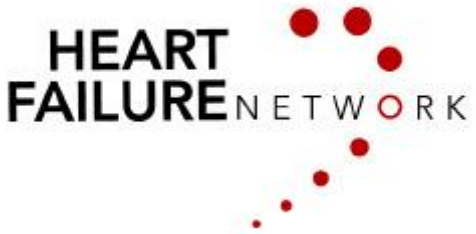


Heart Failure Network

Protocol
Reliable Evaluation of Dyspnea in the Heart Failure Network ROSE Study

RED ROSE

Compiled by:

The Heart Failure Network Research Group

May 4, 2011

Distributed by the Data Coordinating Center:

Duke Clinical Research Institute
Duke University
P.O. Box 17969
Durham, NC 27715

Investigators: O Abou Ezzeddine, MD, R Kociol, MD, J Ho, MD, R Shah, MD, J Nativi, MD, MM Redfield, MD

HFN Consultants: HH Chen, MD, M Felker, MD, M Semigran, MD, G Lewis, MD, LW Stevenson, MD, E Braunwald, MD

External Consultant: P Pang, MD

NHLBI Clinical Trials Specialist: Julianna Keleti, PhD

DCC Protocol Leader: Gayle Paynter

Email: gayle.e.paynter@duke.edu

Study Sponsor: National Heart, Lung, and Blood Institute
National Institutes of Health

Project Officer: Alice Mascette, MD

Network Chair: Eugene Braunwald, MD

Principal Investigators:

Clinical Centers:

David Bull, MD
University of Utah Health Sciences Center
Salt Lake City, UT

Steven Goldsmith, MD
University of Minnesota
Minneapolis, MN

Martin LeWinter, MD
University of Vermont
Burlington, VT

Anita Deswal, MD
Baylor College of Medicine
Houston, TX

Christopher O'Connor, MD
Duke University
Durham, NC

Margaret Redfield, MD
Mayo Clinic
Rochester, MN

Jean-Lucien Rouleau, MD
University of Montreal
Montreal, Quebec, Canada

Lynne Stevenson, MD
Harvard University
Boston, MA

Elizabeth Ofili, MD
Morehouse School of Medicine
Atlanta, GA

Data Coordinating Center:

Kerry Lee, PhD
Duke Clinical Research Institute
Durham, NC

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Title:	Reliable Evaluation of Dyspnea in the Heart Failure Network ROSE Study
Indication:	Acute heart failure
Location:	Regional Clinical Centers and associated hospitals in the United States and Canada.
Rationale	The dyspnea Visual Analog Scale (VAS) has been suggested to be superior to other scales in assessment of dyspnea in acute heart failure syndromes yet it may not optimally reflect the variability in dyspnea severity in these patients.
Objectives:	To determine whether the Provocative Dyspnea Severity Score (pDSS) is a more sensitive index of variability in clinical status than the dyspnea VAS assessed without standardization of conditions at assessments.
Study Design:	Approximately 250 patients
Treatment Regimens:	None for RED ROSE
Primary Objectives:	1) To determine whether the pDSS is a more sensitive index of variability in dyspnea status than the dyspnea VAS assessed without standardization of conditions at assessment 2) To determine whether changes in pDSS or dyspnea VAS correlate with the response to decongestive therapy.
Secondary Objectives:	1) To determine whether changes in worst reported symptom (WRS) (dyspnea, body swelling or fatigue) VAS (WRS-VAS) correlate with the response to decongestive therapy. 2) To compare the predictive characteristics of clinical stability assessments scores (pDSS-2, dyspnea VAS, worst symptom VAS (WRS-VAS), 6MW distance and NT-proBNP) assessed at 72 hours for predicting 60-day post-discharge outcomes (combined endpoint of ED visit or re-hospitalization for HF or death) in patients hospitalized for Acute Heart Failure Syndromes (AHFS).

FUNDAMENTAL CONCEPTS:

The dyspnea visual analog scale (dyspnea VAS) has been suggested to be superior to other ordinal (Likert) scales in assessment of dyspnea in acute heart failure syndromes (AHFS)[1]. However, there is no standardization of conditions (oxygen supplementation, position, activity) at the time of VAS assessment and thus, it may not optimally reflect the *variability in dyspnea severity* in AHFS patients. This insensitivity to variability at baseline and subsequent assessment may limit the ability to reflect variation in response over time and with alternate treatment strategies. A standardized and sequentially provocative assessment of dyspnea (provocative dyspnea severity score, pDSS) may better reflect variation in dyspnea severity and variation in response over time and with alternate treatment strategies.

Further, in a subset of patients with AHFS hospitalized with volume overload, other symptoms (body swelling or fatigue) are reported as their most bothersome symptom. In these patients, assessment of dyspnea may not reflect their clinical status or response to therapy.

Equipoise is provided by the possibility that, dyspnea relief - no matter how sensitively assessed - may or may not correlate with the extent of response to therapy. There may be a threshold of decongestion needed for dyspnea relief such that patients with variable reduction in volume overload will have a similar relief of dyspnea. With treatment strategies aimed at enhancing volume removal and maintaining renal function (such as being tested in ROSE), dyspnea relief may be a poor measure of differential response to the tested therapies.

Primary Objectives:

1) To determine whether the pDSS is a more sensitive index of variability in clinical status than the dyspnea VAS assessed without standardization of conditions at assessment. *Hypothesis: The pDSS and change in pDSS overtime are correlated with the dyspnea VAS and change in dyspnea VAS over time respectively. However, the distributions of pDSS and change in pDSS over time are broader than the distributions of dyspnea VAS and changes in dyspnea VAS over time.*

2) To determine whether changes in pDSS or dyspnea VAS correlate with the response to decongestive therapy. *Hypothesis: Changes in pDSS over the first 72 hours correlate more strongly than changes in dyspnea VAS with markers of clinical response to AHFS treatment (Net fluid loss, net weight change and % change in NT-proBNP levels at 72 hours).*

Secondary/Exploratory Objectives:

3) To determine whether changes in worst reported symptom (dyspnea, body swelling or fatigue) VAS (WRS-VAS) correlate with the response to decongestive therapy.

4) To compare the predictive characteristics of clinical stability assessments scores (pDSS-2, dyspnea VAS, worst symptom VAS (WRS-VAS), Six Minute Walk (6MW) distance and NT-proBNP) assessed at 72 hours for predicting 60-day post-discharge outcomes (combined endpoint of ED visit or re-hospitalization for HF or death) in patients hospitalized for AHFS.

