Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE)

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1. Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
AE	adverse event
ANP	atrial natriuretic peptide
BNP	brain natriuretic peptide
CHF	congestive heart failure
CEC	Clinical Events Committee
CK(-MB)	creatine kinase (-myocardial band isoenzyme)
CPX	cardiopulmonary exercise
CRF	case report form
DCF	data-clarification form
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram, electrocardiographic
ESCAPE	Evaluation Study of Congestive heart failure and Pulmonary Artery Catheterization Effectiveness
ICF	Informed consent form
IRB	Institutional Review Board
IVRS	Interactive Voice-Response System
LVAD	left ventricular assist device
MI	myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NYHA	New York Heart Association
PAC	pulmonary-artery catheter
PAS	pulmonary-artery systolic pressure
PAD	pulmonary-artery diastolic pressure
PCWP	pulmonary-capillary wedge pressure
RAP	right atrial pressure
RV	right ventricular
SVR	systemic vascular resistance
ULN	upper limit of normal

2. Primary Hypothesis

The primary hypothesis of this trial is that for patients with severe heart failure, therapy guided by pulmonary-artery catheter monitoring and clinical assessments will lead to fewer deaths and hospital days over a 6-month period than therapy guided by clinical assessment alone.

3. Background

The prevalence of congestive heart failure (CHF) continues to increase, affecting an estimated 4.7 million Americans, with 400,000 new cases diagnosed each year.[1,2] Daily life is limited for the 800,000 to 1 million patients with New York Heart Association (NYHA) Class III or IV heart failure.[3,4] These patients account for most of the morbidity and cost of CHF. Direct costs related to CHF in 1999 are estimated to be $19.6 billion in the U.S. alone, 77% of which will be due to hospitalizations.[4] Comprehensive heart-failure programs that combine tailoring of medical therapy, patient education, and care from a multidisciplinary team appear to reduce such hospitalizations by 50% to 80%, with concomitant improvement in functional capacity.[5,6]

Standard care for patients in these programs includes adjustments to therapy that often are based on results of hemodynamic monitoring via pulmonary-artery catheter (PAC). Experience and competence in such monitoring, although assumed, have not been formally defined. A recent trial of inpatients with various diagnoses has suggested that those selected for PAC monitoring have higher mortality, although this was not true for the subgroup diagnosed with CHF.[7] As addressed both in a recent National Heart, Lung, and Blood Institute (NHLBI) Workshop[8] and by a Consensus Committee of the American College of Cardiology,[9] the initial evaluation and treatment of CHF decompensation often may be aided by the use of PAC, but it remains to be determined whether its benefits and safety in this setting result in better outcomes over therapy guided only by clinical assessments.

The purpose of this study, the Evaluation Study of Congestive heart failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, is to examine the long-term efficacy and safety of treatment guided by hemodynamic monitoring and clinical assessment versus that guided by clinical assessment alone in patients hospitalized with severe symptoms of CHF. A secondary objective is to compare the costs and resource use associated with the PAC-guided treatment strategy versus the clinical assessment treatment strategy. The impact of the two treatment strategies on levels of natriuretic peptides, severity of mitral regurgitation, and exercise capacity (measured by peak oxygen consumption and performance on the 6-minute walk test), also will be compared. Each of these variables has correlated with outcomes in patients with CHF.[10-12]

4. Study Design and Objectives

The study will include 500 patients who have been hospitalized with NYHA Class IV symptoms of CHF. The patients will be randomized 1:1 to the clinical assessment-guided arm (CLIN arm) or the PAC arm. The primary endpoint will be a composite of the number of days patients are hospitalized and the number of days they are dead, over a 6-month period. Secondary endpoints will include physiological variables that can reflect the effect of treatment on the progression of CHF. Unlike the primary endpoint, changes in the physiological endpoints will be assessed without knowledge of treatment allocation. Costs and resource use and patient-assessed quality of life also will be compared in the two treatment arms.

A secondary objective is to determine the incidence and significance of PAC-associated complications when the device is inserted and maintained by experienced personnel.

The tertiary objective is to assess the value of physiological variables and integrated clinical assessments as potential surrogate endpoints for outcomes in advanced CHF.

5. Patient Population

Recruitment for ESCAPE will span a period of 27 months. All participants will be recruited from a population of patients hospitalized for exacerbation of documented heart failure. Patients (or a

representative) must provide written, informed consent before any study procedures occur (see Appendix 1 for sample Informed Consent Form [ICF]). All decisions about patient recruitment, adjustment of therapy in the hospital, and later follow-up will be made in conjunction with the patient's primary physician.

5.1. Inclusion Criteria

Patients eligible for the trial must comply with all of the following **at randomization**:

1. Age ≥16 years
2. Current admission under the care of the heart-failure service at the site
3. Current admission for NYHA Class IV heart-failure symptoms (see Appendix 2 for NYHA Classifications)[13]
4. At least one prior admission for exacerbation of CHF within 6 months before randomization
5. Left ventricular ejection fraction <30% by contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within 1 year before randomization. The most recent measure of left-ventricular function should be used.
6. Documented history of heart failure for ≥3 months
7. Attempted therapy with angiotensin-converting enzyme (ACE) inhibitors and diuretics for ≥3 months before randomization
8. Systolic blood pressure ≤125 mm Hg
9. Elevated filling pressures, indicated by one symptom AND one physical sign:

   Symptoms: Dyspnea at rest, in the supine position, OR immediately upon routine activity within 1 room; abdominal discomfort, severe anorexia, or nausea without apparent cause other than hepatosplanchnic congestion

   Signs: Jugular venous pressure elevation >10 cm above the right atrium; square-wave Valsalva response; hepatomegaly, ascites, or edema in the absence of other obvious causes; rales greater than 1/3 lung fields

5.2. Exclusion Criteria

1. Acute decompensation thought by the attending heart-failure physician to require or be likely to require PAC during the next 24 hours. Such patients should be entered into the PAC Registry (see below).
2. Inability to undergo PAC placement within the next 12 hours
3. Active listing for cardiac transplant
4. Present or anticipated mechanical ventilation
5. Present or anticipated mechanical circulatory assist device insertion, including intra-aortic balloon pumps and left ventricular assist devices (LVAD)
6. Any administration of intravenous milrinone within the previous 48 hours
7. Current administration of intravenous dopamine or dobutamine at >3 μg/kg/min, OR dopamine or dobutamine administration for >24 hours before randomization
8. Acute myocardial infarction (MI) or cardiac surgery within the last 6 weeks
9. Current admission for an acute coronary syndrome, including acute MI or unstable angina
10. Documented moderate-to-severe mitral or aortic stenosis
11. Anticipated revascularization procedure during the admission
12. Other planned surgical procedure during the admission
13. Documented primary pulmonary hypertension
14. Pulmonary infarction within the past month

15. Current pneumothorax
16. Current serum creatinine >3.5 mg/dL
17. Temperature >37.8°C
18. White blood cell count >13,000/mm^3
19. Exacerbation of CHF due to a primary factor requiring specific therapy, such as severe anemia, clinical hypothyroidism, or active systemic infection
20. Presence of any noncardiac disease, such as cancer, likely to shorten life expectancy to <1 year
21. Inability to return to the site's CHF program at 14±7 days, 30±14 days, 60±14 days, 90±14 days, and 180±14 days after randomization
22. Pregnancy or lactation, or childbearing potential in the absence of contraception by oral contraceptives, an intrauterine device, or surgical sterilization. All women of childbearing potential must have a negative pregnancy test before randomization.

Additional exclusion criteria (for which patients may be rescreened during same admission):

23. Estimated large volume reservoir (major ascites or anasarca) thought to require extensive diuresis (>48 hours) before major adjustment of other medications such as vasodilators
24. Temporary inability to place and monitor PAC, due either to patient factors such as excessive anticoagulation, or to logistical factors such as temporary lack of bedside monitoring equipment

Patients enrolled in other investigational drug studies are potential candidates for ESCAPE. As the ESCAPE protocol does not involve any investigational agents or techniques, patients would be eligible for dual randomization if they are on stable doses of the investigational drugs. Patients should not be considered for dual randomization if they are being started on investigational drugs or if such doses are being adjusted. The Clinical Helpline physician will need to obtain permission from the Steering Committee of the concurrent study before randomization of the patient in ESCAPE. Investigators must contact the Clinical Helpline to receive confirmation that the patient may be enrolled.

