



Edwards

PARTNER 3:

A Prospective, Randomized, Controlled, Multi-Center Study to
Establish the Safety and Effectiveness of the SAPIEN 3
Transcatheter Heart Valve in Low Risk Patients who have Severe,
Calcific, Aortic Stenosis Requiring Aortic Valve Replacement

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PARTNER 3 - Low Risk

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Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter
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PROTOCOL SYNOPSIS

Title	A prospective, randomized, controlled, multi-center study to establish the safety and effectiveness of the SAPIEN 3 transcatheter heart valve in low risk patients who have severe, calcific, aortic stenosis requiring aortic valve replacement.
Purpose	To establish the safety and effectiveness of the Edwards SAPIEN 3 (Edwards Lifesciences, Irvine, California) Transcatheter Heart Valve (THV) in patients with severe, calcific aortic stenosis who are at low operative risk for standard aortic valve replacement (AVR).
Study Device	Edwards SAPIEN 3 THV system Model 9600 TFX (20, 23, 26 and 29 mm) with the associated delivery systems.
Control	Commercially available surgical bioprosthetic aortic valve replacement
Study Design	<p>Prospective, randomized, controlled, multi-center.</p> <p>Patients will be randomized 1:1 to receive either transcatheter heart valve replacement (TAVR) with the Edwards SAPIEN 3 or aortic valve replacement with a commercially available surgical bioprosthetic valve. A subset of eligible patients from each study arm will be enrolled in a computed tomography (CT) sub-study and/or an Actigraphy/QOL sub-study [enrollment closed] at select sites.</p>
Patient Population	Patients with severe, calcific, aortic stenosis requiring aortic valve replacement who are at low operative risk
Sample Size	<p>PARTNER 3 Randomized Trial: Up to 1182 patients will be enrolled.</p> <p>PARTNER 3 Sub-studies: Of the 1182 patients, a subset of patients will be enrolled in the following sub-studies:</p> <ul style="list-style-type: none">• CT Sub-study (up to 440)• Actigraphy/QOL Sub-study (up to 400) [Enrollment Closed] <p>PARTNER 3 Single-Arm Registries: Additional patients will be enrolled in the following single-arm registries:</p> <ul style="list-style-type: none">• Alternative Access Registry (100) [Enrollment Closed]

- Bicuspid Registry (up to 75)
- Underrepresented Populations Registry (up to 100)

Study Sites Up to 85 actively enrolling sites will participate. Selected sites will participate in a CT sub-study, an Actigraphy/QOL sub-study [enrollment closed], or the Underrepresented Populations Registry.

Visit Schedule Screening, Procedure, Post Procedure, Discharge, 30 day, 6 month, and annually through 10 years.

Primary Endpoint

Safety and Effectiveness:

Composite endpoint of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year post procedure.

Secondary Endpoints for Labeling

1. New onset atrial fibrillation at 30 Days
2. Length of index hospitalization
3. Death, KCCQ < 45 or KCCQ decrease \geq 10 points at 30 days
4. Death or All Stroke at 30 days
5. All Stroke at 30 days

Additional Safety and Effectiveness Endpoints

1. Mortality (all cause & cardiovascular) at 30 days and 1 year
2. Stroke (disabling and nondisabling) at 30 days and 1 year
3. Death or stroke at 1 year
4. Death or disabling stroke at 30 days and 1 year
5. Vascular complications (major) at 30 days and 1 year
6. Bleeding complications (life-threatening, disabling, or major) at 30 days and 1 year
7. Myocardial infarction at 30 days and 1 year
8. Acute kidney injury at 30 days

9. Renal replacement therapy at 1 year
10. New permanent pacemaker implantation resulting from new or worsened conduction disturbances at 30 days and 1 year
11. Coronary obstruction requiring intervention at 30 days and 1 year
12. New York Heart Association class at 30 days and 1 year
13. Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular & central) at 30 days, and years 1, 2, 3, 4, 5, 7, and 10
14. Rehospitalization (valve- or procedure-related including heart failure) at 30 days, 1 year and annually (up to year 10)
15. New onset atrial fibrillation at 1 year
16. ICU days and discharge location
17. Structural valve deterioration at years 1-5, 7 and 10
18. Days alive and out of hospital at 1 year
19. Six-minute walk test at 30 days and 1 year
20. Health status as evaluated by Quality of Life questionnaires
 - KCCQ at 30 days and 1 year
 - EQ-5D-5L at 30 days and 1 year
 - SF-36 at 30 days and 1 year

Inclusion Criteria

Candidates for this study must meet all of the following inclusion criteria:

1. Severe, calcific aortic stenosis as follows:
 - $AVA \leq 1.0 \text{ cm}^2$ or $AVA \text{ index} \leq 0.6 \text{ cm}^2/\text{m}^2$
 - Jet velocity $\geq 4.0 \text{ m/s}$ or mean gradient $\geq 40 \text{ mmHg}$ AND
 - 1) NYHA Functional Class ≥ 2 OR 2) exercise test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia OR 3)

asymptomatic with LVEF <50%

Note: Qualifying echo must be within the 90 days prior to randomization.

2. Heart team agrees the patient has low risk of operative mortality and has an STS < 4.
3. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site.

Exclusion Criteria

Candidates will be excluded from the study if any of the following conditions are present:

1. Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29 mm THV based on 3D imaging analysis
2. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
3. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before randomization
4. Aortic valve is unicuspid, bicuspid, or is non-calcified
5. Severe aortic regurgitation (>3+)
6. Severe mitral regurgitation (>3+) or ≥ moderate stenosis
7. Pre-existing mechanical or bioprosthetic valve in any position. (of note, mitral ring is not an exclusion).
8. Complex coronary artery disease:
 - Unprotected left main coronary artery
 - Syntax score > 32 (in the absence of prior revascularization)
 - Heart Team assessment that optimal revascularization cannot be performed.
9. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
10. Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states.

11. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
12. Hypertrophic cardiomyopathy with obstruction (HOCM)
13. Ventricular dysfunction with LVEF < 30%
14. Cardiac imaging (echo, CT, and/or MRI) evidence of intracardiac mass, thrombus or vegetation
15. Inability to tolerate or condition precluding treatment with anti-thrombotic/anticoagulation therapy during or after the valve implant procedure
16. Stroke or transient ischemic attack (TIA) within 90 days of randomization
17. Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy
18. Active bacterial endocarditis within 180 days of randomization
19. Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
20. Severe pulmonary hypertension (e.g., PA systolic pressure \geq 2/3 systemic pressure)
21. History of cirrhosis or any active liver disease
22. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters).
23. Significant abdominal or thoracic aortic disease (such as porcelain aorta, aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system or cannulation and aortotomy for surgical AVR .
24. Hostile chest or conditions or complications from prior surgery that preclude safe reoperation (e.g., mediastinitis, radiation damage, abnormal chest wall, adhesion of aorta or IMA to sternum, etc.)
25. Patient refuses blood products
26. BMI > 50 kg/m²
27. Estimated life expectancy < 24 months
28. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication

29. Immobility that would prevent completion of study procedures (e.g. six-minute walk tests, etc.)
30. Patient is not a candidate for both arms of the study (not applicable to single-arm registries)
31. Currently participating in an investigational drug or another device study.
Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

CT Imaging Sub-Study Inclusion Criteria

Sites with the ability to perform high quality multi-phasic, ECG-gated CT scans (i.e., 4D) will be selected to participate in a CT sub-study

All CT sub-study participants must meet inclusion criteria 1-3 above

CT Imaging Sub-Study Exclusion Criteria

In addition to the exclusion criteria noted above, patients will be excluded from the sub-study if the following is present:

1. Condition requiring or planned use of anticoagulants following the valve implant procedure
2. GFR < 50
3. Inability to perform high-quality MDCT study for any reason (e.g., atrial fibrillation with rapid ventricular response)

Actigraphy/QOL Sub-Study Eligibility Criteria [Enrollment Closed]

Select sites will be invited to participate in an Actigraphy/QOL sub-study. Patients must meet all the eligibility criteria of the PARTNER 3 study. In addition, they must demonstrate a basic working knowledge of and ability to use the devices specified in the sub-study. Patients who are non-ambulatory (i.e., wheelchair bound) will not be eligible.

Alternative Access Registry Eligibility Criteria [Enrollment Closed]

Patients who do not have appropriate iliofemoral access as defined in exclusion criterion number 2 but meet all other inclusion and exclusion criteria should be considered for enrollment in the alternative access registry.

Bicuspid Registry Eligibility Criteria

Patients with a bicuspid valve as determined by the CT core lab (e.g., exclusion criterion 4) should be considered for enrollment in this registry if they meet all other eligibility criteria and none of the following additional exclusion criteria:

1. Aneurysmal ascending aorta (i.e., >4.0 cm)
2. Severe or bulky calcification of the left ventricular outflow tract (LVOT) or raphe that

would increase the risk of annular injury or significant paravalvular leak (PVL) post TAVR

3. Coronary anatomy that increases the risk of coronary artery obstruction post TAVR
4. Positive urine or serum pregnancy test in female subjects of childbearing potential

Underrepresented Populations Registry Eligibility Criteria

Up to ten (10) sites from underrepresented geographical locations will be selected to enroll patients in a single-arm registry for underrepresented populations. Patients at these sites are eligible for this registry if they meet all eligibility criteria above for the randomized cohort.

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INVESTIGATOR SIGNATURE PAGE**A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients who have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement**

I have read this protocol and agree to adhere to its requirements. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice and all applicable regulatory requirements.

Investigative Site Name

Site Principal Investigator Name (print)

Site Principal Investigator Signature

Date

1.0 INTRODUCTION

1.1 Background

Prolonged average life expectancy has resulted in an aging population and consequently an increase in the number of patients with acquired, calcific, severe, symptomatic aortic stenosis (AS). Surgical aortic valve replacement (SAVR) has been the standard of care therapy for patients suffering from severe AS. In the aged population, many patients are too sick to undergo AVR, or have extensive comorbidities that preclude the option for surgery [1].

AS is a progressive, debilitating and life-threatening disease if left untreated. Affected individuals are typically > 65 years of age. Bicuspid aortic valve morphology is a common congenital valvular abnormality, occurring in 0.5% to 2% of the general population [2]. AS is also a frequent complication in this population and may occur at a younger age in patients with a bicuspid valves, when compared with patients with a tricuspid aortic valve morphology [3, 4]. The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole.

The pathophysiology of AS includes an increase in afterload, progressive hypertrophy of the left ventricle, valve obstruction, and a subsequent decrease in systemic and coronary blood flow. Cellular aging and degeneration have been implicated in this form of the disease; diabetes mellitus and hypercholesterolemia are risk factors.

Typically, patients with AS are free from cardiovascular symptoms (e.g. angina, syncope, and/or heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor without intervention. Survival analyses have demonstrated that the interval from onset of symptoms to time of death is approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina [5]. Gardin [6] reported that among symptomatic patients with moderate-to-severe AS treated medically, mortality rates after the onset of symptoms were approximately 25% at 1 year, and 50% at 2 years. More than 50% of the reported deaths were sudden.

Grading the severity of AS is based on a variety of hemodynamic and natural history data. According to the ACC/AHA guidelines, AS is best described as a continuum. Relief of aortic valve obstruction typically results in a reduction of symptoms and improvements in hemodynamic parameters, global left ventricle systolic function, as well as a reversal of left ventricular hypertrophy [7].

Echocardiographic criteria for determining the severity of AS, as defined by the 2006 published practice guidelines of the joint ACC/AHA Task Force are described below in Table 1.1-1.

Table 1.1-1 Criteria for Determining Severity of Aortic Stenosis

Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	< 3.0	3.0 - 4.0	> 4.0

Mean Gradient (mmHg)	< 25	25 - 40	> 40
Valve area (cm²)	> 1.5	1.0 - 1.5	< 1.0
Valve area index (cm²/m²)			< 0.6

1.1.1 Treatment options prior to introduction of transcatheter aortic valve replacement (TAVR)

Treatment options for patients suffering from symptomatic aortic stenosis, prior to the introduction of transcatheter aortic valve replacement (TAVR), included palliation of symptoms without valve replacement (non-surgical standard therapy), or surgical aortic valve replacement (AVR). Treatment options were determined by patient risk for morbidity or mortality after surgery and patient choice. Non-surgical treatment options, including balloon aortic valvuloplasty, did not provide sustained hemodynamic improvement and have led to poor quality of life and shortened life expectancies [8-10]. Patients considered poor candidates for AVR typically present with significant multiple morbidities or anatomical limitations [11].

Patient frailty may also contribute to the decision to forego surgery. Surgical AVR has demonstrated excellent long term outcomes for patients with aortic valve stenosis, even in high risk populations (STS PROM > 10) [8-10,12-14].

1.1.2 Transcatheter aortic valve replacement (TAVR)

Transcatheter aortic valve replacement (TAVR) was first performed in man in 2002 [15], followed by clinical trials and approval for commercialization in Europe in 2007 [16, 17]. It is currently estimated that approximately 300,000 patients have undergone TAVR worldwide. The Edwards THV global clinical research program includes more than 30,000 patients enrolled in 18 clinical studies that include first-in-man, feasibility, and pivotal studies as well as randomized controlled trials and post market registries. Results and outcomes from these trials have been publically reported at medical congresses and in peer-reviewed scientific journals. References are provided in [18-25]. The randomized PARTNER I Trial produced the most conclusive evidence of safety and effectiveness of the Edwards SAPIEN THV in high surgical risk (Cohort A) and inoperable (Cohort B) patients with severe, symptomatic aortic stenosis [cite Cohort A and B papers]. The PARTNER II trial has shown safety and effectiveness of the next generation SAPIEN XT THV in high risk and inoperable patients (Cohort B). More recently results of the SAPIEN 3 THV have also demonstrated safety and effectiveness in high risk or greater risk patients with symptomatic heart disease due to severe native calcific aortic stenosis. Early results in intermediate risk patients treated with SAPIEN 3 THV have been presented and longer term intermediate risk results with the SAPIEN XT THV and SAPIEN 3 THV are pending.

1.1.3 General Overview of the Study Valve Technology

Edwards Lifesciences has pioneered three variations of heart valve implantation devices over the past 50 years, starting with the first mechanical heart valve in 1960,

followed by the introduction of bioprosthetic tissue valves in 1976 and the advancement of bovine pericardial bioprostheses in the 1980's. The evolution of valve replacement therapy was again expanded in 2004, with the acquisition of transcatheter heart valve technologies from percutaneous valve technologies (PVT). Edwards's research and development expertise in bioprosthetic heart valves was applied to the development of the first generation SAPIEN™ transcatheter heart valve (THV) in 2006 and the introduction of the second generation Edwards SAPIEN XT™ THV in 2008. The current generation Edwards SAPIEN 3 THV was approved by the FDA in June 2015 for patients with aortic valve stenosis who are inoperable or high risk.

Figure 1.1.3-1 Edwards TAVR Technology



The original Edwards SAPIEN THV was comprised of a radiopaque, stainless steel expandable support structure (stent), with an integrated unidirectional trileaflet tissue valve, and a polyethylene terephthalate (PET) fabric cuff. The SAPIEN XT THV has incorporated a cobalt chromium alloy stent and a proprietary valve leaflet shape. The valve tissue is fabricated from three equal sections of bovine pericardium that have been preserved in low concentration solutions of buffered glutaraldehyde to fully crosslink the tissue, while preserving its flexibility and strength. All SAPIEN family THV valves are treated with the Edwards ThermaFix™ process.

The SAPIEN 3 system was designed to improve the rates of procedure related adverse events such as paravalvular leak, major vascular complications and major bleeding. The SAPIEN 3 system also improves ease of use over previous

generations by improving coaxial valve alignment with a greater degree of distal flex in the transfemoral Commander delivery system, with a flex indicator on the handle that shows the degree of articulation in the delivery system, and smaller expandable sheaths with minimum access vessel diameter requirements as low as 5.5 mm.

The inflow aspect of the SAPIEN 3 THV contains an external layer of polyethylene terephthalate (PET) with integral scalloped geometry that is intended to acutely fill the voids between the valve frame and native annulus caused by eccentric calcium deposits and enhances the chronic re-endothelialization process to create a tissue bridge across these voids.

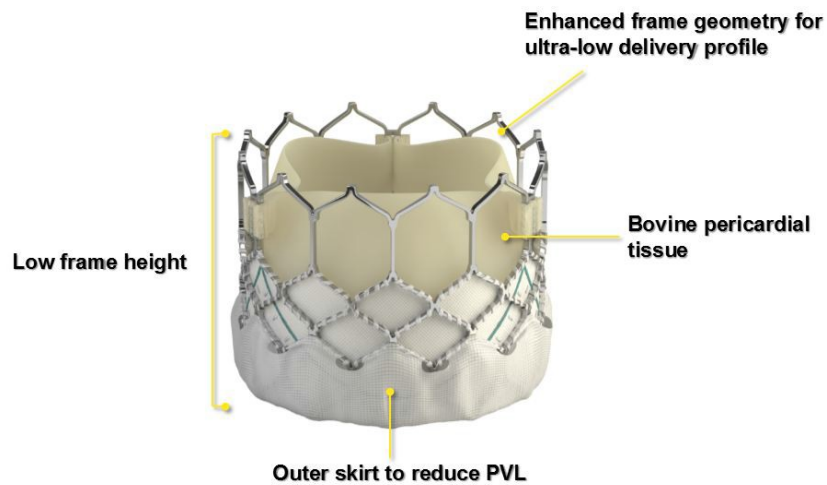


Figure 1.1.3-2: SAPIEN 3 THV

As with the previous generation valve (SAPIEN XT THV), the SAPIEN 3 THV leaflets are designed to be in the semi-closed configuration at the first heartbeat. The SAPIEN 3 THV leaflets, however, were given a small “cap” at the leaflet tips to accommodate proper coaptation under all deployment configurations (i.e., nominal, under, over, and oval). The commissure attachments of the SAPIEN 3 THV also differ slightly from the SAPIEN XT THV; the leaflets are attached via a soft integral tissue tab that is inserted into slots on the frame (rather than attached to a metal bar, as is the SAPIEN XT THV).

Delivery of the SAPIEN 3 THV may be preceded by dilation of the stenotic native aortic valve by means of balloon aortic valvuloplasty (BAV). Predilation tests the expansion capacity of the native valve and prepares the annulus for implantation of the THV. For the Commander delivery system, the THV is carefully mounted and crimped proximal to the balloon. The delivery system is then inserted into the femoral artery (retrograde approach), through the Edwards Expandable Introducer Sheath Set (eSheath), and into a straight section of the descending aorta. The balloon catheter is then brought underneath the valve, in the correct location for valve delivery. The steerable delivery system is then advanced over the aortic arch and delivered to the site of the native stenotic aortic valve.

1.2 SAPIEN 3 Clinical History

There were two cohorts, in the PARTNER II (PII) Trial assessing the latest SAPIEN 3 (S3) THV in patients with symptomatic severe aortic stenosis: the high risk operable/inoperable cohort (PIIS3 HR), with nested registry (NR7 – size 20mm) and the intermediate risk cohort (PIIS3i). All patients receiving the S3 THV presented with severe symptomatic calcific aortic stenosis requiring aortic valve replacement (AVR) and due to co-morbidities were at intermediate or higher risk for open chest surgery.

1.2.1 PIIS3HR Cohort of the PARTNER II Trial Results

The PIIS3HR Cohort of the PARTNER II trial was a single arm, non-randomized, historical- controlled study to compare the third generation Edwards SAPIEN 3 THV system with the first generation Edwards SAPIEN THV system in patients who either have high risk for surgery or cannot undergo surgery (inoperable). The 20 mm valve size was introduced into the trial after enrollment was completed with the three larger sizes (23, 26, and 29 mm), thus a separate nested registry, NR7, with identical inclusion/exclusion criteria as the PIIS3HR Cohort except for the aortic annulus diameter, was created to collect data for the 20 mm valve.

Data was collected on 583 eligible patients enrolled at 29 investigational sites in the United States, who were successfully implanted with a SAPIEN 3 THV, which constitutes the Valve Implant (VI) population. Among the VI population, 491 patients were implanted via the transfemoral (TF) access route, and 92 patients via the transapical (TA) or transaortic (TAo) access route. The overall (N=583) average patient age was 82.6 ± 8.1 years, and the average STS score was 8.6 ± 3.7 .

The primary endpoint; composite rate of all-cause mortality, all stroke, and AI \geq moderate at 30 days was 6.7% in the SAPIEN 3 cohort and 15.6% in the SAPIEN cohort, as shown in Table 1.2.1-1. The resulting proportion difference in the average treatment effect on the treated (ATT) was -6.9% (90% CI: [-13.3%, -0.5%]). Since the upper limit of the CI was $< 7.5\%$, the non-inferiority was met.

Table 1.2.1-1: Primary Endpoint Analysis – Non Inferiority Test SAPIEN 3 vs. SAPIEN

(PIIS3HR VI Population) Event at 30 days	SAPIEN 3 (N=583)	SAPIEN (N=326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)
Composite of Death, Stroke and AI \geq Moderate	6.7% [5.1%, 8.6%] ¹	15.6% [12.6%, 19.5%] ¹	-6.90% [-13.3%, -0.5%]
1. 90% stratified Wilson confidence interval 2. Wald-type two-sided 90% confidence interval using weighted mean and SD			

The Kaplan-Meier (K-M) estimates for all-cause mortality, cardiac mortality, and all stroke at 30 days for the SAPIEN 3 cohort and the SAPIEN cohort are provided in Table 1.2.1-2.

Table 1.2.1-2: Death and Stroke at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

Events at 30 Days	SAPIEN 3 (N= 583)			SAPIEN (N= 326)		
	No. Events	No. Pts with Events	K-M Estimated Event Rate ¹ (95% CI)	No. Events	No. Pts with Events	K-M Estimated Event Rate (95% CI)
Death	13	13	2.2% ([1.3%, 3.8%])	15	15	4.6% ([2.8%, 7.5%])
Cardiac Death	8	8	1.4% ([0.7%, 2.7%])	10	10	3.1% ([1.7%, 5.7%])
All Stroke	9	9	1.6% ([0.8%, 3.0%])	14	14	4.3% ([2.6%, 7.2%])

¹Kaplan-Meier (K-M) estimates at 30 days used time to first event for each patient. Events occurring after 30 days were not included in this analysis.

The proportion of patients with AI \geq moderate at 30 days was 3.0% in the SAPIEN 3 cohort and 14.3% in the SAPIEN cohort, which were found to be statistically significantly different ($p=0.0051$; Table 1.2.1-3).

Table 1.2.1-3: Aortic Insufficiency at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

Event at 30 Days	SAPIEN 3 (N = 583)	SAPIEN (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
AI \geq Moderate, n/Total no. (%) [95% CI]	16/532 (3.0%) [1.7%, 4.8%] ¹	40/280 (14.3%) [10.4%, 18.9%] ¹	-13.1% [-22.2%, -3.9%] ²	0.0051

1. 95% Clopper-Pearson Exact confidence interval.
2. The Wald-type two-sided 90% confidence interval using weighted mean and SD.

The rate of major vascular complications at 30 days post implantation is shown in Table 1.2.1-4. The rate was 5.0% for the SAPIEN 3 cohort and 10.1% for the SAPIEN cohort, which were found to be not statistically significantly different ($p=0.0578$).

Table 1.2.1-4: Major Vascular Complications at 30 Days (SAPIEN 3 vs. SAPIEN VI Population)

Event at 30 Day	SAPIEN 3 (N=583)	SAPIEN (N=326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
Major Vascular Complications, n/Total no. (%) [95% CI]	29/583 (5.0%) [3.4% , 7.1%]	33/326 (10.1%) [7.1% , 13.9%] ¹	-8.0% [-16.2%, 0.3%] ²	0.0578

1. 95% Clopper-Pearson Exact confidence interval.
2. The Wald-type two-sided 90% confidence interval using weighted mean and SD.

Professor Howard Hermann presented the 1-year results from the PIIS3HR cohort at the TCT annual meeting (15 October 2015, San Francisco, California, USA). There were 384 high surgical risk patients (HR) (66.0%) and 199 inoperable patients (INOP) (34%) in this cohort. Between the 30-day and 1-year follow-up there were 71 additional deaths and 5 patients withdrew their participation in the study.

Table 1.2.1-5: PIIS3 – Clinical Outcomes at 30 Days and 1 Year in Combined S3HR/INOP Cohort (AT Population)

Clinical Outcomes (%)	30 Days	1 Year
All-Cause Mortality	2.2	14.4
Cardiac Mortality	1.4	8.1
All Strokes	1.4	4.3
Disabling Stroke*	0.9	2.4
Rehospitalization	8.0	17.1
New Permanent Pacemaker	13.3	16.9
Surgical AVR	0.2	0.6
Structural Valve Deterioration	0	0
Valve Thrombosis	0	0
*No differences between TF and TA/TAo or between HR and INOP subgroup defined as modified Rankin Score ≥ 2 – CEC adjudicated.		

A paired analysis of paravalvular regurgitation (PVL) confirmed a sustained change in the none/trace measurement of 64.3% at 30 days and 68.1% at 1 year (Figure 2). No severe PVL was reported and only 2.5% and 2.7% moderate PVL at 30 days or 1 year. A Kaplan- Meier survival analysis by 30 day PVL demonstrated no difference in survival between patients with none/trace and mild PVL (88.0% and 85.9%) but a significant difference in survival between moderate/severe PVL (61.9%) and none/trace PVL (log rank $p=0.0015$) and mild PVL (log rank $p=0.0058$).

1.2.2 PIIS3i Cohort of the PARTNER II Trial Results

The PIIS3i Cohort consists of intermediate operable risk patients, who received the Edwards SAPIEN 3 THV. To assure that patients were of “intermediate” risk, an STS score of 4 – 8% was selected as the inclusion criteria.

The PIIS3i Cohort is a single arm non-randomized, historical-controlled study to compare the transcatheter heart valve therapy with the third generation SAPIEN 3 THV system, to surgical AVR in patients who have an intermediate risk for surgery (control arm patients from PARTNER II Cohort A). The S3 THV was available in 20, 23, 26, and 29 mm sizes. The primary endpoint for the PIIS3i Cohort is a non-hierarchical composite endpoint of death, all stroke, and AI \geq moderate at 1 year. The primary analysis is a non-inferiority analysis.

A total of 1078 patients were enrolled in S3i, across 51 different sites. The majority of patients were male (62%) and the average patient age was reported as 81.9 years. The average STS score was 5.3% (median 5.2%). The transfemoral access approach was used for valve delivery in 89.0%, transapical approach in 7% and

transaortic approach in 4.0%.

Treatment was conducted with the implantation of a size 26mm valve in 43.7% of patients, followed by size 23mm in 32.2%, size 29mm in 20.0% and size 20mm in 4.1% of patients.

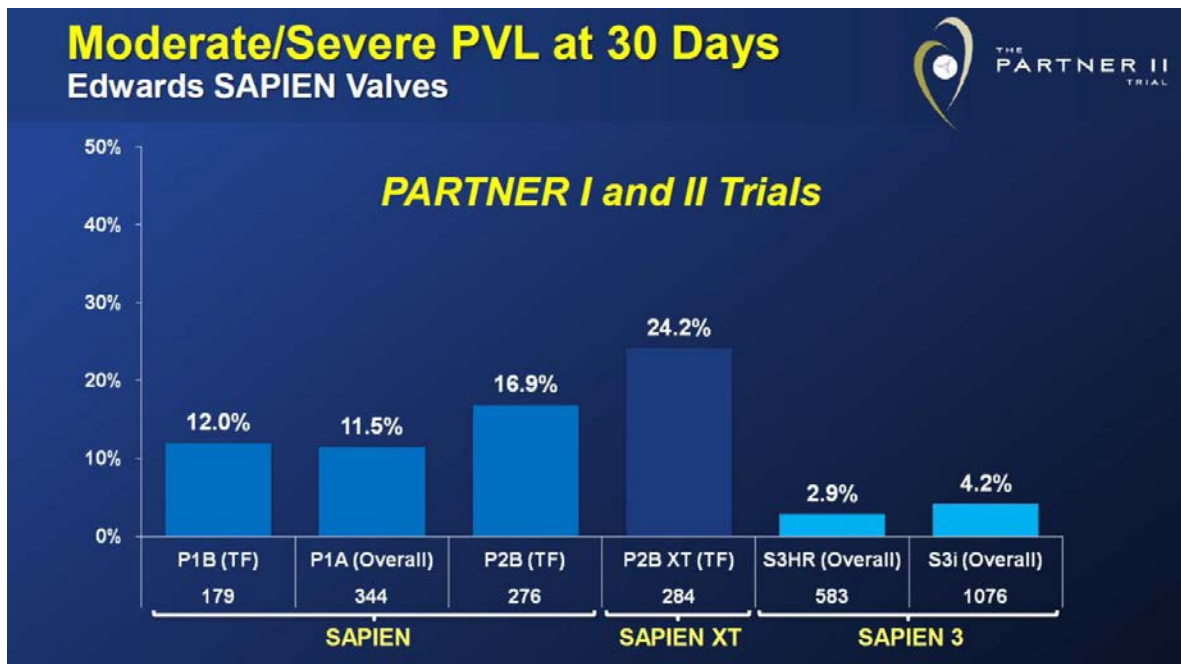
Functional improvement was observed in the AT population of the S3i Cohort, as the number of patients with NYHA classification III/IV decreased from baseline to 30 days from 90% to 13% and 73% to 6%, respectively.

At ACC in 2015, Dr. Susheel Kodali presented 30-day data for S3i, as seen in Table 1.2.2-1 below. S3i clinical events and historical SAPIEN family moderate/severe paravalvular leak at 30 days are described below in Table and Figure 1.2.2- 1 respectively.

Table 1.2.2-1: PIIS3 - 30-Day Clinical Events in S3i (AT Population)

Event (%)	S3i Overall (n=1076)	S3i TF (n= 951)	S3i TA/TAo (n=125)
All-Cause Death	1.1	1.1	1.6
Cardiovascular Death	0.9	0.9	0.8
All Strokes	2.60	2.42	4.00
Disabling*	1.02	0.95	1.60
Non-Disabling	1.58	1.47	2.40
TIA	0.37	0.42	0
Major Vascular Complication	5.6	5.9	3.2
Life-Threatening Bleeding	5.4	4.4	12.9
Annular Rupture	0.2	0.2	0
Myocardial Infarction	0.3	0.3	0
Coronary Obstruction	0.4	0.4	0
Acute Kidney Injury	0.5	0.3	1.6
New Permanent Pacemaker	10.1	10.4	7.2
Aortic Valve Reintervention	0.7	0.8	0
Endocarditis	0.1	0.1	0

Figure 1.2.2-1: Moderate/Severe PVL at 30 Days of SAPIEN Valves



Although patients with bicuspid valve morphology have historically been excluded from TAVR studies and are not included in the data summaries above, recent reports on the use of S3 in these patients is feasible and effective with favorable valve performance [38].

1.3 Design Rationale for the Expanded Indication Trial

Earlier TAVR studies, such as those evaluating the SAPIEN (2006) and SAPIEN XT (2009) THVs, had very selective inclusion criteria that required that the patient populations be high risk for surgery (STS>8) and non-operable, due to concerns of procedural complications including stroke, vascular complications, paravalvular leak (PVL), and conduction disturbances.

As TAVR technology has evolved (Figure 1.1.3-1), such as with the introduction of the S3 enhanced frame geometry, lower frame height, outer skirt to reduce PVL, and improved delivery system utilizing reduced access-vessel diameter requirements, and new studies demonstrate procedural complication rates similar to AVR, there has been a natural progression towards indications including operable patients with decreasing risk profiles.

The tenacious pursuit of technological advances in THV, in combination with over a decade of clinical outcomes, operator experience and input has yielded favorable and steadily improving safety and efficacy. Ongoing studies of the latest generation valve (S3) demonstrate very low rates of significant paravalvular regurgitation, major vascular complications, and bleeding complications; and in intermediate-risk patients - markedly low mortality and stroke at 30 days.

1.3.1 Rationale for CT Sub-Study

There have been recent reports of abnormal imaging findings as assessed by multi-phasic, ECG-gated CT (i.e., 4D CT) in some patients in the absence of clinical symptoms or echocardiographic abnormalities following TAVR [29, 30]. The abnormal imaging has been described as “leaflet thickening” and “reduced leaflet mobility”. This imaging phenomenon has not been definitely linked with clinical valve thrombosis which occurs in 1% or less of TAVR and SAVR bioprostheses. The purpose of the CT sub-study is to further investigate this phenomenon with the following specific objectives:

1. Establish the prevalence of the imaging abnormality.
2. Establish the relationship between the imaging abnormality and patient, procedural and pharmacology factors.
3. Establish the relationship between imaging abnormalities and clinical events.

1.3.2 Rationale for Actigraphy/QOL [Enrollment Closed]

Traditional, face-to-face methods for measuring quality of life (QOL) and functional status at defined time points can lack the precision needed to detect changes on a more frequent or even day to day basis. Advances in mobile health (mHealth) technology may enable more regular, convenient and accurate tracking of QOL and physical activity information through applications and wearable devices. These technologies have the potential to help gather more and better data on patients’ response to therapy and progression of disease.

The purpose of this sub-study is to investigate the feasibility of assessing change in QOL and activity levels using electronic patient-reported outcome (ePRO) applications and wearable activity trackers. The end goal is to publish study results and explore new and innovative ways of assessing QOL and functional status of aortic stenosis patients with low surgical risks.

1.3.3 Rationale for Underrepresented Registry

With the growing use of TAVR for heart valve repair, some US centers are considered “high-volume” due to the number of TAVR procedures performed each year. Results from past TAVR trials have shown that these centers enroll predominately Caucasian patients. Many patients that would benefit from TAVR are not enrolled into trials due to their inability to travel to the larger TAVR centers, due to cultural/socio-economic pressure to remain within their own community, or because there is no referral base for reaching these patients and increasing awareness of TAVR. In order to expand the study of TAVR to a broader group of patients, Edwards is reaching-out to these underrepresented patients by selecting ten additional sites with a predominantly diverse ethnic, cultural, non-Caucasian patient base that perform a more limited number of TAVR procedures per year.

2.0 STUDY OBJECTIVE

The purpose of this trial is to establish the safety and efficacy of the Edwards SAPIEN 3 THV device in patients with severe, calcific, aortic stenosis who are at low operative risk for SAVR.

3.0 STUDY DESIGN

This is a prospective, randomized, controlled, multi-center study. Qualified study patients will be randomized 1:1 to receive either the Edwards SAPIEN 3 transcatheter heart valve through iliofemoral access, or SAVR with a commercially available bioprosthetic valve. Selected sites will enroll qualified patients into a CT sub-study. Selected sites may also enroll patients in an Actigraphy/QOL sub-study [Enrollment Closed].

Additional patients will be enrolled in the following single-arm registries:

- Alternative Access Registry (100) [Enrollment Closed]
- Bicuspid Registry (up to 75)
- Underrepresented Populations Registry (up to 100)

4.0 ENROLLMENT

Up to 1182 qualified patients will be randomized at up to 65 actively enrolling sites in the US. It is anticipated that approximately 5-10 sites may be selected outside of the US. Further, up to ten (10) separate US sites from targeted geographic areas will be selected to enroll patients in a single-arm registry for underrepresented populations. No site will be allowed to enroll more than 15% of patients. Edwards will notify investigative sites of enrollment closure.

Sub-studies

Of the 1182 patients, a subset of patients will also be enrolled in the following randomized sub-studies:

- CT sub-study (up to 440)
- Actigraphy/QOL sub-study (up to 400) [Enrollment Closed]

Registries

Additional patients will be enrolled in the following single-arm registries:

- Alternative Access Registry (100) [Enrollment Closed]
- Bicuspid Registry (up to 75)
- Underrepresented Populations Registry (up to 100)

5.0 STUDY DEVICE

The commercially available Edwards SAPIEN 3 THV and Commander Delivery System will be provided for use in this study for transfemoral delivery of the SAPIEN 3 THV.

Alternative Access Registry [Enrollment Closed]

The Edwards Commander Delivery System will be provided for subclavian delivery and the Edwards Certitude Delivery System will be provided for transapical and transaortic delivery of the SAPIEN 3 THV as part of Alternative Access Registry.