BACKGROUND:

Dyspnea: Dyspnea is the most common presenting symptom in patients hospitalized with AHFS[2, 3]. Current practice guidelines target relief of symptoms as a primary goal of AHFS therapy[4, 5]. As such; the resolution of dyspnea has become a key endpoint in clinical trials of AHFS[6]. Moreover, it is the basis on which regulatory agencies evaluate drug efficacy and approve novel therapeutic agents[6, 7].

Dyspnea in AHFS: Despite its importance, dyspnea is a poorly understood phenomenon and no standardized methodology exists for its assessment in the setting of AHFS[7, 8]. Some have suggested that the paucity of positive AHFS therapy trials may be a reflection of inadequate dyspnea assessment tools rather than ineffective therapeutic interventions[8]. To date, there is no consensus on how to best measure such a subjective symptom to ensure sensitivity to variation in clinical status, inter-observer reproducibility and uniformity across trials. This is evidenced by the myriad of sub-optimally validated instruments used in major AHFS clinical trials[9].

Current dyspnea assessment tools and their limitations in HF: Most of the available dyspnea assessment tools are quality of life questionnaires extrapolated from the pulmonary literature[10, 11]. The Medical Research Council Dyspnea Scale, the Borg scale and the Chronic Heart Failure Questionnaire are such examples. They respectively reflect the impact of dyspnea on activities of daily living, exercise and patients' overall well being[9]. Despite their validation in the pulmonary patient population, these tools have their shortcomings when applied to AHFS patients. They do not correlate with objective changes in clinical exercise tolerance, they involve cardiopulmonary testing that is not widely used in AHFS, and they lack sufficient sensitivity to track a response to therapy during the average length of AHFS hospitalization[9].

Dyspnea assessment in recent AHFS therapy trials: Considering these limitations, the most widely accepted measures of dyspnea in AHFS therapy trials have become the Visual Analog Scale (VAS) and the Likert scale. However, they too have their limitations. As with any patient-reported symptom measure, subjectivity limits reproducibility and inter- and intra- patient comparisons are difficult to make. Also, the minimal clinically important difference (MCID) of these scales is yet to be validated[9]. Only one HF study has addressed what change in dyspnea VAS suggests a clinically meaningful therapeutic response[12]. No such substantiation exists for the Likert scale. Finally, there are conflicting data on the accuracy of VAS to reflect true symptom relief, improvement of clinical status and outcomes in AHFS[13]. While some attention has been given to use of ordinal (Likert) scales assessing dyspnea severity (ie mild, moderate or severe dyspnea), ordinal scales reflecting degree of change in dyspnea severity (mildly improved, moderately improved, etc) and more continuous scales of dyspnea severity (the visual analogue scale (VAS), only one study examined the impact of *patient conditions during the assessment* (see below, the URGENT-dyspnea study).

Dyspnea VAS, clinical status and outcomes: In an ancillary analysis from DOSE-AHF, Kociol et al found that dyspnea VAS AUC did not or only weakly correlated with objective markers of decongestion - weight change, net fluid loss and % change in serum NT-proBNP- each of which otherwise correlated significantly with the combined endpoint of ED visit or rehospitalization for HF and death at 60 days. An ancillary analysis from the Pre-RELAX-AHF study has recently shown that early dyspnea relief (Likert scale over first 24 hours) did not correlate with outcomes. However, the lack of persistent dyspnea relief measured by VAS AUC over the first 5 days or the presence of worsening HF after initial response predicted longer length of stay or worse post-discharge outcomes[13]. Other studies have suggested that assessment of exercise capacity (6MW distance) predicts post-discharge outcomes[14, 15].

Provocative Dyspnea Severity Score (pDSS): Considering the above, there has been a paradigm shift towards novel, standardized approaches to assess dyspnea in AHFS. One such example is the URGENT-dyspnea study, in which dyspnea was uniformly assessed in the sitting position within 1 hour of presentation. Those patients with less severe dyspnea ('no', 'mild' or 'moderate' shortness of breath) were further challenged with postural stress[16]. In patients mildly-moderately dyspneic at rest in the seated position, provocation unmasked more severe symptoms in 46% of patients using an ordinal scale and 72% of the patients using a VAS scoring system. This study suggests that provocation may

better reflect the variability in dyspnea severity and thus, may potentially better discriminate between response to tested therapeutic strategies.

The AHFS International Working Group has proposed a more rigorous provocative Dyspnea Severity Score (pDSS) [8]. The pDSS consists of asking patients to rate their breathing on a 5-point Likert scale ('worst possible', 'severe', 'moderate', 'mild' or 'no'-shortness of breath) at each stage of a provocative dyspnea assessment as described by Pang et al [8].

The pDSS stages are as follows:

A) Sitting upright (>60°) with supplemental oxygen (minimum of 2 L)

B) Sitting upright (>60°), no oxygen

C) Supine (<20° head elevation), no oxygen

D) Walking the equivalent of 50 m as fast as possible

E) Six minute walk test

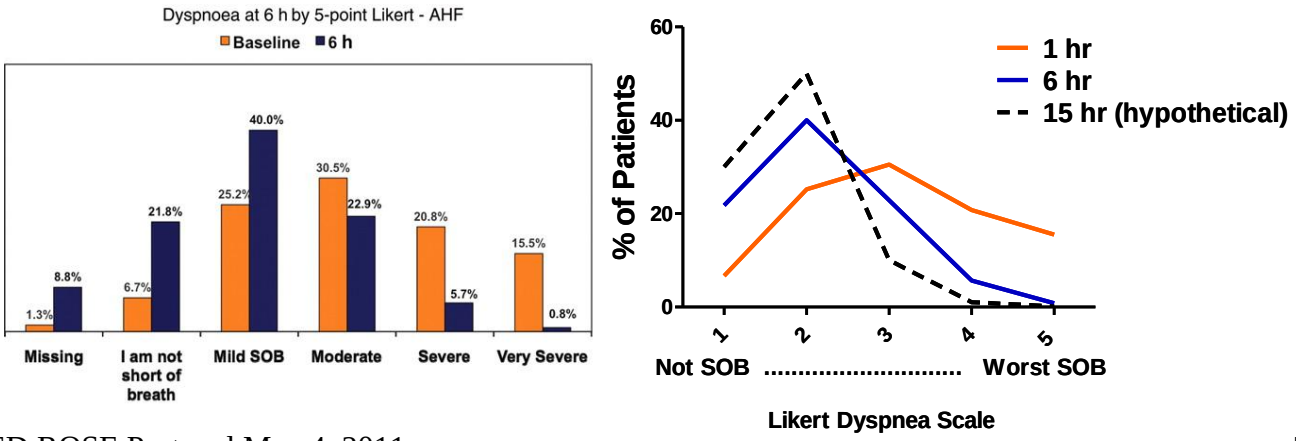
We propose to stratify the pDSS as pDSS-1 (stages A-D) and pDSS-2 (stages A-E) with pDSS-1 assessed at baseline, 24, 48, and 72 hours and pDSS-2 assessed at 72 hours only.