5.3. Registry

During the 27 months of the trial, all patients hospitalized for CHF, who undergo PAC placement, and who are under the care of a heart-failure service, will be entered into a PAC Registry.

The following data will be collected for the Registry: demographics, medications, reasons for PAC insertion, initial hemodynamic profile, complications of PAC, and major outcomes during the index admission (discharge, death, transplantation, listing for transplantation, LVAD insertion, or cardiac surgery).

6. Randomization

Eligible patients (or a representative) will have the study procedures and potential risks explained to them, and written informed consent will be obtained (see Appendix 1 for a sample ICF). If the patient meets the inclusion criteria and none of the exclusion criteria, a treatment will be randomly assigned by a central telephone allocation service (Interactive Voice-Response System, IVRS). Patients will be randomized into the CLIN Arm or the PAC Arm in a 1:1 ratio. Each patient will be assigned a unique identification number, called the Patient Number.

7. Treatment and Study Procedures

7.1. Definitions of Treatment Arms

7.1.1. CLIN Arm

This strategy will adjust therapy according to the signs and symptoms of heart failure, without PAC information. Therapy will be adjusted to achieve the following clinical goals:

1. Absence of elevated intracardiac filling pressures, as judged by absence of symptoms: orthopnea, abdominal discomfort, nausea, or vomiting attributable to hepatosplanchnic congestion

2. Absence of signs: jugular venous pressure ≥8 cm above the right atrium, rales, peripheral edema, detectable ascites or hepatomegaly
3. Evidence of adequate peripheral perfusion, as judged by warm extremities, pulse pressure ≥25% if possible, and walking without dizziness
4. Serum creatinine ≤3.0 mg/dL and stable or improving by discharge

7.1.2. PAC Arm

This strategy will adjust therapy using information from both PAC monitoring and the signs and symptoms of heart failure (CLIN Arm). Therapy in this arm will be adjusted to achieve specific hemodynamic goals, as well as the clinical goals outlined for the CLIN Arm.

1. Pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg
2. Right atrial pressure (RAP) ≤8 mm Hg (unless Goal #1 already has been achieved)
3. Maintenance of systolic blood pressure to avoid symptomatic hypotension

When possible, hemodynamic measures should be continued until an oral vasodilator regimen has been selected for discharge.

7.1.3. Crossovers

Patients randomized to the CLIN Arm can cross over to the PAC Arm at any time, if they deteriorate to the point that hemodynamic monitoring is considered necessary. Criteria for which crossover from the CLIN Arm to the PAC Arm could be considered include:

- Progressive hemodynamic decompensation leading to the need for high-dose inotropic or mechanical support
- Inability to wean intravenous inotropic agents
- Progressive, oliguric renal insufficiency
- Need for mechanical ventilation due to respiratory failure
- Acute coronary syndrome, refractory symptomatic hypotension, sepsis, worsening pulmonary edema
- Persistent concern that failure to relieve symptoms or signs of severe CHF despite 7-10 days of clinically-guided therapy could reflect diagnostic uncertainty of the primary process producing the clinical picture, or incorrect assessment of the hemodynamic profile

To record reasons for crossovers to the PAC Arm, investigators should contact the Clinical Helpline beforehand. The primary reason for crossover will be assessed and recorded. In addition, investigators must complete a Randomization Crossover Form when the crossover occurs.

Patients should not be randomized until they are ready to undergo PAC insertion. Criteria for which crossover from the PAC Arm to the CLIN Arm might be considered include:

- Failure to insert PAC due to technical difficulties, such as unusual patient anatomy
- Development of fever or other signs and symptoms of infection. In these cases, the investigator may need to remove the PAC, as it may be a potential source of infection.

Investigators also should call the Clinical Helpline before **any insertion or reinsertion** of PACs after randomization, and complete a PAC Insertion/Reinsertion Form, regardless of the original treatment allocation. Repeat PAC in a patient who has been randomized to the PAC Arm is not anticipated to be useful under most conditions, as the initial hemodynamic profile and drug responses already have been established. Even though repeat PACs in these patients do not represent crossovers, investigators must contact the Clinical Helpline.

7.2. Selection and Adjustment of Therapy for All Patients

For all patients, therapy should be adjusted to the following three goals:

1. Discharge on an oral drug regimen for relief of CHF symptoms

2. Reduction of filling pressures as shown by physical signs or achievement of hemodynamic targets
3. Maintenance of adequate perfusion. Initial therapy after randomization may include temporary stabilization with intravenous drugs, such as vasodilators, diuretics, and inotropic agents. These agents then should gradually be discontinued and replaced with oral medications.

The therapies will be chosen from those now in standard use for this population, according to the experience and expertise of the individual investigators. Any available therapy may be used for an individual patient regardless of treatment assignment. Diuresis generally will begin with intravenous agents. Current intravenous vasodilators that may be used include nitroprusside and nitroglycerin. Dopamine and dobutamine also may be used at any dose after randomization, but patients are excluded from ESCAPE for administration of dopamine or dobutamine at >3 μg/kg/min or for >24 hours before randomization. The use of milrinone after randomization, while not encouraged, is permitted at low doses, but again, the use of intravenous milrinone within 48 hours before randomization is an exclusion criterion. The prolonged biological half-life of milrinone should be taken into account when recording the optimum hemodynamic measures achieved through an oral regimen.

The oral medical regimen for discharge will consist of standard medications for CHF, which includes combinations of ACE inhibitors, nitrates, and hydralazine. Angiotensin-II receptor antagonists also may be used. Titration to hemodynamic goals is aided by use of the shorter-acting vasodilators. Diuretics should be given orally for ≥48 hours before discharge. Beta blockers should not be started during the index admission or for 1 month afterward. After then, they can be considered if the patient is clinically stable and has been free from congestion for ≥1 month. For patients with successful titration of beta blockers before admission, these drugs can be continued during this period if the investigator judges that compensation can be restored. Calcium-channel blockers other than amlodipine should not be used. Options and dosing for standard therapy may change during the course of this study, due to the ongoing release of results from other studies.

7.3. Eligibility for Discharge

Regardless of the patient's treatment allocation, the following goals should be achieved before discharge:

- ≥48 hours with no intravenous inotropic agents
- 24 hours on an oral drug regimen with no major change in doses (except for anticoagulation)
- Stable fluid balance, defined by net fluid status and weight. Investigators should try to attain patients' "dry" weights while they are in the hospital, rather than planning for further diuresis after discharge.
- Completion of patient education. Education should include both oral and written instructions about symptoms, CHF medications, flexible diuretic regimens, and maintenance of daily logs. Patients also should receive information about how to contact the heart-failure team. Patient education is described in further detail in the Manual of Operations.
- Arrangements for follow-up visits. The Study Coordinator should ensure that the patient has an appointment for the next scheduled follow-up visit (see Appendix 3 for complete Schedule of Events). Provisions for a visiting nurse, if necessary, also should be arranged.

7.4. Study Procedures

7.4.1. PAC Procedures

See Appendix 4 for detailed standards for PAC insertion, maintenance, and waveform analysis.

7.4.2. Echocardiography

Echocardiograms will be performed at randomization, discharge, and 90±14 days. Echocardiograms will be obtained with standard views for two-dimensional, Doppler, and color Doppler imaging. The

Echocardiographic Core Laboratory (Brigham and Women's Hospital) will analyze films for quantitated mitral regurgitation as an absolute volume and as a fraction of total stroke volume, calculated as the sum of [regurgitant volume and forward stroke volume measured in the left ventricular outflow tract]. Pulmonary-artery systolic pressures will be estimated from tricuspid regurgitation jets. Diastolic filling will be assessed from early and late mitral-inflow patterns and from inflow deceleration time. Left ventricular and left atrial dimensions will be measured in systole and diastole, and ejection fractions calculated.

