Appendix I: Echocardiographic Image Acquisition Protocol

For the echocardiogram, the patient will be positioned in left lateral recumbency or in the position that permits optimal imaging. It is strongly recommended that a customized echocardiography bed be used with a standard cut-out mattress to expose the cardiac apex. With digital archiving, at least 3 and no more than 5 cardiac cycles are requested for two-dimensional imaging. At least 5 cardiac cycles are required for spectral pulsed wave (PW) and continuous wave (CW) Doppler. For patients in atrial fibrillation, a minimum of 2 captures of 5 consecutive cardiac cycles are required. Unless otherwise specified, depth should be adjusted to maximize the image while including all necessary structures. All images will be acquired at end-expiration held during quiet respiration. Harmonic imaging should be employed to optimize visualization of endocardial borders. All PW, CW Doppler and m-mode recordings will be performed at a sweep speed of 100 mm/sec. Color Doppler Nyquist limits will be adjusted to the range of 0.5 – 0.7 m/sec, unless otherwise specified. The following protocol is required however additional images should be obtained at the discretion of the sonographer/physician.

Protocol for Transthoracic Echocardiogram (TTE)

1. PLAX with and without magnification of the left ventricular outflow tract; with and without color flow Doppler interrogation of the aortic and mitral valves. Careful attention will be paid to identifying the vena contracta of the mitral regurgitant jet using zoom views.

2. An m-mode recording of the left ventricle just below the tips of the mitral leaflets.

3. Parasternal inflow view of the tricuspid valve; with and without color flow Doppler (CW if jet imaged parallel to beam).

4. Parasternal outflow view of the pulmonic valve; with and without color flow Doppler and PW and CW of the PV.

5. PSAX (ensure on-axis views)
   a. Apex
   b. Mid-papillary muscle level.
   c. Level of the mitral valve when both anterior and posterior leaflets are visualized. Position the Color Doppler scan box over the mitral orifice to visualize the regurgitant jet origin.
   d. Tips of the mitral valve leaflets (identity minimum diastolic orifice).

6. Basal PSAX (at the aortic valve level). Evaluation of PV and TV performed; with and without color flow Doppler. Pulsed Doppler sample of pulmonary flow at the level of the pulmonary valve to measure pulmonary velocity time interval (VTI) opening and closing transients of the pulmonary valve should be recorded. Optimize the pulmonary valve annulus for measurement of the pulmonary annular diameter.

7. Apical 4-chamber view
    a. Full sector and zoom/res of individual valves with and without color flow interrogation of mitral and tricuspid valves. The color flow Doppler interrogation should include the entire left atrium taking care to include wall-impinging eccentric jets in the region of interest. Gain should be adjusted to reduce excess noise. Spectral Doppler interrogation in this view includes:

        i. PW Doppler of mitral inflow at mitral leaflet tips.
        ii. PW Doppler of mitral inflow at the level of the mitral annulus at end diastole with a small sample volume.
        iii. CW of the mitral inflow signal.
        iv. CW of the mitral regurgitant jet with care to record a complete signal and maximize the peak velocity. Contrast should be used to enhance this signal when incomplete and when a peak velocity cannot be determined. NOTE: Occasionally eccentric CW jets may require interrogation of additional views (e.g., PLAX, Apical 2C view) to obtain the true maximal jet velocity.
        v. CW of tricuspid regurgitant jet for estimation of pulmonary artery systolic pressure. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
        vi. PW Doppler of right pulmonary vein flow. The sample volume should be placed at least 1 cm within the pulmonary vein, if possible. If jet is inadequate for measurement, this recording should be repeated following contrast injection (see below).
        vii. Color flow Doppler visualization of regurgitant jets (mitral and tricuspid).
        viii. PISA (proximal isovelocity surface area) using zoomed views for estimation of regurgitant orifice area.
            1. Mitral Regurgitation: the Nyquist limit will be lowered and the baseline shifted in the direction of flow (toward left atrium) to maximize the PISA signal. The PISA aliasing velocity should be set between 0.3 and 0.4 m/sec. Record 3-5 cycle (more for atrial fibrillation) clip of PISA as well as still frame of maximum PISA radius.
            2. Tricuspid regurgitation: : the Nyquist limit will be lowered and the baseline shifted in the direction of flow (toward left atrium) to maximize the PISA signal. The PISA aliasing velocity should be set as close to 0.28 m/sec as possible. Record 3-5 cycle clip of PISA as well as still frame of maximum PISA radius.
        ix. Tissue Doppler of the mitral annulus (lateral and septal) and the tricuspid annulus.
        x. Velocity of propagation across the mitral valve.

   b. Apical 4-chamber zoom/res image of the left atrium with mitral annulus in the middle of sector.
   c. Apical 4-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus).