The Likert assessment is to take place after 3 minutes of equilibration at each of stages A, B, C but during/immediately after the step test or walk for stages D and E. In a 'stress-test'-like fashion, only patients who report moderate, mild or no breathlessness should proceed to the next stage. The step test in stage D will be performed at the bedside. Blood pressure will be checked in the upright position and patients who have symptomatic hypotension or asymptomatic severe hypotension (systolic BP < 80 mmHg) without severe dyspnea in the standing position or who are orthopedically or neurologically limited will not undergo the step test and will receive the highest score obtained in Stages A-C. The step test is to be aborted if they become severely dyspneic or if they are hemodynamically unstable. In each of these situations, patients will receive the lowest possible score of that specific stage. ***The pDSS-1 ranges from 1 to 20 and will be transformed (multiply score by 5) to provide the same scale as the VAS (100 mm) to enhance ease of comparison.*** Of note, both the pDSS and the dyspnea VAS used in the network trials rank dyspnea from most severe (lowest numerical value) to least severe (largest numerical value). The directional convention of VAS and Likert scales has varied in different trials but is maintained as above for consistency among Network trials.

The URGENT dyspnea study showed that *resting* dyspnea improves rapidly in the first 6 hours after presentation, narrowing the distribution of Likert dyspnea severity score. The average time from presentation to consent was 15 hours in DOSE and will likely be similar in ROSE. We postulate that improvement continues from 6 to 15 hours yielding an even narrower and skewed distribution of dyspnea scores at the 15 hr time point (Figure 1.).

Figure 1. Distribution of Dyspnea Severity Narrows Rapidly over Time after Presentation

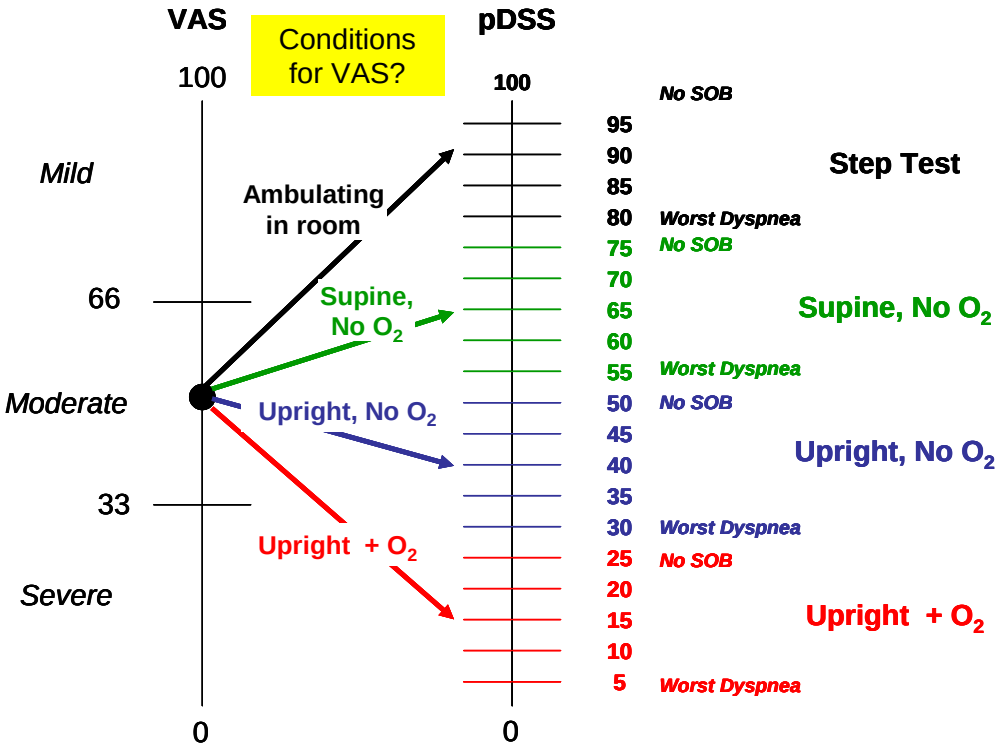
(URGENT-Dyspnea Study)



The postulated advantage of the pDSS is an increase in the variability (broadening of the distribution) of the dyspnea assessment reflecting true variation in severity of dyspnea that is under-recognized by not accounting for different conditions (oxygen, position, activity) under which dyspnea VAS scores are assessed. This is particularly important in studies such as DOSE and ROSE, where patients are enrolled many hours after initial presentation as above. Figure 2. illustrates this potential range of pDSS scores (transformed to have same scale as VAS, multiplied x 5) possible for a patient with a "moderate" degree of dyspnea on the dyspnea VAS depending on the conditions under which the VAS was assessed. A patient with moderate dyspnea on the VAS could have a "worse" or "better" pDSS score depending on the VAS conditions. Similarly, patients indicating mild or severe symptoms on the VAS, may fall over a range of scores on the pDSS, depending on the conditions under which the VAS was collected.

Figure 2. Potential relationships between a "moderate" degree of dyspnea on VAS and the pDSS

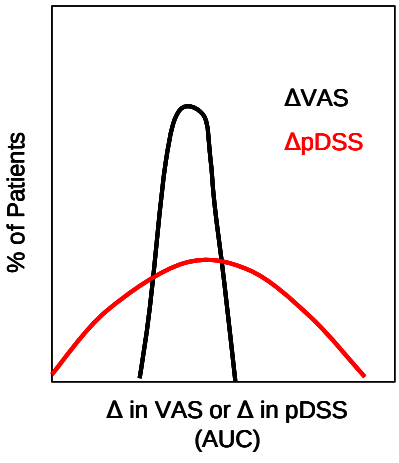
(pDSS transformed to similar scale as the 100 mm VAS)



By more accurately reflecting the range of severity of dyspnea present at baseline and sequentially after treatment, the pDSS may result in more variability in the change in dyspnea over time as assessed by the Area Under Curve (AUC) (Figure 3.), and ultimately better reflect differences in response to different treatments.