7.4.3. Six-minute Walk Test

Although performance on the 6-minute walk may have only limited value to detect changes during therapy for CHF,[14] it appears to be most sensitive in the range of very low performance expected for this population (in the ESCAPE pilot study, the average peak oxygen consumption was 10 mL/kg/min at randomization). Patients will perform the 6-minute walk at randomization, discharge, 90±14 days, and 180±14 days. The investigators used established methods[15] to design the 6-minute walk protocol. Study Coordinators at each site will conduct the test in a level hallway equipped with accessible chairs. This involves walking for 6 minutes along an inside corridor, under supervision of a member of the study team. Patients will be encouraged to walk as far as they can during the 6 minutes but stop to rest when necessary.

7.4.4. Cardiopulmonary Exercise Testing

Cardiopulmonary exercise (CPX) testing will be performed at randomization, discharge, and 90±14 days. Patients will be asked to perform exercise with gas-exchange analysis. Patients will be encouraged to exercise to an RER-value of ≥1, if possible. Centers are encouraged to use cycle ergometry exercise testing as much as possible, but have the option to use either cycle ergometry or treadmill testing. In addition, centers should use the following protocols when performing CPX testing:

- Cycle Ergometry – 2 minutes rest data, then 2 minutes unloaded exercise, then 15W per minute ramp to peak exercise
- Treadmill – 2 minutes rest data (patient may sit if unable to stand), then modified Naughton protocol

Peak oxygen consumption may be slightly higher with treadmill exercise. Differences in testing modes between sites should not complicate data analysis, as the change in exercise performance will be the endpoint for each patient. Patients must perform all exercise tests on the same type of equipment (either cycle or treadmill) each time, however.

7.4.5. Blood Tests

Atrial natriuretic peptide (ANP), proatrial natriuretic peptide, and brain natriuretic peptide (BNP) will be measured at randomization, discharge, 90±14 days, and 180±14 days. Blood samples for these tests (15 mL) will be drawn when the patient undergoes venipuncture for routine clinical assessment, with no need for additional needlesticks to participate in this study. The 6-month samples will be held at the core laboratory (Mayo Clinic) in the event that they need to be analyzed at a later date. Unused serum also will be stored, for confirmation of initial results or measurement of other related hormones. All analyses will be performed at the core laboratory by personnel unaware of treatment assignment.

7.4.6. Questionnaires

To assess their quality of life, patients will complete the Minnesota Living with Heart Failure questionnaire[16] at randomization, 30±14 days, 90±14 days, and 180±14 days. Patients also will complete a time trade-off assessment,[17] which asks how much time in their current state of health the patient would be willing to trade for a shorter time in good health. This assessment will be completed at the same intervals as the Minnesota questionnaire, with an additional assessment at 60±14 days.

To assess their symptoms, patients will complete a Visual Analog Scale indicating the severity of their dyspnea, other dominant CHF symptoms, and overall comfort. This will be completed at

randomization, discharge, 14±7 days, 30±14 days, 60±14 days, 90±14 days, and 180±14 days.

Patients may still continue with the study even if they elect to forego the questionnaires.

7.4.7. Other Inpatient Procedures

Please see Appendix 3 for the complete schedule of events.

7.5. Postdischarge Management

Management will be provided according to standard care after hospitalization for CHF. This includes a return visit for standard clinical assessment and review of medications at 14±7 days, 30±14 days, 60±14 days, 90±14 days, and 180±14 days after randomization. Additional visits may be scheduled as needed to establish and maintain clinical stability after discharge (see Manual of Operations). Data collected during these additional visits do not need to be recorded on the Case Report Form (CRF).

8. Data Collection

The majority of the data for this study will be collected as part of standard care.

8.1. Standard Data

8.1.1. Baseline Data

The entry data recorded at the time of randomization will include patient demographics, social support and resuscitation status, presumed etiology of CHF, documentation of coronary angiography, duration of CHF symptoms , documentation of ejection fraction and method, number of admissions in the past 6 months, and baseline medications, including ACE inhibitors, diuretics, digoxin, beta blockers, amiodarone, hormone-replacement therapy, lipid-lowering agents, antiplatelet agents, and warfarin. Medications will be recorded daily during the index admission.

8.1.2. Clinical Assessments

Clinical assessments will be performed at randomization and at 3 days, 5 days, 7 days, optimal status, discharge, 14±7 days, 30±14 days, 60±14 days, 90±14 days, and 180±14 days after randomization. Optimal status is defined as the day that, in the physician's opinion, the patient has achieved the best condition possible in the hospital. While there are no specific criteria for "optimal status", physicians should make this determination using data from the patient's clinical assessment, volume status, and medication doses.

After randomization, assessments on days 3, 5, and 7 should be performed only if the patient is still hospitalized. If the patient has been discharged before these days, then additional clinical assessments are not required. If the patient achieves optimal status on days 3, 5, or 7, then data should be recorded only once for that day. Later assessments should be completed according to the specified follow-up time frames, regardless of where the patient is located (outpatient or in-hospital).

Clinical assessments should include the following:

- Evaluation of CHF symptoms, including orthopnea, dyspnea on exertion, and gastrointestinal discomfort
- Blood pressure and heart rate measured while the patient is supine and standing
- Weight
- Evaluation of physical signs of congestion, such as estimated height of jugular venous pressure, rales, hepatosplenomegaly, edema, temperature of extremities, and pattern of Valsalva response (if performed routinely at the site)
- For patients randomized to the PAC Arm, physicians will be asked to estimate hemodynamic variables before insertion, using information from the clinical assessment. This will provide information about the accuracy of clinical assessment among expert heart-failure physicians.

8.1.3. Laboratory Results

During the index admission, patients will have laboratory work drawn at randomization, and at 3 days, 5 days, 7 days, and optimal status after randomization. Additional samples should be drawn

whenever clinically indicated, but these results do not need to be recorded on the CRF.

8.1.4. Volume Status

A summary of the patient's net fluid status and weight should be recorded daily on the CRF.

8.2. Hemodynamic Data

For patients randomized to the PAC-Guided Therapy Arm, investigators will need to record the following hemodynamic variables:

- Right atrial pressure (RAP)
- Pulmonary-artery systolic pressure (PAS)
- Pulmonary-artery diastolic pressure (PAD)
- Pulmonary-artery mean pressure (PA mean)
- Mean pulmonary capillary wedge pressure (PCWP mean)
- PCWP A wave (PCWP A wave)
- PCWP V wave (PCWP V wave)
- Systemic vascular resistance (SVR)
- Mixed venous oxygen saturation
- Arterial blood pressure

Hemodynamic data should be collected according to the following schedule and guidelines:

- One set of screening measures should be recorded within 1 hour after PAC insertion
- Two sets of baseline measures should be recorded before medical therapy begins (excluding intravenous diuretics). The PCWP readings on two successive measurements should be within 15% of each other. The average of three cardiac-output readings taken during the first measurement should be within 15% of the average of three such readings taken during the second measurement.

Three sets of hemodynamic measures should be recorded daily while the PAC is in place. These should include:

- Standard readings (including all hemodynamic variables) at 8 AM and 4 PM. The study coordinator should obtain these measurements herself, ensuring that transducer placement and patient positioning are consistent with previous measurements.
- The lowest PCWP achieved each day, and all hemodynamic variables associated with this PCWP. The lowest PCWP recorded each day should be within 15% of a previous PCWP. The study coordinator should review the hemodynamic data recorded each day and record the lowest PCWP on the CRF. If two PCWP readings are of equal value, then the study coordinator should select the value associated with the highest cardiac output.

Two sets of hemodynamic measures should be recorded 1 hour before PAC removal. These should include:

- A reading obtained while the patient is supine
- A reading obtained after the patient has been standing for at least 3 minutes

Study coordinators and ESCAPE nurses may use the hemodynamic results indicated on the bedside monitor, but these results should be verified with paper-tracing results. If there is any discrepancy between the monitor values and the paper tracing results, the paper-tracing data should be used.