Edwards SAPIEN 3 System

- Edwards SAPIEN 3 Transcatheter Heart Valve [Model 9600TFX (in 20 mm, 23 mm, 26 mm and 29 mm sizes)]
- Edwards Commander Delivery System (Models 9600LDS20, 9600LDS23, 9600LDS26 and 9600LDS29)
- Edwards Certitude Delivery System (Models 9620TA20, 9620TA23, 9620TA26 and 9620TA29, 9600SDS20, 9600SDS23, 9600SDS26 and 9600SDS29)
- Edwards Certitude Introducer Sheath Set [Models 9620IS18 (18F) and 9620IS21 (21F), 9600IS18 and 9600IS21]
- Edwards Crimper (Model 9600CR)

5.1 Device Descriptions**5.1.1 Edwards SAPIEN 3 THV**

The SAPIEN 3 THV (Figure 5.1.1-1) is a catheter-delivered heart valve that combines a balloon expandable stent and bioprosthetic valve technology.

The device is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing ring. The valve tissue is treated with Edwards ThermoFix process, packaged and terminally liquid sterilized in a buffered glutaraldehyde solution.

Figure 5.1.1-1 Edwards SAPIEN 3 Model 9600TFX



The device leaflets are designed to be in the semi-closed configuration at the first heartbeat. The leaflets have a small “cap” at the leaflet tips to accommodate proper coaptation under all deployment configurations (i.e., nominal, under, over and oval). The leaflets are attached via a soft integral tissue tab that is inserted into slots on the frame.

The SAPIEN 3 is available in 4 sizes (Table 5.1.1-1).

Table 5.1.1-1 Device Sizing

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		THV Size	Valve Height
	Area	Area Derived Diameter		
16-19 mm	273 – 345 mm ²	18.6-21 mm	20 mm	15.5 mm
18-22 mm	338 – 430 mm ²	20.7-23.4 mm	23 mm	18 mm
21-25 mm	430 – 546 mm ²	23.4-26.4 mm	26 mm	20 mm
24-28 mm	540 – 683 mm ²	26.2-29.5 mm	29 mm	22.5 mm

THV size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography (TEE) or computed tomography (CT). Patient anatomical factors and multiple imaging modalities should be considered during THV size selection.

5.1.2 Edwards Commander Delivery System

The Commander Delivery System includes:

- Loader
- Qualcrimp Accessory
- 2-piece Crimp Stopper

Commander Delivery System

The Edwards Commander Delivery System consists of a balloon catheter for deployment of the THV and a Flex Catheter to aid in valve alignment to the balloon, tracking and positioning of the THV. The delivery system includes a tapered tip to facilitate crossing of the aortic valve. The handle contains a Flex Wheel to control flexing of the Flex Catheter, and a Balloon Lock and Fine Adjustment Wheel to facilitate valve alignment and positioning of the valve within the aortic annulus. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the working length of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. A radiopaque Triple Marker proximal to the balloon indicates the Flex Catheter position during deployment.

Certitude Delivery System

The Edwards Certitude Delivery System includes a handle with a Flex Wheel for articulation of the Balloon Catheter and a Loader. The loader allows for the delivery of the crimped THV through the hemostasis valves of the sheath. Three radiopaque indicators on the catheter shaft define the position on the balloon where the THV should be crimped and also provide visualization of the balloon. The THV is crimped between the two radiopaque shoulders on the distal and proximal ends of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. An inflation and guidewire hub is housed in the handle assembly. A 2-piece crimp stopper and the Qualcrimp crimping accessory are packaged with the delivery system for use during crimping of the THV.

Loader

The loader is used to aid insertion of the delivery system into the sheath, and may be removed to utilize the full working length of the inserted device.

Qualcrimp Accessory

The Qualcrimp accessory is a foam tube composed of polyurethane sponge covered in an outer layer of PET. The SAPIEN 3 THV is placed within the Qualcrimp accessory prior to placing it in crimper. The Qualcrimp accessory is intended to protect the leaflets of the SAPIEN 3 THV during crimping.

2-piece Crimp Stopper

This component is discussed in section 5.1.4.

5.1.3 Certitude Delivery System

The Certitude Delivery System includes:

- Loader (see 5.1.2)
- Qualcrimp Accessory (see 5.1.2)
- 2-piece Crimp Stopper (see 5.1.4)

The Edwards Certitude Delivery System includes a handle with a Flex Wheel for articulation of the Balloon Catheter and a Loader. The loader allows for the delivery of the crimped THV through the hemostasis valves of the sheath. Three radiopaque indicators on the catheter shaft define the position on the balloon where the THV should be crimped and also provide visualization of the balloon. The THV is crimped between the two radiopaque shoulders on the distal and proximal ends of the balloon. A radiopaque Center Marker in the balloon is provided to help with valve positioning. An inflation and guidewire hub is housed in the handle assembly. A 2-piece crimp stopper and the Qualcrimp crimping accessory are packaged with the delivery system for use during crimping of the THV.

5.1.4 Edwards Crimper

The Crimper reduces the diameter of the SAPIEN 3 THV to mount it to the delivery system. The Crimper is comprised of a compression mechanism that is closed with a handle located on the housing. The Crimper is used with a 2-piece Crimp Stopper (packaged with the delivery system) to correctly crimp the THV to the appropriate size.

The SAPIEN 3 THV, the associated Delivery Systems and components will be used per the Instructions for Use (IFU) and after sufficient training of physicians/site personnel has been achieved as determined by the study sponsor. Further descriptions of these devices are provided in the respective IFUs (Appendix C).

6.0 STUDY ENDPOINTS

6.1 Primary Endpoint Safety and Effectiveness:

Composite endpoint of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year post procedure.

6.2 Secondary Endpoints for Labeling

1. New onset atrial fibrillation at 30 Days
2. Length of index hospitalization
3. Death, KCCQ < 45 or KCCQ decrease \geq 10 points at 30 days
4. Death/All Stroke composite at 30 days
5. All Stroke at 30 days

6.3 Additional Safety and Effectiveness Endpoints

1. Mortality (all cause & cardiovascular) at 30 days and 1 year
2. Stroke (disabling and nondisabling) at 30 days and 1 year
3. Death or stroke at 1 year
4. Death or disabling stroke at 30 days and 1 year
5. Vascular complications (major) at 30 days and 1 year
6. Bleeding complications (life threatening, disabling, or major) at 30 days and 1 year
7. Myocardial infarction at 30 days and 1 year
8. Acute kidney injury at 30 days
9. Renal replacement therapy at 1 year
10. New permanent pacemaker implantation resulting from new or worsened conduction disturbances at 30 days and 1 year
11. Coronary obstruction requiring intervention at 30 days and 1 year
12. New York Heart Association class at 30 days and 1 year
13. Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular & central) at 30 days, and years 1, 2, 3, 4, 5, 7, and 10.

14. Rehospitalization (valve-related or procedure-related and including heart failure) at 30 days, 1 year, and annually (up to 10 years).
15. New onset atrial fibrillation at 1 year
16. ICU days, and discharge location
17. Structural valve deterioration at years 1-5, 7 and 10
18. Days alive and out of hospital at 1 year
19. 6-minute walk test at 30 days and 1 year
20. Health status as evaluated by Quality of Life questionnaires
 - a. KCCQ at 30 days and 1 year
 - b. EQ-5D-5L at 30 days and 1 year
 - c. SF-36 at 30 days and 1 year

6.4 Actigraphy/QOL Substudy Outcome Measures [Enrollment Closed]

Primary Outcome Measures:

1. Quality of life as assessed by visual analog scale for pain (VAS Pain) through 30 days.
2. Activity during daytime hours (6 am to 10 pm) as assessed by mean daily steps walked through 30 days.

Secondary Outcome Measures:

1. Quality of life as assessed by
 - a. VAS Pain 31-44 days
 - b. Kansas City Cardiomyopathy Questionnaire (KCCQ-12) through 44 days
 - c. PF-10 Physical Component Summary through 44 days
2. Activity during daytime hours (6 am to 10 pm) through 44 days
 - a. Mean daily steps walked
 - b. Number of minutes active
 - c. Number of minutes sedentary
 - d. Total activity count of the most active 10 hours in the day (which need not be 10 consecutive hours)

7.0 STUDY POPULATION

The study population will be comprised of patients with severe, calcific, aortic stenosis who are at low operative risk for SAVR.

7.1 Inclusion Criteria

All study participants must meet the following inclusion criteria.

1. Severe, calcific aortic stenosis meeting the following criteria:
 - $AVA \leq 1.0 \text{ cm}^2$ or $AVA \text{ index} \leq 0.6 \text{ cm}^2/\text{m}^2$
 - Jet velocity $\geq 4.0 \text{ m/s}$ or mean gradient $\geq 40 \text{ mmHg}$ AND

 - 1) NYHA Functional Class ≥ 2 OR 2) exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia OR 3) asymptomatic with LVEF $<50\%$

Note: Qualifying echo must be within the 90 days prior to randomization.

2. Heart team agrees the patient has a low risk of operative mortality and an STS < 4 .
3. The study patient has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB)/Ethics Committee (EC) of the respective clinical site.

7.2 Exclusion Criteria

Candidates will be excluded from the study if any of the following conditions are present:

1. Native aortic annulus size unsuitable for sizes 20, 23, 26, or 29mm THV based on 3D imaging analysis
2. Iliofemoral vessel characteristics that would preclude safe passage of the introducer sheath
3. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before randomization
4. Aortic valve is unicuspid, bicuspid, or non-calcified
5. Severe aortic regurgitation ($>3+$)
6. Severe mitral regurgitation ($>3+$) \geq moderate stenosis
7. Pre-existing mechanical or bioprosthetic valve in any position. (of note, mitral ring is not an exclusion).
8. Complex coronary artery disease:

- a. Unprotected left main coronary artery
 - b. Syntax score > 32 (in the absence of prior revascularization)
 - c. Heart Team assessment that optimal revascularization cannot be performed
9. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomization
 10. Leukopenia (WBC < 3000 cell/mL), anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL), history of bleeding diathesis or coagulopathy, or hypercoagulable states
 11. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomization
 12. Hypertrophic cardiomyopathy with obstruction (HOCM)
 13. Ventricular dysfunction with LVEF < 30%
 14. Cardiac imaging (echo, CT, and/or MRI) evidence of intracardiac mass, thrombus or vegetation
 15. Inability to tolerate or condition precluding treatment with anti-thrombotic/anticoagulation therapy during or after the valve implant procedure
 16. Stroke or transient ischemic attack (TIA) within 90 days of randomization
 17. Renal insufficiency (eGFR < 30 ml/min per the Cockcroft-Gault formula) and/or renal replacement therapy at the time of screening.
 18. Active bacterial endocarditis within 180 days of randomization
 19. Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
 20. Severe pulmonary hypertension (e.g., PA systolic pressure \geq 2/3 systemic pressure)
 21. History of cirrhosis or any active liver disease
 22. Significant frailty as determined by the Heart Team (after objective assessment of frailty parameters).
 23. Significant abdominal or thoracic aortic disease (such as porcelain aorta, aneurysm, severe calcification, aortic coarctation, etc.) that would preclude safe passage of the delivery system or cannulation and aortotomy for surgical AVR
 24. Hostile chest or conditions or complications from prior surgery that would preclude safe reoperation (i.e., mediastinitis, radiation damage, abnormal chest wall, adhesion of aorta or IMA to sternum, etc.)

25. Patient refuses blood products
26. BMI > 50 kg/m²
27. Estimated life expectancy < 24 months
28. Absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication
29. Immobility that would prevent completion of study procedures (e.g. six-minute walk tests, etc.)
30. Patient is not a candidate for both arms of the study (not applicable to single-arm registries)
31. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. Observational studies are not considered exclusionary.

7.3 CT Imaging Sub-Study

Sites with the ability to perform high quality 4D scans will be selected to participate in a CT sub-study.

7.3.1 Inclusion Criteria

All CT sub-study participants must meet inclusion criteria listed in Section 7.1.

7.3.2 Exclusion Criteria

In addition to the exclusion criteria in section 7.2, candidates will be excluded from the sub- study if the following is present:

1. Condition requiring or planned use of anticoagulants following the valve implant procedure.
2. GFR <50
3. Inability to perform high-quality MDCT study for any reason (e.g., atrial fibrillation with rapid ventricular response)

7.4 Actigraphy/QOL Sub-Study Eligibility Criteria [Enrollment Closed]

Select sites will be invited to participate in an Actigraphy/QOL sub-study. Patients must meet all the eligibility criteria of the PARTNER 3 study in sections 7.1 and 7.2. In addition, they must demonstrate a basic working knowledge of and ability to use the devices specified in the sub-study. Patients who are non-ambulatory (i.e, wheelchair bound) will not be eligible.

7.5 Alternative Access Registry Eligibility Criteria [Enrollment Closed]

Patients who do not have appropriate iliofemoral access as defined in exclusion criterion 2 in Section 7.2 but meet all other inclusion and exclusion criteria should be considered for enrollment in the alternative access registry.

7.6 Bicuspid Registry Eligibility Criteria

Patients who have a bicuspid valve as determined by the CT core lab (e.g., exclusion criterion 4) should be considered for enrollment in this registry if they meet all other eligibility criteria in Sections 7.1 and 7.2 and none of the following additional exclusion criteria:

1. Aneurysmal ascending aorta (i.e., >4.0 cm)
2. Severe or bulky calcification of the left ventricular outflow tract (LVOT) or raphe that would increase the risk of annular injury or significant paravalvular leak (PVL) post TAVR
3. Coronary anatomy that increases the risk of coronary artery obstruction post TAVR
4. Positive urine or serum pregnancy test in female subjects of childbearing potential

7.7 Underrepresented Populations Registry Eligibility Criteria

Up to ten (10) sites from underrepresented geographical locations will be selected to enroll patients in a single-arm registry for underrepresented populations. Patients at these sites are eligible for this registry if they meet all eligibility criteria in Sections 7.1 and 7.2.

8.0 STUDY PROCEDURES

8.1 Screening Period

The screening period is designed to obtain patient consent, determine patient eligibility for the study, and to submit the presentation for case review. The Screening Visit procedures will occur within the 30 days prior to the valve implant procedure, unless otherwise noted below. All patients that sign an informed consent will be entered into the electronic database (EDC) and be assigned a Subject ID. All assessments performed will be entered into EDC.

Patients that have signed the informed consent and do not meet the inclusion/exclusion criteria in Section 7.1 and 7.2 will be considered a Screen Failure (SF). All assessments performed and the inclusion or exclusion criteria that was not met will be entered into EDC.

The patient status will be considered 'Discontinued' if the following occur during the screening period:

- The patient withdraws consent or expires prior to or after the Case Review.
- The patient completes all of the screening procedures, including Case Review call, and the Case Review is not approved.

All assessments performed and the reason for discontinuation will be entered into EDC and the Exit form will be completed.

The following information will be collected during the screening period:

Consent:

- Patient informed consent completion, (section 8.1.1)

Operability:

- STS Risk Score

Other Assessments:

- Logistic EuroSCORE
- EuroSCORE II

Systems:

- Medical history and physical assessment (including height, weight, blood pressure, and heart rate).
- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors.

Cardiopulmonary:

- Canadian Cardiovascular Society (CCS) status of angina
- 12-lead ECG
- New York Heart Association Class (NYHA Classification)
- Comprehensive transthoracic (TTE) echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, left ventricle systolic function (global and segmental). Qualifying echo must be performed within 90 days prior to randomization.
- Cardiac imaging (TEE, CT, or cardiac MRI) with 3D reconstruction to determine aortic valve annulus area. Qualifying cardiac imaging must be performed within 1 year prior to randomization, unless clinically indicated.
- CT Angiography, including thoracic and abdomen scan with visualization of iliac and femoral arteries. Qualifying iliofemoral CT must be performed within 1 year prior to randomization.
- Left heart catheterization to assess the severity of aortic stenosis and severity of coronary artery disease, if applicable. Qualifying catheterization must be performed within 1 year prior to randomization, unless clinically indicated.
- SYNTAX Score for significant native coronary artery disease (CAD)
- Pulmonary Function Test for patients with a history of lung disease

Neurological Assessments:

- Mini Mental State Examination (MMSE), (Appendix G)
- National Institutes of Health Stroke Scale (NIHSS), (Appendix H)
- Modified Rankin Scale (mRS), (Appendix I)

Every effort should be made to have a neurologist (or neurology fellow) perform the NIHSS and mRS assessments. If it is not possible to have the neurologist/fellow perform the assessments within the protocol-specified visit window, a certified study team member may perform the assessments.

Functional Assessments:

- Six Minute Walk Test (6MWT), (Appendix E)
- Frailty Index (5 Meter Walk Test (5MWT), grip strength, Activities of Daily Living (ADL), and Albumin laboratory) (Appendix F)
- Quality of Life Assessments
 - KCCQ (Appendix N)
 - EQ-5D-5L (Appendix M)
 - SF-36 (Appendix O)

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- CK/CKMB and/or troponins \leq 72 hours before the valve implant procedure
- Creatinine
- eGFR
- Albumin (as part of Frailty Index)
- Total Bilirubin
- AST/ALT (required for patients with chronic liver disease)
- B-type natriuretic peptide (BNP)

8.1.1 Informed Consent

The study investigator(s) and support staff will approach patients with severe, aortic stenosis to assess their interest in participating in the study by providing them an overview of the study including the background, risks, benefits and study procedures. If patients are interested in participating in the study, the study patient will sign the Institutional Review Board (IRB) approved informed consent form prior to any study specific procedures are performed. All patients consented should be entered into the study's electronic database (EDC).

8.1.2 Case Review

The Case Review Board is a select review committee comprised of Investigators who are participating in the trial. The role of the Case Review Board is to review submitted cases to determine if the patient is an appropriate candidate for the trial, with a focus on confirming patient operative risk, valve sizing, appropriate vascular

access, valve morphology and any relevant clinical factors impacting enrollment eligibility. In addition, the Heart Team's strategy for treatment of concomitant coronary artery disease will be reviewed, as applicable. Before a case is submitted for review, the site Principal Investigator and Heart Team will screen the patient for operative risk and fundamental enrollment criteria. It is required that at least one site surgeon Investigator personally examine the patient to determine operative risk. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the Case Review Board. The Sponsor will maintain a record of the case presentation and case approval notes.

8.2 Randomization and Enrollment

Once all screening procedures have been completed, all inclusion/exclusion criteria have been confirmed and the Case Review has been completed and approved, the patient is eligible to be randomized or enrolled into one of the single-arm registries.

Randomization will occur centrally. To randomize a patient, the investigative site will enter the subject into the designated electronic system and obtain the treatment assignment (TAVR or SAVR). Once the assignment has been made, the subject will be considered randomized and enrolled into the study.

All randomized patients will be considered part of the Intent to Treat (ITT) population. Randomized patients are considered enrolled in the study; for the randomized patients, the terms "randomized" and "enrolled" have the same meaning.

If the patient has been enrolled and the patient withdraws consent prior to the valve implant procedure start, the patient will be considered discontinued. All assessments performed and the reason for withdrawal will be entered into EDC and the Exit form will be completed.

8.3 Procedure (Day 0)

The valve implant procedure should occur within 14 days of randomization and no later than 30 days after informed consent is obtained. The date of the valve implant procedure is considered Day 0. The valve implant procedure will be considered to have started when:

- The first interventional access related puncture (venous or arterial) is established for TAVR.
- The first skin incision is performed for SAVR.

Performance of TEE does not by itself constitute start of procedure.

For those patients receiving TAVR, the commercially available SAPIEN 3 THV with the Commander Delivery System, or the Certitude Delivery system if treated with a transapical or transaortic approach as part of the Alternative Access registry [enrollment closed], and components will be used per the most current Instructions for Use (IFU) at all times for device sizing, preparation, and recommended implant

procedure. Refer to Appendix C for the IFUs to be used in this study.

For those patients receiving SAVR, a commercially available bioprosthetic surgical valve and associated components will be used according to institution standard of care.

Day 0 will be used to schedule all subsequent visits and calculate visit windows. Patients who receive the assigned TAVR or SAVR implant will continue in the study and complete the study through year 10 according to the visits and events described in section 8.0 and Schedule of Procedures.

Day 0 valve implant procedure assessments will include the following:

Systems:

- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors.
- Adverse event assessment

Cardiopulmonary:

- Comprehensive transthoracic (TTE) or transesophageal (TEE) echocardiogram
- Supra-aortic angiogram or TEE

If the valve implant is aborted (prior to or after the start of the valve implant procedure), the Day 0 visit may be re-scheduled if the patient continues to meet all inclusion/exclusion criteria.

8.3.1 Device Preparation

A detailed description of device preparation and required equipment is supplied in the Instructions for Use (Appendix C).

8.3.2 Procedure Recommendations

Table 8.3.2-1 outlines the recommended anticoagulation/antithrombotic regimen. The categories were developed by The PARTNER II Trial Patient and Procedure Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines [26].

NOTE: The CHAD score only applied to patients in Atrial Fibrillation (AF) and had not been validated in non-AF patient populations; therefore the CHAD score reference was used as one among many guidelines to establish the risk stratification for intensity of anticoagulation regimen.

Table 8.3.2-1 Recommended anticoagulation/antithrombotic regimen

	AVR	TAVR
Pre valve implant procedure		
	Aspirin 81-100 mg QD	Aspirin 81-100 mg QD
	<ul style="list-style-type: none"> • Patients with BMS within one month or drug eluting stent (DES) within 12 months should be continued on Clopidogrel/prasugrel prior to their implant procedure • Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the implant procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to the implant procedure. If intra-procedural TEE during AVR reveals thrombus, implant procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. In patients in the surgical group with LA clot seen on intraoperative TEE, implant procedure can proceed per surgical standard of care 	<ul style="list-style-type: none"> • Patients with BMS within one month or DES within 12 months should be continued on Clopidogrel/prasugrel prior to their implant procedure • Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the implant procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to implant procedure. If intra-procedural TEE during TAVR reveals thrombus, implant procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. Note: thrombus must be eliminated in order to proceed with TAVR. • In patients undergoing concomitant TAVR/PCI, clopidogrel loading with either 300mg or 600mg prior to the implant procedure is recommended in addition to ASA
Intraprocedural		
	Heparin will be given to achieve/ maintain ACT _≥ 250	Heparin will be given to achieve/ maintain ACT _≥ 250 sec.

AVR		TAVR
Post valve implant procedure		
<p>Category I for Stroke Risk No atrial fibrillation, No recent stents</p>	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel 75qd started 24 hours post-surgery for at least one month if clinically safe and at the discretion of the surgical team. In centers that use warfarin post-surgical AVR, Clopidogrel will not be started 	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel 300mg load within 6 hours of the implant procedure (either pre or post) • Clopidogrel 75mg qd for at least one month post implant procedure
<p>Category II for Stroke Risk No atrial fibrillation, recent stents</p>	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel should not be discontinued prior to surgery if patient had BMS within one month or DES in 12 months • Clopidogrel 75qd started 24 hours post-surgery if clinically safe and continued for at least one month post-surgical AVR in those with BMS and a total 	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel 75mg qd should be continued prior to the implant procedure and after the implant procedure without interruption for at least one month after BMS and 12 months after DES
<p>Category III for Stroke Risk Atrial fibrillation, no recent stents</p>	<ul style="list-style-type: none"> • ASA 81mg qd • Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patient's being started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for warfarin or dagibatran, Clopidogrel 75mg qd (in addition to ASA 81 mg) can be 	<ul style="list-style-type: none"> • ASA 81mg qd • Patients should be started on warfarin or dabigatran 24 hours post TAVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patients started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for warfarin or dagibatran, Clopidogrel 75mg qd can be considered as an alternative

	AVR	TAVR
Category IV for Stroke Risk Atrial fibrillation, recent stents	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES • Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and continued indefinitely. If clinically safe, patients being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic. 	<ul style="list-style-type: none"> • ASA 81mg qd • Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES • Patients should be started on warfarin or dabigatran 24 hours post TAVR if clinically safe and continued indefinitely. If clinically safe, patient's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.

Note: Any changes to antithrombotic/anticoagulation regimen from study visit to study visit will be noted on the Case Report Form (CRF) including reason for change.

8.3.3 Antibiotic Prophylaxis

Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association.

8.3.4 Contrast Media

Careful management of contrast media is required. Accurate measurement of the contrast used will be captured in the case report form.

8.3.5 Radiation Precautions

Radiation precautions will be adhered to per institutional standards. Total procedural radiation exposure will be documented on the case report forms in accordance with institutional measures (i.e. total procedural fluoroscopy time, dosage, etc.).

Radiation exposure of 6-15 mSv is estimated for the Screening CT and each Sub-study CT [27]. If a radiation induced skin injury is suspected, the Investigator should see the patient at an office visit, and should arrange for appropriate follow-up care.

8.4 Post Procedure

The post implant procedure time period is defined as the 48 hours after the patient exits the cath lab/ operating room. Study patients will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local, systemic side effects and complications. After completion of the implant procedure, all study patients will be monitored per institution standard of care. Subsequent monitoring will also be continued according to institutional standard of care.

The following information will be collected during the Post Procedure time period:

Systems:

- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors .
- Adverse event assessment

Cardiopulmonary:

- 12-lead ECG

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- CK/CKMB and/or Troponins will be performed to monitor the patient's cardiac enzymes at 3 different time intervals. Of note, patients discharged prior to the completion of 24 hour series of lab tests will not be issued deviations.
 - The first lab draw post implant procedure (within 8 hours of exit from the cath lab / operating room)
 - The second lab draw, (6 – 8 hours after the first lab draw)
 - The third lab draw, (6 – 8 hours after the second lab draw)
- Creatinine

Neurological assessments:

- NIHSS

All patients should be assessed post-procedure to determine if there is evidence of neurological impairment. If symptoms of stroke are suspected, the NIHSS should be performed. For all patients diagnosed with stroke after procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

8.5 Discharge

Discharge is the actual date and time the patient is discharged. For patients discharged within 48 hours of exiting the cath lab / operating room, it is not required to repeat tests collected during the Post Procedure period that are also required for the discharge visit. If the patient was discharged over a weekend or holiday, the discharge assessments may be completed on the last weekday prior to discharge.

The following information will be collected for study patients within 24 hours of the date and time of discharge.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors.
- Adverse event assessment

Cardiopulmonary:

- NYHA classification
- Comprehensive transthoracic echocardiogram (TTE)

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- PT or INR
- Creatinine
- BNP

Neurological Assessments:

- NIHSS

All patients should be assessed at Discharge to determine if there is evidence of neurological impairment. If symptoms of stroke are suspected, the NIHSS should be performed. For all patients diagnosed with stroke after procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

8.6 Post Procedure Follow Up Visits**8.6.1 30 Day Post Procedure Visit**

The 30 day post procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +7 days.

The following data will be collected for all study patients 30 days post implant procedure.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors.
- Adverse event assessment

Cardiopulmonary:

- 12-lead ECG
- NYHA classification
- Comprehensive transthoracic echocardiogram (TTE)
- CT Scan (only for those patients in the CT sub-study) (section 12.5.2.1)

Neurological Assessments:

- MMSE
- NIHSS
- Modified Rankin Scale

For all patients diagnosed with stroke between discharge and 30 days post-procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) complete the NIHSS and mRS assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

Functional Assessments:

- 6MWT
- Quality of Life Questionnaires
 - KCCQ
 - EQ-5D-5L
 - SF-36

Clinical Laboratory Tests:

- WBC, Hgb, and platelet count
- Creatinine
- BNP

8.6.2 6 Month Post Procedure Visit

The 6 month post implant procedure visit window will be calculated from the Day 0 visit date. The visit window is +14 days.

The following data will be collected for all study patients 6 months post valve implant procedure.

Systems:

- Physical assessment including weight, blood pressure, and heart rate
- Medications including all antithrombotics/anticoagulants and HMG-CoA reductase inhibitors.
- Adverse Event assessment

Cardiopulmonary:

- NYHA classification

Neurological Assessments:

The following assessments should be completed for all patients diagnosed with stroke after the procedure:

- NIHSS
- Modified Rankin Scale

For all patients diagnosed with stroke between 30 days and 6 months post-procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

Functional Assessments:

- Quality of Life Questionnaires
 - KCCQ
 - EQ-5D-5L
 - SF-36

8.6.3 12 Month Post Procedure Visit

The 12 month post implant procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +30 days.

The following data will be collected for all study patients 12 month post implant procedure.

Systems:

- Physical assessment, (including weight and blood pressure)
- Medications including all antithrombotics/anticoagulants and HMG-CoA reductase inhibitors.
- Adverse Event assessment

Cardiopulmonary:

- 12 lead ECG
- NYHA classification
- Comprehensive transthoracic echocardiogram (TTE)
- CT Scan (only for those patients in the CT sub-study)

Neurological Assessments:

- MMSE

The following assessments should be completed for all patients diagnosed with stroke after the procedure:

- NIHSS
- Modified Rankin Scale

For all patients diagnosed with stroke between 6 months and 12 months post-procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

Functional Assessments:

- 6MWT
- Quality of Life Questionnaires
 - KCCQ
 - EQ-5D-5L
 - SF-36

8.6.4 Years 2 through 10 Annual Post Procedure Visit

The yearly post implant procedure visit window will be calculated from the Day 0 valve implant date. The visit window is +45 days.

The following data will be collected for all study patient's years 2 through 10 annually post implant procedure visit.

Systems:

- Physical assessment including weight, blood pressure and heart rate
- Medications including all antithrombotics/anticoagulants and HMG coA reductase inhibitors.
- Adverse event assessment

Cardiopulmonary:

- NYHA classification
- Comprehensive transthoracic echocardiogram (TTE) [years 2, 3, 4, 5, 7, and 10 only]

Functional Assessments:

- Quality of Life Questionnaire
 - KCCQ
 - SF-36

Neurological Assessment (2 Year Post Procedure Visit only):

For all patients diagnosed with stroke between 1 year and up to 2 years post-procedure, a follow-up mRS assessment 90 days after the diagnosis should be performed (on site or phone calls). Evaluation of stroke by mRS between 30 and 90 days is acceptable if 90-day follow-up not available. Every effort should be made to have a neurologist (or neurology fellow) perform the assessment. If it is not possible to have the neurologist/fellow complete this within the protocol-specified visit window, a certified study team member may perform the assessments.

8.7 Missed Visits

Site personnel should make all reasonable efforts to locate and communicate with the subject at each visit time point. For each missed visit, a minimum of 3 attempts to contact the subject should be recorded in source documentation, including date, time and name of site personnel trying to make contact.

8.8 Lost to Follow-Up

If the patient has missed multiple visits (with multiple attempts to contact as noted in section 8.9) and no record of death is found, the patient may be considered a lost to follow up. All assessments performed and the reason for discontinuation will be entered into EDC and Exit form completed.

8.9 Discontinuation after entering procedure room

Every patient should be encouraged to remain in the study until they have completed the protocol required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented. All attempts should be made to have the patient come into the clinic for an Exit visit.

If the following situations occur, the patient status will be considered 'Discontinued':

- The patient has entered the cath lab or operating room (procedure room) and an inclusion or exclusion criteria failure has been found.
- The patient has entered the procedure room and expires prior to the start of the valve implant procedure.
- The patient expires after the procedure has started.
- The patient withdraws consent after the valve implant procedure and prior to the final study visit.
- The patient expires after the valve implant procedure and prior to the final study visit.

If the patient is randomized to TAVR but has a THV other than the SAPIEN 3 implanted, the patient status will be considered discontinued and the patient will be monitored through Day 30 or until any AEs occurring are resolved.

All assessments performed and the reason for discontinuation will be entered into EDC and Exit form completed.

8.10 Randomized TAVR patient receives SAVR

Patients who are randomized to TAVR but undergo SAVR will continue in the study and complete all remaining study visits. The reason for conversion from TAVR to SAVR will be entered into EDC.

8.11 Death Registries

In the event of a patient lost to follow-up or early withdrawal, Edwards may opt to search the Social Security Death Index and/or other death registries. If the patient is confirmed to be expired, Edwards may opt to obtain the death certificate.

Schedule of Procedures

	Screening	Procedure (Valve Implant)	Post Procedure	Discharge	30D	6M	12M	2-10Y
Visit Window	Day -30 ^d	Day 0			+7 days	+14 days	+30 days	+45 days
Physical Assessment								
Informed Consent	X							
Medical History	X							
Physical Assessment	X			X	X	X	X	X
CCS Angina	X							
NYHA Classification	X			X	X	X	X	X
MMSE	X				X		X	
STS Risk Score	X							
Logistic EuroSCORE	X							
EuroSCORE II	X							
SYNTAX Score	X							
Medications	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X
NIHSS ^a	X		X ^a	X ^a	X	X ^a	X ^a	
Modified Rankin Scale ^a	X				X	X ^a	X ^a	
6 Minute Walk Test	X				X		X	
Frailty Index ^k	X							
Laboratory Measurements								
WBC, Hgb, Platelet Count	X		X	X	X			
PT or INR	X		X	X				
CK/CKMB and/or Troponins	X ^b		X ^c					
eGFR	X							
Creatinine	X		X	X	X			
Albumin, Total Bilirubin	X							
AST/ALT ^m	X							
BNP	X			X	X			

	Screening	Procedure (Valve Implant)	Post Procedure	Discharge	30D	6M	12M	2-10Y
Visit Window	Day -30 ^d	Day 0			+7 days	+14 days	+30 days	+45 days
Non-Invasive Tests								
Pulmonary Function Test (PFT)	X ^l							
ECG	X		X		X		X	
Echocardiogram (TTE)	X ^e	X ^j		X	X		X	X ^e
Final Eligibility Review								
Case Review ⁱ	X							
Invasive Tests								
Sub-study CT ^f					X		X	
3D Cardiac imaging (CT, TEE, or cardiac MRI) ^h	X							
Iliofemoral CT Angiography ^g	X							
Valve implant procedure (TAVR or SAVR)		X						
Cardiac Catheterization	X							
Supra-aortic angiogram or TEE		X ⁱ						
Quality-of-Life Assessments								
KCCQ	X				X	X	X	X
EQ-5D-5L	X				X	X	X	
SF-36	X				X	X	X	X

- a All patients should be assessed post-procedure to determine if there is evidence of neurological impairment. If symptoms of a stroke are suspected, the NIHSS should be performed. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments. 6M and 1Y assessments to be performed only for patients diagnosed with a stroke after the procedure.
- b CK/CKMB and/or Troponins are required ≤ 72 hours before the valve implant procedure.
- c Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1.) At the first lab draw post valve implant procedure (within 8 hours of exiting the cath lab or operating room) 2.) At the second lab draw 6 – 8 hours after the first lab draw 3.) At the third lab draw 6 – 8 hours after the second lab draw.
- d Screening procedures will be completed within 30 days prior to the valve implant procedure unless otherwise noted.
- e Qualifying echocardiogram must have been performed within the 90 days prior to randomization. Echocardiograms to be obtained years 2, 3, 4, 5, 7, and 10.
- f Only for those patients participating in the CT sub-study (section 12.5.2.1). Additionally, if the patient presents with symptoms, an unscheduled CT scan should be performed,
- g Includes thoracic and abdomen scan with visualization of iliac and femoral arteries.
- h All patients will have cardiac imaging at the screening visit regardless of participation in the CT sub-study.
- i Case Review will be completed when all screening procedures have been completed, all inclusion/exclusion criteria have been fundamentally confirmed and the site is ready to present a case.
- j TTE or TEE on date of valve implant procedure.
- k Frailty Index includes activities of daily living (ADLs), 5 meter walk test (5MWT), grip strength, and albumin laboratory.
- l Only for patients with a history of lung disease.
- m Only required for patients with chronic liver disease.

8.12 Procedures for Actigraphy/QOL Sub-study [Enrollment Closed]

Patients will receive a tablet and wearable activity tracker during the screening process and prior to randomization. A trained research assistant at each site will instruct patients on how to wear and use the devices. Baseline QOL and activity will be established during a pre-procedure phase (between screening and the procedure date). A preprogrammed algorithm will send alarm prompts to complete the VAS Pain assessment on the tablet every other day beginning at screening and ending on day 44 post procedure. The KCCQ-12 and PF-10 Physical will be completed via the tablet at 1, 2, 3, 5 and 6 week time points following the procedure. Activity data will be tracked continuously in 15-minute increments from screening through 44 days post procedure. Quality of life data will be captured via Medidata's Patient Cloud ePRO system, which allows patients to enter questionnaire data into commercially available smartphones and tablets that automatically synchronize with the Medidata platform. Activity data will be captured via Medidata's mobile health offering, which involves direct integration with wearable devices (i.e., Garmin Vivofit2). Activity data is authenticated and securely ingested by the Medidata Clinical Cloud, where it is then audited, processed and integrated with the rest of the clinical record.