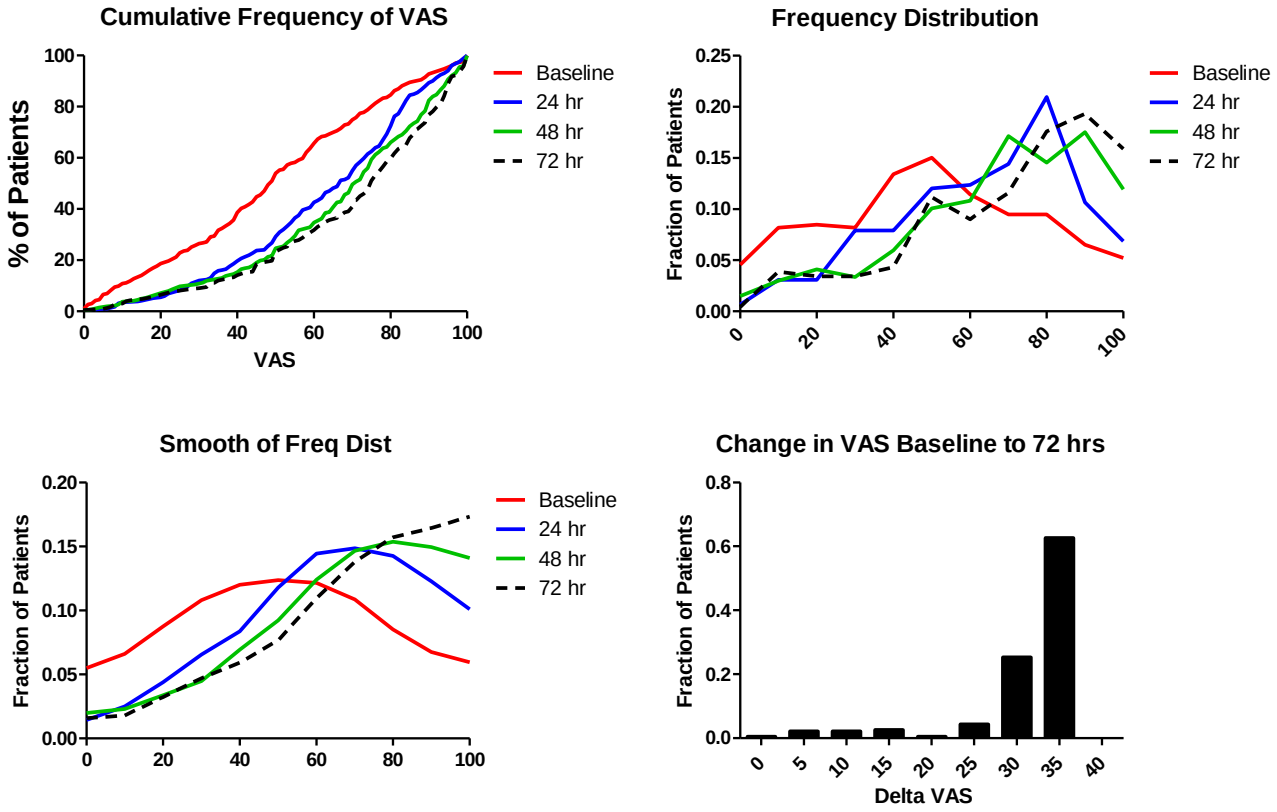
We examined the distribution of VAS scores over time in the DOSE trial (data supplied by DCC). The distribution of VAS scores at baseline was fairly broad but was skewed by 24 hours and subsequent time points with a very narrow distribution of change in VAS from

Figure 3. Postulated Difference in Change In Dyspnea VAS and pDSS



baseline to 72 hours (Figure 4) where nearly all patients had a change in VAS of between 27.5 and 37.5. We postulate that the pDSS will show a broader distribution at all time points and that the change in pDSS will be more variable.

Figure 4. Distribution of Dyspnea VAS and Change in VAS in DOSE



While changes with oxygen and position (stages A through C of pDSS) may reflect acute changes in dyspnea in response to AHFS therapy over hours, exertional provocation (step test in pDSS-1 and 6 minute walk in pDSS-2) may reflect clinical status as treatment progresses over days. Also, having been validated as a predictor of early hospital readmission and mortality [14, 15], the 6-minute walk test, may render the pDSS-2 predictive of clinical outcomes in patients hospitalized for AHFS.

Is provocative dyspnea assessment safe? Previous studies have supported the safety of such provocative assessment. Kaddoura et al. have illustrated that a 9-minute walk test on a patient-powered treadmill in patients with decompensated chronic heart failure (NYHA III-IV) was a safe, practical and objective assessment of functional capacity[17]. Also Spertus et al. assessed 6MW distance within hours of admission without adverse outcomes reported [15]. Moreover, this is a very brief duration of activity (see table below) and Stage D is only performed in a patient who is hemodynamically stable.

Is dyspnea the only symptom which should be assessed? Although the most common, dyspnea is not consistently the most dominant symptom perceived by patients presenting with AHFS. In a sub-study of the ESCAPE trial, Kato et al. exposed the spectrum of *"worst"* reported symptoms whereby 48% of patients reported 'fatigue', 'abdominal discomfort' or 'body swelling', rather than dyspnea, as their most bothersome symptom. This heterogeneity of symptoms could further explain the negative AHFS therapy trials in which dyspnea is often the only symptom to be assessed. Although very plausible, the use of "worst" symptoms to gauge the therapeutic response of novel agents has not been studied in major AHFS therapy trials to date.

In summary, although theoretically promising, the pDSS has not been validated in any AHFS trial. Whether there is greater variability in dyspnea severity in response to provocative measures is unclear although suggested by the URGENT-dyspnea study as above. Further, whether optimally assessed dyspnea severity changes in tandem with the degree of response to therapy such as net fluid loss, weight change and change in NT-proBNP levels is unclear. Moreover, its use as a predictor of rehospitalization and mortality is yet to be established. Finally, should a patient's worst presenting symptom of AHFS not be dyspnea, it would be worthwhile to study the relationship between provocative dyspnea assessments and the "worst" presenting symptom. RED-ROSE presents a unique opportunity to accomplish these goals.

STUDY DESIGN:

ROSE-AHF is a randomized, double-blinded, placebo controlled trial studying the effects of low dose dopamine and low dose nesiritide on renal function (Cystatin C) and diuretic responsiveness in patients with AHFS and renal dysfunction. Secondary and tertiary objectives of the study include assessing each of dyspnea VAS AUC, serum NT-proBNP levels, body weight and fluid balance at baseline (randomization) 24, 48 and 72-hrs post-randomization. Rehospitalization and vital status check are to be performed at 60 days post randomization.