The study coordinators and ESCAPE nurses should manually identify on paper tracings the RAP, PAS/PAD/PA mean, and PCWP mean/PCWP A wave/PCWP V wave. The study coordinator should collect the tracings of the hemodynamic measures obtained as part of the ESCAPE protocol. These will include the 8 AM, 4 PM, and the lowest PCWP tracings obtained each day. These tracings will be considered source documents. Study coordinators should instruct the ESCAPE nurses to collect

the paper tracings of all hemodynamic measurements taken each day.

Assessment of the PAC insertion site should be recorded daily on the Daily Summary of Volume Status and Insertion Site Status Form.

8.3. Complications and Procedures during the Index Admission

Any complications that occur during the index admission or during the follow up period should be recorded on the CRF. In addition, the Complications of Pulmonary Artery Catheterization section of the CRF should be completed for all PAC-associated complications.

All procedures that occur during the index hospitalization or during the follow up period also should be recorded on the CRF.

8.4. Discharge Data

At discharge, the following information should be recorded on the CRF:

- Discharge date
- Endpoint summary
- Complete list of discharge medications
- Discharge instructions for sodium and fluid restriction
- Patient discharge status
- Physician estimate of likelihood of death
- Physician estimate of likelihood of readmission
- Nurse estimate of likelihood of death
- Nurse estimate of likelihood of readmission

8.5. Follow-up Data

The following data should be collected during each follow-up visit. These visits are scheduled at the following times after randomization: 14±7 days, 30±14 days, 60±14 days, 90±14 days, and 180±14 days. Please refer to the Schedule of Events (Appendix 3) for complete information.

- Clinical assessment, symptom assessment
- Physical examination
- Patient assessment of symptoms and global status
- Medication log
- Endpoint summary – interval events, death or readmission reports
- Documentation of patient education

The following data should be collected only during the specified follow-up visits.

- Physician estimate of likelihood of death — 30±14 days
- Physician estimate of likelihood of readmission — 30±14 days
- Nurse estimate of likelihood of death — 30±14 days
- Nurse estimate of likelihood of readmission — 30±14 days
- Cardiopulmonary exercise testing — 90±14 days
- Echocardiogram — 90±14 days
- Natriuretic peptides — 90±14 and 180±14 days
- 6-Minute walk — 90±14 and 180±14 days
- Quality-of-life questionnaires (Minnesota Living with Heart Failure and patient time trade-off) — 30±14, 90±14, and 180±14 days

9. Endpoints and Definitions

9.1. Endpoints

Note: Clinical events identified by the investigator as possible primary or secondary endpoints will be adjudicated by a Clinical Events Committee (CEC) unblinded to treatment assignment.

9.1.1. Primary Endpoint

- Number of days patients are hospitalized or dead during the 6 months after randomization

9.1.2. Secondary Endpoints

- Components of the primary endpoint (time to readmission or death, and time to death throughout the 6 months after randomization)
- Enhanced primary endpoints: cost and resource utilization, patient preference-adjusted survival
- Physiological endpoints: changes in mitral regurgitation, ANP, BNP, changes in peak oxygen consumption, and 6-minute walk distance
- Quality-of-life endpoints: changes in the Minnesota Living with Heart Failure score and in the patient time trade-off assessment

9.1.3. PAC-Associated Complications

- Composite of complications associated with PAC: bleeding requiring transfusion, bleeding requiring surgical intervention, cannulation of the carotid artery, complete heart block requiring pacemaker, complication requiring cardiopulmonary resuscitation, ventricular tachycardia >30 seconds or requiring intervention, infection, pneumothorax, or pulmonary infarction or hemorrhage

9.1.4. Clinical Performance Measures

- PAC Arm only: accuracy of physicians' estimate of hemodynamics. Estimate to be made before insertion of PAC.
- Both Arms: accuracy of physicians' and nurses' estimates of patient death and of readmission over the next 6 months. Estimates to be made at randomization, discharge, and 1 month.

9.1.5. Health Economics

The objective of the health economic evaluation is to determine the impact on direct medical resource use incurred by patients who undergo PAC versus those who undergo heart-failure care without PAC use. Clinical data will be used as a measure of resource use and will be captured on the CRF. The clinical data captured during the index admission will include: number and type of hospital days, cost of the PAC, cost of medications (intravenous drugs, oral drugs, intravenous home infusions), level of hospital care (intensive-care unit, standard unit), and procedures (e.g., intra-aortic balloon pump, pacemaker, mechanical ventilation).

During each follow-up visit, a section of the CRF will capture the following: number of readmissions, number of hospital days, level of hospital care, procedures, emergency-department visits, and cost of medications.

9.2. Definitions

9.2.1. Causes of Death

All deaths shall be considered cardiovascular unless an unequivocal noncardiovascular cause can be established. Deaths will be classified into the following categories: pump failure, fatal MI, sudden death, other cardiovascular, noncardiovascular, or unable to determine, defined below.

Pump failure: Cardiogenic shock or collapse with insufficient pressure to maintain clinically adequate perfusion, symptomatic pulmonary edema, CHF symptoms or signs requiring continuous intravenous therapy or oxygen administration, or confinement to bed due only to worsening symptoms and signs of CHF. NYHA Class IV heart-failure patients who are being treated in the hospital for pump failure and who have a "sudden" arrhythmic event as the terminal event should be

classified as having a pump-failure death. If this category is marked, investigators must complete a CHF Report.

Fatal MI: An MI is defined as the presence of a clinical syndrome consistent with acute MI and one of the following: new ST-segment or T-wave changes ≥1.0 mm in two or more contiguous leads, new Q or QS waves in 2 or more contiguous leads, or new left bundle branch block; OR total creatine kinase (CK) >1.5 times the upper limit of normal (ULN), CK-MB >1.5 times the ULN, or troponin I or T >1.5 times the ULN. If more than one cardiac enzyme is available, CK-MB takes precedence over troponin I or T, and troponin I or T takes precedence over total CK. For death to be classified in this category, the MI must be the primary precipitating event leading to death. If this category is marked, investigators must complete an MI Report.

Sudden death. This is defined as sudden, unexpected cardiovascular death such as: death due to an identified arrhythmia (ECG or monitor recording, witnessed arrhythmia by either medic or paramedic); unwitnessed deaths; or cardiac arrest or cardiovascular collapse without exacerbation of pump failure, myocardial infarction, or other modes of death. This includes patients resuscitated from sudden cardiac arrest who later die from the sequelae, or similar patients who die during attempted resuscitation.

Other Cardiovascular. This is defined as cardiovascular procedure-related death (death occurring during a cardiovascular procedure such as bypass or angioplasty, or PAC, LVAD, or IABP placement), stroke (fatal ischemic or hemorrhagic stroke documented by autopsy, computed tomography, or angiography, or clinical criteria--rapid onset [<48 hours] of either localizing neurological deficits or change of consciousness that leads to death, with documentation of the deficit by computed tomography or angiography), pulmonary embolism (fatal pulmonary embolism diagnosed by pulmonary angiography, high-probability lung scan, or autopsy), other cardiovascular death (due to great-vessel or peripheral vascular disease or other vascular-related deaths).

Noncardiovascular. These are deaths from cancer and other noncardiovascular causes.

Unable to Determine. This category is reserved for cases with insufficient clinical information to permit the CEC to make a determination.

9.2.2. Reason for Readmission

Hospitalization is defined as a hospital admission or an emergency-department visit that spans >24 hours. Readmissions will be classified into the following categories: CHF exacerbation, acute coronary syndrome, arrhythmia, other cardiovascular, noncardiovascular, or unable to determine, defined below.

CHF exacerbation. Hospitalization for cardiogenic shock or cardiovascular collapse with insufficient pressure to maintain clinically adequate perfusion, symptomatic pulmonary edema, or CHF symptoms or signs requiring intermittent or continuous intravenous therapy or adjustment of other medications for heart failure. This includes downward adjustment of medication required by progressive heart failure. This category should also be marked for hospitalizations due to heart failure precipitated by or associated with other diseases such as pulmonary disease, renal disease, and infections.

Acute coronary syndrome. This includes MI (defined above). This category also includes unstable angina, defined as: 1) chest pain at rest, new exertional chest pain, or acceleration of chest pain (increased severity, duration, or frequency) **and** 2) either ST-T–wave deviation ≥0.5 mm or the same enzyme criteria as for MI.