Schedule of Procedures Actigraphy/QOL Sub-Study [Enrollment Closed]

	Screening	Procedure Day	Post-Procedure																							
			Time window: + 12 hours																							
			+ 2	+ 4	+ 6	+ 8	+ 10	+ 12	+ 13	+ 14	+ 16	+ 18	+ 20	+ 22	+ 24	+ 26	+ 28	+ 30	+ 32	+ 34	+ 36	+ 37	+ 38	+ 40	+ 42	+ 44
VAS Pain	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
			Time window: + 1 day																							
KCCQ-12	X				X					X				X								X			X	
PF-10	X				X					X				X								X			X	

Notes:

- ePRO based VAS pain assessment will be completed every other day. A 12 hour time window will be allowed for patients to complete each assessment
- ePRO based KCCQ-12 and PF-10 assessments will be completed at 1-week, 2-weeks, 3-weeks, 5-weeks and 6-weeks post procedure. A one day time window will be allowed for patients to complete each assessment. Note: to lessen patient burden, ePRO based KCCQ-12 and PF-10 assessments will not be completed at baseline and 30-day follow-up as paper based assessments are already administered at those time points
- Paper based KCCQ, EQ-5D-5L and SF-36 will be administered at screening, 30-days, 6 months, 12 months. Note: KCCQ-12 and PF-10 scores can be derived from the longer KCCQ and SF-36 instruments
- Daily activity data is defined based on the subject’s time zone and day

9.0 ADVERSE EVENTS

9.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device.

Adverse events may be volunteered by patients, elicited by the Investigator or designee, the CEC, safety team, monitoring team, or collected via observation by the Investigator. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or implant procedure, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF.

In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events occurs between study visits.

All clinically significant AEs will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations as indicated below section 9.5.

9.2 Serious Adverse Event

An Adverse Event is considered serious if the event:

- Leads to death;
- Leads to a serious deterioration in the health of the study patient that:
 - Results in life-threatening illness or injury;
 - Results in a permanent impairment of a body structure or a body function;
 - Requires inpatient hospitalization or prolongation of existing hospitalization;
 - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Led to fetal distress, fetal death or congenital abnormality or birth defect;
- Significant medical event.

Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.

Death should not be recorded as an adverse event, but should only be reflected as an outcome to another specific AE.

9.3 Anticipated Adverse Events

Anticipated adverse events are AEs that have been identified as possible adverse events related to the investigational device or implant procedure.

9.4 Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients.

The Investigator shall submit to the Sponsor and the reviewing EC/IRB a report of any UADE occurring during an investigation **as soon as possible, but no later than 10 working days of awareness**.

All UADE adverse events must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the UADE adverse event must be recorded.

Edwards will notify FDA as well as all participating clinical investigators and IRBs of all UADEs that occur during this study within 10 working days after becoming aware of the event. Investigators are responsible for reviewing information received about UADEs.

9.5 AE Reporting Requirements

All relevant AEs will be captured from the time of randomization/enrollment until the study patient's participation has ended (i.e. completion of study or withdrawal of consent).

Adverse events must be followed until resolution, stabilization or study completion. The AE and/or SAE should be reported, and CRF Forms completed **as soon as possible but no later than 10 working days of awareness**.

In the event that the EDC system is not in service, a paper copy of the AE Case Report Form (CRF) must be faxed or emailed to Sponsor THV Medical Safety at (949) 809-2933 or emailed to THV_Safety@edwards.com **within 10 business days of becoming aware of the event**. At the time of initial notification, the following minimal information must be provided:

- Study site
- Patient ID
- Adverse event description
- Causal relationship to device and implant procedure
- Aware date

The site will provide a copy of supporting documentation (example: admission H&P, implant procedure reports, anesthesia records, discharge summary, echocardiogram and ECG reports, laboratory results, etc.) for all endpoint-related and device or procedure-related events and UADEs to Edwards Lifesciences (or designee). Source documentation may be requested by the Edwards Medical Safety Officer for other AEs in order to verify that events are being assessed appropriately.

Enrolling sites must provide to the Sponsor at a minimum an admission history and physical, index procedure report and discharge from index hospitalization along with relevant echocardiographic reports. This will be done irrespective of subject having any AE/SAE.

All AEs must be reported over the 12 month period following the initial valve implant procedure. Reportable AEs after year 1 through year 10 or study exit include only the following events:

- All AEs that are assessed or suspected to be device or implant procedure related
- All AEs that meet the criteria for serious adverse event irrespective of device or implant procedure relationship
- All AEs considered to be an Unanticipated Adverse Device Effect

The site Principal Investigator is responsible for informing the Institutional Review Board (IRB) of SAEs, UADE and/or AEs as required. A copy of this report should be provided to the Sponsor (or designee).

Events that do not Require Reporting to the Sponsor:

For purposes of this study, the following events will not be required to be reported as adverse events to the Sponsor, because they are normally expected to occur in conjunction with transcatheter valve implantation and surgical valve replacement or are associated with customary, standard care of patients undergoing THV implantation or surgical AVR:

- Post-operative pain.
- Post-anesthesia emesis, nausea, or headache (within 24 hours of procedure).
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction.
- Pre-planned future surgical procedures not associated with the study procedure or device.
- Low grade temperature increase ($\leq 101^{\circ}\text{F}$ or 38.5°C).
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo without signs of TIA or stroke.
- Elevated white blood count, outside the standard laboratory normal value, without signs and symptoms of infection.

- Minor, localized tenderness, swelling, induration, oozing, etc. at incision / delivery system insertion site.
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Thrombocytopenia: does not become an AE until treatment is administered; Suspected heparin-induced thrombocytopenia (HIT) should be reported
- Hyperglycemia - The use of insulin in the post-operative period does not constitute hyperglycemia if during the index hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post-operative does not constitute hyperglycemia.
- Expected, non-clinically significant events such as non-significant lab variances.

9.6 Pre-existing Condition

Pre-existing medical conditions or symptoms reported prior to subject enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition or symptoms due to the device, implant procedure, or study related procedures, then an AE must be recorded.

Death should not be recorded as an adverse event, but should only be reflected as an outcome to another specific AE.

9.7 Causality of AEs

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, and whether the event meets the definition of a SAE as outlined in section 9.2.

The causal relationship of the event to the device and the implant procedure will be categorized as follows:

- **None:** The event is not associated with the device or implant procedure. There is no relation between the event and the device or implant procedure.
- **Possibly Related:** The temporal sequence between the device or implant procedure and the event is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the study patient's condition. There is a possibility of any relation between the event and the device or implant procedure.
- **Definitely Related:** The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the patient's condition or comorbidities. The event is related or most likely associated with the device or implant procedure.

9.8 Sponsor Assessment of AEs

All AEs will be reviewed by the Medical Safety Officer. Each AE will be assessed as to its relationship to the study device and/or implant procedure, whether it was

anticipated or not anticipated, (based on the list of potential risks provided in section 10.2), and whether it qualifies as an SAE.

9.9 Device Malfunctions

A device malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

All device malfunctions with or without adverse events should be reported to Edwards Lifesciences **as soon as possible (preferably within 24 hours) but no later than 10 working days of awareness.**

10.0 RISKS AND BENEFIT ANALYSIS

There are potential risks associated with transcatheter valve replacement. There are risks related to the overall procedures (complications associated with standard cardiac catheterization, balloon valvuloplasty, local and/or general anesthesia) as well as additional possible risks uniquely associated with the use of the study valve and its delivery systems.

10.1 Potential Benefits

There are no guaranteed benefits from participation in this study. Information gained from this study may be of benefit to other people with the same medical condition in the future. The long-term results of using the SAPIEN 3 THV are not known at the present time. Alternative treatments include surgical AVR and BAV.

Implantation of the transcatheter heart valve may result in improved valvular function, acute alleviation of symptoms related to aortic stenosis, and improved quality of life in patients with low operative risk of mortality.

10.2 Potential Risks

There are potential risks associated with transcatheter valve replacement. There are risks related to the overall procedures (complications associated with standard cardiac catheterization, balloon valvuloplasty, local and/or general anesthesia) as well as additional possible risks uniquely associated with the use of the study valve and its delivery systems.

Potential risks associated with anesthesia and interventional procedures include but are not limited to:

- Abnormal lab values (including electrolyte imbalance)
- Allergic reaction to anesthesia, contrast media or device materials
- Anemia

- Angina
- Arrhythmia
- Bleeding
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Conduction system injury (defect) which may require a permanent pacemaker
- Death
- Embolization including air, calcific/thrombotic valve material, or thrombus
- Exercise intolerance or weakness
- Femoral AV fistula or pseudoaneurysm
- Fever
- Heart failure
- Heart murmur
- Hematoma
- Hemorrhage requiring transfusion or intervention
- Hypertension or hypotension
- Infection including septicemia and endocarditis
- Inflammation
- Myocardial infarction
- Pain or changes at the access site
- Paralysis
- Pericardial effusion or cardiac tamponade
- Peripheral ischemia or nerve injury
- Permanent disability
- Pleural effusion
- Pulmonary edema
- Renal insufficiency or renal failure
- Reoperation
- Respiratory insufficiency or respiratory failure
- Restenosis
- Retroperitoneal bleed
- Stroke/transient ischemic attack, clusters or neurological deficit
- Syncope

In addition to the risks listed above, additional potential risks specifically associated with the use of the SAPIEN 3 THV, the delivery systems and/or accessories include, but may not be limited to, the following:

- Cardiac arrest
- Cardiac failure or low cardiac output
- Cardiogenic shock
- Coronary flow obstruction/transvalvular flow disturbance
- Device degeneration
- Device embolization
- Device explants
- Device migration or malposition requiring intervention
- Device thrombosis requiring intervention

- Emergency cardiac surgery
- Hemolysis
- Injury to mitral valve
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation
- Nonstructural dysfunction
- Paravalvular or transvalvular leak
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Valve deployment in unintended location
- Valve regurgitation
- Valve stenosis
- Valve thrombosis

10.2.1 Risk Minimization

Product handling and implant procedure guidance are provided in the IFU and training manual, which will be used for device training to minimize risks associated with device use.

Additionally, efforts will be made to minimize risks through site/investigator selection and management. First, site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures as well as support the associated requirements for research. Second, the trial management structure is designed to provide disciplined oversight of the trial activities including close monitoring of site and personnel performance and also support opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

The SAPIEN 3 THV represents a third generation THV for Edwards Lifesciences and was developed with the experience from the first and second generation SAPIEN THVs. The SAPIEN 3 System has undergone extensive clinical testing in the aortic position and is commercially available for TAVR in the US and countries that honor the CE mark.

11.0 STATISTICAL ANALYSIS

11.1 Sample Size Calculations

The sample size for the trial is based on obtaining at least 90% power to pass the 1-year safety and effectiveness endpoint.

Event rate estimates for the primary safety and effectiveness endpoint were based on data from prior studies. Since the current study patients are a lower risk

population, and to account for procedural refinement over time in both arms as well as changes in definitions for components of the endpoint, the rates have been lowered.

The sample size is based on the composite primary endpoint which assumes an event rate of 16.6% in the SAVR arm and 14.6% in the TAVR arm. A randomized sample size of 864 patients with 1-year data would produce 90% power for passing the endpoint. The test statistic used for this computation is the one-sided Z test (Unpooled), at $\alpha = 0.025$, using the specified non-inferiority margin of 6.0%. The sample size was computed in PASS.

The sample size determination was based on a pure frequency analysis, whereas the endpoint analysis will use the Kaplan-Meier estimates. Since the two methods are equivalent in the absence of censoring, and a sufficient number of uncensored patients is anticipated, the sample size should be adequate.

Because the feasibility assumptions are uncertain in this previously unstudied population, an actual sample size of 1000 has been chosen, which is higher than the minimum statistically justified size to allow for trial contingencies, such as withdrawals and lost to follow-up.

11.2 Analysis Populations

- The Intent to Treat (ITT) population consists of all randomized patients.
- The As Treated (AT) population is the subset of the ITT population consisting of all patients for whom the index procedure is begun, whether or not the index procedure is completed. If multiple procedures were attempted, the last procedure with the study valve deployed will be considered the index procedure and used for determining the As Treated trial arm assignment and the date of the index procedure will be used for determining all follow-up visits and related assessment. A randomized TAVR patient for whom the TAVR procedure is never started will not be part of the AT population, even if that patient should receive a SAVR implant.
- The Valve Implant (VI) population is the subset of the AT population consisting of all patients who receive and retain the intended valve during the index procedure. Patients who receive a valve in valve implant will be part of the VI population. Patients who are converted from TAVR to SAVR during the procedure will not be part of the VI population.

The AT population will be the primary population for trial endpoint analysis. The VI population will be used for analysis of echo data and related endpoints. Selected sensitivity analyses will be performed using the ITT population.

11.3 Timing

- The index procedure date is defined as Day 0. For randomized patients who do not have the procedure attempted, the randomization date will be used as Day 0.
- Time intervals for events will be computed by subtracting the event date minus day 0. For example, if the procedure occurs on January 1, and the patient dies on January 31, the death will be considered a 30 day death for analysis.
- The timing for all visits will be based on the index procedure date. If the patient never receives the procedure the 30-day visit will never be due; later visits for such patients will be based on the randomization date.
- In analysis of time-dependent variables, one year is defined as 365.25 days, and one month as 30.4375 (= 365.25/12) days.

For information depending on follow-up windows any visit within the specified window will be used, without regard to the actual timing of the visit.

- Analysis close date:
 - The analysis close date for the initial analysis will be the earlier of the following two dates: One year past the last index procedure
 - One year plus 60 days past the last randomization. This condition is in order to account for a potential patient with a severely delayed procedure.
- The analysis close date for later reports will be determined prior to the report. Unless otherwise specified such dates will be at annual intervals past the initial analysis close date.
- All database information will be used to determine patient survival as of the analysis close date.
- Adverse events occurring after the relevant analysis close date will not be included in adverse event analysis.
- Information dependent on a visit window, such as echo or NYHA, will be included in analysis as long as the window starts on or before the analysis close date.

11.4 Primary endpoint analysis (Non-inferiority)

The primary safety and effectiveness endpoint is the composite of all-cause mortality, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year post procedure. The endpoint will be evaluated as a non-inferiority analysis based on a non-inferiority margin of 6.0%. The components of

the composite endpoint will be evaluated by the CEC.

To precisely formulate the test, let r_T denote the true event proportion in the test arm at 1 year, and r_C denote the true event proportion in the Control arm at 1 year. The hypotheses are:

$$\begin{aligned} H_0: r_T - r_C &\geq \Delta \\ H_A: r_T - r_C &< \Delta \end{aligned}$$

The value Δ is the non-inferiority margin, and is taken to be 0.06. The test will be performed as a one-sided test at $\alpha = 0.025$.

A 95% confidence interval for the difference $r_T - r_C$ will be computed using the Kaplan-Meier algorithm with the standard errors being computed using Greenwood's formula. The null hypothesis shall be rejected at $\alpha = 0.025$ if the upper confidence limit is less than 0.06.

Covariates will not be included in analysis of the primary endpoint.

11.5 Primary Endpoint (Superiority) and Secondary endpoints for labeling

The analysis for the superiority in the primary endpoint and secondary endpoints for labeling will be performed only if the primary endpoint passes the non-inferiority test.

The superiority in the primary endpoint and secondary endpoints will be evaluated for labeling purposes in the order shown below. Each endpoint will be tested between the treatment arms by a two-sided test at $\alpha = 0.05$. If any of the endpoints does not achieve statistical significance at $\alpha = 0.05$, the lower endpoints in the list will not be considered for this purpose. The analyses will be performed in the As Treated population.

1. New onset atrial fibrillation, as a superiority analysis comparing trial arms (Secondary endpoint for labeling)

Let r_T and r_C be the true new onset atrial fibrillation rate at 30 days for test and control arms respectively. The hypotheses for the superiority test are:

$$\begin{aligned} H_0: r_T &= r_C \\ H_A: r_T &\neq r_C \end{aligned}$$

The endpoint will be evaluated as a binary endpoint. The trial arms will be compared using the Fisher's exact test. The null hypothesis shall be rejected and the superiority will be established if the p-value of test is less than 0.05 and the point estimates $\hat{r}_T < \hat{r}_C$.

The counts and percentages of the new onset atrial fibrillation at 30 days will be presented for TAVR and SAVR arms, the p-value of trial arm comparison will

also be presented. The subjects with pre-procedural atrial fibrillation or those undergoing concomitant ablation will be excluded from the analysis unless CEC adjudicated the event as “new onset” or “both”.

2. Length of index hospitalization, as a superiority analysis comparing trial arms (Secondary endpoint for labeling)

Let d_T and d_C be the distribution of the true lengths of index hospitalization for test and control arms, respectively. For this analysis, patients who die before discharge will be considered to have been discharged on the death date. The hypotheses for the superiority test are:

$$\begin{aligned} H_0: d_T &= d_C \\ H_A: d_T &\neq d_C \end{aligned}$$

Length of index hospitalization will be treated as a continuous variable, with trial arms compared using the Wilcoxon rank-sum test. The null hypothesis shall be rejected and the superiority will be established if the p-value of test is less than 0.05 and the point estimates of the median lengths $\hat{d}_T < \hat{d}_C$.

The mean, standard deviation, median, minimum and maximum of Length of index hospitalization will be presented for TAVR and SAVR arms, the p-value of trial arm comparison will also be presented.

3. Primary endpoint as a superiority analysis comparing trial arms

The superiority test for the primary endpoint will be performed as a one-sided test at 0.025, where α is the amount of Type I error passed, The hypotheses for the superiority test are:

$$\begin{aligned} H_0: r_T &\geq r_C & \text{or equivalently} & & H_0: r_T - r_C &\geq 0 \\ H_A: r_T &< r_C & & & H_A: r_T - r_C &< 0 \end{aligned}$$

The following Z statistic will be used for the superiority test.

$$Z = \frac{\hat{r}_T - \hat{r}_C}{\sqrt{s_T^2 + s_C^2}}$$

The null hypothesis shall be rejected and the superiority will be established if the p-value of the one-sided Z test is less than 0.025.

4. KCCQ and death composite at the 30 day visit, as a superiority analysis comparing trial arms (Secondary endpoint for labeling)

Let r_T and r_C be the true rate of the composite events at 30 days for test and control arms respectively. The hypotheses for the superiority test are:

$$H_0: r_T = r_C$$

$$H_A: r_T \neq r_C$$

The endpoint will be evaluated as a binary endpoint. The trial arms will be compared using Fisher's exact test. The null hypothesis shall be rejected and the superiority will be established if the p-value of test is less than 0.05 and the point estimates $\hat{r}_T < \hat{r}_C$.

A patient will be counted as meeting this endpoint if one or more of the following three conditions hold.

- a) The patient dies on day 30 or earlier, whether or not a KCCQ score has been collected within the follow-up window.
- b) The KCCQ score at the 30 day visit is < 45 .
- c) The KCCQ score at 30 days is ≥ 10 points decreased from the baseline score.

Missing data will be handled as described in section 11.8.5.

5. Death/All Stroke composite at 30 days, as a superiority analysis comparing trial arms (Secondary endpoint for labeling)

Let r_T and r_C be the true rate of the death/all stroke composite events at 30 days for test and control arms, respectively. The hypotheses for the superiority test are:

$$H_0: r_T = r_C$$

$$H_A: r_T \neq r_C$$

The endpoint will be evaluated as a binary endpoint. The trial arms will be compared using the Fisher's exact test. The null hypothesis shall be rejected and the superiority will be established if the p-value of test is less than α and the point estimates $\hat{r}_T < \hat{r}_C$.

The counts and percentages of the composite event at 30 days will be presented for TAVR and SAVR arms, the p-value of trial arm comparison will also be presented.

6. All Stroke at 30 days, as a superiority analysis comparing trial arms (Secondary endpoint for labeling)

Let r_T and r_C be the true stroke rate at 30 day for test and control arms, respectively. The hypotheses for the superiority test are:

$$H_0: r_T = r_C$$

$$H_A: r_T \neq r_C$$

Stroke will be evaluated as a binary endpoint. The trial arms will be compared using the Fisher's exact test. The null hypothesis shall be rejected and the superiority will be established if the p-value of test is less than α and the point estimates $\hat{r}_T < \hat{r}_C$.

The number of events, number of patients with event and Kaplan-Meier estimates of stroke rate at 30 day will be presented for TAVR and SAVR arms, the p-value of trial arm comparison will also be presented.

11.6 Additional Safety and Effectiveness Endpoints

The endpoints in this section will be evaluated according to the general statistical methods described in section 11.8. These endpoints will not be subject to the formal multiple comparisons correction; they are presented as part of the totality of information. All the statistical tests between the treatment arms will be two-sided tests at $\alpha=0.05$.

- Mortality (all cause & cardiovascular) at 30 days and 1 year
- Stroke (disabling and nondisabling) at 30 days and 1 year
- Death or stroke at 1 year
- Death or disabling stroke at 30 days and 1 year
- Vascular complications (major) at 30 days and 1 year
- Bleeding complications (life threatening, disabling or major) at 30 days and 1 year
- Myocardial infarction at 30 days and 1 year
- Acute kidney injury at 30 days
- Requirement for renal replacement therapy at 1 year
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances at 30 days and 1 year.
- Coronary obstruction requiring intervention at 30 days and 1 year

- New York Heart Association class at 30 days and 1 year
- Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation at 30 days and years 1, 2, 3, 4, 5, 7, and 10. Echo readings to be evaluated include aortic valve area, mean gradient, peak gradient, perivalvular aortic regurgitation, total aortic regurgitation, and mitral regurgitation.
- Rehospitalization (valve-related or procedure-related and including heart failure) at 30 days, 1 year and annually (up to 10 years)
- Days alive and out of hospital at 1 year
- Six-minute walk test at 30 days and 1 year
- Health status as evaluated by Quality of Life questionnaires at 30 days and 1 year
- New onset atrial fibrillation at 1 year
- ICU days and discharge location
- Structural valve deterioration at years 1-5,7 and 10

11.7 Additional analyses

- Baseline data will be reported by summary statistics, separately by trial arm with p - values.
- The various procedural variables will be reported by summary statistics, separately by trial arm with p -values.
- Visit compliance data will be presented.
- Analysis of echo and procedural variables will be presented by valve size, at the various echo collection time points.
- Analyses past one year will be the same as the analyses for 1 year, but limited to those variables collected after the 1 year visit.

11.8 General Statistical Methodology

11.8.1 Time Dependent Variables

Time-dependent variables will be analyzed using the Kaplan-Meier algorithm, with standard errors computed by Greenwood's formula. The number of patients-at-risk will be computed at exact time points, without reference to any nominal follow-up windows. The log-rank statistic will be used for any comparison among groups.

Thirty day analysis will present both pure frequency and Kaplan-Meier rates; for later analyses only Kaplan-Meier rates will be presented. Kaplan-Meier rates will be presented at 30 days and 1 year as well as other time points as appropriate.

11.8.2 Continuous and ordinal variables

- For continuous variables, summary statistics will include means, standard deviations, medians and quartiles. Confidence limits will be computed using the t -distribution. Groups will be compared using t-tests or analysis of variance. Where severe departures from normality are observed, comparisons will also be performed using the Wilcoxon rank-sum test.
- For ordinal variables, summary statistics will include medians and quartiles; means will also be presented when appropriate. Group comparisons will be performed using the Wilcoxon rank-sum test.
- NYHA and regurgitation will be considered as ordinal variables. Group counts and means will be presented for these variables.

11.8.3 Categorical Variables

- For categorical variables, summary statistics will include counts and percentages. Confidence limits for binary variables will be computed using the exact binomial distribution.
- Categorical variables will be compared by Fisher's exact test.

11.8.4 Non-Inferiority Analyses

- Non-inferiority tests at a point in time are based on the rate difference approach.
- The test is performed at a point in time T , using the Kaplan-Meier estimates for freedom from the endpoint being evaluated, and the Greenwood standard errors for these estimates. The test will be performed by computing the two-sided 95% confidence limit for the event rate difference (TAVR - SAVR). The acceptance criterion is that the upper confidence limit is less than Delta, where Delta is the predetermined non-inferiority margin of 6.0%.
- In analysis of the primary endpoint, there will be little or no censored data. The only censoring would be due to lost to follow-up or withdrawal from the trial.
- It is conceivable that there will be no censored data at all in evaluating the primary endpoint. In such a case the Kaplan-Meier estimators are pure proportions, and the Greenwood variance is the standard variance for an estimated proportion. The confidence limits would agree with those produced by

standard frequency analysis.

- For the primary endpoint in this trial the non-inferiority margin of 6.0% has been chosen.

11.8.5 Missing Data

- Missing variables will not be imputed for planned analyses, except where otherwise specified.
- The primary safety and effectiveness endpoint will be based on Kaplan-Meier estimates, which automatically account for censored data.
- For sensitivity purposes, tipping point analyses for the primary endpoints are defined in the SAP.
- Tipping point analysis will also be presented for the secondary endpoint involving KCCQ.

11.8.6 Multiple comparisons

A formal multiple comparisons analysis is presented in section 11.5 for the named secondary endpoints for labeling purposes. In all other cases p-values will be presented as computed, without any adjustments for the comparisons.

11.8.7 Adverse event analysis

- Adverse event analysis will involve both site and CEC reporting.
 - Where events have been adjudicated by the CEC, those adjudications will be used in preference to site reports.
 - Where site events are analyzed, the MedDRA coding will be used. The underlying site evaluations will not be used for analysis, but may appear in listings as appropriate.
- Adverse events to be analyzed include the composites involved in the primary and secondary endpoints, as well as all events contained in these composites. All events adjudicated by the CEC will also be analyzed.
- Adverse event tables will present data at 30 days, 6 months, and 1 year. The tables will include counts of events, patients with event, and Kaplan-Meier event rates at the specific time point. The trial arms will be compared by the log-rank test
- Late adverse events (> 30 days) will be analyzed by a constant hazard model, and upper one-sided confidence limits will be given for the rates.

- Adverse event data past 1 year will be presented as counts of events and patients with event. No formal analyses will be performed for such data.

11.8.8 Periodic analyses

Periodic analyses will be performed during the trial to the extent required by the appropriate regulatory authorities and the DSMB. The sample size and endpoint timing for this trial is fixed in advance, and not based on these periodic analyses. Accordingly, there is no adjustment to alpha.

Other than the required reports mentioned in the previous paragraph, there will be no reporting of trial outcome data prior to the 1-year analysis close date.

It is anticipated that reporting will continue throughout the trial, with formal reports based on analysis close dates at annual intervals.

11.8.9 Quality of life questionnaires

Quality of life questionnaires will be scored according to algorithms provided by the vendor. The various summary scores produced by the algorithms will be analyzed as continuous variables.

11.8.10 General Specifications

- Trial arm comparisons will be presented wherever meaningful. *P*-values will be computed using a null hypothesis of no difference.
- Unless otherwise specified, Wald *p*-values will be presented.
- Unless otherwise specified, confidence limits and hypotheses tests will be two sided, using alpha = 0.05.
- Unless otherwise specified, the precise form of each algorithm will be the default of SAS, using the latest release installed at Edwards at the time of analysis. This will be version 9.3 or later.
- Various CRFs will contain comment fields. Data in these fields will not be analyzed, but listings will be provided for internal use on request.

11.9 CT Sub-Study

The purposes of the study are to:

1. Investigate the prevalence of the imaging abnormality.

The prevalence data come in two forms. A Yes/No value, which will be analyzed as a binary variable. A grading, which will be analyzed as an ordinal variable.

2. Investigate the relationship between the imaging abnormality and patient, procedural and pharmacology factors.

The Yes/No value will be the dependent variable in logistic regression models, with the independent variables chosen based on potential clinical relevance.

Multivariable models will be developed if the univariate analyses so suggest.

3. Investigate the relationship between imaging abnormalities and clinical events.

The clinical events to be considered will include stroke, TIA, and death. These will be modeled as time-dependent variables using proportional hazards regression, with the Yes/No value of the imaging abnormality as an independent variable.

Key echo parameters (valve area, mean gradient, and AR) will be modeled, with the Yes/No value of the imaging abnormality as an independent variable.

This sub-study analysis is unpowered.

The choice of variables for items 2 and 3 will be based on the tables presented in the papers of Makkar [26] and Pache [27].

It should be noted that the prior studies found few statistically significant baseline predictors of the imaging abnormality, and they found only minor clinical impact resulting from the abnormality. There is no reason to expect any different results in this sub-study.

12.0 STUDY ADMINISTRATION

12.1 General Study Organization

Edwards Lifesciences is the Study Sponsor and has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies.

Edwards Lifesciences will be responsible for obtaining IDE approval for the study, selecting investigators, ensuring that sites have IRB/EC approval prior to investigational device shipment, and conducting clinical site monitoring to ensure that patients are being properly consented and the study is being conducted according to the protocol.

As appropriate, Edwards Lifesciences will submit changes in the Investigational Plan to the FDA and Investigators to obtain IRB/EC re-approval.

Edwards Lifesciences will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial as appropriate.

Edwards Lifesciences will submit all reports required by the FDA as identified in 21 Code of Federal Regulations (CFR) 812.150(B). This includes UADEs, withdrawal of IRB/EC approval, current investigators list, annual progress reports, recall information, final reports and protocol violations.

12.2 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will monitor all AEs and SAEs to provide safety oversight. DSMB members will not be involved in the study and have no conflict of interest. At least one member will be a cardiothoracic surgeon with specific expertise in aortic stenosis. DSMB activities, including stopping rules for early termination, will be defined in the DSMB Charter.

12.3 Clinical Event Adjudication Committee (CEC)

The Clinical Events Committee (CEC) will adjudicate endpoint events and provide assessment of SAEs and device/procedure relatedness from enrollment through the primary endpoint. The CEC will include cardiologists and cardiothoracic surgeons with experience in the field of aortic stenosis who are not involved in the study and have no conflict of interest. CEC activities will be defined in the CEC Charter.

12.4 Study Procedures

12.4.1 Echocardiogram

Study patients will receive an echocardiogram at the visits specified in section 8.0. A central imaging core lab will be established to independently review and analyze echocardiographic images. A standardized protocol for acquiring images will be developed by the core lab and be provided to the clinical sites prior to study initiation. Sites will be trained on acquiring images prior to study initiation. Appendix J includes the echocardiogram manual of operations.

12.4.2 Computed Tomography (CT)

All study patients will have a screening CT as referenced in section 8.0. Sites will be trained on acquiring images prior to study initiation. In addition, all Screening CTs will be independently analyzed with regards to annular measurements by a CT/angiographic core lab. Appendix K-1 includes CT acquisition information.

12.4.2.1 CT Sub-Study

Study patients enrolled in the CT sub-study will have a 4D CT at visits specified in section

8.1. A central imaging core lab will independently review sub-study CTs. Appendix K-2 includes the sub-study CT acquisition information.

Investigational sites will be blinded to the resulting images unless specific clinical or echo abnormalities are present.

If any of the following events occur, a repeat 4D CT will be mandated unless the event occurs within 24 hrs of the 30 day CT; in which case the CT will be unblinded.

:

- Any neurological event
- Any potential embolic event
- Myocardial infarction
- A change in echo parameters including an increase in mean gradient of 10-20 mm Hg or a change in DVI of 0.05 - 0.1

Patients whose initial imaging data are determined to be unevaluable will not undergo subsequent imaging.

12.4.3 Quality of Life Questionnaires

Investigational sites will be provided with paper QoL questionnaires (KCCQ, EQ-5D-5L, and the SF-36). Patient questionnaires will be IRB approved prior to patient administration.

Investigational staff will administer patient questionnaires to study patients. Patients will be instructed to complete each questionnaire at visits specified in section 8.0. The patient will be instructed by the investigational staff to sign and date the paper questionnaire once the questionnaire is completed. Patients will be instructed by the investigational staff not to change questionnaire answers once the questionnaire has been completed. Investigational sites should retain the completed questionnaire in the patients' source documents. Site staff will enter data collected from the completed patient questionnaire into the EDC.

The patient level summary scores will be computed by the Edwards Biostatistics group, and these scores will be used in evaluating protocol endpoints. A QoL core lab may prepare reports of additional analyses.

Quality of life will be measured through standard surveys:

- 1) The Kansas City Cardiomyopathy Questionnaire (KCCQ) is an assessment of disability and quality of life impairment due to congestive heart failure.
- 2) EQ-5D-5L is a standardized questionnaire for describing and valuing patients' health-related quality of life for clinical and economic appraisal.

- 3) The SF- 36 is a generic health status instrument and rating scale that allows mapping of health status to population-level utility weights. This is an important metric for cost- effectiveness analysis.

12.4.4 Image Management

A central image management lab will be established to receive, maintain, and provide cardiac images (echocardiogram and CT) to the appropriate core lab for analyzing.

Instructions for image upload will be provided to investigative staff prior to study initiation. Investigative staff should upload all images to the image management core lab within 5 business days of data collection.

12.4.5 Histopathology

Histopathology studies of explanted valves will be performed. Explants will be appropriately prepared and preserved and sent to the independent histopathology laboratory for macroscopic and microscopic analysis. Investigational valves that are removed at any time with an allegation of device malfunction should be returned to the Sponsor for evaluation. All other explants (those not with an allegation of device malfunction) should be sent to the Histopathology Core Lab. Appendix L contains a complete explant protocol which includes detailed procedures for the histopathology studies.

Gross pathological examination of the entire valve and the support structure (i.e., and shape, if occurrence of intravascular trauma, tissue abrasion, uniformity of the frame, position the natural valve cusps) will be assessed.

The valves will be assessed for cusp excursion and the presence of leaflet fenestrations, rigidity tears, hematoma, thrombi and calcified nodules, cell proliferation tissue overgrowth,

fibrous sheath, and local inflammatory reaction. (One half of each leaflet must be used for the quantitative determination of inorganic calcium and phosphate).

12.5 Training

To ensure proper device usage, uniform data collection, and protocol compliance, training is required for relevant study site personnel in accordance to roles outlined in the Delegation of Authority (DoA).

At the beginning of the study, Edwards Lifesciences will provide training to site personnel. Training will include review of the instructions for use of the device, study protocol, case review process, identification of eligible patients, instructions on in-hospital data collection, standardized data collection for core laboratory analysis,

methods for soliciting data from alternative sources, and regulatory requirements.

Documentation of site personnel qualification and training should be maintained in the site's clinical trial files and copies collected and forwarded for the Sponsor site file.

Ongoing training may be provided in one of the following formats by the Sponsor or its designee: live training sessions, teleconference, WebEx, online, or read and review. The Sponsor reserves the right to enforce retraining for sites who have demonstrated study or implant procedure compliance issues.

12.6 Device Management

12.6.1 Study Device

All SAPIEN 3 products will be supplied by Edwards Lifesciences. Each SAPIEN 3 THV will have a unique identifier which should be recorded in the patient's medical file as well as on the implant card that is given to the patient.

Refer to Appendix C for the IFUs to be used in this study. The IFUs will also be available electronically.

12.6.2 Device Storage

All SAPIEN 3 System components provided for the study should be stored in a secure location where only study personnel can access the device for use. Only physicians identified in the Investigator's Delegation of Authority Log on file at Edwards Lifesciences may implant this device in study patients.

12.6.3 Device Accountability

The study site will maintain detailed records of the receipt and disposition of all investigational devices on the Device Accountability Log (DAL). Device disposition will be verified by the clinical monitor periodically throughout the study. The Investigator will return unused devices to Edwards along with the completed device disposition log at completion of the investigation. Use of the SAPIEN 3 THV and accessories provided for use in the study is prohibited outside of this protocol.

12.7 Data Management

Edwards Lifesciences will provide data management through a secure, password protected Electronic Data Capture (EDC) system accessible via the Internet. A unique Patient ID will be assigned for each patient enrolled in the study. All pertinent data will be entered by the study site and core lab personnel into the electronic Case Report Forms (eCRFs).

Every reasonable effort should be made to complete data entry within 5 business

days of data collection. Data review by Edwards Lifesciences personnel will occur remotely as well as during on site monitoring. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate eCRFs. Changes to data previously submitted to the Sponsor will require a new electronic signature to acknowledge/approve the changes.

12.8 Monitoring Procedures

All clinical sites will be monitored periodically by Edwards Lifesciences or designee to ensure compliance with the protocol and the Investigator's Agreement and that all study patients have been properly consented. The monitor will ensure that the completed eCRFs match the source documents and work with the site to resolve differences through electronically generated queries or formal action items.

Edwards Lifesciences will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove either the investigator or the investigational site from the study.