In our ancillary study, we will measure the dyspnea VAS score under the (non-standardized) conditions the patient was in at the time of scheduled assessment at baseline, 24, 48 and 72 hrs *as is currently specified in the protocol. .* ***The additional data to be collected in this ancillary study include:***

1. For all dyspnea VAS assessments, the conditions present will now be recorded (position (<20°; 20-59°, ≥ 60°, or ambulatory in room; use of oxygen and flow rate).

2. Subsequent to each VAS, the pDSS-1 will then be assessed at each time point (baseline, 24, 48 and 72 hrs).

3. At the 72 hour time point only, a six minute walk test will also be assessed if maximal severity of dyspnea at any Stage of the pDSS-1 is moderate or milder. Subjects with severe or worst possible dyspnea at any stage of the pDSS-1 will not under go a six minute walk test. A standard six minute walk test form similar to those used in RELAX and EXACT will be used with an additional data point for severity of dyspnea with or after the six minute walk test. This information along with the pDSS-1 will be used to calculate the pDSS-2.

A standardized script and a timer will be used in the assessments which will be performed by the study staff. The actual day and time of the assessment will be recorded on each form. Given the severity of symptoms of patients admitted with AHFS, the original version of the pDSS (including the 6-minute walk test) was felt not to be feasible during the first 48 hours of hospitalization. Moreover, to standardize the 50-meter walk across the trial centers and make it clinically practical, we propose that its time-equivalent should be performed at the bedside as a "step-in-place" walk. This is a relatively brief exertional challenge with pilot studies indicating that the 50-meters take from 37 to 85 seconds depending on the speed of stepping (Table). As such, a 2-minute "step-in-place" walk as fast as possible is felt to be sufficient exertional provocation to elicit worsening dyspnea in a specific subset of patients. If patients develop more than moderate dyspnea at any point during the "step-in-place" walk and can not proceed any further, they will indicate this to the examiner and may stop before completing the full 2 minutes. This modified pDSS is illustrated in appendix I. The 6MW test (6MWT) is to be performed at 72-hours post-randomization under the supervision of skilled personnel according to the standard protocol as described by the American Thoracic Society [18].

SPEED	TIME (Seconds)
Brisk	37
Moderate	45
Slow	85

4. Patients will be asked what their "worst reported symptom" is at baseline. At the time of enrollment, patients will be asked to select their most bothersome symptom from a list of 'fatigue', 'body swelling' or 'difficulty breathing'.

5. A worst reported symptom VAS (WRS-VAS) will be collected at baseline, 24, 48, and 72 hours if the patient's WRS is not dyspnea. Should dyspnea ('difficulty breathing') not be a patient's worst symptom, a 100-mm VAS will subsequently be used to assess this alternative symptom at baseline, 24, 48 and 72 hours post-randomization. Similar to the original study protocol, symptom (fatigue or body swelling) severity will be assessed on a VAS using a 100 mm vertical line, upon which patients are required to draw a horizontal line rating their symptoms (100 representing the 'best imaginable health state' and zero 'the worst imaginable health state').

Recognizing that assessments may not take place at precisely 24, 48 and 72 hours post-randomization, the cumulative change in dyspnea VAS, pDSS-1 and worst symptom VAS will be calculated using the area under the curve (trapezoid) method (pDSS score on Y axis and minutes post-randomization on theX axis) which provides the most accurate assessment of cumulative symptom relief over time as described in DOSE and the main ROSE study protocol.

Both the 6MWT and the NT-proBNP have been established as good prognosticators of outcomes[14, 19] and will be used to further validate the pDSS2 as a predictor of outcomes.

ANALYSIS:

Primary Objectives:

1) To determine whether the pDSS is a more sensitive index of variability in clinical status than the dyspnea VAS assessed without standardization of conditions at assessment. *Hypothesis: The pDSS and change in pDSS overtime are correlated with the dyspnea VAS and change in dyspnea VAS over time respectively. However, the distributions of pDSS and change in pDSS over time are broader than the distributions of dyspnea VAS and changes in dyspnea VAS over time.*

The Pearson and Spearman correlation coefficients will be used to examine the correlation between the pDSS, change in pDSS over time, dyspnea VAS, and changes in dyspnea VAS over time. The pDSS-1 will be transformed to have a similar distribution as the dyspnea VAS by multiplying the pDSS-1 score by 5. We postulate that the dyspnea VAS and pDSS and their changes (AUC) will have a non-zero correlation coefficient. Thus, methods for comparing the variance of the distributions of related, non-independent variables will be used and could include the method of Pitman et al[20] or Boot-strapping methods[21].

2) To determine whether changes in pDSS or dyspnea VAS correlate with the response to decongestive therapy. *Hypothesis: Changes in pDSS over the first 72 hours correlate more strongly than changes in dyspnea VAS with markers of clinical response to AHFS treatment (Net fluid loss, net weight change and % change in NT-proBNP levels at 72 hours).*

The bivariate relationship between measures of pDSS and dyspnea VAS (at baseline and AUC to 72 hours) and clinical response will be examined using regression models. For continuous outcome variables we will use general linear models and for binary response variables we will use logistic regression models. Multivariable regression models will be used to describe the relationship between changes in pDSS and dyspnea VAS and clinical response at 72 hours.

Secondary Objectives:

3) To determine whether changes in worst reported symptom (dyspnea, body swelling or fatigue) VAS (WRS-VAS) correlate with the response to decongestive therapy. Multivariable regression models will be used to describe the relationship between WRS-VAS AUC and response to decongestion therapy including wt change, fluid loss and % change in NT-proBNP as well as the VAS AUC and the pDSS-1 AUC.

4) To compare the predictive characteristics of clinical stability assessments scores (pDSS-2, dyspnea VAS, worst symptom VAS (WRS-VAS), 6MW distance and NT-proBNP) assessed at 72 hours for predicting 60-day post-discharge outcomes (combined endpoint of ED visit or re-hospitalization for HF or death) in patients hospitalized for AHFS.

The relationship between pDSS-2, dyspnea VAS, WRS-VAS, 6MW distance and NT-proBNP and the time to an event response will be modeled using Cox proportional hazard regression models. Unadjusted analyses using Kaplan-Meier survival curves and log-rank tests will be used to describe the bivariate relationship between tertiles of the clinical stability scores and 60-day outcomes.

Approach for handling missing data:

Informative missing data due to death or mechanical ventilation will be imputed to the lowest score for pDSS or WRS VAS for the data analysis.

If data are missing for any other reason, the last value carried forward approach will be applied.