Arrhythmia. This includes admissions due to sudden death with resuscitation, supraventricular arrhythmia, ECG or monitor recording showing sustained or unsustained ventricular arrhythmia, monitor-witnessed sustained or unsustained ventricular arrhythmia by a medic or paramedic, firing of an intracardiac defibrillator, or Type II second- or third-degree atrioventricular block.

Other cardiovascular. These are admissions for cardiac procedures such as bypass surgery, angioplasty, or LVAD; stroke or transient ischemic attack documented by history or computed

tomography; pulmonary embolism documented by high-probability lung scan or angiography, or another cardiovascular cause that does not fall into the categories above.

Noncardiovascular. This is any admission due to cancer or other noncardiovascular causes (e.g., pneumonia, foot ulcer, gastrointestinal bleeding).

Unable to determine. This category is reserved for cases with insufficient clinical information to permit the CEC to make a determination.

10. Adverse Events

The recording and reporting of adverse events (AEs) in ESCAPE is crucial to better understand the risks and benefits associated with the PAC. During this trial, the reporting of AE information may lead to important changes in the way the PAC is used and monitored, and provide critical safety data.

10.1. Expedited Event Notification

In ESCAPE, investigators are required to complete an Event Notification Form for all deaths and specific PAC-associated complications that occur between randomization and 6 months. These events will include 1) all **deaths**, 2) all PAC-associated **pulmonary infarctions or hemorrhages**, and 3) any PAC-associated complication that **results in cardiopulmonary resuscitation or death**.

Investigators must fax the completed Event Notification Form to the DCRI within 1 business day after identification of the event. The DCRI will forward the information immediately to the NIH. The NIH, in turn, will determine which events meet "unanticipated" criteria and report these events to the FDA and investigators. Investigators also must submit such data promptly to their IRB for review, and report any other **unusual** or **unanticipated** events directly to the FDA.

The intent of expedited reporting is rapid communication of only those events necessary to evaluate the safety of the PAC, which translates to the relay of information only about death and PAC-associated events that lead to increased mortality. Other PAC-associated complications will be recorded on the relevant pages of the CRF. These data will be tabulated and summarized for periodic review by the Data and Safety Monitoring Board (DSMB).

10.1.1. PAC-Associated Events to be Captured Only on the CRF

- Bleeding requiring transfusion
- Bleeding requiring surgical intervention
- Cannulation of the carotid artery
- Complete heart block requiring pacemaker
- Ventricular tachycardia >30 seconds or requiring intervention
- Infection
- Pneumothorax

10.1.2. Procedures in Case of Pregnancy

Any patient who becomes pregnant during the study period must be discontinued from the study. The investigator will continue to follow the patient until she delivers, and provide a follow-up report to the study monitor about the outcome.

10.2. Event Notification Form Collection and Processing

The investigator faxes the completed Event Notification Form to the DCRI Safety Desk within 24 hours of learning of the event. The DCRI Safety Desk reviews the Form for completeness, follows-up with the site for incomplete or unclear data, logs and tracks Forms, provides the data to the Data Manager for entry into the ClinTrial database, and faxes the Forms to the NIH within 1 business day of receipt by the DCRI.

The NIH reviews the Form for completeness, queries the Safety Desk for incomplete or unclear data, reviews the event for regulatory criteria (unanticipated PAC complications), reports events to regulatory agencies if necessary, and provides the Safety Desk with copies of regulatory reports to

fax to investigators.

11. Data Management

Database management and quality control for the ESCAPE trial are the responsibility of the DCRI.

Investigators will collect all information required by the protocol on CRFs; any omissions to these data should be explained. The CRFs will be printed on three-part no-carbon-required (NCR) paper. All entries to the CRF must be made clearly with a black ball-point pen, to ensure the legibility of self-copying pages. Corrections are made by placing a single horizontal line through the incorrect entry, so that the original entry remains visible, and placing the correct entry beside it. Members of the investigator's research team authorized to make CRF entries must initial and date each revision. The investigator must sign each CRF before submission to the DCRI. Upon completion, CRFs are separated into two parts, with the site maintaining the pink copy in their study files and forwarding the white and yellow copies to the DCRI. The CRFs should be forwarded to the DCRI within 5 days of discharge or the follow-up visit.

The DCRI will process the CRFs upon receipt, according to their Standard Operating Procedures. The DCRI will generate queries at each stage of the data-management process (review upon receipt and automated and manual data-validation checks) and send Data Clarification Forms (DCFs) by fax, mail, or e-mail to sites for resolution. The site will review the DCFs, respond appropriately on the DCF, and return them to the DCRI. Quality-control methods will be use throughout to maintain the data's integrity, and audits will be performed at designated times during the study.

When all queries have been addressed and all expected data has been received, the database will be locked. Any changes to the database after then can be made only by joint, written agreement between the Project Leader, the statistician, and the clinical data specialist.

12. Statistical Analysis Plan

12.1. General Statistical Methods

All analyses will use the intention-to-treat principle, except the analyses of PAC-related complications, which will include only patients who received a PAC. All statistical tests will be two-sided. An overall alpha of 0.05 will be used for the primary hypothesis. To monitor the statistical significance of interim treatment differences, we will use the group-sequential methods of Lan and DeMets.[18] Our approach will incorporate a spending function with an upper boundary that approximates the O'Brien-Fleming boundary.[19] If the test statistic crosses the upper boundary at an interim analysis, it will indicate that benefit is established. Interim analyses (see Section 13.5, Data and Safety Monitoring Board) will be assessed using smaller alpha levels. All continuous variables will be summarized medians with interquartile ranges for each group, and categorical variables will be presented as frequencies and percentages. Baseline demographic variables, risk factors, and relevant clinical variables will be descriptively summarized and statistically tested to characterize and compare the treatment groups.

12.2. Primary Endpoint

The primary endpoint is defined as the number of days either hospitalized or dead during the 6 months after randomization. We will use the Cox proportional-hazards model to assess whether there is a statistical difference between the two treatment groups in the number of days hospitalized or dead.[20] The test statistic will be the likelihood-ratio statistic.

12.3. Secondary Endpoint(s)

The components of the primary endpoint will be analyzed separately as secondary endpoints. The number of days spent in the hospital during the 6-month follow-up interval will be analyzed and compared between treatments using the same approach outlined above for the primary endpoint. For the mortality component, treatments will be compared using a conventional Cox model (log-rank) analysis of failure-time data allowing for censoring. Kaplan-Meier survival estimates[21] will be calculated for each treatment group to display the mortality results graphically. Additional analyses

will be done using baseline variables as covariates. The analysis of hospital days will be modeled with and without adjustment for censoring.

13. Study Network, Training, and Responsibilities

13.1. Research Network

We expect participation by 30 experienced investigators and 22 study coordinators from 22 U.S. sites. To qualify, physicians responsible for PAC placements will be required to show proof of insertion of ≥50 PACs in the previous year with a complication rate of <5%. Further, clinicians will need to show competence in the following areas to participate in the study: 1) insertion techniques and cardiovascular anatomy; 2) oxygen dynamics; 3) knowledge of pharmacological agents used to manipulate hemodynamics; 4) waveform interpretation and technical skills; 5) clinical application of hemodynamic information; 6) patient preparation and comfort during PAC insertion and maintenance; and 7) common PAC complications.[22,23] These topics are addressed in a PAC educational module (PACEP) developed by a consortium of professional medical societies, and in the Hemodynamic Pre-Test and Hemodynamic Post-Test. Therefore, we will assume basic competence in these areas after satisfactory completion of the PACEP module.

13.2. Training

The NHLBI has mandated that a primary goal of ESCAPE should be to implement among centers with recognized expertise a standard educationalprocess that ensures proper use of the PAC. This has been the focus of a specific working group, PACCO, composed of representatives from the NHLBI and critical care subspecialties. A systematic training program will ensure that the ESCAPE investigators will be able to describe a standard of expertise in PAC use and that PAC data can be compared across centers. The PACCO group has developed a PAC education program (PACEP) that will be used in ESCAPE to promote uniform data collection and interpretation.