8. Anteriorly angulated 4-chamber view:
   a. Color flow Doppler to exclude aortic insufficiency. If present, aortic insufficiency jet will be optimized to permit measurement of the pressure half time using CW Doppler.
   b. PW Doppler in left ventricular outflow tract positioned such that closing artifact but not opening artifact of the valve is visible.
   c. CW Doppler through the aortic valve.

9. Apical 2-chamber view
   a. Mitral valve with and without color Doppler.
   b. Apical 2-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus).

10. Apical 3-chamber view
    a. Mitral valve and aortic valve with and without color Doppler.
    b. Apical 2-chamber zoom/res images of the left ventricle (excluding most of LA but including all of the basal LV/annulus)

11. Subcostal imaging
    a. Inferior vena cava with and without a “sniff”.
    b. Color Doppler of inter-atrial septum to interrogate presence of ASD.
    c. 4-chamber and SAX views (particularly if parasternal evaluation was limited).

12. Contrast will be used for endocardial border delineation when less than 80% of the endocardium can be visualized on the harmonic image. Contrast can also be employed for enhancement of the tricuspid regurgitant and pulmonary venous flow signals. During the contrast imaging, the mechanical index (MI) should be adjusted according to manufacturer recommendations.

Note: Addition of any non-standard imaging will be coordinated in collaboration with the selected Core Laboratory under a protocol amendment and should be obtained at the discretion of the sonographer/physician.

Protocol for Intra-operative Transesophageal Echocardiogram (TEE)

Intra-operative TEE imaging will be performed on all specified index operative procedures in the CTSN clinical trials, consistent with standard clinical care. For the purposes of the CTSN trials, the clinically indicated TEE’s will be performed according to the standardized protocol below. The echos will be over-read by the echo core lab.

Valvular evaluation should always include Color Doppler and Pulsed/Continuous Wave Doppler as appropriate.

Pre-Procedure Imaging
A comprehensive intra-operative multiplane TEE as defined by the ASE/SCA Guidelines (Shanewise JS et al. J Am Soc Echocardiogr 1999;12:884-900) should be performed. The following checklist may be used with appropriate Doppler performed for valvular assessment:

Mid and High esophageal views

- 4 Ch view (of entire LV/RV)
- Mitral Valve: (lower depth) with appropriate color Doppler and recording of CW in at least one plane
  - Transverse Plane (0°)
  - Commissural View (60°)
  - Two-chamber View (90°)
    - Change depth to imaged entire LV as well
  - Three-chamber View (120-140°)
    - Change depth to imaged entire LV as well
- LVOT/AV/Aorta
  - Long-axis view (120-140°) with color Doppler
  - Ascending aorta (mid to high esophageal view) (90°)
  - Ascending aorta SAX views (0°, high esophageal)
  - AV SAX (30°, mid esophageal) with color Doppler
- Main PA/PV
  - Bifurcation view (0-30°, high esophageal)
  - RVOT view (70°, mid esophageal)
- LA/LAA (0-180°)
- RA/TV/IAS:
  - 4 Ch view (all of RV then change depth for TV)
  - TV/IAS rotation (0-90°) with color Doppler
  - Bicaval view (90-110°)
  - Pulmonary veins (either at 90° or 0°)

Transgastric views

- Three horizontal 2D short axis views are requested
  - Mitral valve level
  - Mid papillary muscle
  - Apical level.
- Horizontal 2D images of the right ventricle and tricuspid valve.
- Deep Gastric views
  - 5Ch view Aortic valve (with color, PW and CW Doppler)