12.9 Auditing

The study may be subject to a quality assurance audit by Edwards Lifesciences or a designee, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the Investigator should contact Edwards Lifesciences as soon as possible.

12.10 Record Retention

All clinical sites will maintain study records for a minimum of two years after marketing for this patient population approval is obtained or after the site is notified by Edwards

Lifesciences that the study has been terminated. Record retention dates will be provided to all parties concerned by Edwards Lifesciences.

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Compliance with Good Clinical Practices

The Investigator will ensure that this study is conducted in accordance with Good Clinical Practice (GCP) and applicable regulatory (local) requirements.

13.2 Institutional Review Board/Ethics Committee

This protocol, the proposed Informed Consent Form (ICF), other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and ICF must be received by Edwards Lifesciences before recruitment of patients into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF.

The Investigator is responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to Edwards Lifesciences.

13.3 Patient Informed Consent

Edwards Lifesciences will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF must be in agreement with current GCP guidelines.

Edwards Lifesciences must approve the site-specific ICF prior to submission to the IRB. The reviewing IRB must approve the ICF before use at that site.

Before participating in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained in a language that is easily understood by the patient. The subject must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

A copy of each patient's signed and dated consent form must be maintained by each Investigator in a designated clinical trial administrative file. A signed copy of the consent form must be given to each subject. The consent process must be documented in the subject's medical chart.

Any modifications to the site-specific ICF must be approved by Edwards Lifesciences and the IRB.

13.4 Confidentiality

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient. Authorized personnel assigned by Edwards Lifesciences will have access to the confidential files and will have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

13.5 Investigator Records

Records to be maintained by the Investigator include, but are not limited to, the following:

- Clinical trial protocol and all amendments
- Signed Clinical Trial Agreement and any amendments
- IRB approval letters, including continuing reviews and all amendments/changes
- IRB approved informed consent documents

The following records must be maintained for each subject enrolled in the trial:

- Signed patient informed consent
- All relevant source documentation for study visits and study-related procedures
- Supporting documentation of any adverse events

13.6 Investigator Reports

Adverse event reporting requirements are discussed in section 9.0.

Withdrawal of IRB Approval. Within 5 working days, the Principal Investigator will report to Edwards Lifesciences a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

Informed Consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to Edwards Lifesciences and the reviewing IRB within 5 working days after the use occurs.

Progress Reports. The Principal Investigator will submit progress reports on the investigation to Edwards Lifesciences and the IRB at least yearly.

Final Report. Upon completion or termination of this Trial, the Principal Investigator must submit a final written report to Edwards Lifesciences and the IRB as required by the regulations. The report must be submitted within 3 months of completion or termination of the trial.

13.7 Amending the Protocol

This protocol must be followed exactly. It can be altered only by written amendments made by Edwards Lifesciences. Following appropriate approval by Edwards Lifesciences, the amended protocol will be submitted to the required regulatory agencies before being distributed to all enrolling sites. Each site must obtain IRB/EC approval, complete required training (if any, and as required by DoA role), and receive written approval from Edwards Lifesciences before implementing the revised protocol.

13.8 Protocol Deviations

An investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Emergency changes to protect the life of the patient do not require prior approval, but must be reported to Edwards Lifesciences and the reviewing IRB within 5 days of the incident.

Each deviation from the protocol must be documented with the date and reason for the deviation and reported to Edwards Lifesciences as soon as possible, and to the IRB per local guidelines and government regulations.

13.9 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards Lifesciences. If Edwards Lifesciences approves the publication or presentation of the overall clinical study results and/or site-specific results, then Institutions and Investigators will comply with the Publications and Public Disclosure section of the Clinical Trial Agreement. Edwards Lifesciences will provide statistical support for the publication process.

Appendix A Abbreviations

Abbreviation	Full Term
ACT	Activated Clotting Time
AE	Adverse Event
AR	Aortic Regurgitation
ASD	Atrial Septal Defect
AT	As Treated
AV	Atrioventricular
AV	Aortic Valve
BARC	Bleeding Academic Research Consortium
BAV	Balloon Aortic Valvuloplasty
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHD	Congenital Heart Defects
CHF	Congestive Heart Failure
CK-MB	Creatine Kinase MB
CPB	Cardiopulmonary Bypass
CT	Computed Tomography
CTA	Computed Tomography Angiography
CV	Curriculum Vitae
DAL	Device Accountability Log
DOA	Delegation of Authority
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
ePRO	Electronic Patient-Reported Outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization

Abbreviation	Full Term
KM	Kaplan Meier
LAR	Legally Authorized Representative
LBBB	Left Bundle Branch Block
LVOT	Left Ventricular Outflow Tract
MI	Myocardial Infarction
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
NYHA	New York Heart Association
PA	Pulmonary Artery
PCWP	Pulmonary Capillary Wedge Pressure
PET	Polyethylene Terephthalate
PLT	Platelets
QOL	Quality of Life
RA	Right Atrium
RBC	Red Blood Cell
RV	Right Ventricle
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
STS	Society of Thoracic Surgeons
TAVR	Transcatheter Aortic Valve Replacement
THV	Transcatheter Heart Valve
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
VARC	Valve Academic Research Consortium
VAS	Visual Analogue Scale
VI	Valve Implant
WBC	White Blood Cell

Appendix B Definitions

Term	Definition	Reference/ Justification
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device	ISO 14155-1:2011 GCP
Access Site	Any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath for TAVR or skin incision for SAVR	VARC 1
Access site related complication	Any adverse clinical consequence possibly associated with any of the access sites used during the procedure	VARC 1
Acute kidney injury	<p>An abrupt loss of kidney function, resulting in the retention of urea and other nitrogenous waste products</p> <p>The increase in creatinine meeting at least Stage 1 must occur within 48 hours. Staging will be based on the worse stage that occurs within 7 days of the index procedure.</p> <p>Stage 1</p> <ul style="list-style-type: none"> Increase in serum creatinine to 150-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR Urine output <0.5 ml/kg per hour for >6 but <12 hours <p>Stage 2</p> <ul style="list-style-type: none"> Increase in serum creatinine to 200-299% (2.0-2.99 × increase compared with baseline) OR Urine output <0.5 ml/kg per hour for >12 but <24 hours <p>Stage 3</p> <ul style="list-style-type: none"> Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR Urine output <0.3 ml/kg per hour for ≥24 hours OR Anuria for ≥12 hours <p>Patients receiving renal replacement therapy (dialysis, hemodialysis, peritoneal dialysis, hemofiltration, transplant) are considered to meet Stage 3 criteria irrespective of other criteria irrespective</p>	Sponsor/VARC 2
Anemia	A condition in which the blood is deficient in red blood cells, in hemoglobin, or in total volume, without clear evidence of overt bleeding, that is actionable (e.g. requires medications, transfusion etc)	Sponsor

Term	Definition		Reference/ Justification
Angina / Cardiac chest pain	Chest pain due to an inadequate supply of oxygen to the heart muscle		Sponsor
Angina, grading scale	Grade	Description	Canadian Cardiovascular Society
	Grade I	Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or during recreation	
	Grade II	Slight limitation of ordinary activity. Angina occurs with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, walking in the cold, into the wind, while under emotional stress, or during the first hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions, does not cause angina	
	Grade III	Marked limitation of ordinary physical activity. Angina occurs with walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at a normal pace	
	Grade IV	Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest	
Aortic coarctation	A narrowing of the aorta usually in the area of the ligamentum arteriosum		Groenemeijer BE, Bakker A, Slis HW, Waalewijn RA, Heijmen RH. An unexpected finding late after repair of coarctation of the aorta. <i>Netherlands Heart Journal</i> . 2008;16(7-8):260-263.

Term	Definition	Reference/ Justification
Aortic dissection	Aortic dissection is a separation of an intimal of wall that may or may not require intervention	Sponsor
Aortic stenosis, native	Aortic stenosis is classified as "severe" when the following are present: <ul style="list-style-type: none"> • Jet velocity > 4.0 m/s • Mean gradient > 40mmHg • Valve area < 1.0 cm² • Valve area index < 0.6cm²/m² 	2014 AHA/ACC
Arrhythmia / Conduction System Injury (Defect)	Arrhythmia: an irregular heart rate or abnormal rhythm resulting in symptoms or requiring medical intervention. Conduction system defect: an impairment of the electrical pathways and specialized muscular fibers that conduct impulses through the heart (ex. bundle branch block, heart block, etc.).	Sponsor
Bicuspid aortic valve	Congenital malformation resulting in 2 functioning leaflets as defined by Sievers and Schmidtke	<i>A classification system for the bicuspid aortic valve from 304 surgical specimens. Sievers HH, Schmidtke C. J Thorac Cardiovasc Surg. 2007 May;133(5):1226-33.</i>
Bioprosthetic valve dysfunction	Bioprosthetic valve dysfunction can be structural (ex. leaflet tears, leaflet mobility restriction, etc.) or non-structural (ex. paravalvular leak or endocarditis) or hemodynamic(aortic regurgitation or aortic stenosis) or a combination of these dysfunctions. Patients with BVD maybe asymptomatic or symptomatic requiring medical therapy (ex. addition of anticoagulation), hospitalization, or require intervention and/or valve explant.	Sponsor
Bleeding	Bleeding, including, but not limited to fatal bleed, bleeding associated with transfusion, drop in Hgb or visible sign of blood loss For the purposes of this trial, an overt source of bleeding for subjects undergoing TF-TAVR is > 100 mL blood loss during the procedure. For subjects undergoing SAVR and for subjects undergoing TAVR using an alternative approach (i.e. TAO, TA), an overt source of bleeding is considered to be > 600 mL bloody chest tube output (as captured on Intake and Output Chart, I/O) within 24 hours of leaving the OR/cath lab or bleeding requiring a transfusion of RBCs	Sponsor
CABG	Coronary artery bypass surgery	Sponsor

Term	Definition	Reference/ Justification
Cardiac arrest	Cardiopulmonary arrest or circulatory arrest, is a sudden stop in effective blood circulation due to the failure of the heart to contract effectively or at all	Sponsor / STS
Cardiogenic shock	Sustained (>30 min) episode of systolic BP <90 mmHg and/or cardiac index <2.2 L/min/m ² determined to be secondary to cardiac dysfunction, and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulatory support, ventricular assist device) to maintain BP and cardiac index above those specified levels	2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials
Cardiac tamponade	Evidence of a new pericardial effusion associated with hemodynamic instability evident by: 1. Echo showing pericardial fluid and signs of tamponade such as right heart compromise, or 2. Systemic hypotension due to pericardial fluid compromising cardiac function	VARC 2 / STS
Hypertrophic Cardiomyopathy	Cardiomyopathy is a term applied to a wide spectrum of cardiac diseases in which the predominant feature is poor myocardial function in the absence of any anatomic abnormalities. Idiopathic hypertrophic subaortic stenosis (IHSS) is also known as hypertrophic obstructive cardiomyopathy (HOCM), and is characterized by a primary hypertrophy of the myocardium. The obstructive forms involve different degrees of dynamic subvalvar aortic obstruction from a thickened ventricular wall and anterior motion of the mitral valve. Cardiomyopathies are into three entities: 1. Dilated, characterized by ventricular dilatation and systolic dysfunction 2. Hypertrophic, characterized by physiologically inappropriate hypertrophy of the left ventricle 3. Restrictive, characterized by diastolic dysfunction, with a presentation often identical to constrictive pericarditis.	STS Congenital Heart Surgery Database Data Specifications

Term	Definition	Reference/ Justification																											
Cerebrovascular disease	<p>Cerebrovascular disease includes all disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process</p> <p>It includes:</p> <ul style="list-style-type: none"> • Stroke • TIA • Noninvasive or invasive arterial imaging test demonstrating $\geq 50\%$ stenosis of any of the major extracranial or intracranial vessels to the brain • Previous cervical or cerebral artery revascularization surgery or percutaneous intervention <p>This does not include chronic (nonvascular) neurological diseases or other acute neurological insults such as metabolic and anoxic ischemic encephalopathy</p>	STS																											
CHADS ₂ Score (Annual Stroke Risk)	<p>The CHADS2 score can help physicians estimate stroke risk in patients with non-valvular atrial fibrillation and determine which antithrombotic therapy is most appropriate.</p> <p>The CHADS2 score is one of several risk stratification schema that can help determine the 1 year risk of an ischemic stroke in a non-anticoagulated patient with non-valvular AF.</p> <table border="1" data-bbox="427 1192 1105 1591"> <thead> <tr> <th colspan="3" style="text-align: center;">Annual Stroke risk</th> </tr> <tr> <th>CHADS₂ Score</th> <th>Stroke Risk %</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>1.9</td> <td>1.2–3.0</td> </tr> <tr> <td>1</td> <td>2.8</td> <td>2.0–3.8</td> </tr> <tr> <td>2</td> <td>4.0</td> <td>3.1–5.1</td> </tr> <tr> <td>3</td> <td>5.9</td> <td>4.6–7.3</td> </tr> <tr> <td>4</td> <td>8.5</td> <td>6.3–11.1</td> </tr> <tr> <td>5</td> <td>12.5</td> <td>8.2–17.5</td> </tr> <tr> <td>6</td> <td>18.2</td> <td>10.5–27</td> </tr> </tbody> </table>	Annual Stroke risk			CHADS ₂ Score	Stroke Risk %	95% CI	0	1.9	1.2–3.0	1	2.8	2.0–3.8	2	4.0	3.1–5.1	3	5.9	4.6–7.3	4	8.5	6.3–11.1	5	12.5	8.2–17.5	6	18.2	10.5–27	<p>Gage BF, Waterman AD, Shannon W, Boehler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: <i>Results From the National Registry of Atrial Fibrillation</i>. <i>JAMA</i>. 2001;285(22):2864-2870. doi:10.1001/jama.285.22.2864</p>
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Chest deformity (see also “Hostile chest”)	Chest deformities that would preclude an open chest procedure and include pectus excavaatum, mastectomy, iatrogenic radiation exposure	Sponsor																											

Term	Definition	Reference/ Justification																																								
Child-Pugh Classification	<p>The Child-Pugh score consists of five clinical features and is used to assess the prognosis of chronic liver disease and cirrhosis:</p> <table border="1" data-bbox="423 317 1094 842"> <thead> <tr> <th>Measure</th> <th>1 point</th> <th>2 points</th> <th>3 points</th> </tr> </thead> <tbody> <tr> <td>Total bilirubin, $\mu\text{mol/l}$ (mg/dl)</td> <td><34 (<2)</td> <td>34-50 (2-3)</td> <td>>50 (>3)</td> </tr> <tr> <td>Serum albumin, g/dl</td> <td>>3.5</td> <td>2.8-3.5</td> <td><2.8</td> </tr> <tr> <td>Prothrombin time, prolongation (secs)</td> <td><4.0</td> <td>4.0-6.0</td> <td>> 6.0</td> </tr> <tr> <td>Ascites</td> <td>None</td> <td>Mild</td> <td>Moderate to Severe</td> </tr> <tr> <td>Hepatic encephalopathy</td> <td>None</td> <td>Grade I-II (or suppressed with medication)</td> <td>Grade III-IV (or refractory)</td> </tr> </tbody> </table> <p>Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above:</p> <table border="1" data-bbox="423 930 1084 1125"> <thead> <tr> <th>Points</th> <th>Class</th> <th>One year survival</th> <th>Two year survival</th> </tr> </thead> <tbody> <tr> <td>5-6</td> <td>A</td> <td>100%</td> <td>85%</td> </tr> <tr> <td>7-9</td> <td>B</td> <td>81%</td> <td>57%</td> </tr> <tr> <td>10-15</td> <td>C</td> <td>45%</td> <td>35%</td> </tr> </tbody> </table>	Measure	1 point	2 points	3 points	Total bilirubin, $\mu\text{mol/l}$ (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)	Serum albumin, g/dl	>3.5	2.8-3.5	<2.8	Prothrombin time, prolongation (secs)	<4.0	4.0-6.0	> 6.0	Ascites	None	Mild	Moderate to Severe	Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	Points	Class	One year survival	Two year survival	5-6	A	100%	85%	7-9	B	81%	57%	10-15	C	45%	35%	<p>CHOLONGITAS, E., PAPTAEODORIDIS, G. V., VANGELI, M., TERRENI, N., PATCH, D. and BURROUGHS, A. K. (2005), Systematic review: the model for end-stage liver disease – should it replace Child-Pugh's classification for assessing prognosis in cirrhosis. <i>Alimentary Pharmacology & Therapeutics</i>, 22: 1079–1089. doi: 10.1111/j.1365-2036.2005.02691.</p>
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Coagulopathy	<p>A pathologic condition that affects the ability of the blood to coagulate. Examples include <u>hemophilia</u>, <u>drug-induced clotting disorder</u>, <u>thrombocytopenia</u> and <u>Von Willebrand's disease</u></p>	Sponsor																																								
Continuous Atrial fibrillation	<p>Atrial fibrillation > 24 hours, requiring new drug treatment / anticoagulation OR requiring chemical or electrical cardioversion</p>	Sponsor																																								

Term	Definition	Reference/ Justification
Congestive Heart Failure (CHF)	<p>Diagnosis requires physician documentation or report of any of the following:</p> <ul style="list-style-type: none"> • Unusual dyspnea on light exertion • Recurrent dyspnea occurring in the supine position • Fluid retention; or the description of rales, jugular venous distension • Pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction <p>A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure. An elevated BNP without other supporting documentation should not be reported as CHF</p>	STS
Cardiopulmonary bypass (CPB)	Bypass of the heart and lungs as in open heart surgery	Sponsor
Conversion to open surgery	Any conversion to complete TAVR procedure secondary to any procedure-related complications	Sponsor
Coronary artery disease (CAD)	Coronary artery disease is characterized by a narrowing or "stenosis" of the blood vessels to the heart resulting in inadequate blood flow to the heart muscle itself.	STS
Coronary obstruction	<p>Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR or SAVR procedure.</p> <p>Mechanical coronary artery obstruction following TAVR or index SAVR includes:</p> <ul style="list-style-type: none"> • impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy; OR • displacement of native aortic valve leaflets towards the coronary ostia during TAVR ; OR • suture-related kinking or obstruction or cannulation-related obstruction of the coronary ostia associated with SAVR. 	VARC 2/STS
Device	<p>For the determination of device relationship, the study device consists of:</p> <ul style="list-style-type: none"> • The Edwards SAPIEN 3 valve • The Edwards Valve Delivery System • The Edwards Expandable Sheath • Any surgical valve used implanted during index procedure 	Sponsor
Device (Valve) fracture	The separation of any portion of the frame into two or more parts; as may be determined by radiography, computed tomography, magnetic resonance imaging or by direct examination.	Sponsor

Term	Definition	Reference/ Justification
Device malfunction	The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device.	FDA., 21 CFR 803.3(m)
Device (Valve) thrombosis	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis	VARC 2
Endocarditis	<p>Endocarditis must meet at least 1 of the following criteria:</p> <ol style="list-style-type: none"> 1. Patient has organisms cultured from valve or vegetation 2. Patient has 2 or more of the following signs or symptoms: <ul style="list-style-type: none"> • Fever (>38°C) • New or changing murmur • Embolic phenomena • Skin manifestations (i.e., petechiae, splinter hemorrhages, painful subcutaneous nodules) • CHF • Cardiac conduction abnormality <p>With no other recognized cause and at least 1 of the following:</p> <ol style="list-style-type: none"> a. organisms cultured from 2 or more blood cultures b. organisms seen on Gram's stain of valve when culture is negative or not done c. valvular vegetation seen during an invasive procedure or autopsy d. positive laboratory test on blood or urine (e.g., antigen tests for H influenzae, S pneumoniae, N meningitidis, or Group B Streptococcus) e. evidence of new vegetation seen on echocardiogram and if diagnosis is made antemortem, physician institutes appropriate antimicrobial therapy. Infection of the endocardial surface of the heart which may include one or more heart valves, the mural endocardium, or a septal defect 	STS
EuroSCORE II	http://www.euroscore.org/calc.html	European System for Cardiac Operative Risk Evaluation
EuroSCORE, logistic	http://www.euroscore.org/calcold.html	European System for Cardiac Operative Risk Evaluation
Explant	Removal of the investigational valve implant for any reason	Sponsor

Term	Definition	Reference/ Justification
Hemolysis	Evidence of RBC destruction best explained by hemolysis (LDH >350 u/L and decreased haptoglobin based on site lab normals) and no other explanation for the findings. Microscopic evidence may be considered supportive.	Sponsor
Hospitalization (repeat)	Any <i>unplanned</i> admission to the hospital (including an emergency department visit) for either a diagnostic or therapeutic purpose (e.g. diuretics, inotropes, chronotropes, oral or intra-venous therapy) following discharge from the index hospitalization	Sponsor
Hospitalization for CHF	An event where the patient is admitted to the hospital with a primary diagnosis of CHF where the length of stay is at least 24 h (or extends over a calendar date if the hospital admission and discharge times are unavailable), and the patient exhibits new or worsening symptoms of CHF on presentation, has objective evidence of new or worsening CHF, and receives initiation or intensification of treatment specifically for CHF. Clinical symptoms of CHF include, but not limited to a pulmonary edema, hypoperfusion, or documented volume overload AND administration of IV diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (IABP or ventilation for pulmonary oedema) or haemodialysis for volume overload.	2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials/VARC 2
Hypertension	Systolic pressure > 140 or a diastolic pressure > 90 mmHg	Sponsor
Hypotension	Systolic pressure < 90 or a diastolic pressure < 60 mmHg	Sponsor
Index hospitalization	The beginning of the Index Hospitalization is defined as the day the patient is admitted for valve implant procedure and continues until the patient is discharged from the hospital.	Sponsor
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization	Sponsor
Lung disease, severe	FEV1 < 50% predicted or currently on home oxygen	Sponsor
Liver disease, chronic	MELD Score ≥ 10 or Child-Pugh Class B or C	Sponsor

Term	Definition	Reference/ Justification
Mini-mental state examination (MMSE)	A questionnaire that is used extensively in clinical and research settings to measure cognitive impairment.	Pangman, VC; Sloan, J; Guse, L. (2000). "An Examination of Psychometric Properties of the Mini-Mental State Examination and the Standardized Mini-Mental State Examination: Implications for Clinical Practice". <i>Applied Nursing Research</i> 13 (4): 209–213.
MELD (Model For End-Stage Liver Disease) Score	<p>A scoring system for assessing the severity and quantification of chronic liver disease.</p> <ul style="list-style-type: none"> • It is preferable to using the calculator (http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/) to calculate the MELD as there are several caveats relating to minimum and maximum values assigned in the MELD • Values should be no more than 48 hours old <p>In interpreting the MELD Score in hospitalized patients, the 3 month mortality is:</p> <p>40 or more — 71.3% mortality 30–39 — 52.6% mortality 20–29 — 19.6% mortality 10–19 — 6.0% mortality <9 — 1.9% mortality</p>	Wiesner et al. Model for end-stage liver disease (MELD) and allocation of donor livers. <i>Gastroenterology</i> (2003) vol. 124 (1) pp. 91-6
Modified Rankin Scale (mRS)	<p>A commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke, as follows:</p> <ol style="list-style-type: none"> 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead 	Van Swieten, J. C., et al. "Interobserver agreement for the assessment of handicap in stroke patients." <i>Stroke</i> 19 .5 (1988): 604-607.

Term	Definition	Reference/ Justification
Mortality, all-cause	<p>Cardiovascular mortality</p> <p>Any of the following criteria:</p> <ul style="list-style-type: none"> • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause <p>Non-cardiovascular mortality</p> <ul style="list-style-type: none"> • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide). 	VARC 2
Myocardial Infarction	<p>An acute ischemic event that is associated with documented and clinically significant myocardial necrosis Any one of the following criteria meets the diagnosis for MI:</p> <ul style="list-style-type: none"> • Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following: <ul style="list-style-type: none"> - Symptoms of ischemia - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB) - Development of pathological Q waves in the ECG - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography 	STS

Term	Definition	Reference/ Justification										
National Institutes of Health Stroke Scale (NIHSS)	The NIHSS can help physicians determine the severity of a stroke, predict clinical outcomes and can help guide management.	NIHSS										
New York Heart Association Classification (NYHA)	<table border="1"> <thead> <tr> <th data-bbox="423 390 540 472">NYHA Class</th> <th data-bbox="540 390 1070 472">Functional Capacity</th> </tr> </thead> <tbody> <tr> <td data-bbox="423 472 540 627">I</td> <td data-bbox="540 472 1070 627">Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td> </tr> <tr> <td data-bbox="423 627 540 783">II</td> <td data-bbox="540 627 1070 783">Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td> </tr> <tr> <td data-bbox="423 783 540 938">III</td> <td data-bbox="540 783 1070 938">Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.</td> </tr> <tr> <td data-bbox="423 938 540 1146">IV</td> <td data-bbox="540 938 1070 1146">Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td> </tr> </tbody> </table>	NYHA Class	Functional Capacity	I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	The Criteria Committee of the New York Heart Association. (1994). <i>Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels</i> . (9th ed.). Boston: Little, Brown & Co. pp. 253–256.
NYHA Class	Functional Capacity											
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IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.											
Paravalvular Leak	<p>Paravalvular or paraprosthetic leak (PVL) is a complication associated with the implantation of a prosthetic heart valve whether traditional (surgical) or a transcatheter (TAVR) approach.</p> <p>PVL refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue as a result of a lack of appropriate sealing</p>	ESC										

Term	Definition	Reference/ Justification
Peripheral vascular disease (PVD)	<p>Includes peripheral arterial disease of upper and lower extremity, renal, mesenteric, and abdominal aortic systems, as follows:</p> <ul style="list-style-type: none"> • Claudication , either with exertion or at rest • Amputation for arterial vascular insufficiency • Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities (excluding dialysis fistulas and vein stripping) • Documented abdominal aortic aneurysm with or without repair • Positive noninvasive test (e.g., ankle brachial index =< 0.9, ultrasound, magnetic resonance or computed tomography imaging of > 50% diameter stenosis in any peripheral artery, i.e., renal, subclavian, femoral, iliac) or angiographic imaging <p>Peripheral arterial disease excludes disease in the carotid, cerebrovascular arteries or thoracic aorta. PVD does not include DVT.</p>	STS
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.	VARC 2
Pulmonary hypertension	A mean pulmonary artery pressure >or equal 25 mm Hg in presence of LAP/wedge <= 15 mm Hg	ACC
Pre-existing condition	A pre-existing condition is one that is present at the start of study treatment. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.	Sponsor

Term	Definition				Reference/ Justification	
Prosthetic aortic valve stenosis criteria ^a		Normal	Mild	Moderate/severe	VARC-2	
	Quantitative Parameters (flow-dependent)^b					
	Peak velocity (m/s)	<3 m/s	3-4 m/s	>4m/s		
	Mean gradient (mmHg)	<20 mmHg	20-40 mmHg	>40 mmHg		
	Quantitative parameters (flow-independent)					
	Doppler velocity index ^c	>0.35	0.35-0.25	<0.25		
	Effective orifice area ^d	>1.1 cm ²	>1.1-0.8 cm ²	<0.8 cm ²		
	Effective orifice area ^e	>0.9 cm ²	>0.9-0.6 cm ²	<0.6 cm ²		
	^a In conditions of normal or near normal stroke volume (50–70 mL). ^b These parameters are more affected by flow, including concomitant aortic regurgitation. ^c For LVOT >2.5 cm, significant stenosis criteria is <0.20. ^d Use in setting of BSA ≥1.6 cm ² (note: dependent on the size of the valve and the size of the native annulus). ^e Use in setting of BSA <1.6 cm ² .					

Term	Definition				Reference/ Justification
Prosthetic aortic valve regurgitation criteria		Normal	Mild	Moderate/severe	VARC 2
	Semi-quantitative Parameters				
	Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic	
	Circumferential extent of prosthetic valve paravalvular regurgitation (%) ^a	<10%	10-29%	≥30%	
	Quantitative parameters^b				
	Regurgitant volume (mL/beat)	<30 mL	30-59 mL	≥60 mL	
	Regurgitant fraction (%)	<30%	30-49%	≥50%	
	EROA (cm ²)	0.10 cm ²	0.10-0.29 cm ²	≥0.30 cm ²	
	<p>^aNot well-validated and may overestimate the severity compared with the quantitative Doppler.</p> <p>^bFor LVOT >2.5 cm, significant stenosis criteria is <0.20.</p>				
	Reintervention	<p>Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include:</p> <ul style="list-style-type: none"> • Balloon aortic valvuloplasty • Surgical aortic valve replacement • Valve in valve • Paravalvular leak closure 			

Term	Definition	Reference/ Justification
Serious Adverse Event (SAE)	<p>Adverse Event that:</p> <ul style="list-style-type: none"> • Leads to death; • Leads to a serious deterioration in the health of the study patient that: <ul style="list-style-type: none"> ○ Results in life-threatening illness or injury; ○ Results in a permanent impairment of a body structure or a body function; ○ Requires inpatient hospitalization or prolongation of existing hospitalization; ○ Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; • Led to fetal distress, fetal death or congenital abnormality or birth defect; • Significant medical event <p>Important medical events that do not meet the above criteria may still be considered an SAE if they seriously jeopardize the patient and require immediate medical or surgical intervention to prevent one of the aforementioned outcomes.</p>	ISO 14155-1:2011 FDA (21 CFR 312.32 (a))
Sternal wound dehiscence	Opening of sternal with negative cultures and no signs of infection requiring a procedure or operation for treatment	Sponsor
Valve implant procedure	<p>Placement of study device and/or additional procedures occurring in the cath lab and/or operating room which are completed prior to subject transfer to a post-procedure recovery unit (e.g. Recovery Room, ICU/CCU, etc.</p> <p>The valve implant procedure will be considered to have started when:</p> <ul style="list-style-type: none"> • The first interventional access related puncture (venous or arterial) is established for TAVR. • The first skin incision is performed for SAVR. <p>Performance of TEE does not by itself constitute start of procedure</p>	Sponsor
Valve Thrombosis	Valve thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment.	VARC2
Stroke / Transient Ischemic Attack	Diagnostic Criteria	VARC 2

Term	Definition	Reference/ Justification
(TIA)	<p><i>Acute episode of a focal or global neurological deficit with at least one of the following:</i></p> <ul style="list-style-type: none"> <input type="checkbox"/> change in level of consciousness <input type="checkbox"/> hemiplegia <input type="checkbox"/> hemiparesis <input type="checkbox"/> numbness or sensory loss affecting one side of the body <input type="checkbox"/> dysphasia or aphasia <input type="checkbox"/> hemianopia <input type="checkbox"/> amaurosis fugax <input type="checkbox"/> or other neurological signs or symptoms consistent with stroke <p><i>Duration of a focal or global neurological deficit >24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death</i></p> <p><i>No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist*</i></p> <p><i>Confirmation of the diagnosis by at least one of the following#:</i></p> <ul style="list-style-type: none"> <input type="checkbox"/> Neurology or neurosurgical specialist <input type="checkbox"/> Neuroimaging procedure (MR or CT scan) <input type="checkbox"/> Clinical presentation alone <p>Stroke definitions†:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Non-disabling: a mRS score of less than 2 at 90 days or the last available clinical visit with evaluable data or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline <input type="checkbox"/> Disabling: a mRS score of 2 or more at 90 days or the last available clinical visit with evaluable data and an increase of at least one mRS category from an individual's pre-stroke baseline <p>Stroke classification:</p> <ul style="list-style-type: none"> <input type="checkbox"/> <i>Hemorrhagic:</i> an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. 	

Term	Definition	Reference/ Justification
	<p>□ <i>Ischemic</i>: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue</p> <p>□ <i>Undetermined</i>: stroke with insufficient information to allow categorization as ischemic or hemorrhagic.</p> <p>Transient Ischemic Attack (TIA)</p> <p>Duration of focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct</p> <p><i>*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.</i></p> <p><i>#If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may still be considered a stroke on the basis of the clinical presentation alone.</i></p> <p><i>†Modified Rankin score assessments should be made by qualified individuals according to a certification process.</i></p>	
Structural performance	Evaluation of migration, embolization, fracture, or thrombosis	FDA
Structural Valvular Deterioration (SVD)	Structural valve deterioration includes dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, leaflet retraction, suture line disruption of components a prothetic valve, thickening, stenosis	Akins, Cary W., et al. "Guidelines for reporting mortality and morbidity after cardiac valve interventions." <i>European Journal of Cardio-Thoracic Surgery</i> 33.4 (2008): 523-528.
STS Adult Cardiac Surgery Risk Calculator	The Society of Thoracic Surgeons' risk models predict the risk of operative mortality and morbidity after adult cardiac surgery on the basis of patient demographic and clinical variables. http://riskcalc.sts.org/stswebriskcalc/#/	STS
Syncope	A fainting spell or loss of consciousness	STS
SYNTAX Score	An angiographic grading tool to determine the complexity of coronary artery disease. http://www.syntaxscore.com/ http://ir-nwr.ru/calculators/syntaxscore/frameset.htm	

Term	Definition	Reference/ Justification
6 Minute Walk Test	A performance-based measure of functional exercise capacity. The test measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. See more at: http://www.rheumatology.org/I-Am-A/Rheumatologist/Research/Clinician-Researchers/Six-Minute-Walk-Test-SMWT#sthash.cFCDWfkn.dpuf	ATS
THV-in-THV	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the valve implant procedure	VARC 2
Transient Ischemic Attack (TIA)	See “Stroke / Transient Ischemic Attack (TIA)”	
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problems associated with a device that relates to the rights, safety, or welfare of patients.	FDA
Vascular injury	Injury that may be caused by a guidewire, vascular sheath, delivery catheter, or any balloon used for aortic valve predilatation and can include arterial dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, or incomplete arteriotomy closure. Venous injuries can include perforation, tears and thromboembolism. Cardiac vascular injury can include perforation or tearing of the major cardiac structures that require repair.	Sponsor
Valve malpositioning	<p>Valve migration</p> <ul style="list-style-type: none"> • After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences <p>Valve embolization</p> <ul style="list-style-type: none"> • The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus <p>Ectopic valve deployment</p> <ul style="list-style-type: none"> • Permanent deployment of the valve prosthesis in a location other than the aortic root 	VARC 2

Appendix C Instructions For Use (IFU)

Refer to device package label to access electronic IFU or contact an Edwards Clinical Affairs representative.

Appendix D Physician and Support Staff Training

Title: Edwards Lifesciences Physician Training and Procedural Case Support Plan

Date: October 2017

Purpose: The purpose of this plan is to document and standardize the requirements for physician training for transcatheter heart valve (THV) implantation. It further describes the procedural case support provided by an Edwards Lifesciences representative (e.g., Clinical Specialist).

Scope: This plan applies to the implanting physician Investigators (Interventional Cardiologists/Surgeon for the PARTNER 3 trial. This plan addresses training for current users who have previously completed training under prior Edwards's trials and newly designated implanting physicians.

I. Current User Physician Training Plan**1. Didactic Presentation and Device Demonstration**

A didactic presentation including room set-up and patient preparation, sizing, device description and usage, procedural steps, complications and technical tips is given to the implanting physicians. In addition, a hands-on device demonstration is given. Both the didactic presentation and device demonstration are provided by an Edwards Lifesciences representative (e.g., Edwards Clinical Specialist).

2. Documentation

Training for the implanting physicians will be documented on the appropriate Training Forms (i.e., checked-off, dated and signed) by an Edwards Lifesciences representative as training is completed. Training records are maintained by Edwards Lifesciences in addition to being filed in the site study files.

II. New User Physician Training Plan includes:

1. THV Fundamentals Training Program

All new implanting physicians must attend the Edwards THV Fundamentals Training Program, which consists of the following:

- a) Didactic training/review of training manual: Focuses of key aspects of patient evaluation, device overview, procedural and technical tips, potential complications and troubleshooting tips.
- b) Device demonstration
- c) Simulation: Not required. Used as an enhancement to device demonstration and procedure training when available or applicable.
- d) Case observation or Case Review: 1 case observation or case review prior to first THV case.

- e) Certain requirements may be waived for physicians with applicable prior experience including but not limited to: prior involvement in THV or procedural development, or prior clinical experience in the aortic position. Any requirements waived to be indicated by a letter to file summarizing the reason for waiver and applicable prior experience.