A standard training process has been established to achieve these goals. The proposed process is as follows:

- We will give the PACEP Pre-Assessment to all investigators and study coordinators at the Investigator's Meeting 12/7/99-12/8/99.
- We will present them with an overview of hemodynamic monitoring steps to ensure uniform data collection.
- Study coordinators then will undergo a training program based on the PACEP educational module.
- Study coordinators will receive a PACEP module on computer diskette and an envelope with a PACEP Post-Assessment. They will have 1 week to complete an independent review of the PACEP module and return the PACEP Post-Assessment. The DCRI Site Manager will follow-up with sites and keep a log of those returning the PACEP Post-Assessment, to ensure proper completion of this phase.
- Once the study coordinators have completed the PAC educational program, they will be considered "ESCAPE Certified."
- Study coordinators then will identify at least four to five nurses at their sites who will be "ESCAPE Nurses."
- Study coordinators will administer the PACEP Pre-Assessment to the "ESCAPE Nurses." After the Pre-Assessment, study coordinators will distribute the PAC educational module to the "ESCAPE Nurses," who will have 1 week to complete and return the independent study program.
- After completing the study program, the "ESCAPE Nurses" will take a PACEP Post-Assessment and, if they pass, will be "ESCAPE Certified." These will be the nurses managing PACs of patients enrolled in the trial.

- Another PACEP Post-Assessment will be given to the "ESCAPE Nurses" at 6 months.

13.3. Study Coordination

The Data and Clinical Coordinating Center will be the DCRI.

13.4. Steering Committee

The Steering Committee will consist of all site investigators. The Steering Committee provides feedback to the Executive Committee on the trial's policies, procedures, and progress.

13.5. Executive Committee

The Executive Committee (Drs. Califf, Stevenson, O'Connor, Shah, and Sopko) is responsible for developing the final version of the protocol, monitoring the progress of the trial, serving as resources for the sites, overseeing the development of policies for trial conduct, and serving as chairs of analysis and writing subcommittees after the trial has ended.

13.6. Data and Safety Monitoring Board

Interim examinations of key safety and endpoint data will be performed at regular intervals during the course of the trial. The primary objective of these analyses will be to evaluate the accumulating data for an unacceptably high frequency of negative clinical outcomes in either of the treatment arms. In addition, however, the interim monitoring will also involve a review of the control-arm event rates, patient recruitment, compliance with the protocol, submission of data forms, and other factors that reflect the overall progress and integrity of the study. The results of the interim analyses will be carefully and confidentially reviewed by the DSMB, whose purpose will be to monitor the progress of the study, the quality of data acquisition, and the various elements mentioned above that are important to the successful conduct of the trial. If necessary, the DSMB has the authority to terminate the study early.

The DSMB will be appointed by the NHLBI and will comprise a clinical chairperson, one cardiologist, one statistician, and one medical ethicist. The nonconfidential portion of the Board meetings will be attended by the Principal Investigators and statisticians from the DCRI. After a discussion of the progress of the trial, a confidential discussion will be held by DSMB members only. A written report will be given to the Study Chair.

The DSMB will meet at roughly 6-month intervals to review accumulating data. Before each meeting, the DCRI will conduct the desired statistical analyses and prepare a summary report for DSMB review. The extracted data files and analysis programs for each DSMB report will be copied to tape and maintained at the DCRI for the life of the study. Reports will be presented by the DCRI describing the progress of enrollment, the rates of compliance with therapy, and the frequency of protocol violations. Detailed tables will be generated presenting the number of forms received, entered, and queried, queries completed, and forms receiving the final, completed entry in the double data-entry system.

14. Ethical Requirements

The study will be performed in accordance with the principles stated in the Declaration of Helsinki.[24] The Institutional Review Board (IRB) or Ethics Board of each site must approve the final study protocol, including the final version of the ICF, before any patients can be randomized at that site. Investigators must forward IRB approval, along with the Office for Protection from Research Risk (OPRR) numbers, to the DCRI, with the approval to include the title and date of the protocol and other documents submitted for review.

Investigators are responsible for informing their IRB of any amendments to the protocol as per national and local requirements. The investigator should file all correspondence with the IRB, after sending a copy to the DCRI.

Investigators must ensure that the patient or a representative is given full, adequate verbal and

written information about the nature, purpose, and possible risks and benefits of the study. Patients also must be notified that they can stop participating in the study at any time. Patients should be given the opportunity to ask questions and, when possible, time for consideration.

Investigators must obtain a signed ICF each patient before any study-related procedures are performed, including randomization. Patients should retain a copy of the signed ICF.

15. Changes to the Protocol

No study procedure can be changed without the agreement of the Executive Committee and the NHLBI. All changes must be documented by signed protocol amendments.

Changes to the protocol may require approval from the institutional IRBs before implementation. National requirements also must be followed.

The DCRI Site Manager is responsible for distribution of amendments to the Principal Investigator at each site. The DCRI Project Leader is responsible for distribution of the amendment to the Executive Committee and NHLBI. The Principal Investigator at each site is responsible for the distribution of an amendment to the IRB at the site.

16. Substudies

Proposal for substudies within the main ESCAPE program should be presented to the Executive Committee. The Executive Committee will evaluate the proposals and give recommendations to the NHLBI.

17. Publication Policy

The main results from the ESCAPE study will be submitted to a peer-review medical journal as a single manuscript coordinated by the Executive Committee. All site investigators and NHLBI representatives will have an opportunity to review and comment on the manuscript before submission. Participating investigators agree not to submit, without the prior written approval of the Executive Committee, any publications, including those from substudies, before the main manuscript has been accepted for publication. After this time, authors must give the Executive Committee and NHLBI representatives at least 28 days for comment before submitting any manuscripts for peer-reviewed journal articles, including those from any secondary analyses or substudies. The Executive Committee may distribute such manuscripts to other participating investigators for comment. Authorship of the main manuscript and all later publications must conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.[25]

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19. Appendix 1. Sample Informed Consent Form

Consent To Participate As A Research Subject In Medical Research

Evaluation Study of Congestive heart failure and Pulmonary-artery catheterization Effectiveness (ESCAPE)

You are being admitted to the hospital for treatment of worsening heart failure and the need to adjust your medicines. You are being asked to take part in a research study. Your primary cardiologist has given approval for you to be enrolled in this study, but you must read the following and ask as many questions as you need to, so that you understand what participation would involve, before you agree to be a volunteer.

Background and Purpose of the Study

Patients with worsening heart failure are treated with several medicines, which aim to help relieve the symptoms of heart failure and improve heart pressures and blood flow through the heart. Doctors and medical professionals have two ways to adjust medicines when patients come to the hospital with symptoms of worsening heart failure. One is to use your symptoms and physical signs. The other, in addition to your symptoms and physical signs, uses an instrument called a pulmonary-artery catheter (PAC) to measure the pressures and blood flow of the heart. A PAC is a thin, flexible tube that is inserted into a vein in the neck, and then pushed forward through this vein into the place where blood vessels enter the heart. The PAC stays in place for 2 to 5 days. When patients are treated for heart failure in the hospital, the PAC is often used to measure the pressures and blood flow in the heart.

The purpose of this study is to compare these two ways to adjust medicines that improve the pressures and blood flow in the hearts of people with worsening heart failure. It will be important to know, in the long term, which method is better for managing patients suffering from heart failure.

This study will enroll 500 patients at 22 heart-failure centers in the United States. The National Heart, Lung, and Blood Institute, part of the National Institutes of Health (NIH), is sponsoring the study.

Procedures

If you agree to participate in this study:

You will be randomly assigned (as if by coin-toss) to one of the two treatment groups. If you are assigned to the group that uses a PAC, you will have the PAC placed, and it will remain in place for 2 to 5 days. The machine used to place the PAC uses fluoroscopy (a type of X-ray that helps the physician guide the PAC to the exact spot where it needs to be). The study physician also will ask you about your symptoms and perform a physical exam. If you are not assigned to the PAC group, no PAC will be placed, but you still will be asked about your symptoms and receive the physical exam. There is a 50/50 chance you will receive a PAC. Some study procedures will be performed in the hospital (at admission and as you are about to leave the hospital) and some will occur during visits to the clinic, which will occur roughly at 7 days (if you have been discharged), 14 days, 1 month, 2 months, 3 months, and 6 months.