Aorta

- Thoracic aorta
- Aortic arch (SAX and LAX views)
- Pulmonic valve

Post-procedure Imaging
A full post-procedure TEE should be obtained if time permits. Otherwise, the study should be tailored to the procedure performed, including a minimum of the following:

Mitral valve procedures

- Full rotation on mitral valve (with color, pulsed and continuous wave Doppler) with attention to:
  - MR jet area and vena contracta
  - PISA (time permitting)
  - Continuous wave Doppler to assess post-procedure gradients
- LVOT PW (deep gastric) to calculate MR volume or MVA by CE
- Deep gastric SAX views of LV requested
  - Base (MV level)
  - Mid (papillary muscle level)
  - Apex (no papillary muscles seen)

Echocardiographic Analysis

TTE will be performed using parasternal, apical, and subcostal views according to a standardized echo study protocol (see below).

1. *Quantification of MR*
   Quantification of mitral regurgitation will be performed according to the recommendations of the American Society of Echocardiography Recommendations for evaluation of the severity of native valvular regurgitation[1]. The primary measure of mitral regurgitation will be effective regurgitant orifice area (EROA)[2-4].

   Two methods will be used to calculate EROA:

   a. PISA (Proximal Isovelocity Surface Area) method.

$$EROA = \frac{6.28 \text{ x } radius^2 \text{ x } aliasing\ velocity}{Peak\ MR\ velocity}$$

Using this technique, flow convergence area proximal to mitral regurgitant orifice visualized on echocardiography can be used to calculate the rate of mitral regurgitant flow and effective regurgitant orifice area (EROA). Regurgitant flow converges to the regurgitant orifice with multiple isovelocity hemispheric configurations. Manipulation of the color flow map identifies a proximal isovelocity surface area (PISA) at a certain aliasing velocity which is equal to the velocity of the PISA. The region of interest centered on the regurgitant orifice and PISA needs to be zoomed with color-flow imaging and the zero baseline of the color flow map is shifted downward to increase the radius of the PISA. It is recommended that the aliasing velocity be set at 25-40 cm/s. PISA is calculated as 2 л x radius^2. Therefore, flow rate at the PISA is calculated as 6.28 x radius^2 x aliasing velocities. It is divided by peak MR velocity to obtain the EROA. Peak MR velocity is obtained by continuous-wave Doppler from the apex. Mitral regurgitant volume (RVol) is calculated by multiplying MR TVI by EROA.

b. Quantitative Flow method. Flow rate and stroke volume can also be estimated using a combination of PW Doppler and two-dimensional measurements . The hydraulic orifice formula states that the volume of blood crossing any valve-annulus is the product of the cross-sectional area (CSA) and the velocity time integral (VTI) of flow at the annulus. In the presence of mitral regurgitation, the diastolic flow across the mitral annulus represents both the systolic forward stroke volume and systolic regurgitant volume. Subtracting the forward stroke volume (across a nonregurgitant aortic or pulmonic valve) from this diastolic volume, yields the mitral RVol. The EROA is subsequently derived by dividing the RVol by the MR VTI.

The EROA will be used as the measure of MR severity, because (1) it is objective, and (2) because it is less load dependent than regurgitant volume. MR shall be graded by the following scale:

- <20 mm^2 = mild MR
- 20-40 mm^2 = moderate MR
- >40 mm^2 = severe MR

In using MR for statistical calculations, the PISA value will be treated as a continuous variable. PISA has significant limitations (e.g. non-spherical or multiple jets), but will not be ‘overcalled’ for the purpose of this study. Additional secondary TTE measures of MR will be recorded as follows:

a) color flow width and area
b) intensity of the continuous-wave Doppler signal
c) pulmonary venous flow contour
d) peak early mitral inflow velocity
e) vena contracta width
f) regurgitant volume

2. *Quantification of Mitral Valve Area*

Given the possibility of excessive tightening of the mitral annulus with mitral repair, it is important to remember to include the continuous wave Doppler of the mitral inflow (see Protocol 7iii) and if possible, add images of color inflow with baseline shift toward the ventricle, in order to see a diastolic PISA. Mitral valve area will be calculated by at least one of the following methods:

a. Continuity equation: Limited if there is any mitral regurgitation or significant pulmonic or aortic regurgitation
b. Planimetry: from parasternal short-axis view

c. Color Doppler jet width in orthogonal planes: use of 4-chamber color Doppler (diastolic flow) and 2 or 3-chamber color Doppler (diastolic flow)
d. Diastolic PISA: validated for MV area even in the setting of MR
e. Pressure Halftime method