2. Proctoring

The implanting physician must be proctored by an experienced physician for a minimum of two successful valve implantation procedures and deemed ready for independence by both the proctor and Clinical Specialist. These are to be performed at the Investigator's institution with his staff. If the proctor is not satisfied that these two procedures provide sufficient preparation, then subsequent proctoring sessions may be added as needed. Proctor requirements may be waived for physicians with applicable prior experience including but not limited to: prior involvement in THV or procedural development, or prior clinical experience in the aortic position. Any requirements waived to be indicated by a letter to file summarizing the reason for waiver and applicable prior experience.

3. Proctor Requirements

An implanting physician is considered a proctor only after having completed a minimum of eight procedures. Proctors should have extensive experience in recognition and management of intra-procedural complications and advanced troubleshooting skills.

4. Refresher THV Fundamentals Training

Required for implanting physicians if greater than 3 months from THV Fundamentals completion to first case or 5 months in between THV cases.

5. Didactic Presentation and Device Demonstration

Once THV Fundamentals Training and Proctoring have been complete, the implanting physicians required to be trained by an Edwards Representative (e.g., Clinical Specialist) on the study specific didactic presentation and receive a hands-on device demonstration (if different from training received for commercial device).

6. Documentation

Training for the implanting physicians will be documented on the appropriate Training Forms (i.e., checked-off, dated and signed) by an Edwards Lifesciences representative as training is completed. Training records are maintained by Edwards Lifesciences and copies will be filed in the site study files.

III. Procedural Case Support

An Edwards Lifesciences representative (e.g., Clinical Specialist) will attend all procedures to answer device and procedural questions, and is responsible for ensuring that all Edwards THV devices are prepared in accordance to the Instructions for Use Throughout the PARTNER 3 trial in no instance will any site perform a THV procedure without an Edwards's representative (e.g., Clinical Specialist) present.

Appendix E Six Minute Walk Test

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS
MARCH 2002

CONTENTS

Purpose and Scope
Background
Indications and Limitations
Contraindications
Safety Issues
Technical Aspects of the 6-Minute Walk Test
Required Equipment
Patient Preparation
Measurements
Quality Assurance
Interpretation
References

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardio-

pulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (see Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

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Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41-43). Questionnaire indices of functional status have a larger short-term variability (22-33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44-47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocar-

dial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48-50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association-approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
Lung transplantation (9, 10)
Lung resection (11)
Lung volume reduction surgery (12, 13)
Pulmonary rehabilitation (14, 15)
COPD (16-18)
Pulmonary hypertension
Heart failure (19, 20)
Functional status (single measurement)
COPD (21, 22)
Cystic fibrosis (23, 24)
Heart failure (25-27)
Peripheral vascular disease (28, 29)
Fibromyalgia (30)
Older patients (31)
Predictor of morbidity and mortality
Heart failure (32, 33)
COPD (34, 35)
Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

TECHNICAL ASPECTS OF THE 6MWT

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Rationale. A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52-55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400-1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet (see the APPENDIX).

4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO₂) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO₂ should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO₂. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (see Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

TABLE 2. THE BORG SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO₂ and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (see Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by fol-

lowing the standards found in this document and by using a quality-assurance program.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

Factors reducing the 6MWD	
Shorter height	
Older age	
Higher body weight	
Female sex	
Impaired cognition	
A shorter corridor (more turns)	
Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease)	
Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI)	
Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)	
Factors increasing the 6MWD	
Taller height (longer legs)	
Male sex	
High motivation	
A patient who has previously performed the test	
Medication for a disabling disease taken just before the test	
Oxygen supplementation in patients with exercise-induced hypoxemia	

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and SpO₂ should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (1) an absolute value, (2) a percentage change, or (3) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking

an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle-arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

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APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: _____ Race: _____ Height: _____ft _____in, _____ meters

Weight: _____ lbs, _____ kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	____:____	____:____
Heart Rate	_____	_____
Dyspnea	_____	_____ (Borg scale)
Fatigue	_____	_____ (Borg scale)
SpO ₂	_____ %	_____ %

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: _____ (x60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____ %

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

Appendix F Frailty Index

The assessment should be administered by either an investigator or research coordinator. The study patient will first be given a series of questions related to their ability to perform activities of daily living and scored accordingly on their responses. The second portion of the assessment involves a series of three hand grip strength tests which are averaged. Study patients will then be given a score for frailty based on their average score. Finally, study patients will be asked to walk 5 meters. Based on the overall assessment, a score will be given for frailty.

FRAILTY INDEX DATA

1. Was Frailty Index Obtained? Yes No

2. Date Completed: ____/____/____
(mm/dd/yyyy)

3. Height _____.__(cm/in)

4. Weight _____.__(kg/lb)

5. BMI _____

6. Serum Albumin: _____.__g/dL

7. Time (lab): ____:____ (24 Hr)

Katz Activities of Daily Living

ACTIVITIES POINTS (1 OR 0)	INDEPENDENCE: (1 POINT) NO supervision, direction or personal assistance	DEPENDENCE: (0 POINTS) WITH supervision, direction, personal assistance or total care
BATHING POINTS: _____	(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back,	(0 POINTS) Needs help with bathing more than one part of the body, getting in or out of the tub or

	genital area or disabled extremity.	shower. Requires total bathing.
DRESSING POINTS: _____	(1 POINT) Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 POINTS) Needs help with dressing self or needs to be completely dressed.
TOILETING POINTS: _____	(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING POINTS: _____	(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE POINTS: _____	(1 POINT) Exercises complete self control over urination and defecation.	(0 POINTS) Is partially or totally incontinent of bowel or bladder.
FEEDING POINTS: _____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.
TOTAL POINTS = _____		

Grip Strength

Note to the Examiner: Elbow should be at a 90 degree angle, with arm not resting on table or "pinned" against chest wall. All tests should be completed with the dynamometer in the dominant hand.

_____ Grasp 1
 _____ Grasp 2
 _____ Grasp 3
 _____ Average

Men*Cutoff for grip strength (Kg) criterion for frailty*

BMI \leq 24	\leq 29
BMI 24.1-26	\leq 30
BMI 26.1-28	\leq 30
BMI $>$ 28	\leq 32

Women*Cutoff for grip strength (Kg) criterion for frailty*

BMI \leq 23	\leq 17
BMI 23.1-26	\leq 17.3
BMI 26.1-29	\leq 18
BMI $>$ 29	\leq 21

5-Meter Walk

_____ Seconds

Men*Cutoff Time to walk 5 meters criterion for frailty*

Height \leq 173 cm	\geq 7 seconds
Height $>$ 173 cm	\geq 6 seconds

Women

Height \leq 159 cm	\geq 7 seconds
Height $>$ 159 cm	\geq 6 seconds

Appendix G Mini Mental State Examination (MMSE)



Date of Examination _____/_____/_____ Examiner _____
 Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? May I ask you some questions about your memory?

ORIENTATION TO TIME	RESPONSE	SCORE <small>(circle one)</small>
What is the... year?	_____	0 1
season?	_____	0 1
month of the year?	_____	0 1
day of the week?	_____	0 1
date?	_____	0 1

ORIENTATION TO PLACE*		
Where are we now? What is the... state (province)?	_____	0 1
county (or city/town)?	_____	0 1
city/town (or part of city/neighborhood)?	_____	0 1
building (name or type)?	_____	0 1
floor of the building (room number or address)?	_____	0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... **APPLE** [pause], **PENNY** [pause], **TABLE** [pause]. Now repeat those words back to me. [Repeat up to 5 times, but score only the first trial.]

APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0 1
<i>If needed, say: Keep going.</i>	[86]	_____	0 1
<i>If needed, say: Keep going.</i>	[79]	_____	0 1
<i>If needed, say: Keep going.</i>	[72]	_____	0 1
<i>If needed, say: Keep going.</i>	[65]	_____	0 1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

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Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.

Correct forward spelling if misspelled, but score only the backward spelling.

_____ (D = 1) _____ (L = 1) _____ (R = 1) _____ (O = 1) _____ (W = 1) _____ (0 to 5)

RECALL

RESPONSE

SCORE
(circle one)

What were those three words I asked you to remember? [Do not offer any hints.]

APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

NAMING*

What is this? [Point to a pencil or pen.]

_____ 0 1

What is this? [Point to a watch.]

_____ 0 1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[Repeat up to 5 times, but score only the first trial.]

NO IFS, ANDS, OR BUTS. _____ 0 1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.

Take this paper in your right hand [pause], fold it in half [pause], and put it on the floor (or table).

TAKE IN RIGHT HAND	_____	0	1
FOLD IN HALF	_____	0	1
PUT ON FLOOR (or TABLE)	_____	0	1

READING

Please read this and do what it says. [Show examinee the words on the stimulus form.]

CLOSE YOUR EYES _____ 0 1

WRITING

Please write a sentence. [If examinee does not respond, say: Write about the weather.]

0 1

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [Display the intersecting pentagons on the stimulus form.]

0 1

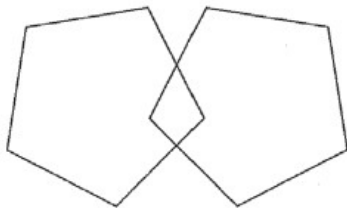
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Assessment of level of consciousness.

Total Score = _____
<small>(Sum all item scores.) (30 points max.)</small>

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive
----------------------	--------	-----------	---------------------------

CLOSE YOUR EYES



Appendix H NIH Stroke Scale (NIHSS)



Date of Exam: ____/____/____

Print Name of Examiner: _____ Signature of Examiner: _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

NOTE: Only a NIHSS certified team member may administer the test.

If there is an increase from the baseline stroke scale score, or evidence of a suspected stroke or TIA, capture the increase as an adverse neurological event and document the reason for the score increase. Administer the NIH Stroke Scale 30 days and 60 days after any neurological adverse event.

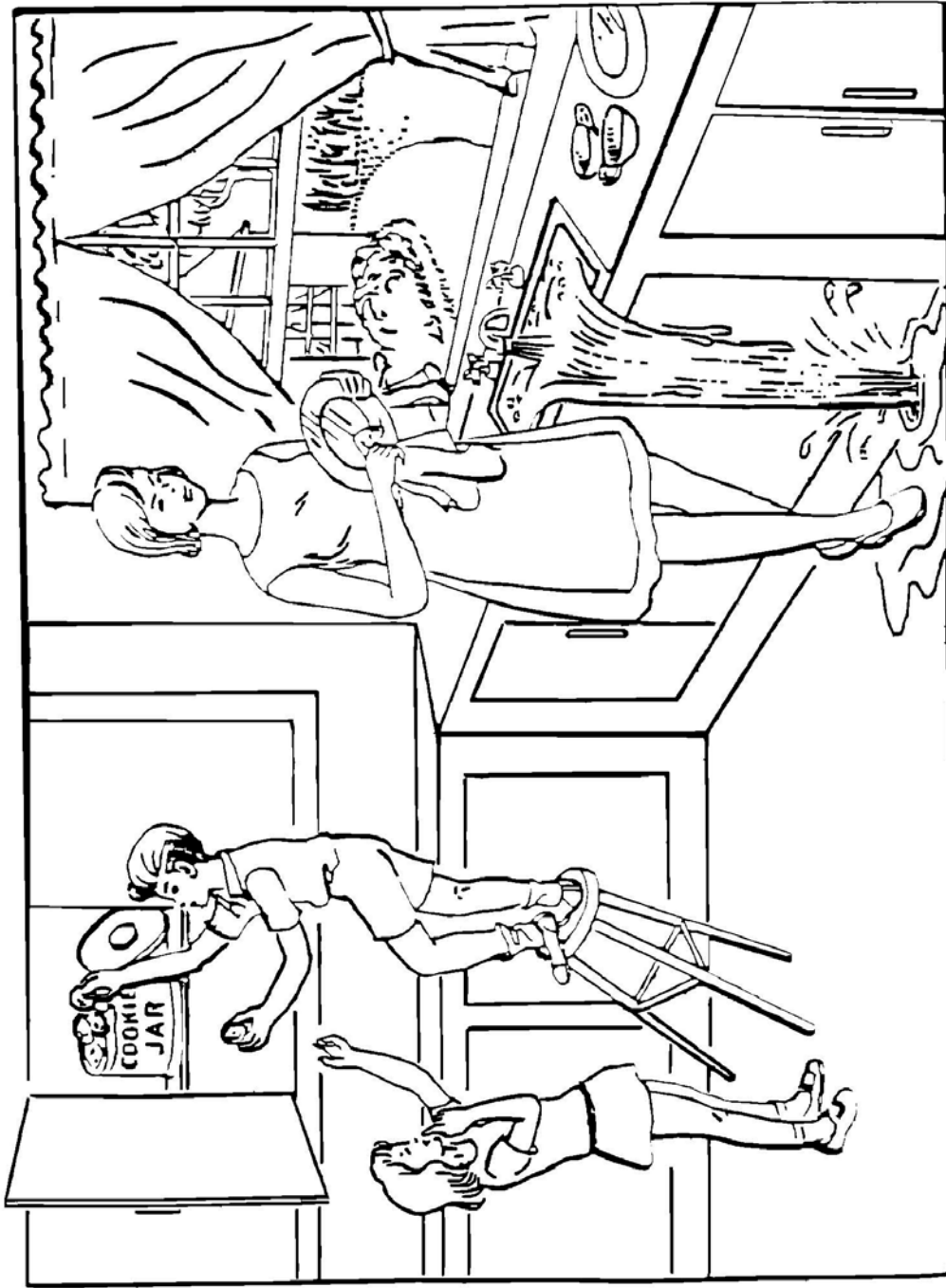
Instructions	Scale Definitions	Score
<p>1a. Level of Consciousness: The Investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 score is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</p>	<p>0 - Alert; keenly responsive.</p> <p>1 - Not alert; but arousable by minor stimulation to obey, answer, or respond.</p> <p>2 - Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped).</p> <p>3 - Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and flexic.</p>	<p>_____</p>
<p>1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not “help” the patient with verbal or non-verbal cues.</p>	<p>0 - Answers both questions correctly.</p> <p>1 - Answers one question correctly.</p> <p>2 - Answers neither question correctly.</p>	<p>_____</p>
<p>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.</p>	<p>0 - Performs both tasks correctly.</p> <p>1 - Performs one task correctly.</p> <p>2 - Performs neither task correctly.</p>	<p>_____</p>
<p>2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the Investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.</p>	<p>0 - Normal.</p> <p>1 - Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.</p> <p>2 - Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.</p>	<p>_____</p>

NIH STROKE SCALE

Instructions	Scale Definitions	Score
<p>3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.</p>	<p>0 - No visual loss. 1 - Partial hemianopia. 2 - Complete hemianopia. 3 - Bilateral hemianopia (blind including cortical blindness).</p>	___
<p>4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 - Normal symmetrical movements. 1 - Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 - Partial paralysis (total or near-total paralysis of lower face). 3 - Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).</p>	___
<p>5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 - No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 - Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 - Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 - No effort against gravity; limb falls. 4 - No movement. UN - Amputation or joint fusion, explain: _____ 5a. Left Arm 5b. Right Arm</p>	___ ___
<p>6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 - No drift; leg holds 30-degree position for full 5 seconds. 1 - Drift; leg falls by the end of the 5-second period but does not hit bed. 2 - Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 - No effort against gravity; leg falls to bed immediately. 4 - No movement. UN - Amputation or joint fusion, explain: _____ 6a. Left Leg 6b. Right Leg</p>	___ ___
<p>7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</p>	<p>0 - Absent. 1 - Present in one limb. 2 - Present in two limbs. UN - Amputation or joint fusion, explain: _____</p>	___

NIH STROKE SCALE

Instructions	Scale Definitions	Score
<p>8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (Item 1a-3) are automatically given a 2 on this item.</p>	<ul style="list-style-type: none"> 0 - Normal; no sensory loss. 1 - Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 - Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg. 	<p>_____</p>
<p>9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (Item 1a-3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<ul style="list-style-type: none"> 0 - No aphasia; normal. 1 - Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 - Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 - Mute, global aphasia; no usable speech or auditory comprehension. 	<p>_____</p>
<p>10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<ul style="list-style-type: none"> 0 - Normal. 1 - Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 - Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN - Intubated or other physical barrier, explain: _____ 	<p>_____</p>
<p>11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<ul style="list-style-type: none"> 0 - No abnormality. 1 - Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 - Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space. 	<p>_____</p>



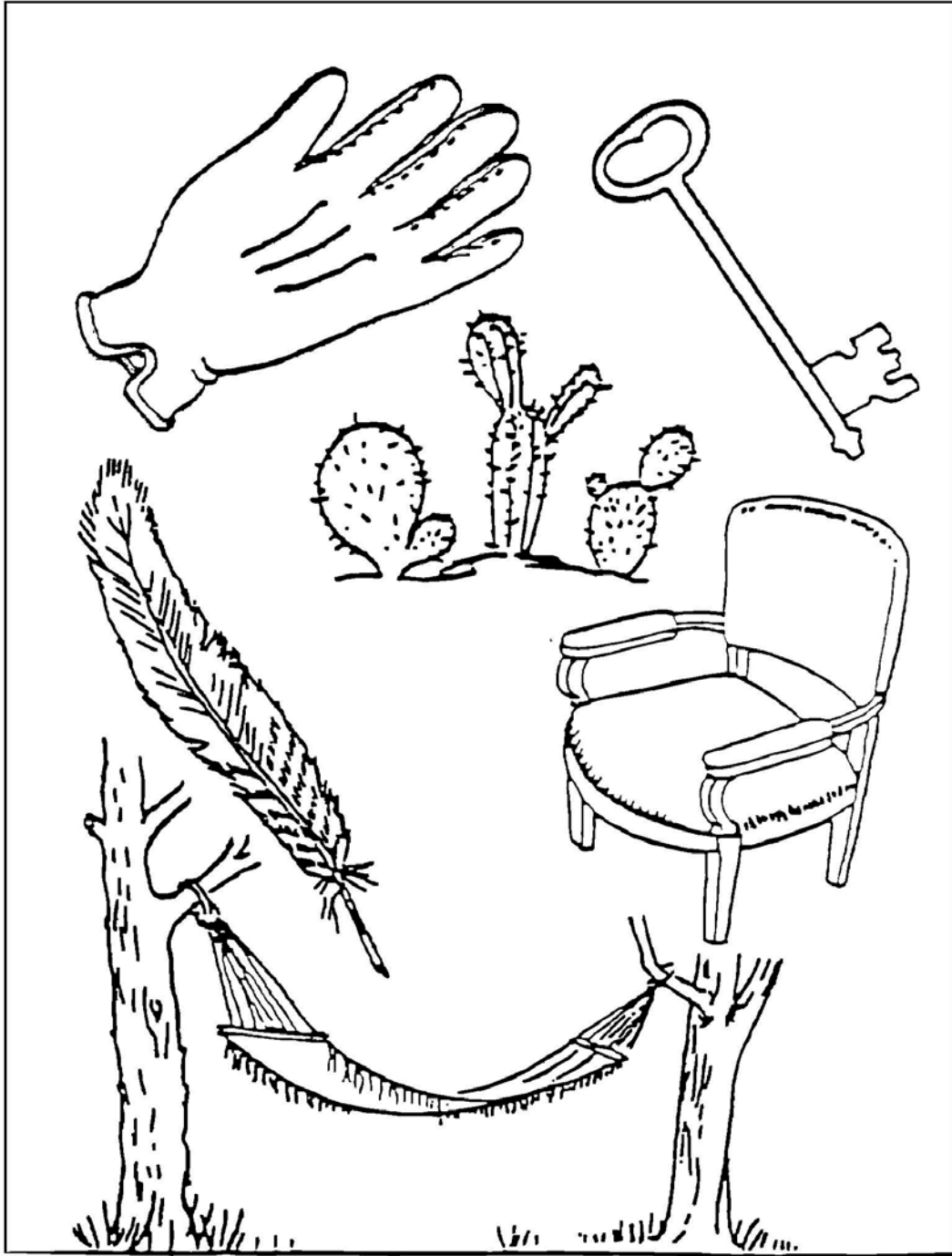
You know how.

Down to earth.

I got home from work.

**Near the table in the dining
room.**

**They heard him speak on the
radio last night.**



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix I Modified Rankin Scale (mRS)

The Modified Rankin Scale (mRS) is a 6-point scale to determine if the patient is severely disabled (5), has a moderately severe disability (4), is moderately disabled (3), is slightly disabled (2), has no significant disability (1), or has no symptoms at all and is not limited (0).

Instructions

The Modified Rankin Scale (mRS) will be administered to all study patients by a neurologist or neurology fellow. The mRS will be completed after the Mini Mental State Examination (MMSE) and the National Institutes of Health Stroke Scale (NIHSS).

Because subjects and family members may understate the severity of disability, it is important for the rating clinician to understand that the mRS is a clinical scale and not a patient-reported outcome. The clinician may ask questions but must assess the disability according to the 6-point scale whether or not in agreement with the subject, family, close friend, or caregiver.

The rater should use the best sources of information available. Information should be obtained from the patient and/or family, friends, nursing staff, physical and occupational therapists, any person who is familiar with the daily routine of the patient, and from medical records. The rater should interview both the patient and a close family member/friend or caregiver whenever possible. If the patient lacks insight into some difficulties, or responses are inconsistent, it is often helpful to interview a caregiver or relative independently.

Modified Rankin Scale Interview

5_Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver.

Question: Does the person require constant care?

4_Moderately severe disability; need for assistance with some basic ADL, but not requiring constant care.

Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?

3_Moderate disability; need for assistance with some instrumental ADL but not basic ADL.

Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?

2_Slight disability; limitations in participation in usual social roles, but independent for ADL.

Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated? Do any of the following interfere with the subject's ability to perform all usual activities: difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?


1_No significant disability; symptoms present but not other limitations.

Question: Does the subject have any symptoms that do not interfere with the performance of all usual activities?

0_No symptoms at all; no limitations and no symptoms.

Note: The above questions are a modification of the questions from Wilson, et. al, *Stroke*. 2002;33:2243-2246 and are modified here for the use in Transcatheter heart valve trials for the FDA Division of CV Devices.

Appendix J Echocardiogram

 Echo Core Lab CRIUCPQ	IUCPQ-CRF	MOP # PARTNER 3-001
	Echo Core Laboratory	Version # 001
	Manual of Procedures	

Title **Echo Imaging Acquisition Manual– PARTNER3 Study -MOP # P3-001**

Locations affected	ADDRESS	Phone: (418) 656-8711 ext. 5938
	Echo CoreLab	
	IUCPQ	
	2725 Chemin Ste-Foy Québec, G1V-4G5	

*Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614*

Document Title: Echo Manual of Operations
 Trial Sponsor: Edwards Lifesciences
 Protocol Title: A Prospective, Randomized, Multi-Center, Controlled, Long-Term Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve (THV) in Patients with Symptomatic, Severe, Calcific Aortic Stenosis Requiring Aortic Valve Replacement (AVR).
 Protocol Identifier: US IDE Pivotal Trial #2015-08

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 Protocol US IDE Pivotal Trial #2015-08

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Protocol US IDE Pivotal Trial #2015-08**1. ABBREVIATIONS AND ACRONYMS**

2D	two dimensional
AO	aorta
AS	aortic stenosis
ASE	American Society of Echocardiography
A2CH	apical 2-chamber
A4CH	apical 4-chamber
A5CH	apical 5-chamber
C5R	Cleveland Clinic Coordinating Center for Clinical
CD	compact disc
DCF	data clarification form
CW	Continuous wave
DICOM	Digital Imaging and Communications in Medicine
DOB	date of birth
EDTF	Echo Data Transmittal Form
DVD	digital video disc
EKG	electrocardiogram
ECHO	echocardiogram
FPS	frames per second
FR	frame rate
ICL	Imaging Core Lab
LA	Left atrium
LV	Left ventricle
MACE	Major Adverse Cardiac Events
NA	Not Applicable
NATIVE DICOM format	Philips proprietary format
PACS	Picture Archiving and Communication System
PLAX	parasternal long axis
PSAX	parasternal short axis
PVC	premature ventricular contraction

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PW	Pulsed wave
RAW Data DICOM format	GE proprietary format
SV	Sample volume
TAVR	Transcatheter Aortic Valve Replacement
THV	Transcatheter Heart Valve

2. STUDY OVERVIEW

2.1 Purpose

The purpose of this Imaging Manual is to instruct sites in: 1) protocol-specific image acquisition requirements; 2) necessary documentation, image data submission instructions and data storage; and 3) the query resolution process for discrepancies and/or non-compliant data.

The goal of the echocardiographic imaging portion of this trial is to assist sites in obtaining high quality, reproducible, quantitative information about structure, function and hemodynamics of the Transcatheter Heart Valve (THV) in the aortic position. Echocardiographic measures of aortic valve area and function are used as markers for determination of success in this trial.

2.2 Study Synopsis

Refer to study protocol.

3. ECHO PROCESS

3.1 Echo Qualification Submission Process

- 3.1.1 All sites new to the PARTNER trials will be asked to submit to the Imaging Core Lab, a de-identified sample of an echocardiogram performed for the Study protocol (Trial #2015-08) via Moving Pictures WebSend at www.mddximage.com. The purpose of the Site Echo Qualification Process is to ensure compatibility between site Echo acquisition and Core Lab analysis tools prior to subject recruitment and to ensure adherence to the imaging protocol.
- 3.1.2 A critique of the Echo qualification scan will be emailed to the site and study sponsor as notification of the qualification status
- 3.1.3 If the site does not qualify with the first submission, the Imaging Core Lab will use the critique to recommend changes for resubmission of another Echo study.

3.2 Echocardiographic Instrumentation

Complete echo-Doppler examinations are required at baseline, discharge, 30 days, 1 year, 2 years, 3 years, 4 years, 5 years, 7 years, 10 years.

Echocardiographic equipment manufacturer and model varies from site to site. Each site must maintain annual documentation by a third party ensuring the equipment has been validated and calibrated. Each enrolling site should strive to use the same echo instrument on all echo exams performed on an individual subject throughout the study. If more than one echo machine will be used in this trial, then the information above should be maintained for all of the machines that will be utilized. Each machine must have the capability to record proper date, time and subject identification (ID).

Digital Capture - Typically the transthoracic images are obtained with the subject in the left lateral decubitus position with head elevated 15 degrees during quiet respiration or end expiration. The two-dimensional images should be recorded on an ultrasound system that ALLOWS DIGITAL CAPTURE and has harmonic imaging capabilities using transducers in the range of 2.5 to 5.0 MHz. A qualified physician or sonographer must perform all ultrasound exams. Whenever possible, the same sonographer should perform all serial echoes on a given subject. At least three to five sinus cardiac cycles (depending on heart rate) of each view should be DIGITALLY CAPTURED during quiet respiration or at end expiration. At least three- to five-second capture should be recorded if the subject is in atrial fibrillation. For digital acquisition, obtain at least two sets of three complete cardiac cycles (normal sinus rhythm <90 beats per minute), and at least two sets of five complete cardiac cycles (normal sinus rhythm >90 beats per

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minute) for each required parameter. Cardiac cycles for assessment should not include PVCs or post-PVCs (compensatory pause). Imaging media provided should be labeled with protocol number, subject ID, study site, time and date of exam. The images MUST be exported in vendor specific proprietary (RAW Data / NATIVE) DICOM data format.

For each view, the gain, compression and image sector width should be optimized to ensure the best echocardiographic image of the endocardial borders.

Frame Rate - A minimum frame rate image acquisition of 40 frames per second (fps) is required for 2D imaging and 20 fps for Doppler imaging.. Optimization of frame rate for 2D imaging is achieved by narrowing the sector width to include entire left ventricular (LV) (or right ventricular) myocardium without compromising LV walls and reduce depth to include 1/3 of left atrium (LA) to ensure full visualization of basal LV. Optimization of frame rate for Doppler imaging is achieved by reducing the color sector without cutting of important region of interest (ROI) segments.

ECG - All images should have a good quality ECG tracing on the screen and clear calibration markings on the imaging sector. ECG leads will be applied and the EKG control setting of the machine optimized to ensure a high quality EKG with adequate amplitude QRS complex for reliable digital capture (lead II equivalent preferred).

Doppler and M-Mode - For Doppler spectral and M-Mode tracings, the sweep speed should be at least 50 mm/sec and preferably 100 mm/sec and the scale and baseline should be adjusted to make sure that the entire Doppler and M-Mode signal is visualized. Time and velocity calibration markers must be present on the Doppler and M-Mode tracing. For spectral and color Doppler, the appropriate gain level should be selected that detects flow without extraneous noise or extension of signal into adjoining tissue.

Color Doppler - As defined in the ASE Guidelines for the Quantification of Native Valve Regurgitation, Nyquist settings for color Doppler assessment of the cardiac valves should be 50-60 cm/sec

Contrast - If visualization of the left ventricular endocardial border is inadequate, then an approved contrast agent can be administered following institutional standards. However, the contrast enhanced imaging should only be performed after all other images and parameters are obtained. Doppler signals should be repeated after 2D contrast images are acquired. When Doppler signals are obtained during the contrast phase of the study, the gain must be reduced to optimize the velocity signal.

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Protocol US IDE Pivotal Trial #2015-08**Echo Visits Schedule –**

Visit	Submit to Core Lab	Range
Baseline	Yes	-90 days
Discharge	Yes	
30 Day	Yes	+7 days
1 Year	Yes	+30 days
2–5 Year	Yes	+45 days
7 Year	Yes	+45 days
10 Year	Yes	+45 days

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3.3 Echo Protocol Parameters and Imaging Guidelines

3.3.1 Begin with subject in the left lateral decubitus position. Echo bed cutout should be utilized to optimize apical views.

3.3.2 Obtain PLAX views of the LV, LVOT, and aortic valve (see Figures 1 and 2)

Figure 1

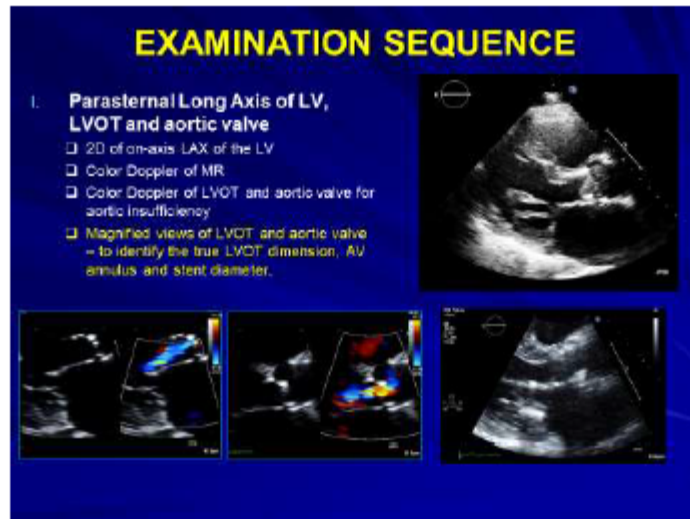
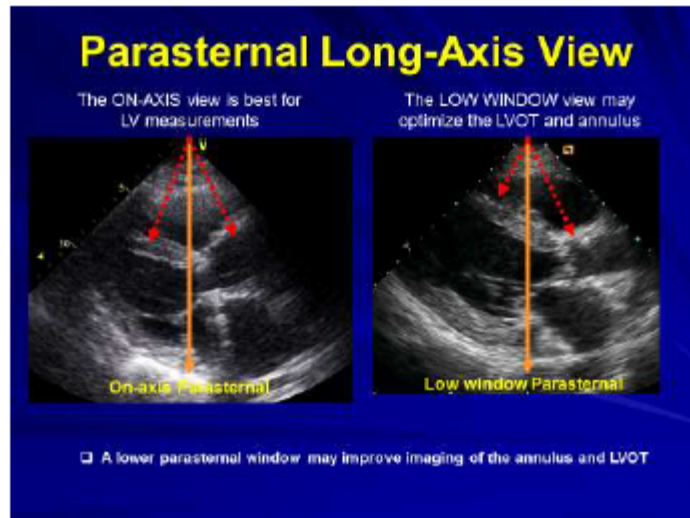


Figure 2



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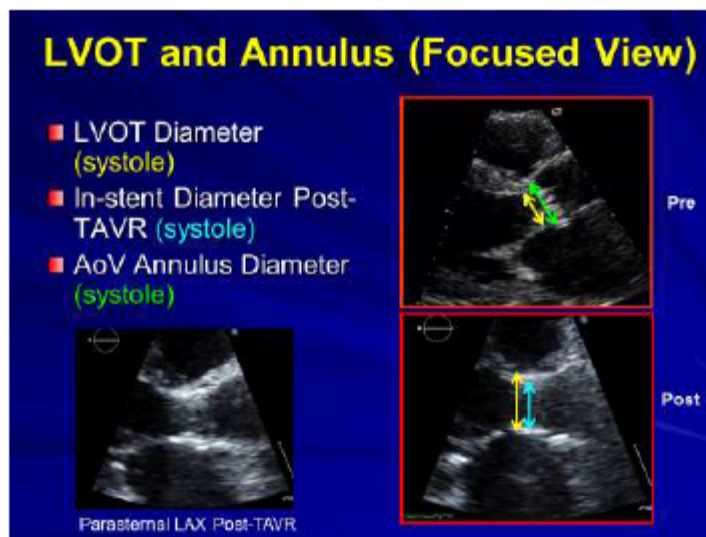
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3.3.3 Zoomed views of the LVOT and Aortic valve in both the PLAX and PSAX are acquired to identify the true LVOT dimension, AV annulus and stent diameter (see Figures 3 and 4).

Figure 3



Figure 4



3.3.4 2D, color, and CW Doppler imaging of the tricuspid valve and pulmonary valve in PSAX view (see Figure 5)

3.3.5 Color Doppler of zoomed Aortic valve must be obtained in the PLAX and PSAX to assess for paravalvular leaks: importance of multi-plane imaging (see Figures 5 and 6).

Figure 5

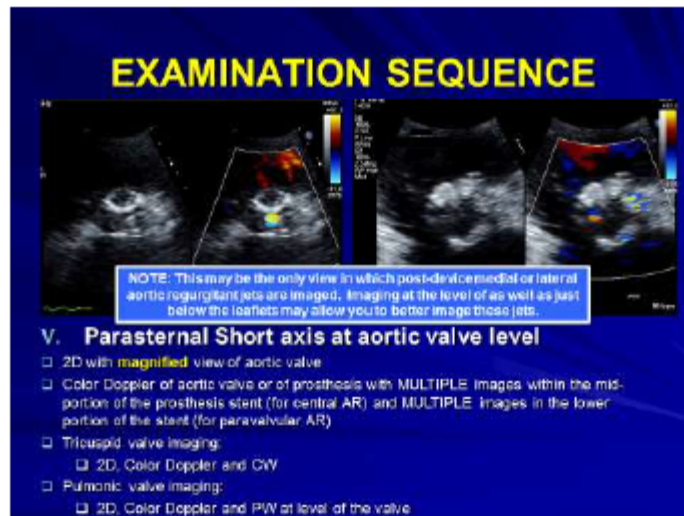
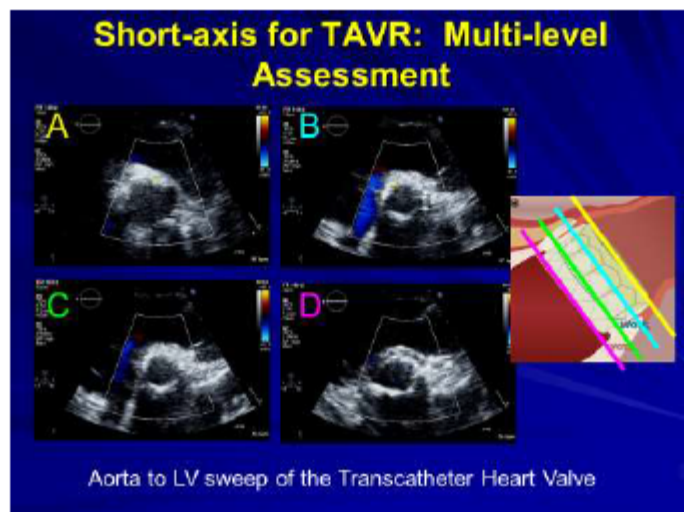
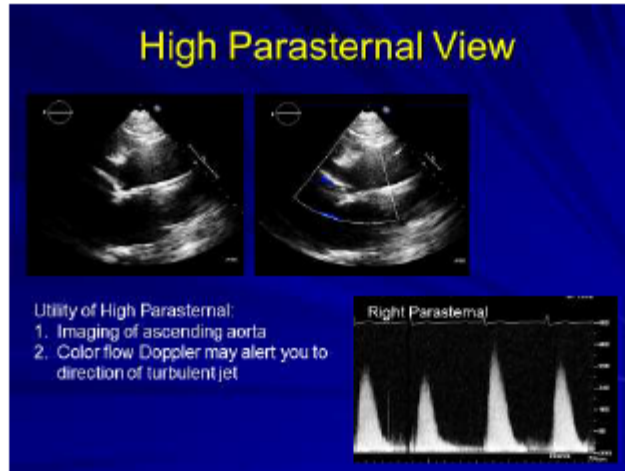


Figure 6



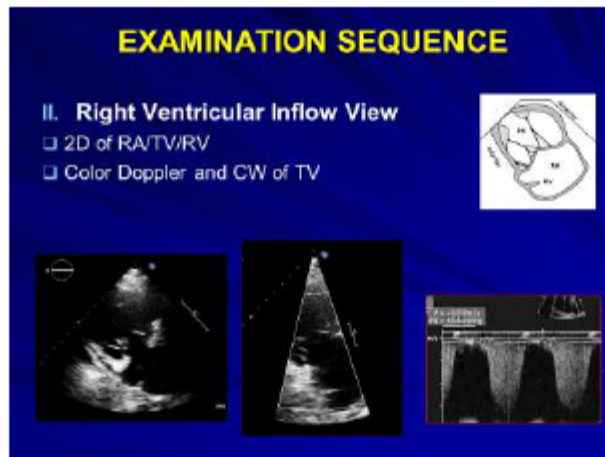
- 3.3.6 Color Doppler of the Mitral valve and Aortic valve should be obtained in multiple planes that can resolve the origins, maximum vena contracta width and maximum paths of the regurgitant jets.
- 3.3.7 Obtain a high PLAX view with transducer in second or third intercostal space to see ascending aorta (see Figure 7).