Blood samples will be taken to measure levels of two hormones, atrial natriuretic peptide and brain natriuretic peptide, produced by your heart and brain, respectively. This will be done four times in the study: when you enroll, when you are discharged from the hospital, and at 3 months and 6 months after you enroll. A **total** of about 10 tablespoons of blood will be taken over the 6 months.

If you enroll, you will be asked questions about living with your heart-failure symptoms and your desire for better health. These questions take about 10 minutes to answer the first time they are asked. These questionnaires will then be repeated at 1 month, 3 months, and 6 months.

You also will be asked to complete a heart-failure questionnaire that takes about 15 minutes. This questionnaire will be given seven times during the study: at enrollment, at discharge, and at 2 weeks,

1 month, 3 months, and 6 months after enrollment.

You will have an echocardiogram (a test that uses sound waves to measure heart function) three times during the study: at enrollment, at discharge, and at 3 months.

You will be asked to perform an exercise test on a bicycle (or a treadmill) with a mouthpiece to measure oxygen use. You will be encouraged to exercise until you are tired, but you can stop at any time. You will do this test at enrollment, at discharge, and at 3 months. The exercise test is the same test that is performed as part of the standard care and evaluation of patients with heart failure.

You will be asked to do a 6-minute walk at enrollment, at discharge, at 3 months, and at 6 months. We will ask you to walk in a specified area for 6 minutes. You may stop to rest if needed.

Risks

Risks associated with participating in the study include the possibility of skin bruising from the taking of blood samples as well as having momentary discomfort. There is a slight risk of infection (1/1000). The risks associated with the insertion of a PAC include infection (1/1000), bleeding (1/1000), a blood clot (1/1000), collapsed lung (less than 1/1000), or heart-rhythm problems (less than 1/1000).

To place the PAC in the correct position, fluoroscopy, X-ray, or both are required. The amount of radiation you will receive for this study has been carefully calculated. The National Committee on Radiation Protection has set "occupational radiation exposure limits." The limits are defined as the "dose of radiation that in light of the present knowledge, is not expected to cause appreciable bodily injury to a person at any time during his/her lifetime." The risks of this amount of occupational exposure for any scientist, radiologist, or technologist who is exposed to radiation nearly everyday, are considered very small, and at these levels, which have been in effect since 1957, there is no indication of harmful effects to the worker or any offspring. We estimate that the maximum exposure that you will get from the combination of these studies is about 1% of the amount allowed by current exposure limits per year. This radiation dose is what you would receive from this study only; it does not include any exposure you may have received or will receive from other tests.

Benefits

You may not receive any benefit from participating in this study, but other patients with heart failure may benefit from the overall findings of the study in the future. Many heart-failure patients participating in studies such as this one are thought to benefit from participation, regardless of the treatment to which they are assigned. This may be due to the extra care they receive during participation.

Alternative Therapy

If choose not to participate in this study, you will continue to receive the standard treatment for heart failure. This may or may not include the use of a PAC, as decided by your doctors.

Significant Findings

As the study continues, we will let you know about any major developments that could affect your willingness to participate. We will provide you with the relevant information so that you can consider whether to continue in the study.

Confidentiality

The confidentiality of study records that identify you will be maintained within _____ (name of the hospital). Your identity will masked if material from your records is used for publication or education. However, authorized representatives from the U.S. Food and Drug Administration (FDA) and the National Heart, Lung, and Blood Institute may inspect the records.

For Women of Childbearing Potential

Some procedures in this study could be harmful to a developing fetus. If you are a woman of childbearing potential, we will perform a pregnancy test to be certain that you are not pregnant. The pregnancy test will involve taking about 1 teaspoon of blood. We also might request a urine sample

from you. If you are sexually active, you must certify that you are using an acceptable form of birth control, such as hormonal contraceptives (birth-control pills), an intrauterine device (IUD), or barriers with spermicide throughout the study.

By signing this consent form, you are agreeing to use an acceptable form of birth control during the study. If you have any questions about this subject, do not hesitate to ask your doctor or the person who is requesting that you participate in the study. During the study, if you think that you might have become pregnant, please notify the study doctor immediately.

You also cannot participate in this study if you are breastfeeding. If you are found to be pregnant or nursing, you will be withdrawn from the study without your consent.

Costs

Both study methods of adjusting medicines are considered standard care for patients with heart failure. Whichever method you receive, your care will be billed as part of standard care to your insurance. All medicines given are those typically used to treat heart failure. The echocardiograms, exercise test, and blood tests performed as part of the study will be provided free.

Voluntary Statement of Understanding And Agreement

Participation in this research is voluntary. You can withdraw your consent and stop participating in this study any time, and this will not affect your regular treatment or medical care in any way. If you decide to end your participation at any time, please notify Dr. _____ at _____ or Dr. _____ at _____, who will explain how to withdraw from the study.

I have read the above and have been given an opportunity to talk about participating in this study and to ask questions. I know that I can contact _____ or _____ to answer any questions I have during the study, and the Office of Risk Management for _____ at _____ if I have any questions about my rights as a research subject. I agree to participate with the understanding that I can withdraw at any time without affecting my regular care. I have been given a copy of this form for my records.

_____	_____
Patient	Date
_____	_____
Parent or Guardian (if patient is less than 18 years old)	Date
_____	_____
Person Obtaining Consent	Date

20. Appendix 2. New York Heart Association Classifications

Class	Description
I	No activity limitations and no discomfort.
II	Patients are comfortable at rest, but ordinary activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients are comfortable at rest, but less-than-ordinary activity results in fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients cannot perform any activity without discomfort, symptoms of cardiac insufficiency or anginal syndrome are present at rest, and discomfort is increased with activity.

*Adapted from reference 14.

21. Appendix 3. Schedule of Events

	Randomization	3 Days	5 Days	7 Days	Optimal Status	Discharge	2 Weeks*	1 Month†	2 Month‡	3 Month§	6 Months‖
Clinical assessment	4	4	4	4	4	4	4	4	4	4	4
Endpoint summary						4	4	4	4	4	4
Drug log	4	4	4	4	4	4	4	4	4	4	4
CPX test	4					4				4	
6-minute walk	4					4				4	4
Echocardiogram	4					4				4	
Peptides	4					4				4	4¶
QOL questionnaires	4							4		4	4
Visual Analog Scale	4					4	4	4	4	4	4
Cost assessment						4	4	4	4	4	4

CPX = cardiopulmonary exercise; QOL = quality of life. *14 ± 7 days after randomization. †30 ± 14 days after randomization. ‡60 ± 14 days after randomization. §90 ± 14 days after randomization. ‖180 ± 14 days after randomization. ¶ Drawn and held.

22. Appendix 4. Guidelines for PAC Insertion, Maintenance, and Waveform Analysis

One of the fundamental goals of ESCAPE is to evaluate the safety and efficacy of the PAC. To properly assess its utility, investigators must ensure that all sites use standard protocols when collecting and interpreting hemodynamic data. Therefore, sites should refer to the following guidelines when managing the PAC.

Insertion Preparation:

Use aseptic technique when preparing to insert the PAC.

1. Flush catheter lumens with sterile solution to ensure patency and remove air.
2. Check balloon integrity by inflating the balloon to the recommended volume (1.5 mL).
3. Connect the catheter injectant and pressure-monitoring system to flush systems and pressure transducer. Make sure there is no air in the lines.