Justification of Statistical Power:

For objectives 2 and 3, a sample size of 250 RED ROSE subjects would provide 89% power to detect a correlation of 0.20 between the predictor variable and the continuous measure of clinical response. A sample size of 200 subjects would provide more than 80% power under the same assumptions. These calculations assume a normal distribution for the predictor variable and a two-sided 0.05 Type I error rate.

For objective 4, based on a similar patient population from the DOSE trial, we anticipate a 43% event rate (ED visit or rehospitalization for HF or death) at 60 days. With 250 RED ROSE study participants, we would expect to observe approximately 107 events. With this number of events we would have more than 80% power to detect a hazard ratio of 1.75 between the groups with above average and below average changes in the clinical stability assessment scores. These calculations are based on log rank test of survival with a two-sided Type I error rate of 0.05.

Future Directions: If the pDSS is found to be a better measure of dyspnea severity than the dyspnea VAS , the AUC of the pDSS-1 will be compared between the three treatment arms in ROSE (placebo, nesiritide and dopamine).

REFERENCES

1. Allen LA, Metra M, Milo-Cotter O, Filippatos G, Reisin LH, Bensimhon DR, Gronda EG, Colombo P, Felker GM, Cas LD, Kremastinos DT, O'Connor CM, Cotter G, Davison BA, Dittrich HC, Velazquez EJ. Improvements in signs and symptoms during hospitalization for acute heart failure follow different patterns and depend on the measurement scales used: an international, prospective registry to evaluate the evolution of measures of disease severity in acute heart failure (MEASURE-AHF). *J Card Fail.* 2008;14(9):777-784.
2. Pang PS, Komajda M, Gheorghiade M. The current and future management of acute heart failure syndromes. *Eur Heart J.*31(7):784-793.
3. Allen LA, Hernandez AF, O'Connor CM, Felker GM. End points for clinical trials in acute heart failure syndromes. *J Am Coll Cardiol.* 2009;53(24):2248-2258.
4. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail.*16(6):e1-194.
5. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol.* 2009;53(15):e1-e90.
6. Teerlink JR. Dyspnea as an end point in clinical trials of therapies for acute decompensated heart failure. *Am Heart J.* 2003;145(2 Suppl):S26-33.
7. Gheorghiade M, Zannad F, Sopko G, Klein L, Pina IL, Konstam MA, Massie BM, Roland E, Targum S, Collins SP, Filippatos G, Tavazzi L. Acute heart failure syndromes: current state and framework for future research. *Circulation.* 2005;112(25):3958-3968.
8. Pang PS, Cleland JG, Teerlink JR, Collins SP, Lindsell CJ, Sopko G, Peacock WF, Fonarow GC, Aldeen AZ, Kirk JD, Storrow AB, Tavares M, Mebazaa A, Roland E, Massie BM, Maisel AS, Komajda M, Filippatos G, Gheorghiade M. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. *Eur Heart J.* 2008;29(6):816-824.
9. West RL, Hernandez AF, O'Connor CM, Starling RC, Califf RM. A review of dyspnea in acute heart failure syndromes. *Am Heart J.*160(2):209-214.
10. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med.* 1999;159(1):321-340.
11. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1998;158(4):1185-1189.
12. Ander DS, Aisiku IP, Ratcliff JJ, Todd KH, Gotsch K. Measuring the dyspnea of decompensated heart failure with a visual analog scale: how much improvement is meaningful? *Congest Heart Fail.* 2004;10(4):188-191.
13. Metra M, Teerlink JR, Felker GM, Greenberg BH, Filippatos G, Ponikowski P, Teichman SL, Unemori E, Voors AA, Weatherley BD, Cotter G. Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. *Eur J Heart Fail.*12(10):1130-1139.
14. Kommuri NV, Johnson ML, Koelling TM. Six-minute walk distance predicts 30-day readmission in hospitalized heart failure patients. *Arch Med Res.*41(5):363-368.
15. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J.* 2005;150(4):707-715.

16. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, Andre S, Mark Courtney D, Hasa J, Spinar J, Masip J, Frank Peacock W, Sliwa K, Gayat E, Filippatos G, Cleland JG, Gheorghiade M. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. *Eur Heart J.*31(7):832-841.

17. Kaddoura S, Patel D, Parameshwar J, Sparrow J, Park A, Bayliss J, Sutton GC, Poole-Wilson PA. Objective assessment of the response to treatment of severe heart failure using a 9-minute walk test on a patient-powered treadmill. *J Card Fail.* 1996;2(2):133-139.

18. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166(1):111-117.

19. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation.* 2004;110(15):2168-2174.

20. Pitman EJG. A Note on Normal Correlation. *Biometrika* 1939;31(1):9-12.

21. Efron B. Bootstrap Methods: Another Look at the Jackknife. *The Annals of Statistics.* 1979;7(1):1–26.

pDSS

The pDSS as proposed by the International Working Group on AHFS

pDSS Stage	5-point Likert scale [Asked of patient at end of each successfully completed stage of the PDA]	Provocative Dyspnea Severity Score (pDSS) [Select number corresponding to Likert assessment on patient's last completed stage of the PDA]
STAGE A Sitting upright (>60°) with supplemental oxygen[c] (minimum 2L Nasal Canula) [assessment after 3 min equilibration]	Worst possible shortness of breath	1
	Severely short of breath	2
	Moderately short of breath	3
	Mildly short of breath	4
	Not at all short of breath	5
STAGE B Sitting upright (>60°), no oxygen [assessment after 3 min equilibration]	Worst possible shortness of breath	6
	Severely short of breath	7
	Moderately short of breath	8
	Mildly short of breath	9
	Not at all short of breath	10
STAGE C Supine (<20° head elevation), no oxygen [assessment after 3 min equilibration]	Worst possible shortness of breath	11
	Severely short of breath	12
	Moderately short of breath	13
	Mildly short of breath	14
	Not at all short of breath	15
STAGE D Bedside “step-in-place” walking as fast as possible for 50-meters[d,e] [post walk assessment]	Worst possible shortness of breath	16
	Severely short of breath	17
	Moderately short of breath	18
	Mildly short of breath	19
	Not at all short of breath	20
STAGE E (pDSS2) Six minute walk test [post-6min walk assessment)]	Worst possible shortness of breath	21
	Severely short of breath	22
	Moderately short of breath	23
	Mildly short of breath	24
	Not at all short of breath	25

Abort test if: patient becomes hemodynamically unstable, reports 'severe shortness of breath', develops oxygen saturation <90%, or is unable to tolerate position of any PDA stage.