Figure 7



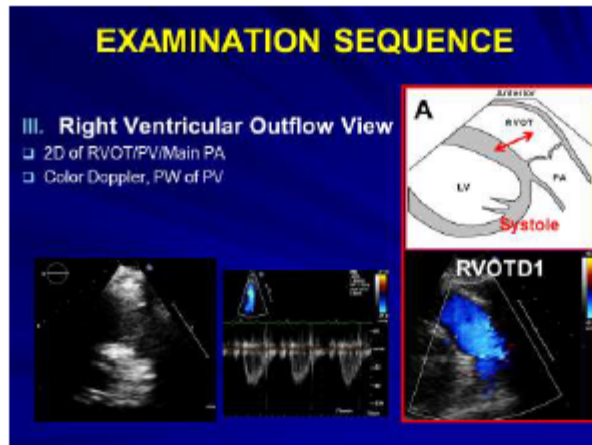
- 3.3.8 Obtain right ventricular inflow view: 2D on right atrium, tricuspid valve, pulmonary valve, Color Doppler and CW Doppler of tricuspid valve (see Figure 8)

Figure 8



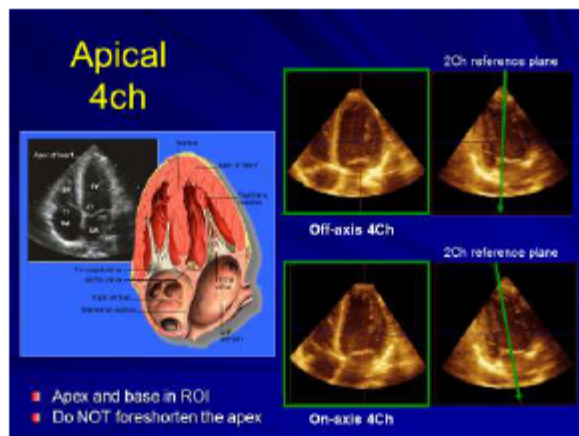
3.3.9 Obtain right ventricular outflow view: 2D of RVOT and main pulmonary artery, color and PW Doppler on pulmonary valve (see Figure 9).

Figure 9



3.3.10 Obtain apical 4-chamber view. It is imperative that all apical views be acquired on axis and not foreshortened. The apical myocardium should appear thin and pointed when in the correct plane. A foreshortened apex will appear rounded with thickened myocardium. If the image is foreshortened, apical contractility will appear to thicken towards the mitral valve rather than towards the contra lateral walls (see Figures 10 and 11).


Figure 10



3.3.11 To ensure high frame rate image acquisition (frame rate of 40 to 90 FPS or 40% of heart rate), sector size should be narrowed to include entire LV myocardium; depth should be reduced to include 1/3 of left atrium to ensure full visualization of basal LV (see Figure 11).

Figure 11

EXAMINATION SEQUENCE



* Image A shows the standard 4 chamber, while image B shows the 4 chamber with decreased depth

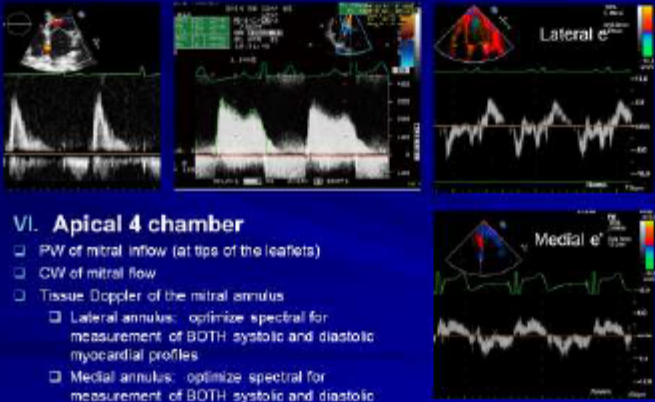
VI. Apical 4 chamber

- 2D optimizing LV endocardial borders : Need to see all aspects of the Lateral Wall, Septum, and Apex
- Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized

3.3.12 Obtain PW and CW Doppler of mitral flow, tissue Doppler velocities at the lateral and medial aspects of the mitral annulus (see Figure 12)

Figure 12

EXAMINATION SEQUENCE

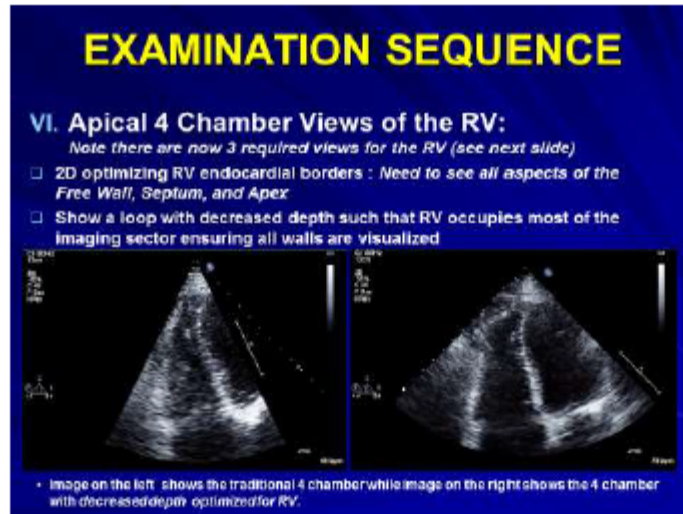


VI. Apical 4 chamber

- PW of mitral inflow (at tips of the leaflets)
- CW of mitral flow
- Tissue Doppler of the mitral annulus
 - Lateral annulus: optimize spectral for measurement of BOTH systolic and diastolic myocardial profiles
 - Medial annulus: optimize spectral for measurement of BOTH systolic and diastolic myocardial profiles

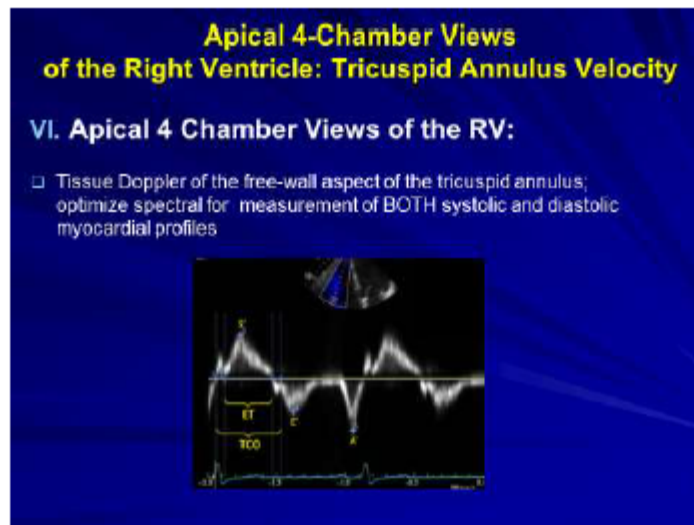
3.3.13 Obtain 4-chamber views of the right ventricle. Show a loop with focused view of the RV (see Figure 13)

Figure 13



3.3.14 Tissue Doppler imaging of the free-wall aspect of the tricuspid annulus (see Figure 14)

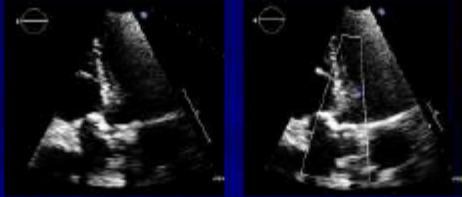
Figure 14



3.3.15 In the apical 5-chamber view, obtain PW Doppler in LVOT and CW of the aortic valve. Obtain color Doppler of LVOT and aortic valve. (see Figure 15 for baseline study and Figure 16 for follow-up studies).

Figure 15

EXAMINATION SEQUENCE: Baseline




VII. Apical 5 chamber view – Native Valve (BASELINE ONLY)

- ❑ 2D imaging (magnified view) of AV
- ❑ Pulse wave Doppler of LVOT: multiple saved PW spectral images are preferred: to avoid the region of flow acceleration - sample volume positioned at valve level and then moved apically until valve noise or "clicks" are no longer detected and then recorded)
- ❑ Continuous wave Doppler through the aortic valve
- ❑ Color Doppler of LVOT and aortic valve

Figure 16

EXAMINATION SEQUENCE: F/U



VII. Apical 5 chamber view – Prosthetic Valve

- ❑ 2D imaging (magnified view) of prosthetic AV focusing on valve position and leaflet motion
- ❑ Pulse Wave Doppler of the following TWO LOCATIONS: (see Doppler images below for a reference)
 - ❑ 1. Sample volume just apical to prosthetic valve stent (TAVR and SAVR)
 - ❑ 2. Sample volume within valve stent on LV side of Aortic Valve leaflets (for TAVR only)
- ❑ Clip of the 2D of pulse wave, sample position (either as moving image or still frame) as well as the Pulse Wave Spectral Doppler for each position is optional but recommended
- ❑ Continuous wave Doppler through the aortic valve
- ❑ Color Doppler of LVOT and aortic valve (attention to paravalvular jets)

3.3.16 For TAVR, obtain PW Doppler at 2 locations pre-stent and in-stent (see Figure 17). For SAVR, obtain PW Doppler pre-stent (see Figure 18).

Figure 17

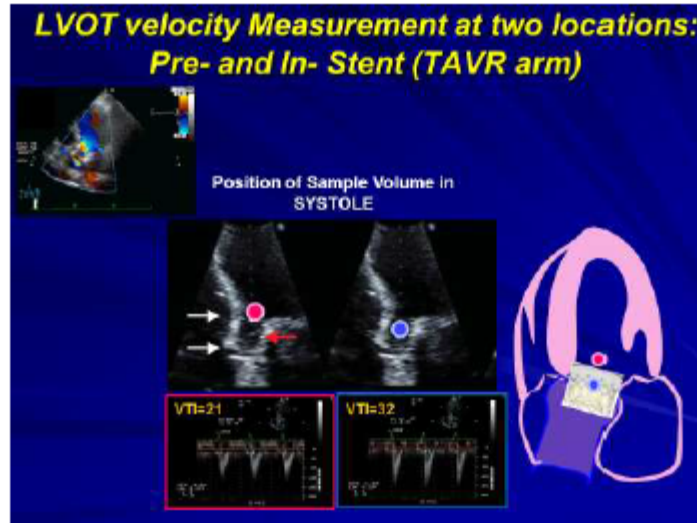
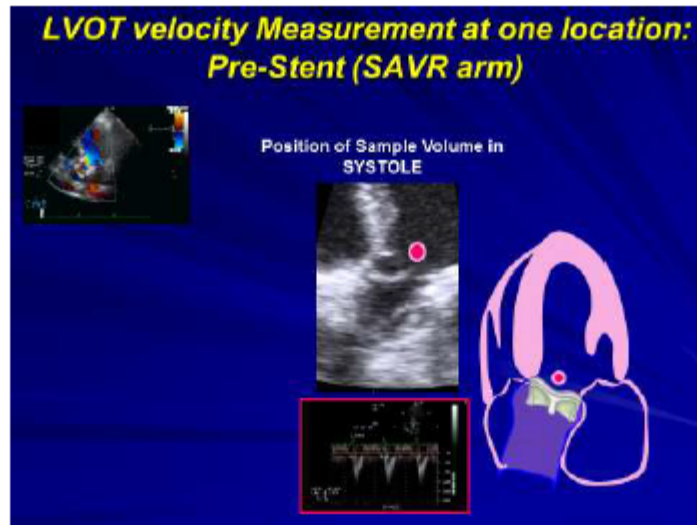


Figure 18

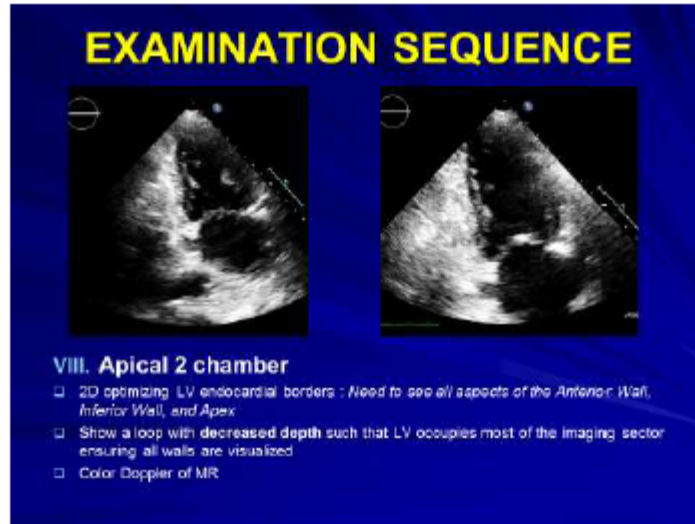


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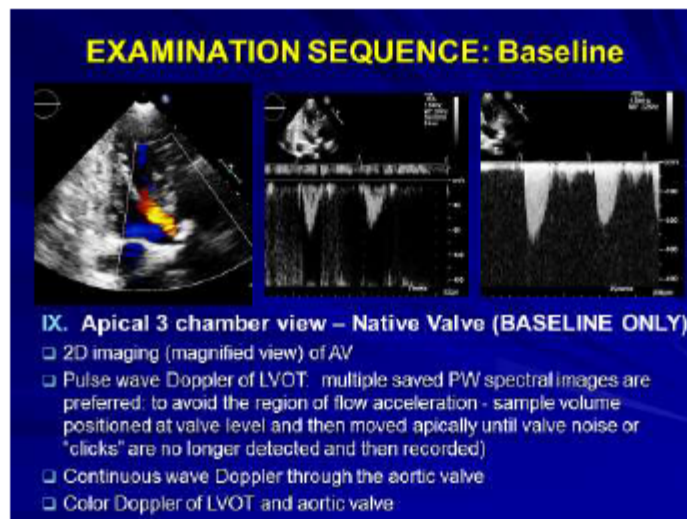
3.3.17 Obtain 2-chamber view: 2D of LV. Color Doppler of MR (see Figure 19)

Figure 19



3.3.18 Obtain 3-chamber view: 2D of aortic valve. PW Doppler of LVOT and CW Doppler of aortic valve. Color Doppler of LVOT and aortic valve. Color Doppler of MR (see Figure 20 for baseline study and Figure 21 for follow-up studies).

Figure 20



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Figure 21

EXAMINATION SEQUENCE: F/U

Position of Sample Volume in SYSTOLE

- Pulse Wave Doppler of the following TWO LOCATIONS: (see Doppler images below for a reference)
 - 1. Sample volume just apical to prosthetic valve stent (TAVR and SAVR)
 - 2. Sample volume within valve stent on LV side of Aortic Valve leaflets (TAVR only)
- Clip of the 2D of pulse wave sample position (either as moving image or still frame) as well as the Pulse Wave Spectral Doppler for each position is optional but recommended
- Color Doppler of LVOT and aortic valve (attention to paravalvular jets)
- Continuous wave Doppler through the aortic valve

3.3.19 Obtain subcostal view: 2D, color Doppler of aortic valve, MR and TR, diastolic flow reversal of upper abdominal aorta (optional) (see Figure 22)

Figure 22

EXAMINATION SEQUENCE

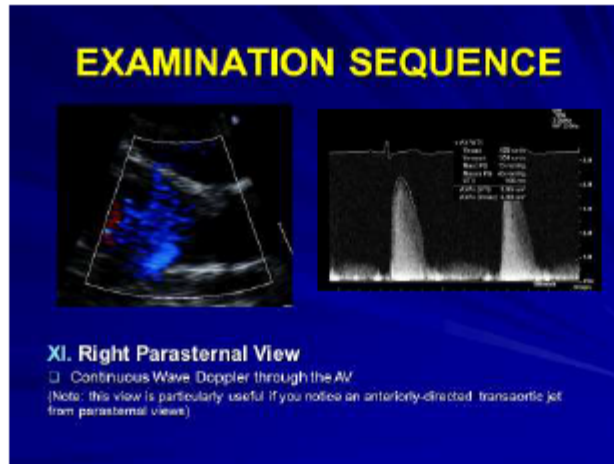
X. Subcostal Views (Long and SAX) chamber

- 2D
- Color Doppler of aortic valve
- Color Doppler of MR and TR (optional)
- Diastolic Flow Reversal (PW) of upper abdominal aorta

Optional

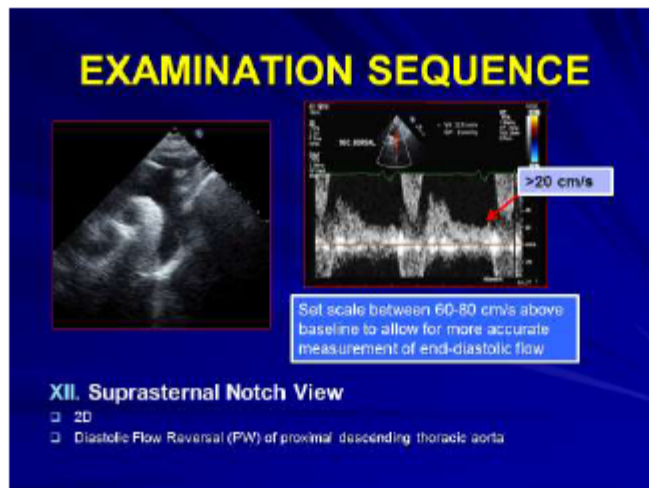
3.3.20 Obtain right parasternal view: CW Doppler of aortic valve (in 40-50% of cases maximum aortic jet velocity is obtained at the right parasternal window (see Figure 23))

Figure 23



3.3.21 Obtain suprasternal notch view: If moderate or severe AR is suspected, then a PW spectral Doppler assessment of the proximal descending aorta should be performed to assess diastolic flow reversal. Place sample volume in the descending thoracic aorta below the take-off of the subclavian artery in the supra-sternal imaging plane. Set velocity scale between 60 and 80 cm/s above baseline (see Figure 24).

Figure 24



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3.3.22 The site is not required to perform any measurements for the study. The ICL will review each image make the required measurements and update the data into the study database.

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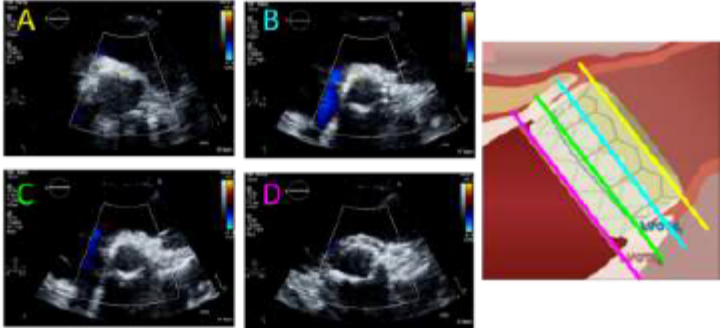
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Table 2: Echo Protocol Imaging Acquisition

<p>Acquisition Requirements</p>	<ul style="list-style-type: none"> • This table can be printed and used as a reference while performing the echo • Secure the study assigned Subject ID from the site coordinator. In the Echo ID field, type LASTNAME as EDWARDS Trial, FIRSTNAME subject initials, and Medical Record Number (MRN) 3-digit trial ID 4-digit site and 3-digit subject number • Obtain 2 digital clips of 3 complete cardiac cycles (normal sinus rhythm) for each required parameter • High 2D imaging frame rate: ≥40 FPS or 40% of heart rate • Spectral Doppler (PW and CW) should be performed with the line of interrogation as parallel to flow as possible. Record Doppler at 100 mm/sec sweep speed. • Pedoff (CW) aortic spectral display Doppler is required from; apical, suprasternal notch (SSN) and right parasternal (RPS) imaging windows. Please annotate on spectral display which view is being acquired. • Per ASE guidelines, if 2 or more contiguous endocardial segments are not visible, echo contrast should be used. If contrast is used, annotate on screed which view is being acquired. Body markers are acceptable forms of annotation. • Ensure good quality ECG signals are recorded on all images. • Distance, time and velocity calibrations must be present on each image. Time, date, subject ID should be accurately captures on each image. • All Image files are to be stored in vendor specific proprietary RAW/NATIVE DICOM data format (see section 7.3 through 7.5 for system specific downloading instructions).
<p>Echo Views</p>	
<p>PLAX</p>	<ul style="list-style-type: none"> • High PLAX focusing on Aortic root • Zoomed view of LVOT and Aortic valve • Standard 2D PLAX imaging to include LV/LA/AO • Color Doppler of Mitral and Aortic valves
<p>PSAX</p>	<ul style="list-style-type: none"> • Standard 2D imaging at these levels: <ul style="list-style-type: none"> ○ 1) Aortic Valve; 2) Mitral Valve; 3) Papillary Muscle; 4) Apical • Color Doppler of the Mitral valve • Color Doppler of Aortic valve at multiple levels, as shown in the image below

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	 <ul style="list-style-type: none"> • Zoomed view of Aortic valve with and without color • Color Doppler of Tricuspid valve and pulmonary valve • CW spectral Doppler of Tricuspid regurgitation
<p>Apical 4CH</p>	<ul style="list-style-type: none"> • Standard 2D imaging at increased depth to evaluate atria • Standard 2D imaging at decreased depth focusing on LV • Views focusing on right ventricle • Color Doppler of Mitral valve and Tricuspid valve • PW spectral Doppler of Mitral inflow • CW spectral Doppler of Mitral flow • CW spectral Doppler of Tricuspid regurgitation • Tissue Doppler Imaging (TDI) of medial and lateral Mitral annulus • Tissue Doppler Imaging (TDI) of free-wall tricuspid annulus
<p>Apical 5CH (BASELINE ONLY)</p>	<ul style="list-style-type: none"> • Zoomed view of LVOT with and without color • PW spectral Doppler of LVOT. Place SV 0.5 cm proximal to the Aortic valve. • CW spectral Doppler of Aortic valve • Color Doppler of Mitral valve
<p>Apical 5CH (FOLLOW-UP VISITS ONLY)</p>	<ul style="list-style-type: none"> • Zoomed view of LVOT with and without color • PW spectral Doppler of stent. Place SV just apical to the prosthesis stent. • PW spectral Doppler within stent (TAVR only) on the LV side of Aortic valve leaflets • CW spectral Doppler of Aortic valve • Color Doppler of Mitral valve

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Apical 3CH (BASELINE ONLY)	<ul style="list-style-type: none"> • Standard 2D imaging at increased depth to evaluate atria • Standard 2D imaging at decreased depth focusing on LV • Zoomed view of LVOT with and without color • PW spectral Doppler of LVOT. Place SV 0.5 cm proximal to the Aortic valve. • CW spectral Doppler of Aortic valve
Apical 3CH (FOLLOW-UP VISITS ONLY)	<ul style="list-style-type: none"> • Standard 2D imaging at increased depth to evaluate atria • Standard 2D imaging at decreased depth focusing on LV • Zoomed view of LVOT with and without color • PW spectral Doppler of stent. Place SV just apical to the prosthesis stent. • PW spectral Doppler within stent (TAVR only) on the LV side of Aortic valve leaflets • CW spectral Doppler of Aortic valve • Color Doppler of Mitral valve
Apical 2CH	<ul style="list-style-type: none"> • Standard 2D imaging at increased depth to evaluate atria • Standard 2D imaging at decreased depth focusing on LV • Color Doppler of Mitral valve
Subcostal	<ul style="list-style-type: none"> • Standard 2D imaging • Color Doppler of Aortic valve • Color Doppler of Mitral and Tricuspid valves • Diastolic flow reversal of upper abdominal aorta (optional)
Right Parasternal (RSB)	<ul style="list-style-type: none"> • CW spectral Doppler of Aortic valve
Suprasternal Notch (SSN)	<ul style="list-style-type: none"> • Standard 2D imaging of aortic arch and descending aorta with and without color • PW spectral Doppler with the SV placed in the proximal descending aorta
Pedoff CW Spectral Doppler	<ul style="list-style-type: none"> • Acquire highest systolic flow velocity through Aortic valve in the following areas: <ul style="list-style-type: none"> ○ 1) Apical, 2) SSN and 3) RSB

3.4 Addendum: Specific Comments on Imaging Planes

IMAGING TIP 1: PARASTERNAL LONG AXIS VIEW

Parasternal long axis view is recorded with the transducer in the third or fourth intercostals space immediately to the left of the sternum. The transducer should be angled so that aortic valve, mitral valve and left ventricle are in their long axis. It is important that the parasternal long-axis view displays the true long axis of the ventricle with the left ventricle lying horizontally on the image. If it is impossible to obtain a single view which optimally displays the long axis of the aortic valve and aortic root as well as the long axis of the left ventricle, record 2 separate views. It is unacceptable to record an off-axis view in which the apex "points up" on the screen. If this type of image is obtained try moving the transducer up an interspace or 2 or having the patient take a breath in. Sometimes having the patient move to a more lateral decubitus position will help as well.

IMAGING TIP 2: PARASTERNAL LONG AXIS VIEW

Measurement of the left ventricular outflow tract and aortic annulus is a key component of the study. In pre-device imaging, it is important to note that the largest annulus may not be in a plane with valve opening centered in the aorta.

Parasternal short axis view is obtained by angling the probe 90° with respect to the parasternal long axis of the LV. The goal of this view is to obtain information about the aortic valve as well as the LV. This is an essential view post-device to completely assess aortic regurgitation.

IMAGING TIP 3: PARASTERNAL SHORT AXIS VIEW

This may be the only view in which post-device medial or lateral aortic regurgitant jets are imaged. Imaging at the level of as well as just below the leaflets may allow you to better image these jets.

Apical four-chamber view provides considerable information including the relative sizes of the right and the left ventricle and the regional function of the LV. The four-chamber view is defined as a view which maximizes the LV long axis and the tricuspid and mitral annular dimensions. In this view, the full excursion of the mitral and tricuspid valves should be seen. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. In the

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apical four chamber view, color Doppler of mitral and tricuspid regurgitation should be recorded. The four chamber view should visualize the Lateral, Septal and Apical walls.

Apical two-chamber view should be obtained for the goal of assessment of LV size and function. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. The degree of MR by color Doppler will also be assessed. The two chamber should visualize the Anterior, Inferior and apical walls.

IMAGING TIP 4: APICAL 4 and 2 CHAMBER VIEWS

Because we will measure volumes from the apical views as an important end-point of the study, please try to avoid apical foreshortening. If the view appears to be foreshortened, please bring the transducer down one interspace and have the patient take a breath in (particularly for the apical two-chamber view). Sometimes this will bring out a better (not foreshortened) view.

Apical 5 chamber and 3 chamber views are obtained to provide detailed information about the aortic valve color, spectral and continuous wave Doppler.

IMAGING TIP 5: APICAL 5 and 3 CHAMBER VIEWS

Both these views are essential in imaging post-device aortic regurgitant jets. Because we will be measuring jet vena contracta and jet length, a Res/Zoom view which includes imaging of the entire jet would be helpful. In addition, the 3Ch view may be used in the biplane Simpson's calculation of LV volume when the 2Ch view is inadequate thus careful attention to endocardial definition is important.

MORE IMAGING TIPS: SEE TEACHING PARTNER 3 TRANSTHORACIC ECHO PROTOCOL TEACHING SLIDES

4. ECHO SCAN SUBMISSION PROCEDURE

4.1 Submitting Echo Images to Imaging Core

- 4.1.1 All images should be uploaded to the image transfer portal at the time of the visit window (or within 2 weeks of image acquisition).
- 4.1.2 The sponsor has provided a check list to be completed by the study qualified sonographer and submitted to the study coordinator for entry in the Electronic Echo Data Transmittal Form (see example 4.1.5) located on the Moving Pictures website <https://mddximage.com>.

(Note: the sonographer check list does not need to be submitted and may be retained at the site for personal records.)
- 4.1.3 The Study Coordinator is responsible for completely and accurately completing the Electronic Echo Data Transmittal Form. To avoid queries, ensure that no required fields are left blank.
- 4.1.4 If there are questions about completing the Electronic Echo Data Transmittal form, refer to the Moving Pictures "Quick Start Guide", or contact a support team member for assistance (support contact information on Moving Pictures website: <https://mddximage.com>).

4.1.5 Echo Data Transmittal Form Example

De-Identify and Upload
Please enter the case ID and identify the information to de-identify.

STEP-BY-STEP

Number Acquired	Weeks	1 Year	2 Year	3 Year	4 Year	5 Year	Next Scheduled
Selected for Upload	Not Uploaded	Not Uploaded	Not Uploaded	Not Uploaded	Not Uploaded	Not Uploaded	Not Uploaded

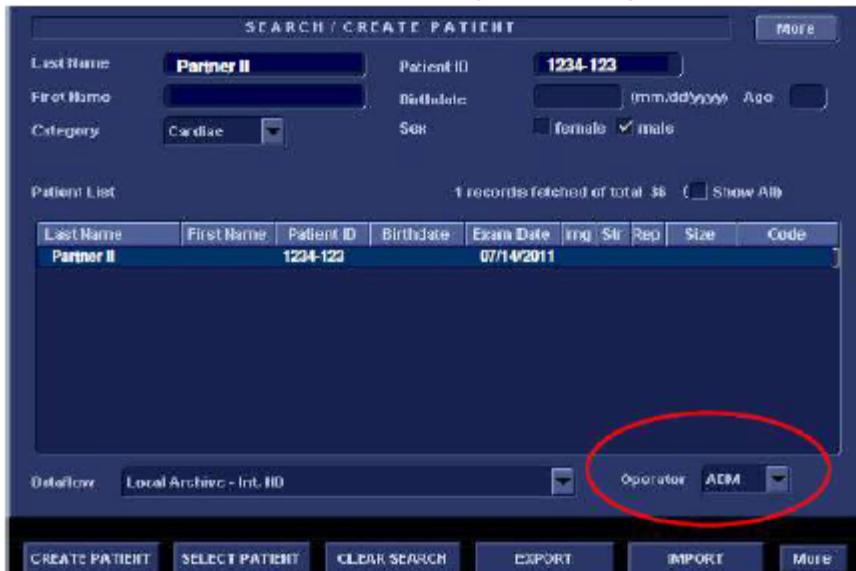
Form fields include: Patient ID, Date of Imaging (19 Aug 2015), Time (07:00), Procedure (TEE), Sonographer (Admin), Position of CT, Angle, Height (75), Weight (60), and Comments (Test Case).

4.2 Archival Instructions

- 4.2.1 Complete the Electronic Echo Data Transmittal Form carefully and completely for each echo exam..
- 4.2.2 Archive the Echo study to digital media (DVD) immediately from the ultrasound system that was used to acquire the images (before archiving to Picture Archiving and Communication System [PACS]). Please note: Image files not stored in DICOM format cannot be interpreted.
- 4.2.3 Retain a copy of the DVD on site with study related materials.
- 4.2.4 Follow routine downloading instructions for all ultrasound systems, with the exception of the systems noted below.
- 4.2.5 If there are problems downloading the study to a DVD, Please contact your local ultrasound system application specialist.

4.3 GE Vivid 7 System Specific Instructions for Archive Export (RAW Data DICOM data)

- 4.3.1 Archive all studies immediately after image acquisition.
- 4.3.2 Select Archive screen and log in as administrator (ADM). Password should be: ulsadm (all lower case)

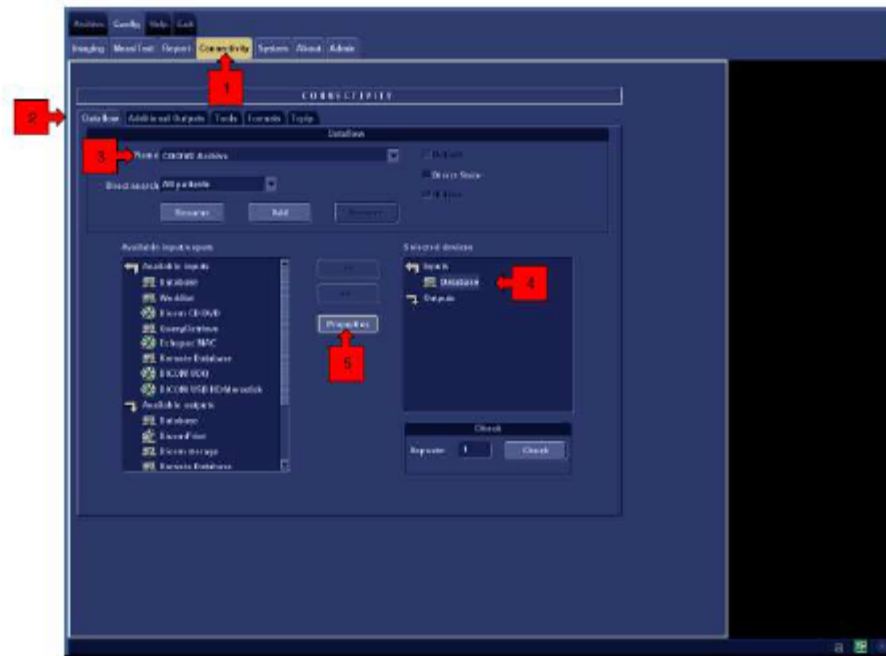


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4.3.3 System Setup

- 1) In **Configuration** screen select "Connectivity"
- 2) On the Connectivity screen choose "Dataflow" from top row of options
- 3) Select CD/DVD Archive from the drop down menu in the "Name" section
- 4) Highlight Database in the "Selected devices" region, then the Properties button will appear
- 5) Activate the Properties button



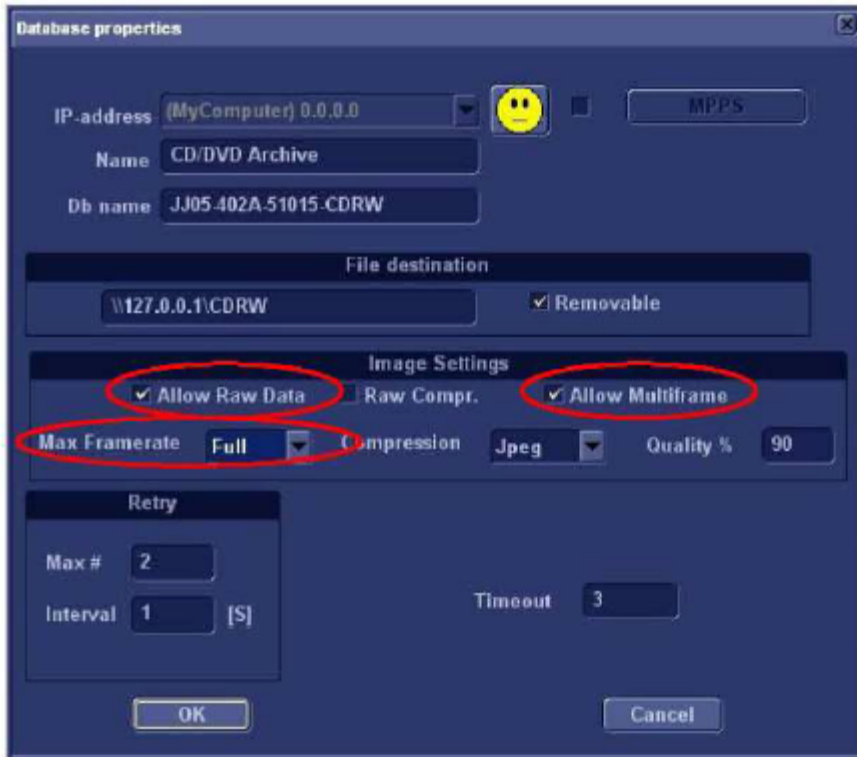
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4.3.4 After activating the Properties button, a new window will appear. Check "Allow Raw Data," and "Allow Multiframe" then change the "Max Framerate" to Full



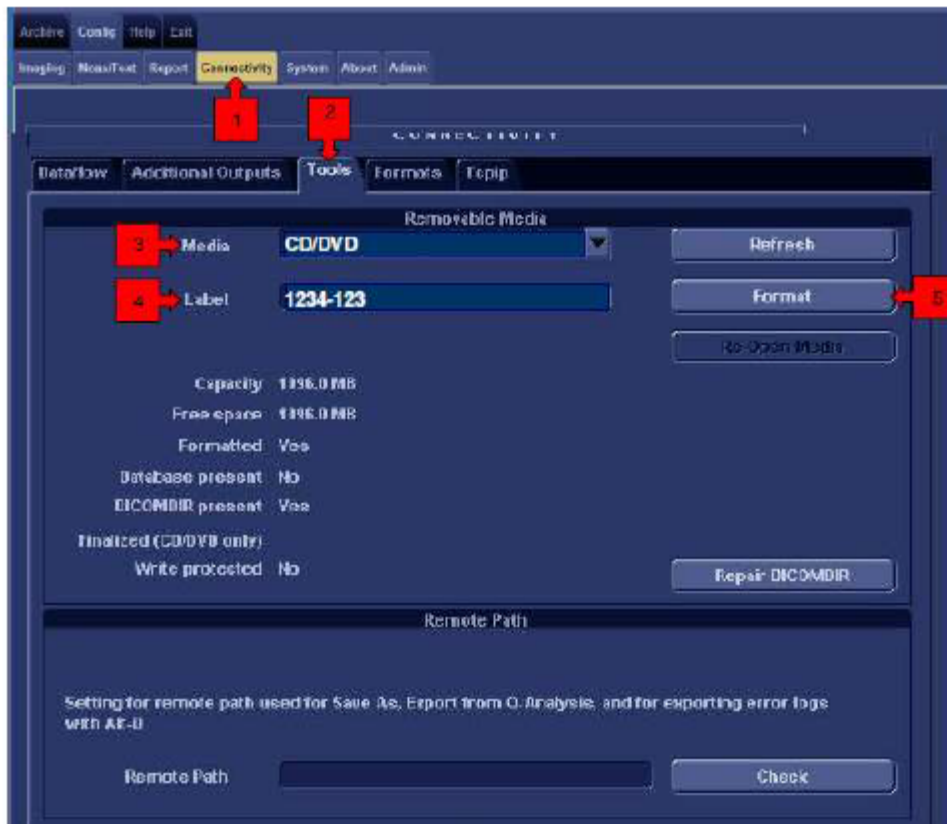
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4.3.5 Formatting DVD

- 1) In **Configuration** screen select "Connectivity"
- 2) On the Connectivity screen choose "Tools" from top row of options
- 3) In the Tools screen the media type should be set to "CD/DVD"
- 4) Type in label for DVD (4 digit site and 3 digit subject number)
- 5) Make sure DVD is in drive and select "FORMAT"

- A dialog box will appear to confirm that you wish to format the DVD– select OK.
- Once the DVD is formatted, exit configuration screen



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4.3.6 .Exporting study from Internal Hard Drive to DVD

- Select **Archive** screen and set "Dataflow" to read "Local Archive – Int. HD"
- Select **EXPORT** from the screen
- The export dialog box will appear. The **FROM** box should read "Local Archive – Int. HD" and the **TO** box should read "CD/DVD Archive" from the drop down menus. Select OK.