3. *Quantification of Left Ventricular Size and Function*
   a. Short axis dimension using the parasternal long-axis view of the LV just distal to the mitral valve and left ventricular outflow.
   b. Long-axis dimension from the apical view.
   c. LV sphericity will be calculated as the ratio of the LV long-axis dimension and the maximum short-axis dimension.
   d. LVEF will be measured by the biplane Simpson's volumetric method (a combination of apical four- and two-chamber views). The LV endocardial border will be traced contiguously from one side of the mitral annulus to the other side excluding the papillary muscles and trabeculations. LVEF will be determined from LV volumes using the formula *LVEF = (EDV-ESV)/EDV* where EDV = end-diastolic volume and ESV = end-systolic volume.
   e. If the definition of the LV endocardial border is not satisfactory for digitization following image acquisition, LVEF will be determined visually.
   f. LV end-systolic volume index shall be calculated using the biplane volumetric method as above, adjusted for body surface area (ml/m^2). [4,5]
   g. Radial strain and twist at different levels of the myocardium will be assessed from apical SAX, mid-papillary SAX and basal SAX views of the left ventricle.

4. *Assessment of Regional Left Ventricular Function and Viability Assessment*
   a. Baseline assessment: Regional left ventricular function will be reassessed echocardiographically using the ASE/ACC/AHA approved 17 segment model. For each segment, function will be scored as normal = 2, hypokinetic = 1, akinetic = 0, dyskinetic = - 1. A wall motion score (WMS) will be calculated as the sum of the individual segment scores and the wall motion score index calculated as WMS/17.
   b. Post-revascularization: Regional left ventricular function will be reassessed echocardiographically using the ASE/ACC/AHA approved 17 segment model. As on the baseline study, for each segment, function will be scored as normal = 2, hypokinetic = 1, akinetic = 0, dyskinetic = - 1. A wall motion score (WMS) will be calculated as the sum of the individual segment scores and the wall motion score index calculated as WMS/17. WMSI (post-revascularization) – WMSI (baseline) will be used as a surrogate for viability. This assumes complete revascularization of all viable segments.

5. *Quantification of Right Ventricular Size and Function*
   a. Tricuspid annular plane systolic excursion (TAPSE) will be measured from apical 4-chamber view of the right ventricle (either by M-mode recording of the annular excursion or two-dimensional estimation).
   b. Tissue Doppler of the tricuspid annulus will be recorded for measurement of peak systolic velocity as well as diastolic E' and A'.

c. Fractional area change: Diastolic and systolic areas will be measured by tracing the endocardial right ventricular cavity from the 4-chamber view, in diastole and systole. The difference between systolic and diastolic area, divided by diastolic area and multiplied by 100, is the fractional area change (%).

6. *Quantification of Tricuspid Regurgitation*
   a. Jet Area will be measured from multiple planes however the accuracy of semi-quantitative measure of TR severity (mild, moderate and severe) is greatest with central jets.
   b. Vena Contracta will be measured from multiple views noting that only a binary classification can be used with this measure (severe and not severe).
   c. PISA: semi-quantitative measure of TR severity (mild, moderate and severe) according to the ASE recommendations[1]:

Table 8 Echocardiographic and Doppler parameters used in grading tricuspid regurgitation severity

Parameter	Mild	Moderate	Severe
Tricuspid valve	Usually normal	Normal or abnormal	Abnormal/Flail leaflet/Poor coaptation
RV/RA/IVC size	Normal*	Normal or dilated	Usually dilated**
Jet area-central jets (cm^2)$	< 5	5-10	> 10
VC width (cm)$^{\Phi}$	Not defined	Not defined, but < 0.7	> 0.7
PISA radius (cm)$^{\psi}$	≤ 0.5	0.6-0.9	> 0.9
Jet density and contour–CW	Soft and parabolic	Dense, variable contour	Dense, triangular with early peaking
Hepatic vein flow†	Systolic dominance	Systolic blunting	Systolic reversal

