluation of haemoglobin oxygen saturation at rest and after exercise in paediatric sickle cell disease patients. *Br J Haematol.* 2009;147(3):352-359.

Connes P, Machado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. *Clin Hemorheol Microcirc.* 2011;49(1-4):151-163.

Dedeken L, Chapusette R, Le PQ, et al. Reduction of the six-minute walk distance in children with sickle cell disease is correlated with silent infarct: results from a cross-sectional evaluation in a single center in Belgium. *PLoS One.* 2014;9(9):e108922.

Gordeuk VR, Minniti CP, Nouraie M, et al. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of follow up in children and adolescents with sickle cell anemia. *Haematologica.* 2011;96(1):33-40.

Hostyn SV, Carvalho WB, Johnston C, Braga JA. Evaluation of functional capacity for exercise in children and adolescents with sickle-cell disease