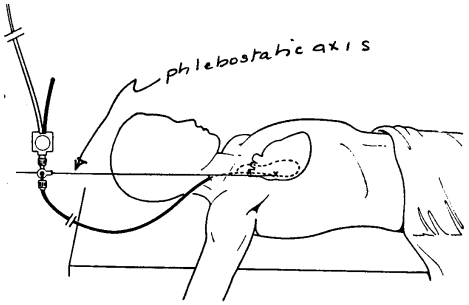
Insertion Procedure:

1. Prepare and drape patient using sterile technique.
2. Introduce catheter into the vein by percutaneous insertion, using a Seldinger-type guidewire, vein dilator, and catheter-introducer sheath.
3. Under continuous-pressure monitoring, with or without fluoroscopy, gently advance the catheter into the right atrium.
4. Inflate the balloon with air to the recommended volume (1.5 mL).
5. Advance the catheter until pulmonary capillary wedge pressure (PCWP) is obtained, then deflate the balloon.
6. If right ventricular (RV) pressure tracing is still observed after advancing the catheter 15 cm beyond the point where the initial RV pressure was obtained, the catheter may be looping in the ventricle. Deflate the balloon and withdraw the catheter into the right atrium. Then reinflate the balloon and advance the catheter again.
7. Observe the cardiac monitor for arrhythmias during insertion.
8. Verify blood return and ease of flush on all catheter ports.

Monitoring:

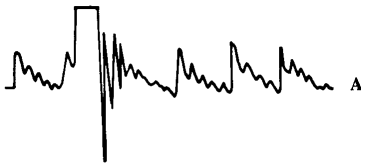
<u>Obtaining Accurate Hemodynamic Values: Basic Set-Up</u>

1. Leveling/Zeroing
   - Purpose – To eliminate hydrostatic pressure differences within the fluid-filled system, by zeroing system at estimated level of the catheter tip
   - Method – Place air reference stopcock at level of mid-chest (phlebostatic axis) and open to room air for a "zero" pressure reading
   - Frequency – Re-zero the transducer before each hemodynamic measurement. Also re-zero if patient has moved, if there are large temperature shifts, before all critical hemodynamic measures, and at least every 4 hours.



2. Square-Wave Test
   - Purpose – Use of fast-flush device to assess damping of fluid filled system. The square-wave test exposes the system to a rapid change in pressure.
   - Method – Run graphic recorder; rapidly activate and release the fast-flush device; record the square wave produced by the fast flush activation; repeat two to three times.
   - Frequency – Perform square-wave test before collection of each hemodynamic measurement. Also may perform more often if clinically indicated.

A. Under-damped Wave



B. Over-damped Wave

C. Normal Wave

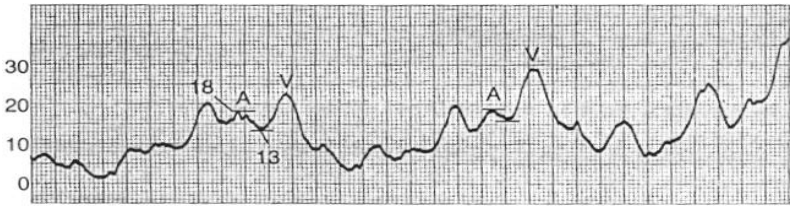
1. Nurses should record insertion length of catheter in their assessment at every shift.
2. Position patient in the supine position for hemodynamic readings. The head of the bed does not need to be flat, but measurements should be made in the same position for consistency. Nurses should record the patient position when readings are taken.

<u>Obtaining Accurate Hemodynamic Values: Waveform Analysis</u>

1. Monitor the PA waveform at all times to ensure proper placement of the catheter.
2. Use the following guidelines when measuring RAP; PAS/PAD/PA mean; and PCWP mean/PCWP A wave/PCWP V wave:
   - To minimize respiratory effects on hemodynamic pressures, always measure hemodynamic waveforms at ***end-expiration.***
   - To identify ***end-expiration,*** locate the waveform just before hemodynamic pressures ***decline*** with inhalation.
   - You may use the hemodynamic results indicated on the bedside monitor. However, these should be verified with paper tracing results. If there is any discrepancy between the monitor values and the paper tracing results, use the paper tracing data.
   - The RAP, PAS/PAD/PA mean, and PCWP mean/PCWP A wave/PCWP V wave should be manually identified on paper tracings. The study coordinator should collect the tracings of the

hemodynamic measures obtained as part of the ESCAPE protocol. These will include the 8 AM, 4 PM, and lowest PCWP tracings obtained each day. These tracings will be considered source documents. Study coordinators should instruct ESCAPE nurses to collect the paper tracings of all the hemodynamic measurements taken each day.

3. When measuring the PCWP, inflate the balloon slowly while observing the waveform. Stop after 1.5 mL of air has been inflated.
4. The mean RAP should be measured as the mean of the "A" wave.
5. The PAP systolic pressure should be measured at the peak of the waveform; the PAP diastolic pressure should be measured at the base of the waveform.
6. The mean PCWP should be measured as the mean of the "A" wave.



Obtaining Accurate Hemodynamic Values: Cardiac Output Measurements

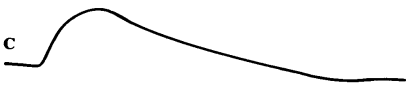
To determine cardiac output by thermodilution, a known amount of sterile solution of known temperature is injected into the right atrium or vena cava, and the resultant change in blood temperature is measured in the pulmonary artery by the catheter thermistor. Cardiac output is inversely proportional to the integrated area under the resulting curve. This method has been shown to provide good correlation with the direct Fick method.

1. Place the patient in a supine position (head of the bed <45°) as tolerated.
2. Verify appearance of PA waveform on monitor to ensure correct placement of catheter.
3. Fill the CO syringe to the 5-mL or 10-ml mark depending on the standard in your hospital. You must use the same volume of injectant for each measurement.
4. You may use either iced or room temperature injectant. However, you should use the same temperature injectant for each measurement.
5. Make sure to adjust the computational constant according to the volume and temperature of the injectant.
6. Open the stopcock position to the injectant syringe at the proximal lumen.
7. At end expiration, press the START button on the thermodilution computer and manually inject the syringe contents rapidly and smoothly over 4 seconds.
8. Observe the thermodilution curve on the monitor.
9. Take at least three consecutive measures.
10. Make sure that the cardiac output curves are smooth and regular. Sample cardiac output curves are in the figures below.

A. Normal Cardiac Output

B. High Cardiac Output

C. Low Cardiac Output



D. Uneven Injection

11. Average all cardiac output values if they are within 10% to 15% of the median value. Do not average any outlying results.
12. Turn the stopcock to close access to the CO flush solution.
13. Verify that the PCWP tracing has not changed.

Removal of Catheter:

1. Remove the catheter as soon as it is clinically indicated.
2. Make sure that the balloon is deflated. Remove syringe from catheter and lock balloon lumen.
3. Remove catheter sheathing from the introducer and remove catheter in swift movement while holding the introducer. Monitor for arrhythmias.
4. Insert obturator under aseptic conditions.
5. Re-dress insertion site.
6. Record the removal of PAC.

Safety Guidelines:

1. Keep catheter tip centrally located in the main branch of the pulmonary artery.
   - During insertion, inflate the balloon to the full recommended volume (1.5 mL).
   - To reduce any redundant length of catheter in the right atrium or ventricle, slowly pull the catheter back 2 to 3 cm.
   - Do not advance the catheter tip too far peripherally.
2. Anticipate spontaneous catheter-tip migration toward the periphery of the pulmonary bed.
   - Monitor the distal tip pressure continuously, to ensure that the catheter is not inadvertently wedged with the balloon deflated
   - Check daily chest X-ray to ensure catheter is properly placed.
   - If migration of catheter tip has occurred, pull catheter back to central pulmonary artery position.
3. Exercise caution when inflating the balloon.
   - If the PCWP reading is obtained with <1 mL of air, pull the catheter back to a position where the full or near-full inflation volume produces a wedge pressure tracing.
   - Never overinflate the balloon beyond the maximum volume printed on the catheter shaft.
   - Do not use liquids for balloon inflation; they may be irretrievable and may prevent balloon deflation.
   - Keep the syringe attached to the balloon lumen of the catheter, to prevent accidental injection of liquids into the balloon.
4. Obtain wedge pressure readings only when necessary
   - Keep PCWP reading time to a minimum – 10 to 15 seconds or two respiratory cycles, maximum.
   - Avoid prolonged maneuvers to obtain PCWP.
   - Never flush the catheter when the balloon is wedged in the pulmonary artery.
5. If a patient has known left bundle branch block, place a transcutaneous pacemaker before PAC

insertion, in the event that complete heart block develops.