Patients who report moderate, mild or no breathlessness should proceed to the next stage

Exercise care with oxygen in patients with severe pulmonary disease to avoid carbon dioxide retention

Do not proceed with Stage D or E if patient is hemodynamically unstable.

Stage D or E can be stopped before completion if patients are severely short of breath or hemodynamically unstable

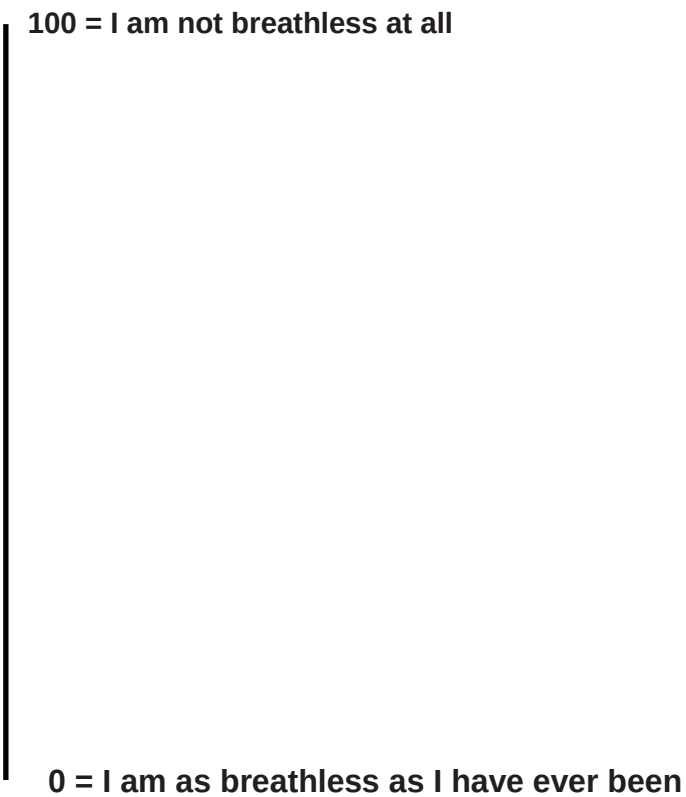
RED ROSE DYSPNEA VAS ASSESSMENT (BASELINE, 24, 48, 72-HR)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___: __ ___
Day month year

Position: ☐ <20°, ☐ 20°- 59°, ☐ ≥ 60°, ☐ Ambulatory in room

Oxygen: ☐Yes ☐ No. If yes, ___ Liters/min

Please draw a line on the scale to show how your breathing feels right now.
The number "0" equals the worst your breathing has ever felt and the number "100" equals the best your breathing has ever felt.



RED ROSE WORSE REPORTED SYMPTOMS ASSESSMENT (BASELINE)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___: ___ ___
Day month year

My most bothersome symptom prompting hospitalization was: (select one):

□ difficulty breathing →Complete dyspnea VAS at baseline, 24, 48 and 72 hrs

□ fatigue→Complete dyspnea VAS ***and*** fatigue VAS at baseline, 24, 48 and 72 hrs

□ body swelling → Complete dyspnea VAS ***and*** body swelling VAS at baseline, 24, 48 and 72 hrs

RED ROSE FATIGUE VAS

(Baseline, 24, 48, 72-hr if Fatigue is worse reported symptom)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___: ___ ___
Day month year

Please draw a line on the scale to show how your most bothersome symptom feels right now.
The number "0" equals the most bothersome ever and the number "100" equals NOT bothersome whatsoever

---

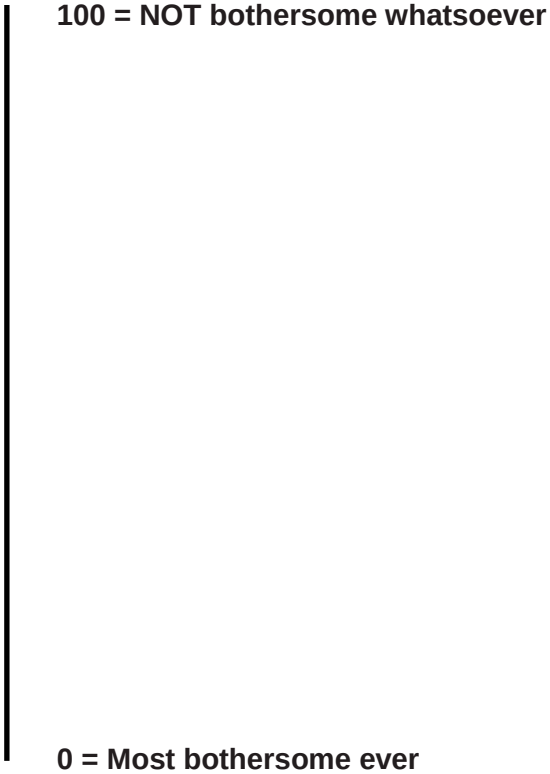
RED ROSE BODY SWELLING VAS

(Baseline, 24, 48, 72-hr if <u>Body Swelling is worse reported symptom</u>)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___: ___ ___
Day month year

Please draw a line on the scale to show how your most bothersome symptom feels right now.
The number "0" equals the most bothersome ever and the number "100" equals NOT bothersome whatsoever

---



RED ROSE pDSS-1 QUESTIONNAIRE

(Baseline, 24, 48, 72-hr)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___: __ ___
Day month year

Is the patient using oxygen? (Check) ☐ Yes → Start assessment at Stage A.
☐ No → Start assessment at Stage B.

Stage A: Position patient with head of bed > 60° with 2 Liters/min of Oxygen. Begin timer. Wait 3 minutes then ask: *"Which ONE of the following accurately describes how your breathing feels right now?" and circle the #:*

1. 'Worst possible shortness of breath'→ Stop assessment, record "pDSS score" in box below.
2. 'Severely short of breath'→ Stop assessment, record "pDSS score" in box below.
3. 'Moderately short of breath'→ Proceed to Stage B
4. 'Mildly short of breath'→ Proceed to Stage B
5. 'Not at all short of breath'→ Proceed to Stage B

Stage B: Position patient with head of bed > 60°. If patient is on oxygen, remove oxygen. Begin timer. Wait 3 minutes then ask: *"Which ONE of the following accurately describes how your breathing feels right now?" and circle the #:*

6. 'Worst possible shortness of breath'→ Stop assessment, record "pDSS score" in box below.
7. 'Severely short of breath'→ Stop assessment, record "pDSS score" in box below.
8. 'Moderately short of breath'→ Proceed to Stage C
9. 'Mildly short of breath'→ Proceed to Stage C
10. 'Not at all short of breath'→ Proceed to Stage C