CW, Continuous wave Doppler; *IVC*, inferior vena cava; *RA*, right atrium; *RV*, right ventricle; *VC*, vena contracta width.
* Unless there are other reasons for RA or RV dilation. Normal 2D measurements from the apical 4-chamber view: RV medio-lateral end-diastolic dimension ≤ 4.3 cm, RV end-diastolic area ≤ 35.5 cm^2, maximal RA medio-lateral and supero-inferior dimensions ≤ 4.6 cm and 4.9 cm respectively, maximal RA volume ≤ 33 ml/m^2(35;89).
** Exception: acute TR.
$ At a Nyquist limit of 50-60 cm/s. Not valid in eccentric jets. Jet area is not recommended as the sole parameter of TR severity due to its dependence on hemodynamic and technical factors.
$^{\Phi}$ At a Nyquist limit of 50-60 cm/s.
$^{\psi}$ Baseline shift with Nyquist limit of 28 cm/s.
† Other conditions may cause systolic blunting (eg. atrial fibrillation, elevated RA pressure).

7. *Additional Chamber and Valve Measurements*
   a. Left atrial dimensions: AP dimension and volume by biplane Simpson's rule and/or biplane area-length method.
   b. Mitral valve: tethering length and area, tethering angle, papillary muscle position and separation.

8. *Doppler*
   a. Intracardiac pressures:
      i. Pulmonary Artery (PA): PA systolic, diastolic and mean pressures will be estimated from TR velocity, PR end-diastolic velocity and PR peak diastolic velocity (if possible). Pulmonary vascular resistance will be estimated from TR velocity and PV VTI.
      ii. PCWP: estimated from E/E' ratio or E/Vp ratio.

9. *TEE Measurements*
   The intra-operative TEE protocol is designed to confirm left ventricular function and severity of mitral regurgitation, understanding that these measures may differ due to changes in loading conditions from the pre-operative TTE.

a. Pre and Post-operative qualitative assessment of left ventricular function (see 4 above).
b. Severity of mitral valve disease:
   iii. Mitral regurgitation jet area, vena contracta and PISA
   iv. Mitral valve area (see 2 above) if possible with peak and mean gradients recorded.

Baseline Transthoracic Echo Assessment of Degree of MR
The assessment of the degree of mitral regurgitation will be based on an integrated method as outlined by ASE document on Valvular Regurgitation outlined below. This is a semi-quantitative technique and would grade MR categorically as: Mild; Moderate; or Severe. The integrated method will use all aspects of the color Doppler jet including jet area/Left atrial area ratio; vena contracta and effective orifice area (EROA) base on the PISA method. In addition, supportive data such as left atrial size, E wave peak, and presence of pulmonary vein flow reversal will be incorporated into the assessment.

1. COLOR DOPPLER CRITERIA

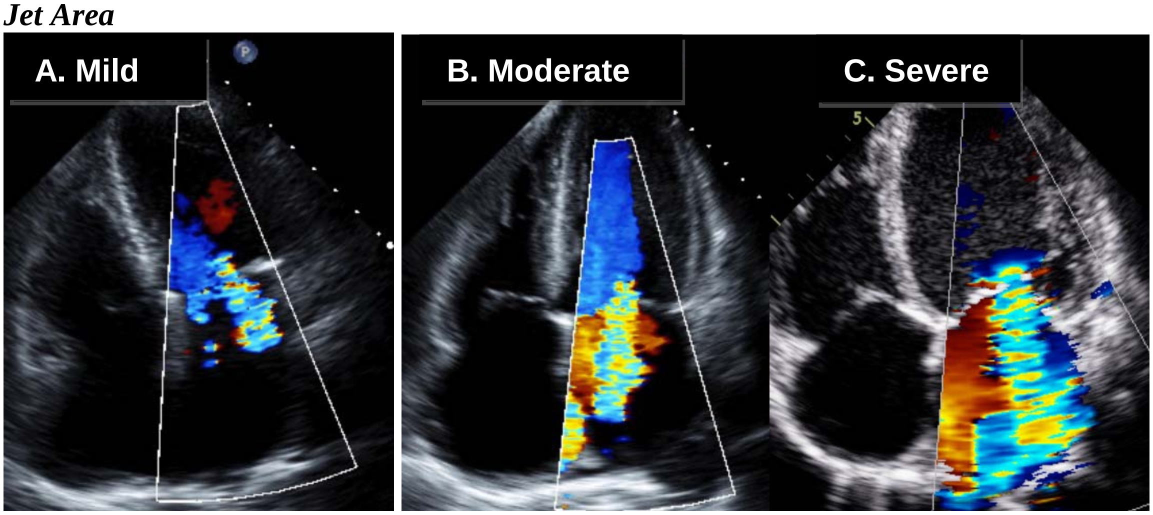
	Mild	**Moderate**	**Severe**
Color Flow Jet Area	< 20% of LA area)	20% to 39% of LA area	Large central jet (usually > 10 cm^2 or > 40% of LA area) or variable size wall- Impinging jet swirling in LA
Quantitative Parameters			
VC width (cm)	< 0.3	0.3 – 0.69	≥ 0.7
EROA (cm^2)	< 0.20	0.20-0.29 0.30-0.39	≥ 0.40