The screenshot shows the 'SEARCH / CREATE PATIENT' interface. The 'Dataflow' dropdown is set to 'Local Archive - Int. HD' and the 'EXPORT' button is highlighted with a red circle. The patient list table is as follows:

Last Name	First Name	Patient ID	Birthdate	Exam Date	img	Str	Rep	Size	Code
Partner II		1234-123		07/14/2011					

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- A screen of patients on the hard drive will appear. Select the patient/subject you wish to export to the DVD and select COPY.
- Once the study has been exported to a DVD, select DONE to finish the copy procedure.
- Select F3 or Alt-E from the keyboard to eject the DVD.



Retain a copy of the DVD on site with study-related materials.

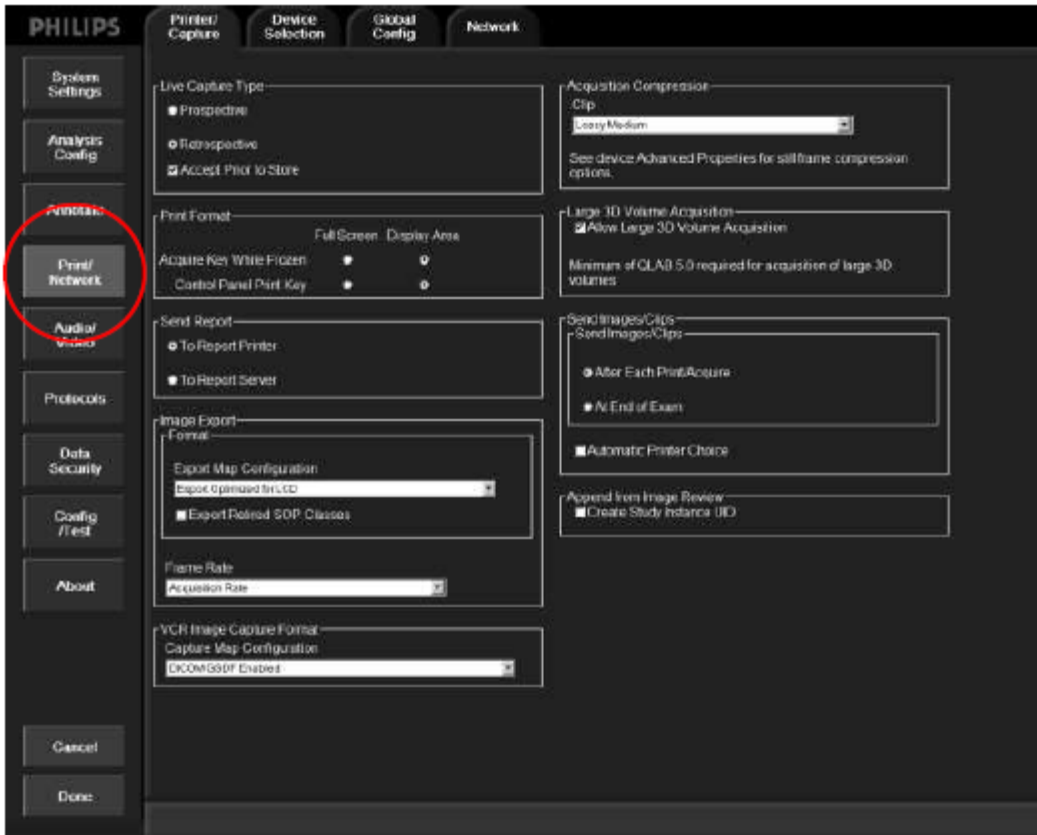
If there are problems downloading the study to a DVD, please contact your local GE application specialist.

4.4 Philips iE33 System Specific Instructions for Archive Export (NATIVE DICOM data)

4.4.1 Archive all studies immediately after image acquisition

4.4.2 System set-up

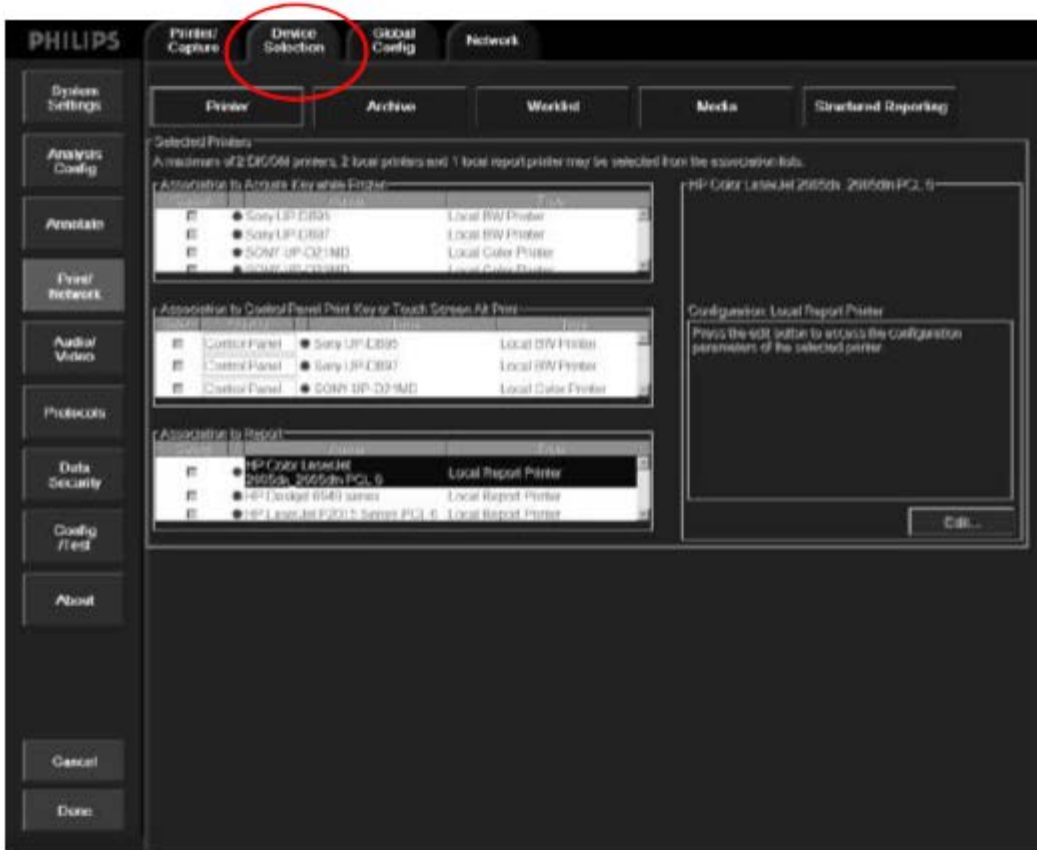
- Select machine "setup" on top row of keyboard to activate set up screen.
- Select "Print/Network" tab on left side of screen (fourth selection down).



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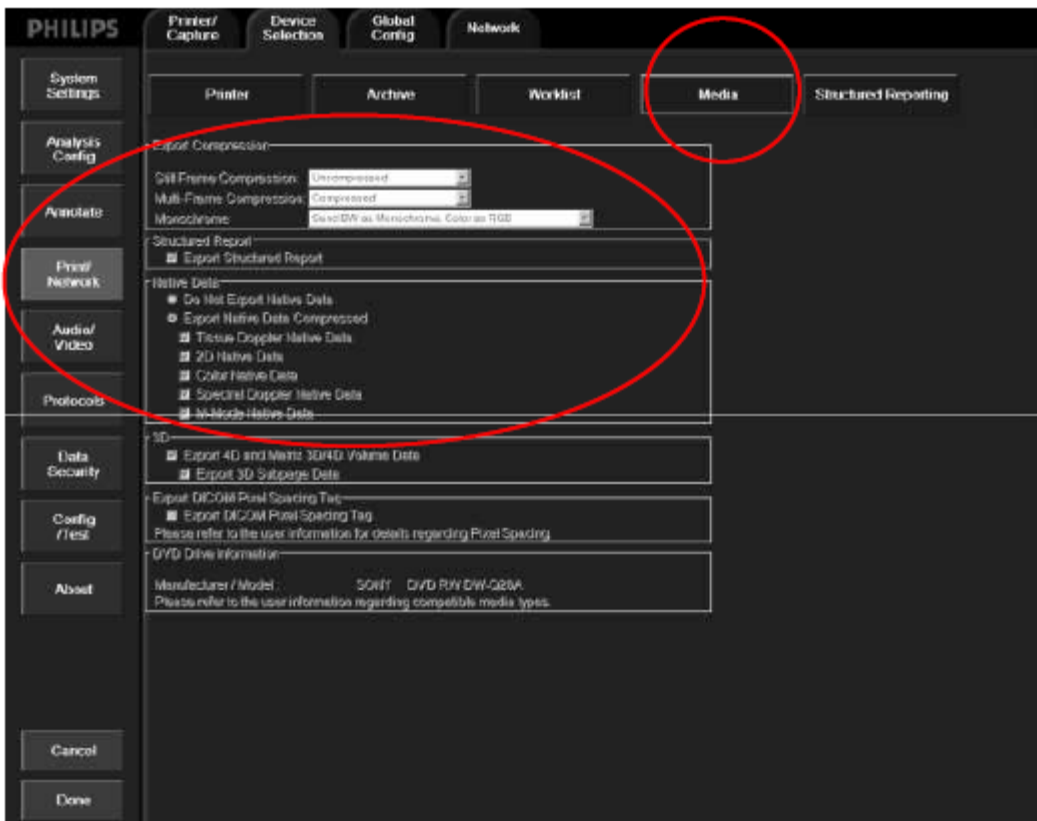
- On the Print/Network screen select "Device Selection" from the top row of options.



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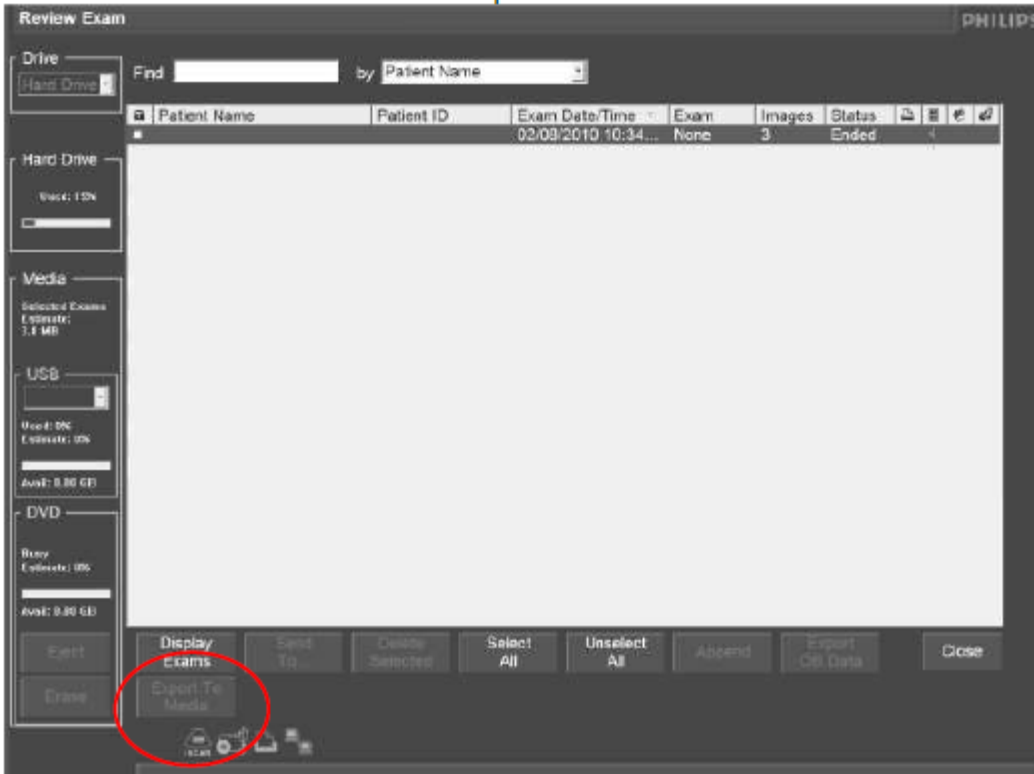
- On the Device selection screen select “Media” from the second row of options.
 - Export Compression
 - Still Frame Compression: Uncompressed
 - Multi-Frame Compression: Compressed
 - Monochrome: Send BW as Monochrome, Color as RGB
-
- Native Data
 - Select Export Native Data Compressed
 - Check Tissue Doppler Native Data
 - Check 2D Native Data
 - Check Color Native Data



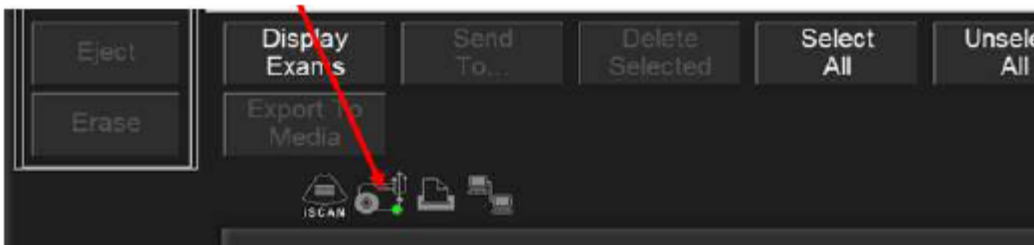
4.4.3 Exporting study from internal hard drive to DVD

- Select "Review" on left side of control panel to activate review screen.
- Select (highlight) subject from exam list.
- On the review screen select "Export To Media"
- Text box will appear

Choose "DVD" and "Export to Media"
Select "OK" to process selections



- Green Icon at bottom left of screen shows active copying



Retain a copy of the DVD on site with study-related materials.

If there are problems downloading the study to a DVD, please contact your local Philips application specialist.

5. ECHO QUALITY CONTROL PROCESS

5.1 Echo Critique

Echocardiograms will be monitored for adherence to study protocol as well as quality. The Imaging Core Labs will provide feedback in the form of a critique to sites via email for each study subject submitted to the core lab. The critique should be shared with the imaging sonographer to ensure research quality data and to help prevent the possibility of missing data.

6. ECHO DATA CLARIFICATION PROCESS (AKA, QUERIES)

6.1 Query Notification

- 6.1.1 The study coordinator (or designee) and the sponsor will receive an email from MDDX asking for the resolution of any issues that were found during the quality control (QC) process. Prompt response is required from the site designee.

6.2 Echo Data Queries

- 6.2.1 Review the variable name, reported value, and comments/suggestions.
- 6.2.2 Record the corrected, missing, or illegible information in the resolution box.

6.3 Echo Media Queries

- 6.3.1 Review the issue and comments/suggestions
- 6.3.2 Record the corrected information and/or comments of action taken (For Example: sent new images).
- 6.3.3 On the Moving Pictures Electronic Echo Transmittal Form, select that images are being re-submitted.

6.4 Echo Query Resolution Form Example

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Query Resolution✕

Patient Name: P2B_0010-034-TTE-65-126284 Query ID: 4798

Data with Query:
Image Count: 28

Query Details:

- Not enough images
- No DICOM present
- Missing Cines
- Low image count, have all images been uploaded?
- Corrupt images, please see comments section for specifics
- Multi-frame images missing, have all images been uploaded?
- Single-frame images missing, have all images been uploaded?
- Color doppler images missing, have all images been uploaded?
- Continuous wave/pulse wave doppler images missing, have all images been uploaded?

SITE QUERY OPEN SQ

By: J Vasiljelic on: 20 May 2016 01:54:15 PST

Site Query Description:

Status changed from Pending Review to Site Query Open

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Written by: Philippe Pibarot Signature: Date:

Checked by: Signature: Date:

Checked by: Signature: Date:

Approved by Director: Signature: Date:

MOP # P3-001 Date Issued: Date Effective:

Appendix K-1 Computed Tomography (CT)

CT Manual of Operations, Appendix K-1

Edwards Lifesciences LLC
Protocol US IDE Trial #2015-08

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*Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614*

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Trial Sponsor: Edwards Lifesciences
Protocol Title: A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Requiring Aortic Valve Replacement who have Severe, Calcific, Symptomatic Aortic Stenosis

Protocol Identifier: US IDE Trial #2015-08

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Acquisition Recommendations for Combined Assessment of the Aortic Root and Aorto-Iliofemoral Vasculature

Contrast-enhanced computed tomography (CT) allows for anatomical assessment of the aortic root and the aorto-iliac femoral vasculature within a single examination. Data acquisition strategies and scanning protocols may vary based on scanner system and institutional preferences. The key component of all approaches is an ECG-assisted data acquisition which covers at least the aortic root, while the remainder of the data acquisition may be performed without ECG assistance. If employed properly, ECG assistance allows for artifact-free depiction of the aortic root.

The sequence of patient preparation and data acquisition, and the relevant principles of CT data acquisition will be explained in brief below.

ECG-ASSISTED CT DATA ACQUISITION

ECG-assisted data acquisition implies that in parallel to the CT data acquisition, the patient's ECG signal is recorded to do the following:

- Direct the data acquisition itself
- Direct the image reconstruction

Currently, there are three different types of ECG-assisted data acquisition techniques commonly employed in the clinical environment:

- Retrospective ECG Gating
- Prospective ECG Triggering
- High-Pitch Helical

Data Acquisition

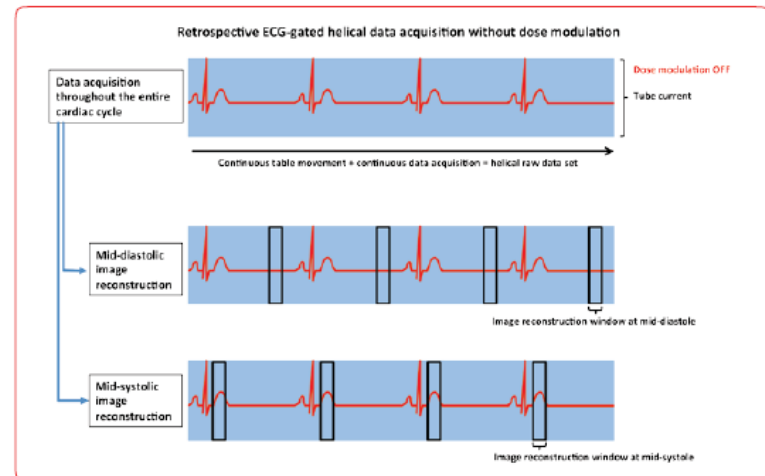


Figure 1 – Retrospective ECG-gated helical data acquisition without dose modulation. The tube current (blue bar) is set at its peak during the entire cardiac cycle. The black boxes indicate the time point of image reconstruction within the cardiac cycle.

Retrospective ECG Gating (Spiral/Helical Mode)

- Helical data acquisition due to continuous movement of the patient through the gantry while the scanner gantry rotates
- Simultaneously records the ECG signal
- The recorded ECG signal allows for "retrospective" image reconstruction at specific time points of the cardiac cycle (FIGURE 1)

- In general, this technique is available on all scanner platforms capable of cardiac CT
- Advantage: Allows for dynamic (cine) imaging/ image reconstruction throughout the entire cardiac cycle (early systole – late diastole)
- Advantage: Greater flexibility in unstable heart rates or rhythms (eg, atrial fibrillation or premature ventricular contractions) – ability to use data from different phases (eg, systole or

- diastole) and to manually edit the reconstruction (please refer to ECG Editing)
- Disadvantage: Relatively high radiation dose, as full tube current is applied throughout the entire cardiac cycle

ECG Editing with Retrospective ECG Gating

- The in-part redundant image data which is acquired using retrospective ECG gating and helical data acquisition allows for manual editing of the ECG signal with adjustment or deletion of certain trigger points (eg, an entire heart beat may be deleted in case of a premature contraction)
- This technique should be employed in cases of misalignment artifacts due to premature contractions or atrial fibrillation
- ECG editing has to be performed at the scanner console using the raw data

CAVEAT: Raw data is commonly stored for a limited time only.

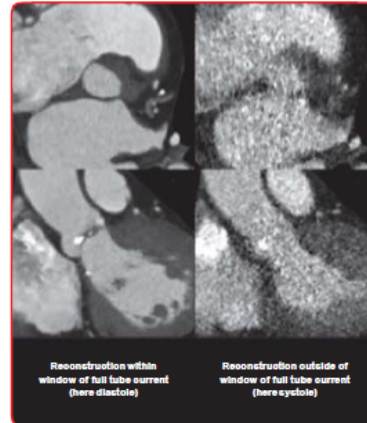


Figure 2 – Example of retrospective ECG gating with dose modulation during systole (not recommended). Images reconstructed during systole outside of the window of peak tube current are noisy and uninterpretable.

Data Acquisition

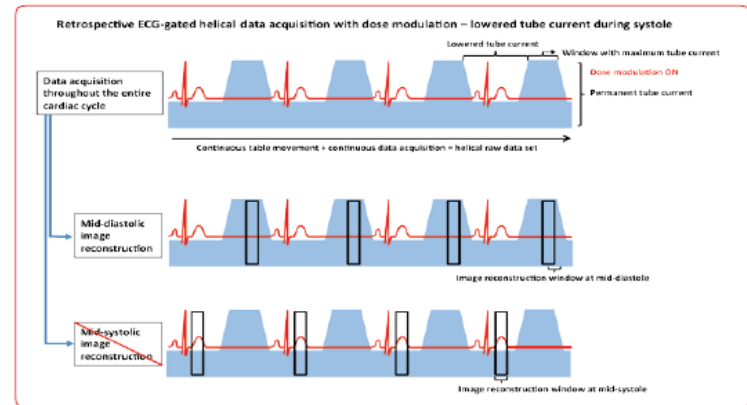


Figure 3 - Retrospective ECG-gated helical data acquisition with dose modulation. Peak tube current is limited to mid-diastole (not recommended). Image reconstruction at systole (lower row) will likely result in uninterpretable image quality.

Recommendation:

- Ideally dose modulation should be switched off to allow for data acquisition with peak tube current throughout the entire cardiac cycle; however, if utilized, it is recommended that dose modulation be used only in diastole set to 20% – 30% peak dose
- It is not recommended, to use dose modulation in systole. *CAVEAT: Most automated coronary CTA protocols with dose modulation reduce tube current during systole.*
- ECG editing should be considered to reduce artifacts due to premature contractions or atrial fibrillation

Dose Modulation in Retrospective ECG Gating:

- Dose modulation is modulation of the tube current throughout the cardiac cycle with peak tube current (mAs) during a predefined phase of the cardiac cycle and lowered tube current during the remainder of the cardiac cycle (FIGURES 3 & 4)
- Although image reconstruction is still technically feasible throughout the cardiac cycle, images reconstructed outside the preselected phase

- will have increased image noise and may not be interpretable
- For aortic root evaluation, images are usually uninterpretable if tube current is lowered below one third of the peak current
- Due to the pulsatile and conformational changes of the aortic annulus throughout the cardiac cycle with larger dimensions usually found in systole, peak tube current is warranted during systole

Data Acquisition

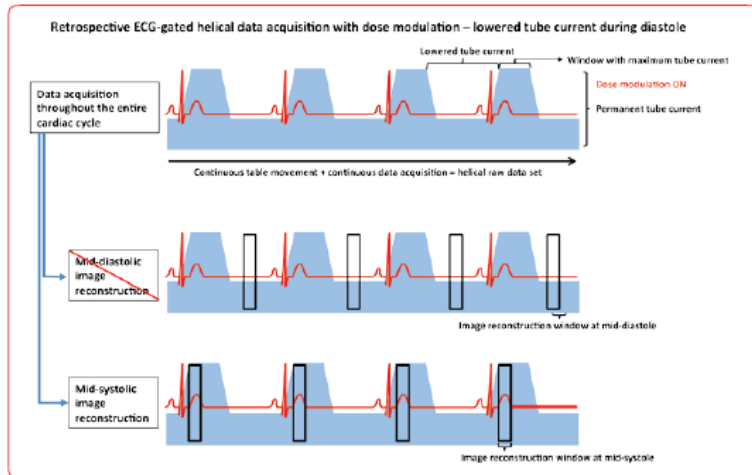


Figure 4 - Retrospective ECG-gated helical data acquisition with dose modulation. Peak tube current is limited to systole. Image reconstruction at diastole (middle row) will likely result in uninterpretable image quality.

- Advantage: Dose reduction
- Disadvantage: Images reconstructed outside of the window of full/peak tube current have increased image noise and may be uninterpretable

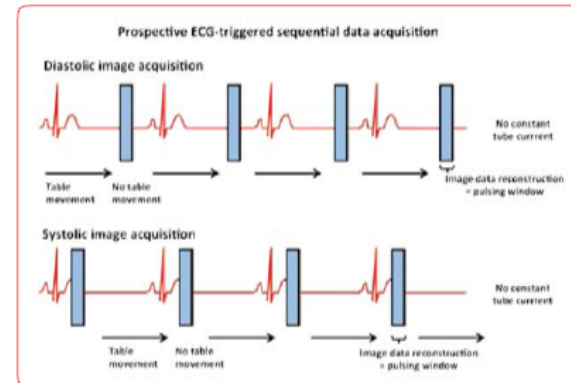


Figure 5 – Prospective ECG-triggered sequential data acquisition. Upper row with diastolic data acquisition (not recommended), lower row with systolic data acquisition.

Prospective ECG Triggering (Sequential/Axial Mode)

- Data acquisition is prospectively triggered by the ECG signal (FIGURE 5)
- Data acquisition is performed in a slab-wise (axial, non-helical) fashion while the patient table does not move. The table is moved in between slabs
- Acquisition windows are usually limited to a specific portion of the cardiac cycle (eg, only mid-diastole) with no radiation exposure or image acquisition occurring outside of the acquisition window

- Limitation of the acquisition window often allows for only one single reconstruction, or if the window is slightly broadened ("padding") for slight variation in the reconstruction window
- Advantage: Lower radiation dose
- Disadvantage: Allows for only limited coverage of the cardiac cycle and almost no correction in case of misregistration or motion artifact

Data Acquisition

Recommendation:

- If prospective ECG-triggering is employed, the acquisition window should be centered in systole.
- Due to the limited potential for image correction, this imaging technique should only be employed if radiation dose is a concern.

High-Pitch Helical Data Acquisition

- High-pitch data acquisition is limited to second and third generation dual-source scanners and employs high pitch factors of 3.2-3.4
- Data acquisition can be ECG triggered to aim for systolic or diastolic data acquisition at the level of the aortic root
- This technique allows only for a single reconstruction
- **Advantage:** Low radiation exposure
- **Disadvantage:** Allows for only a single reconstruction

CT Scan – Patient Preparations

- Positioning of the patient on the scanner table, typically supine, should closely resemble positioning on the cath lab table
- Placement of ECG electrodes and IV access should follow institutional policies
- Patient instruction on breath-holding prior to scanning may improve compliance with the breath-holding instructions during the scan

Note:

Volume scanners with wide z-axis coverage (eg, 256-slice or 320-slice CT scanners) may be capable of covering the entire aortic root with one slab using axial data acquisition and prospective triggering. By extending the acquisition window to cover the entire cardiac cycle, this technique may allow for dynamic imaging, and may then be considered equivalent to retrospective ECG-gating without dose modulation. However, given the prospective nature of the data acquisition, where redundant data is not acquired, ECG editing is not possible.

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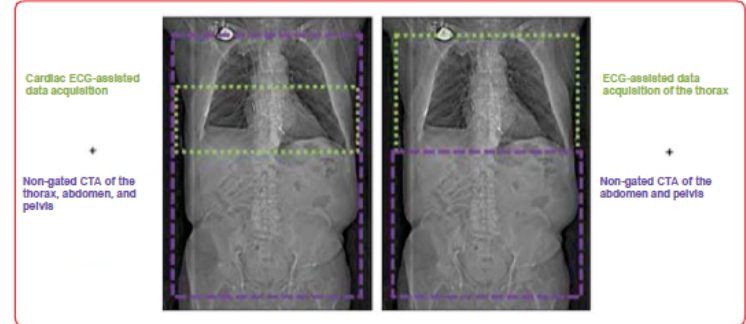


Figure 6 – Scout views highlighting two different imaging strategies: Left, ECG-assisted data acquisition limited to the aortic root and heart (green box) followed by non-gated CTA of the thorax, abdomen and pelvis (purple box). Right, ECG-assisted data acquisition of the entire thorax (green box) followed by the non-gated CTA of the abdomen and pelvis (purple box).

CT Scan – Scan Length and Scan Strategy

In general, there are two different approaches on how to combine the ECG-assisted data acquisition of the aortic root structures and the non-ECG-assisted computed tomography angiography (CTA) of the aorto-iliofemoral vasculature for evaluation of the transfemoral access route (FIGURE 6):

- Cardiac ECG-assisted data acquisition of the heart and aortic root (usually beginning 2 cm below the carina) followed by a non-ECG-assisted CTA of the thorax, abdomen, and

pelvis. Although this approach results in repeat data acquisition of the aortic root and cardiac structures, the time-intensive ECG-assisted data acquisition is kept to a minimum.

- ECG-assisted data acquisition of the thorax followed by a non-ECG-assisted CTA of the abdomen and pelvis. The disadvantage of this approach is the relatively long acquisition time required for the entire thorax (may exceed 15 seconds), which increases the risk of breathing artifacts at the level of the cardiac structures.

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Data Acquisition

In General:

- All studies should be acquired using smallest available scan thickness (≤ 0.75 mm) based on individual system capabilities: Please refer to your system-specific user manual to determine your detector configuration
- The scan coverage should include the entire aortic arch
- The scan coverage for the non-ECG-assisted CTA of the pelvis should include the femoral heads and extend to shortly above the lesser trochanter
- The data acquisition of the non-ECG-assisted CTA should be performed in the cranial to caudal direction
- Tube voltage, tube current, and pitch should be adapted to institutional CTA protocols

Contrast:

- The total dose of contrast varies with scanner, imaging protocol, and body habitus, typically ranging from 60-100 ml.
- Image acquisition timing can be performed using either a timing bolus (test bolus) or bolus tracking. Bolus tracking with a region of interest (eg, in the ascending aorta) is less cumbersome and usually sufficient for imaging of the aortic root.
- Specific contrast protocols should follow institutional policies. A minimum injection rate of approximately 3 to 4 ml/s is usually required to allow for sufficient contrast attenuation of the aortic root.

IMAGE RECONSTRUCTION:

ECG-Assisted Image Data of the Aortic Root/Heart

- A small reconstruction field of view should be used to allow for maximum resolution
- The thinnest possible slice thickness should be employed (eg, 0.6 or 0.75 mm)
- If retrospective ECG gating was employed, image reconstructions should cover the entire cardiac cycle (multiphasic data set)
- Reconstruction phases: 0-90% RR at 5 – 10% increments
- Traditional filtered back projection or iterative reconstruction may be used

Non-ECG-Assisted Image Data of the Thorax, Abdomen, and Pelvis

- The slice thickness should be no thicker than 1.5 mm
- Traditional filtered back projection or iterative reconstruction may be used

Definition and Identification of the Aortic Annulus and the Annular Plane

The aortic annulus is not a discrete structure; rather, it is a "virtual" ring formed by the three lowest attachment points of the aortic valve cusps ("hinge points"). Accurately identifying the aortic annular plane is fundamental to proper transcatheter heart valve prosthesis size selection.

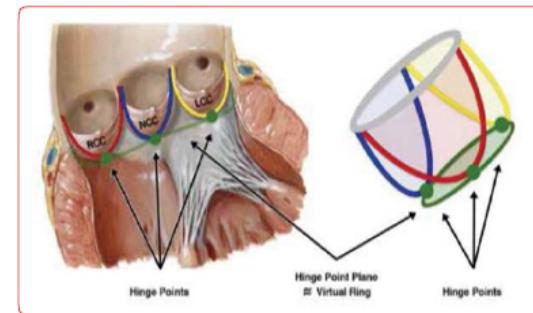


Figure 7 – Aortic root anatomy and definition of the annular plane
(Image source: Kasel et al. JACC: Cardiovascular Imaging, February 2013)

Nomenclature of Viewing Planes

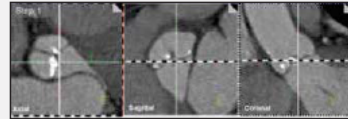
CT images are commonly viewed using multiplanar reformats (MPR). Post-processing platforms provide an axial (transverse), coronal, and sagittal view at the very beginning of processing. Exact orientation of one imaging plane is indicated by the cross hairs in

the two remaining planes. Manipulating the orientation of the cross hairs and the dependent planes results in oblique or double-oblique views, such as a sagittal double-oblique view.