Stage C: Re-position patient with head of bed <20° without oxygen. Begin timer. Wait 3 minutes then ask:
"Which ONE of the following accurately describes how your breathing feels right now?" and circle the #:

11. 'Worst possible shortness of breath'→ Stop assessment, record "pDSS score" in box below.
12. 'Severely short of breath'→ Stop assessment, record "pDSS score" in box below.
13. 'Moderately short of breath'→ Proceed to Stage D
14. 'Mildly short of breath'→ Proceed to Stage D
15. 'Not at all short of breath'→ Proceed to Stage D

Stage D: Prompt patient to stand at bedside. Assess for ability to perform Stage D, measure blood pressure, assess for lightheadedness and check approval for 2-minute walk. Check ONE box below:

☐ Pt. has a mechanical limitation (gait instability, arthritis, paralysis, etc): → Stop assessment, record "pDSS score" from Stage C in box below.
☐ Pt. is unstable in standing position (SBP < 80 or lightheaded): → Stop assessment, record "pDSS score" from Stage C in box below.
☐ Other reason Pt is unable to perform Stage D: → Stop assessment, record "pDSS score" from Stage C in box below and reason for not performing Stage D.

Pt. ☐ stable in standing position (SBP > 80, not lightheaded), has no mechanical limitation and agrees for Stage D: → Continue with Stage D.

"Please take steps in place as fast as you can for a maximum of 2 minutes." **When patient completes 2 minutes or if he/she is unable to complete 2 full minutes because of breathlessness, immediately ask: *"Which ONE of the following accurately describes how your breathing feels right now?" and circle the #:***

16. 'Worst possible shortness of breath' → Stop assessment, record "pDSS score" in box below.
17. 'Severely short of breath' → Stop assessment, record "pDSS score" in box below.
18. 'Moderately short of breath' → Stop assessment, record "pDSS score" in box below.
19. 'Mildly short of breath' → Stop assessment, record "pDSS score" in box below.
20. 'Not at all short of breath' → Stop assessment, record "pDSS score" in box below.

"pDSS score":_____ *Stage D not completed due to:_____*

SIX MINUTE WALK TEST - pDSS2 ASSESSMENT (72-hr)

Site Number: ___ ___ ___ Patient Number: ___ ___ ___ – ___ ___ ___
Assessment Date: ___ ___ /___ ___ /___ ___ ___ ___ Time: ___ ___ : __ ___
Day month year

If the patient completed the pDSS-1 and did not become hemodynamically unstable or report "worst possible" or "severe" shortness of breath at any stage of pDSS (pDSS1 ≥ 18), proceed to Six Minute Walk test.

Perform the Six Minute Walk test as per HF clinical research network Six Minute Walk test protocol

6-MINUTE WALK INSTRUCTIONS

Description: The 6-minute walk is a simple test for assessing exercise capacity as a measure of functional status. It also reflects the normal daily activity levels of patients.

Equipment Needed:

Watch or clock with second hand

Tape measure

Tape

Chairs

6-Minute Walk Worksheet and pen

Preparation:

Measure an indoor course with a chair at each end. Establish a suitable distance between

chairs so that if the patient tires, a chair is easily accessible. A distance of 20 to 25 feet (about 8 meters) is a suitable distance to start with, but this may vary based on the patient's condition and space at your facility. Avoid L-shaped hallways.

Provide patient teaching. Explain the test to the patient by using the suggested wording on the below. Answer any questions the patient may have.

Conducting the 6-Minute Walk Test:

1. Escort the patient to the start of the course. Show the patient the walking course and ask the patient to begin walking as you begin keeping time. Stay with the patient for the entire walk test and record the number of completed laps.
2. Provide encouragement to the patient. At 30 second intervals, encourage the patient using the examples provided below. Notify the patient when 2, 4, and 6 minutes (stop) have elapsed and what the remaining time is. Patients will be allowed to slow or stop and rest during the walk, but will be asked to resume walking as soon as they feel able. After 6 minutes, the distance walked will be measured to the nearest meter. Vital signs (heart rate and BP) will be obtained before and immediately after the test in the standing position. Patients will indicate symptoms limiting the ability to walk during the test (dyspnea, fatigue, chest pain, leg or joint pain, instability, other, none) and these should be recorded on the 6-Minute Patient Walk Worksheet.
3. Stop the test after 6 minutes. Mark the floor where the patient stops with a piece of tape.
4. Determine the total distance walked. Multiply the number of laps by the distance of each lap (round to the nearest meter). Add this figure to the distance covered in the last partial lap. Record the distance.

Suggested explanation of the 6-minute walk:

"*The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and walk back and forth between the two markers I showed you. You will go back and forth as many times as you can in the 6-minute period. If you need to, you may stop and rest. Just remain where you are until you can go again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time and I will let you know when the 6 minutes are up. When I say "stop", please stand right where you are."*

"The aim at the end of the 6 minutes is for you to feel that you couldn't have covered more ground in the time provided. I will stay with you as you walk. We won't talk while you walk because this could affect your performance. I will say some things to you periodically, such as how much time is left.

Please let me know if you are uncomfortable or have pain. The idea is for you to walk at a comfortable pace, but for you to cover as much ground as possible in the 6 minutes. Are you ready?

To start: **"***Begin walking".*

0:30 second intervals: "You're doing well"…"keep up the good work"…"good job"…"you're doing fine"

2 minutes: "You have been walking 2 minutes." "You have 4 minutes left to walk."

4 minutes: "You have walked 4 minutes." "You have 2 minutes left to walk."

6 minutes: **"***Stop."*

Encouragement statements if subject is resting:

1 minute: "*It's been __ minutes. Rest as long as you need and let me know when we can get started again."*
2 minutes:"*__ minute(s) are left in the test. You can keep resting or begin walking again when you feel able."*
Repeat the last statement at each minute if the subject continues to rest.

At the end of the 6MWT ask the patient:

"Which ONE of the following accurately describes how your breathing feels right now or at the time you stopped walking because of trouble breathing?" and circle the #:

21. 'Worst possible shortness of breath'
22. 'Severely short of breath'
23. 'Moderately short of breath'
24. Mildly short of breath'
25. 'Not at all short of breath'

Total Distance Walked: **_____meters**

SAMPLE RED ROSE DYSPNEA ASSESSMENT QUESTION **(pDSS-1 & Six Minute Walk Test)**

"Which of the following accurately describes how your breathing feels right now?"

- Worst possible shortness of breath
- Severely short of breath
- Moderately short of breath
- Mildly short of breath
- Not at all short of breath