2. SUPPORTIVE CRITERIA

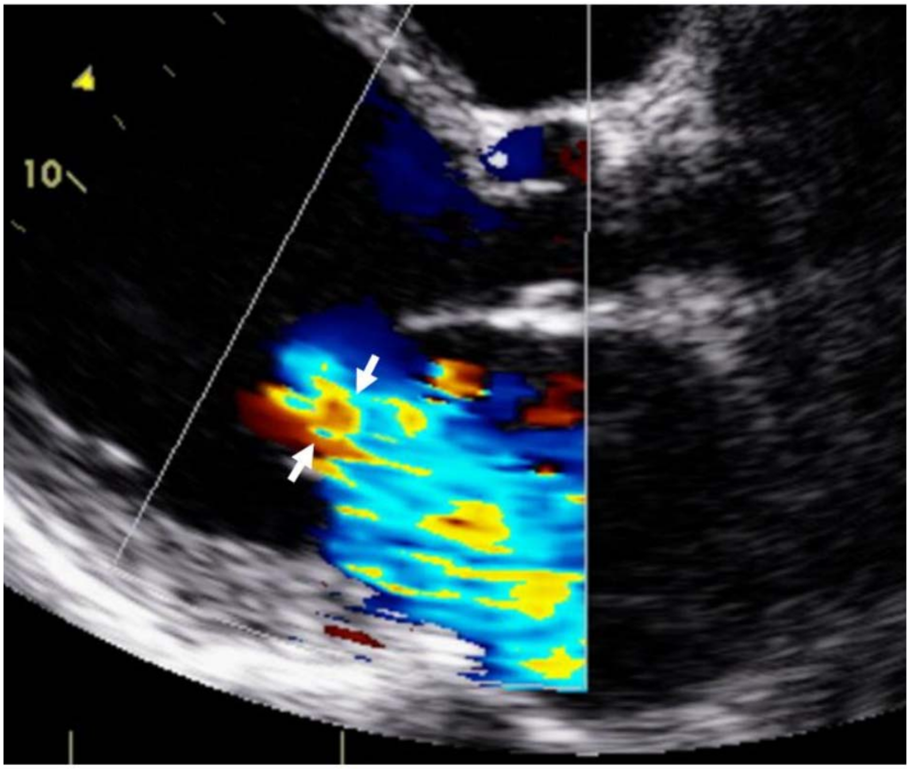
	Mild	**Moderate**	**Severe**
Structural Doppler Parameters			
LA size	Normal	Normal or dilated	Usually dilated
LV size	Normal	Normal or dilated	Usually dilated
Mitral leaflets or support apparatus	Normal or abnormal	Normal or abnormal	Abnormal/ Flail leaflet/ Ruptured papillary muscle
Mitral inflow - PW	A wave dominant	Variable	E wave dominant (E usually 1.2 m/s)
Jet density - CW	Incomplete or faint	Dense	Dense
Jet contour – CW	Parabolic	Usually parabolic	Early peaking-triangular
Pulmonary vein flow	Systolic dominance[§]	Systolic blunting[§]	Systolic flow reversal[†]

Examples:

Jet Area



Measurement of Vena Contracta



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