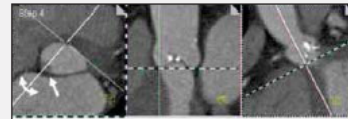
Annular Plane

Techniques for Determining the Annular Plane

There are multiple ways of identifying the correct annular plane using MPRs. Independent of the approach, the final transverse double-oblique view should transect the hinge points of all three cusps. A systematic, step-wise approach has been published by the Society of Cardiovascular Computed Tomography (reproduced with permission):



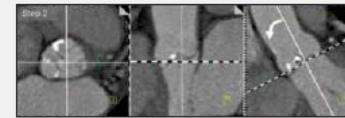
Step 1:
Start out with multiplanar images in axial, sagittal, and coronal orientation.



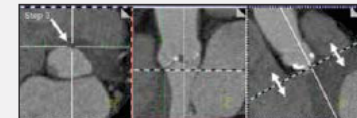
Step 2:
Rotate (without moving up and down or left and right) the reference lines in the former axial plane in a way so that the line that controls the former sagittal plane crosses the lowest insertion point of the noncoronary cusp, which is located at approximately the 8 o'clock position (note: it is not shown here that this may require to interactively change the level of the former axial plane by moving it up and down with the use of the reference line in the former coronal image, without rotating it so that the orientation remains unchanged).

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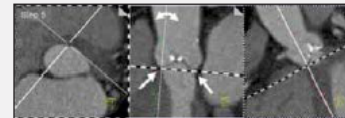
K1-13



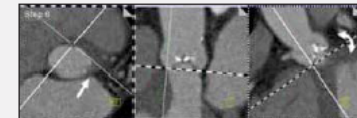
Step 3:
Use the reference line in the coronal image to rotate the former axial plane in a way so that it crudely approximates the plane of the aortic valve.



Step 4:
In the coronal image, move the reference line that controls the former axial plane up and down to identify the lowest insertion point of the right coronary cusp which is usually located at about the 1 o'clock position. Position the formerly axial plane exactly at the level of that cusp insertion point. Then, move the crosshair in the formerly axial plane exactly onto the right coronary cusp insertion point.



Step 5:
The formerly sagittal plane will now show the lowest insertion point both of the right coronary cusp and the noncoronary cusp. In this window, move and rotate the reference line of the former axial plane so that it very exactly crosses both of these insertion points. Once this is achieved, the formerly axial plane will contain 2 of the 3 lowest cusp insertion points.



Step 6:
In the former coronal plane, rotate (without moving it) the reference line of the former axial plane until the lowest insertion point of the left coronary cusp just barely appears in the formerly axial window (arrow). Now, the former axial plane is exactly aligned with the lowest cusp insertion points of all 3 aortic cusps and represents both the orientation as well as the level of the "aortic annulus" (image on left). Measurements of aortic annulus dimensions should be performed in this plane.

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Annular Plane

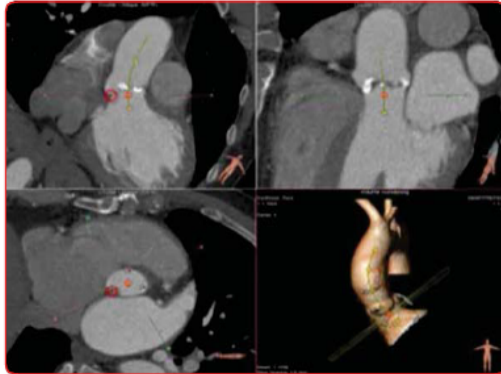


Figure 8 - Facilitated annular segmentation.

Facilitated Annular Segmentation

- Certain post-processing platforms facilitate annular segmentation by manual placement of seeding points at the identified hinge points. After placing a seeding point for all three cusps, the plane transecting all three points is automatically displayed.

Semi-automated Annular Segmentation

- Certain post-processing platforms perform an automated segmentation of anatomical landmarks, including the basal hinge points, allowing for an automated display of the annular plane

Note:

Confirmation of the correct identification of the annular plane is warranted for both the facilitated and semi-automated segmentation, ie, by "turning" the cross hairs and verifying the location of the hinge points on the long axis view.

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K1-15

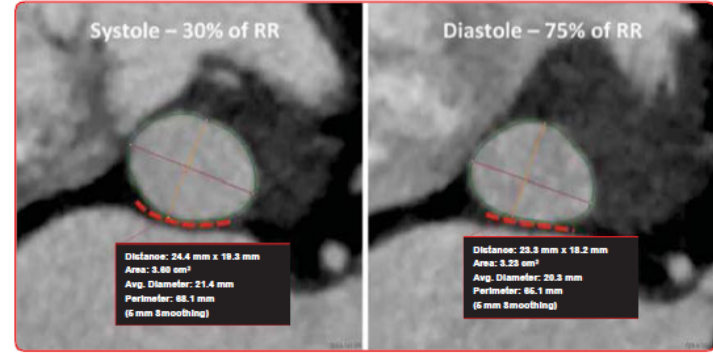


Figure 9 – Dynamic changes in annular dimensions and configuration throughout the cardiac cycle. Conformational changes occur due to bulging of the aorto-mitral junction (red dashes) towards the left atrium during systole.

Annular Plane

Importance of Cardiac Phase for Determining Maximum Aortic Annular Dimensions

- The aortic annulus is subject to pulsatile and deformational changes throughout the cardiac cycle
- The annular area may vary greatly between systole and diastole (FIGURE 9). Edwards sizing charts are based on maximum systolic area. Maximum systolic area is determined by evaluating the aortic annulus in 5 – 10% increments from 25 – 45% of the R – R interval.

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K1-16

Measurements

After proper identification of the annular plane the annulus measurement and ancillary measurements should be performed.

These measurements can be grouped into measurements which depend on the annular plane and measurements which do not depend onto the annular plane.

Measurements Depending on Annular Plane

- Annular dimensions
- Prediction of fluoroscopic angulation
- Distance to coronary ostia (coronary artery height)
- Sinus height (sinotubular junction height)
- Left Ventricular Outflow Tract (LVOT)
- Ascending aorta length

Measurements Independent of Annular Plane

- Sinus of Valsalva width
- Sinotubular junction (STJ) diameter
- Ascending aorta diameter

Although several automated tools are commercially available to expedite the valve analysis workflow, it is important to understand the approach for each measurement in order to be capable of performing the assessment manually and to recognize errors which may occur in an automated analysis.

It is recommended to perform the following actions:

- Identify the annular plane
- Perform measurements dependent on the annular plane
- Perform measurements independent of annular plane

The annular assessment and measurements are used in conjunction with additional imaging modalities as well as patient characteristics to determine the appropriate prosthesis size.

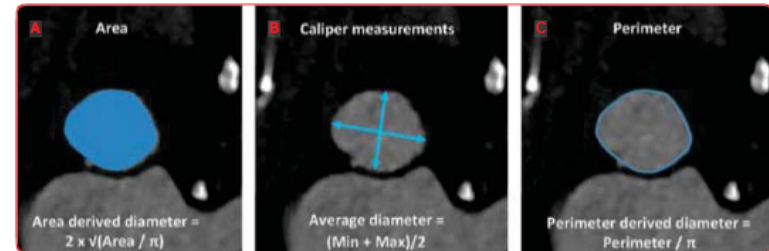


Figure 10 (A, B, C) – Various descriptors of annular dimensions

Annular Dimensions

In general, annular dimensions (FIGURE 10) can be expressed in the following terms:

- Area
- Diameter
- Perimeter

It is important to understand that a diameter can be measured using an electronic caliper (simple distance measurement tool) and derived from perimeter or area using a mathematical equation.

Area and perimeter are assessed by utilizing planimetry by manually drawing a contour, a spline (explained below), or semi-automated contour with contrast-edge detection.

The aortic annulus is usually elliptical. A simple distance measurement, such as a long axis or short axis distance, does not integrate the rather complex dimensions of an ellipse.

Alternatively, the maximum or long axis diameter and minimum or short axis diameter can be assessed and then averaged (FIGURE 10B). This represents a more comprehensive assessment of the elliptical anatomy. However, manual caliper measurements are subject to error as a divergence in a single caliper measurement by 2 mm results in a divergence of 1 mm for the averaged value.

Measurements

Some post-processing platforms provide maximum diameter (long axis) and minimum diameter (short axis) based on annular planimetry. However, these algorithms usually report the most extreme values.

Planimetry is performed by one of the following methods:

- Manual contouring with a region of interest or polygon
- Manual contouring with a spline
- Semi-automated edge detection

Independent of the approach, planimetry yields an area commonly expressed as mm² or cm². The area measurement can be used to calculate an "effective" area-derived diameter calculated using the formula listed in FIGURE 10A. Some advanced post-processing tools perform this calculation automatically.

A "freehand" contour or region of interest follows the path of the cursor while a polygon is created by placing dots along the annular contour which are automatically connected without interpolation. In contrast a spline tool is similar to an elastic ruler which bends to pass through the manually defined points.

Depending on the vendor, these planimetry tools may also yield perimeter. However, a "freehand" contour often results in a irregular line which leads to an artificially increased perimeter. Polygons and splines usually have a smooth contour yielding a more realistic perimeter value. Smoothing algorithms can allow for perimeter assessment using "freehand" contours by correcting the jerky contour.

Edge detection algorithms help to identify the annular contour based on the edge between the contrast-attenuated lumen and the non-enhancing mural components. Importantly, automatically drawn contours should be visually validated and if necessary manually corrected.

Measurements

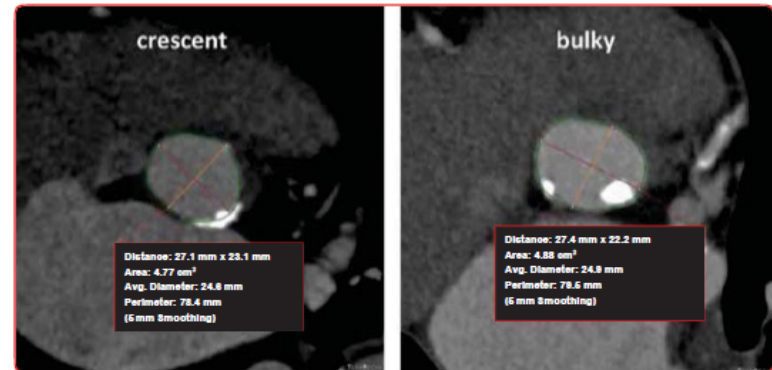


Figure 11 – Annular assessment in the presence of annular calcifications.

Annular Dimensions in the Presence of Annular Calcifications

Annular calcifications can be classified as:

- Adherent (crescent)
- Protruding (bulky)

The annular contour should be traced, extrapolating as if the calcification was not present (FIGURE 11).

It is important to also assess the entire anticipated landing zone for the presence of calcifications, for example, at the level of the annulus, sub-annular region (0 to 2 mm below annulus), and the upper LVOT (2 to 6 mm below annulus).

Prosthesis sizing should take into account calcium distribution, location, and size

Prediction of Fluoroscopic Angulation

- Fluoroscopic angulation required to obtain a coplanar view of the aortic annulus can be obtained prior to the procedure from the CT data set
- This may help to reduce the number of aortograms needed to achieve an acceptable view at the time of the procedure, thus decreasing the amount of contrast material
- Most post-processing platforms report the angulation of each of the three views of the MPR as pairs of degrees [°] RAO/LAO and ° CRA/CAU angulation (FIGURE 12A)
- These angulations are located on an optimal viewing curve (FIGURE 12B)

Step 1:

Following the annular measurement DO NOT change the angulation or level of the annular plane (transverse double-oblique image) (FIGURE 12A).

Step 2:

By manipulating ("spinning") the cross hairs in the transverse oblique view, the orientation of the coronal double-oblique view is moved along the optimal viewing curve which is reflected by a change in the displayed values for °RAO/LAO and °CRA/CAU angulation.

- For example, if the implanter prefers a view with 0° CRA/CAU angulation, the coronal view is adjusted to 0° CRA/CAU angulation, and the corresponding LAO angulation is noted
- Common angulation pairs include the following:
 - 10° LAO, corresponding CRA/CAU angulation
 - 0° LAO/RAO, corresponding CRA/CAU angulation
 - 30° LAO, corresponding CRA/CAU angulation
 - 0° CRA/CAU, corresponding LAO/RAO angulation

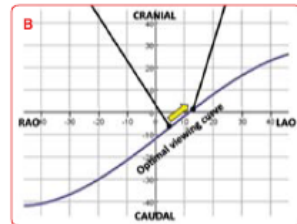
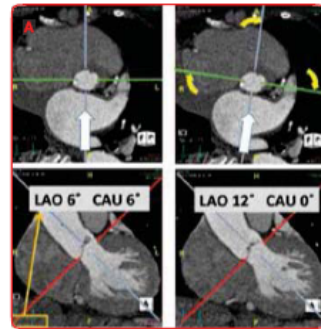


Figure 12 – Required pairs of LAO/RAO and CRA/CAU angulation to achieve a coplanar view of the aortic annulus are located on the patient-specific optimal viewing curve.

Measurements

Coronary Height

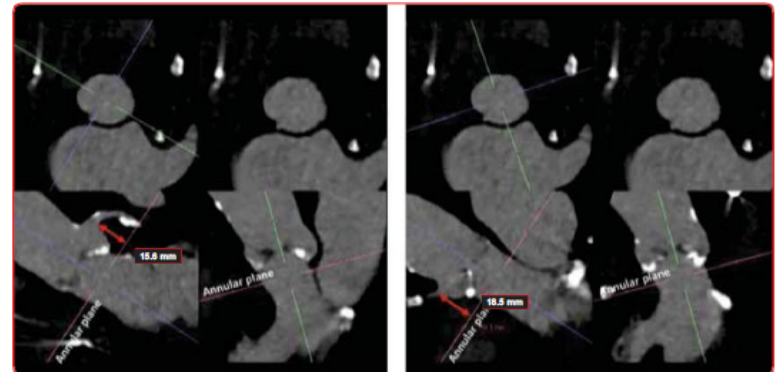


Figure 13 – Assessment of coronary artery height.

The distance from the annular plane to the coronary ostia is critical to identify patients with low coronary height. The prosthesis may displace the native leaflets and/or calcium thereby, possibly occluding the ostium.

Step 1:

Following the annular measurement and fluoroscopy angulation assessment do NOT change the angulation or level of the annular plane (transverse double-oblique image).

Step 3:

Measure the vertical height from the annular plane to the inferior aspect of the left coronary ostia, perpendicular to the annular plane, as shown in the image above (FIGURE 13).

Step 2:

By spinning the cross hairs on the transverse oblique view, adjust so that the coronal double-oblique view transects the left main ostium.

Step 4:

Repeat above steps for the right coronary ostia.

Sinus Height/Sinotubular Junction Height

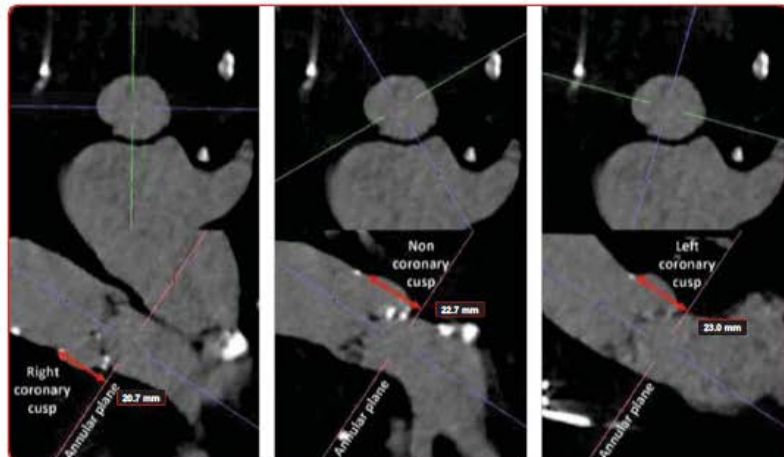


Figure 14 – Assessment of Sinus/STJ Height.

The STJ height is critical in a case of high implantation where the prosthesis may come into contact with the STJ.

Step 1:

Do NOT change the angulation or level of the annular plane (transverse double-oblique image).

Step 2:

By spinning the cross hairs on the transverse oblique view, adjust so that the coronal double-oblique view transects the center of the left coronary sinus.

Step 3:

Measure the vertical height from the annular plane to the STJ, perpendicular to the annular plane, as shown in the image above (FIGURE 14).

Step 4:

Repeat above steps for the right coronary sinus and noncoronary sinus.

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K1-23

Measurements

Left Ventricular Outflow Tract (LVOT)

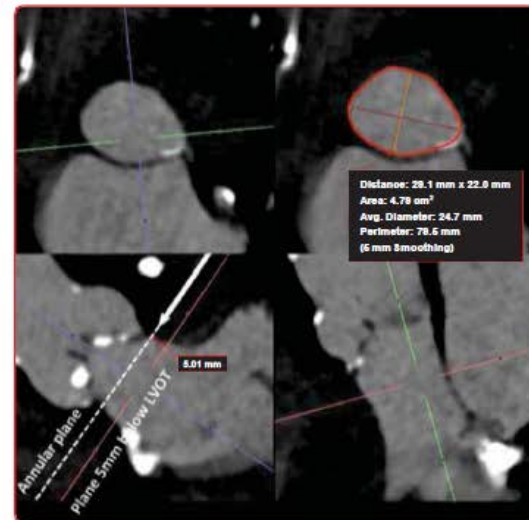


Figure 15 – Assessment of LVOT area 5 mm below annular plane.

It is important to assess the LVOT for the presence and distribution of calcium. LVOT planimetry informs about LVOT geometry and identifies patients with a septal bulge

Step 1:

Do NOT change the angulation or level of the annular plane (transverse double-oblique image)

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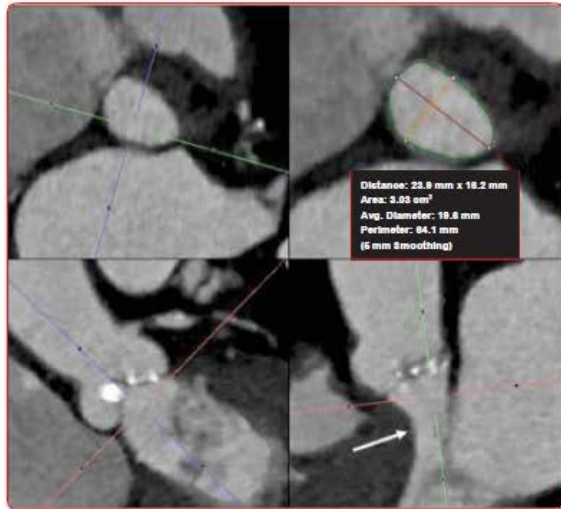


Figure 16 - Pronounced septal bulge (white arrow).

Step 2:

Change the level of the transverse double-oblique plane 4 to 6 mm into the LVOT without changing its orientation (FIGURE 15)

- Assess the LVOT area by means of planimetry or measure the maximum and minimum diameters
- The LVOT anatomy should be assessed for the presence of a septal bulge (FIGURE 16)

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K1-25

Measurements

Ascending Aorta Length

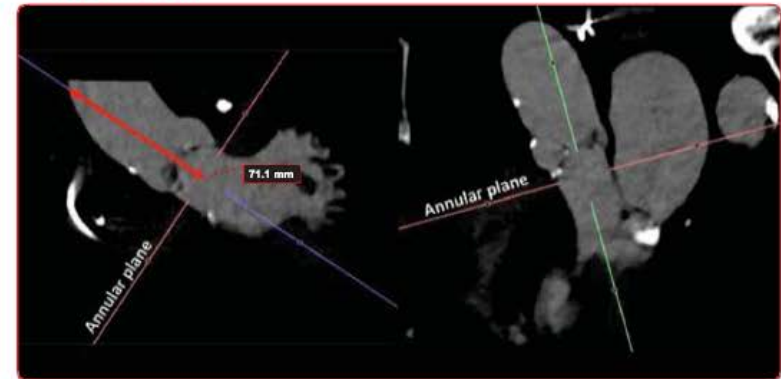


Figure 17 – Assessment of ascending aortic length.

This measurement is needed for evaluating the feasibility of transaortic access.

Step 1:

Do NOT change the angulation or level of the annular plane (transverse double-oblique image).

Step 2:

Measure the distance from the annular plane to the transection point of the cross hairs and the ascending aortic wall on either coronal oblique or sagittal oblique view (both views result in the same measurement) (FIGURE 16).

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K1-26

Sinus of Valsalva Width

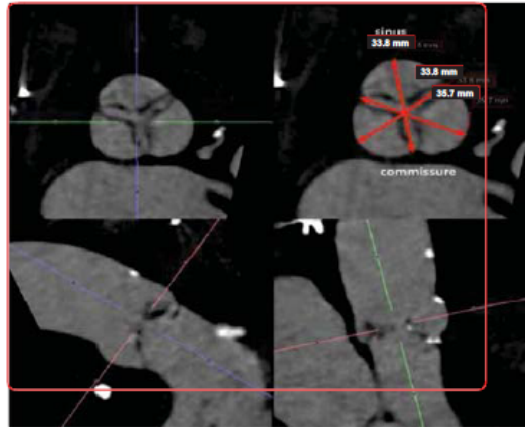


Figure 18 – Assessment of Sinus Valsalva dimensions.

The sinus width is important to assess for shallow, non-capacious sinuses. Non-capacious sinuses may predispose to coronary occlusion.

Step 1:

Change the level of the transverse double-oblique view (annular plane) towards the sinus of Valsalva, usually by scrolling until you reach the widest portion of the sinus of Valsalva.

Step 2:

Measure the distance from the left coronary sinus to the opposing commissure using a distance measurement tool (FIGURE 18)

Step 3:

Repeat for the right coronary sinus and the non-coronary sinus, always measuring to the opposing commissure.

Step 4:

Average all three values by adding them and dividing by three.

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K1-27

Measurements

Sinotubular Junction (STJ) Diameter

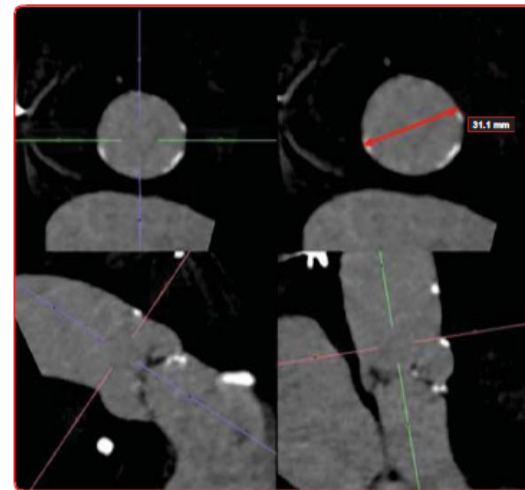


Figure 19 – Assessment of STJ dimensions.

The STJ diameter is critical in a case of high implantation where the prosthesis may come into contact with the STJ.

Step 1:

Change the level of the transverse double-oblique view towards the STJ; the angulation may have to be changed

Step 2:

Identify the STJ and measure the diameter using the distance measurement tool (FIGURE 19)

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K1-28

Ascending Aorta Diameter

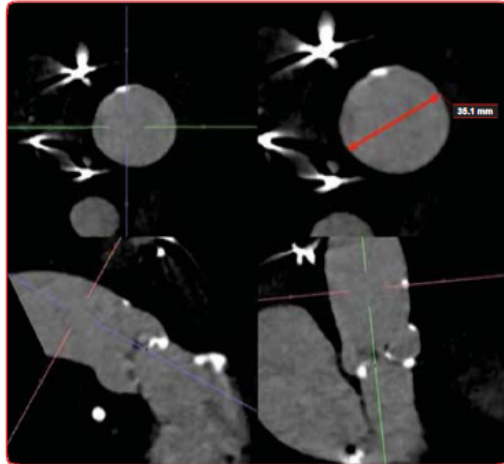


Figure 20 – Assessment of ascending aortic dimensions.

The ascending aorta diameter is important to evaluate for the presence of an ascending aortic aneurysm, in particular in the setting of transaortic approach.

Step 1:

Change the level of the transverse double-oblique view towards the ascending aorta. The angulation has to be changed so that the transverse double-oblique view transects the ascending aorta perpendicular to the long axis (usually resulting in a circular shape of the ascending aorta on the transverse view).

Step 2:

Measure the diameter using the distance measurement tool. The measurement should be performed approximately 4 cm above the annular plane (FIGURE 20).

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K1-29

Measurements

Analysis – Troubleshooting

Good image quality is characterized by sufficient contrast attenuation and images free of artifacts, allowing for proper visualization of the aortic root structures and in particular the aortic annulus, ideally at systole. Artifacts include, but are not limited to, the following:

- Incorrect plane – wrong orientation
- Incorrect plane – wrong angulation and too low
- Incorrect plane – too high
- Misalignment artifact
- Double contours and blurring
- Poor contrast enhancement and image noise
- Breathing artifacts

Importantly, critical measurements such as annular measurements should be documented by means of screen shots (so-called secondary captures) which are ideally archived in, for example in the PACS (Picture Archiving and Communication System).

Screenshots should not only include the view in which the measurement was taken, but also the adjunct views such as the coronal and sagittal double-oblique view in case of an annular measurement on the transverse double-oblique view. These comprehensive screen shots provide valuable information:

- Positioning of the measurement plane
- Overall image quality
- Artifacts, which may be subtle or obscured on the measurement plane but more evident on others

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K1-30

Troubleshooting

Correct Orientation of the Annular Plane

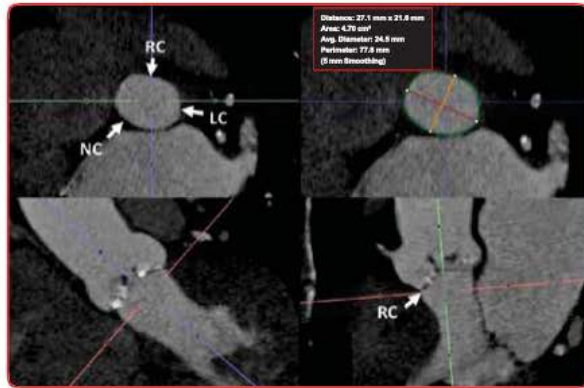


Figure 23 – Appropriate annular plane segmentation and planimetry.

As discussed earlier, the annular plane transects through the most basal hinge points of all three cusps. Commonly, the center of the cross hairs remains in the center of the annular lumen when obtaining the screenshot (FIGURE 23).

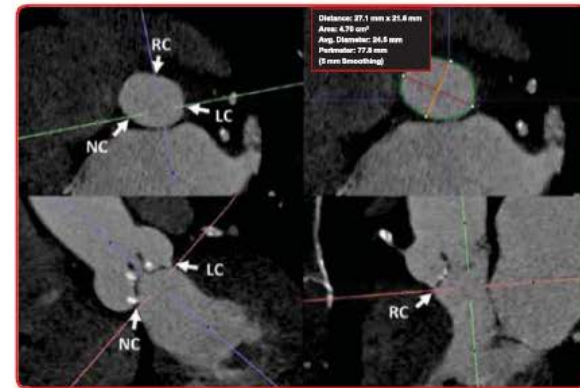


Figure 24 – Appropriate annular plane segmentation and planimetry with cross hairs oriented to show all three hinge points. RC, right coronary cusp; LC, left coronary cusp; NC, non-coronary cusp. Same patient as Figure 23.

The red lines in the oblique coronal and sagittal images indicate the location of the double-oblique transverse image. As the cross hairs actually transect the annular contour four times at 90° intervals, not all of the three hinge points are depicted on the coronal and sagittal oblique views at the same time if the cross hairs remain centered in the annular lumen.

Alternatively, the cross hairs can be oriented to transect all three basal hinge points by eccentric orientation of the cross hair center (FIGURE 24).

Incorrect Plane – Wrong Orientation

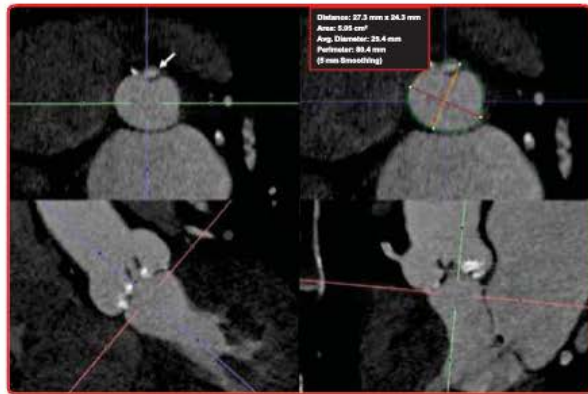


Figure 25 – Incorrect plane due to wrong orientation. The plane cuts through the right coronary sinus.

- Incorrect orientation of the annular plane is a common cause of erroneous annular measurements. Frequently, the annular plane transects the basal portion of one sinus as opposed to the most basal hinge point while the two other most basal hinge points are correctly identified.
- In FIGURE 25 the red lines in the oblique coronal and sagittal images indicate the location of the double-oblique axial image.
- Portions of the right coronary cusp can be visualized (white arrow) in the double-oblique transverse view.
- Incorrect angulation commonly results into too large planimetric measurements.

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K1-33

Incorrect Plane – Wrong Angulation and Too Low

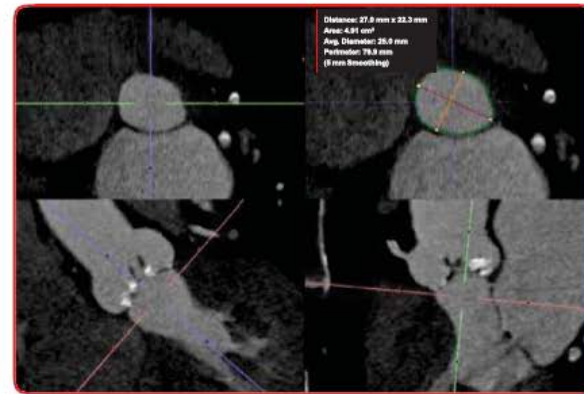


Figure 26 – Wrong angulation and too low. Same angulation as in Figure 24.

- In the setting of wrong angulation (FIGURE 25), a transverse image without sinus tissue can be generated by relocating the level of the transverse double-oblique plane towards the LVOT (FIGURE 26). Although the contour on the transverse double-oblique view appears harmonic, it does not resemble the annular plane. As a consequence, planimetric assessment commonly results in too large measurements.

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K1-34

Incorrect Plane – Too High

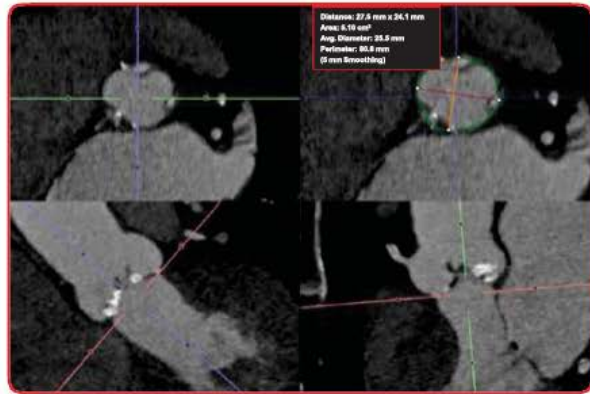


Figure 27 – Transverse plane located above the proper annular plane.

- Red lines in the oblique coronal and sagittal images demonstrate the location of the double-oblique axial image. In the double-oblique axial image, all three coronary cusps are visualized, clearly demonstrating that the plane is too high. This commonly results in overestimation of the annular area. (FIGURE 27)

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K1-35

Misalignment Artifact

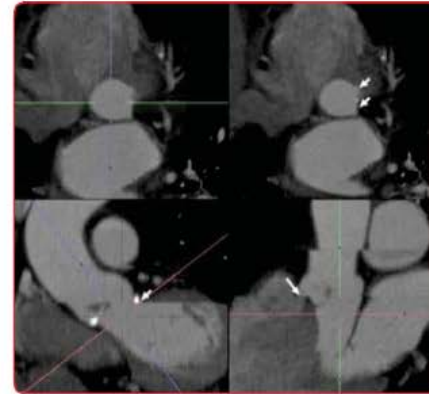


Figure 28 – Misalignment artifacts (white arrows) truncating the annular contour.

- Irregular heart rhythms such as atrial fibrillation or premature contractions may result in misalignment artifacts due to the variable length of the RR intervals
- Severe misalignment artifact at the annular level (white arrows FIGURE 28) precludes accurate annular assessment
- If the image was acquired using retrospective ECG gating, ECG editing at the CT scanner console can be useful to reduce the artifact burden

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K1-36

Double Contours and Blurring



Figure 29 – Double contours (white arrows) impairing proper annular assessment.

- Cardiac motion and pulsation in addition to irregular heart rhythms such as atrial fibrillation or premature contractions may result in double contours and blurring of the annular contour (white arrows FIGURE 29)
- Severe artifacts preclude accurate annular assessment

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K1-37

Poor Contrast Enhancement and Image Noise

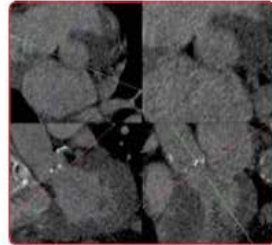


Figure 30 – Poor opacification and increased image noise render this data set uninterpretable.

Breathing Artifacts

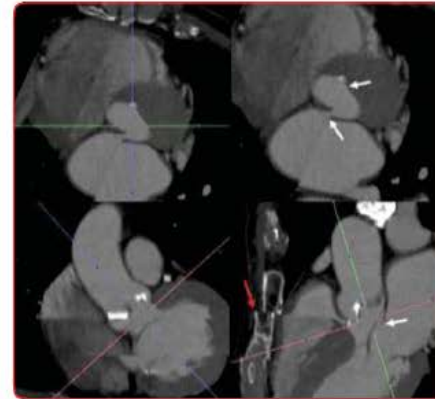


Figure 31 – Breathing artifact at the level of the aortic root (white arrow) and evident as a stair-step also involving the sternum (red arrow).

- Breathing artifacts at the annular level can cause artifacts with a similar appearance as misalignment artifacts (white arrows FIGURE 31)
- Breathing artifacts always involve the chest wall, commonly appreciated as a stair-step along the body surface or sternum (red arrow FIGURE 31)
- They usually preclude accurate annular assessment

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K1-38

Transfemoral Access Analysis

The aorta and iliofemoral vasculature should be evaluated using the acquired CTA data. The aorta can usually be evaluated using axial images and does not necessarily require advanced segmentation. The iliofemoral vasculature should be evaluated using a combination of axial images as well as various post-processing techniques.

Aorta

The thoracic and abdominal aorta should be assessed for the presence of the following:

- Tortuosity/aneurysm, and in particular partially thrombosed aneurysms
- Non-calcified, exophytic plaque (FIGURE 32)

Ilio-femoral Vasculature

The iliofemoral arteries should be assessed for the following:

- Vessel diameters
- Vascular calcification
- Tortuosity
- Dissections

A comprehensive analysis includes the following:

- Review of the vasculature on axial images
- Curved planar reformats (CPRs)
- Volume rendered technique (VRTs)



Figure 32 – Coronal view demonstrating atherosclerotic changes in the aortic arch, including non-calcified plaque (white arrow).

Transfemoral

Vascular Dimensions

Vascular dimensions should be assessed perpendicular to the long axis of the vessel. On true axial images, only the common femoral arteries are oriented in a perpendicular fashion to the imaging plane. Instead of performing measurements on multiple angulated MPRs, most post-processing platforms allow for semi-automated or automated creation of center lines along the iliofemoral vasculature. The centerlines are then used to create multiple views oriented in a radial fashion in regard to these centerlines.

The required vessel diameters depend on the intended device to be used. Please refer to device-specific IFUs.

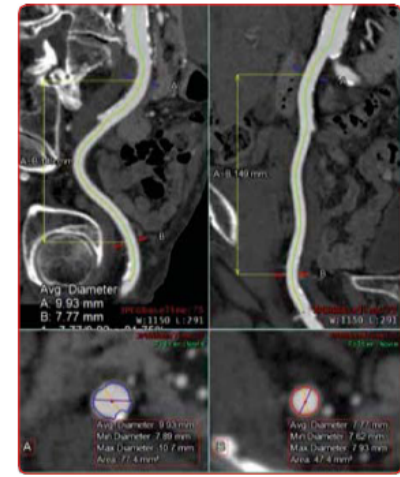


Figure 33 – CPRs (two top images) of the right iliofemoral vasculature with short axis views at the level of the common iliac artery and common femoral artery.

Vascular Calcification

Vascular calcification can be assessed on axial views, CPRs with short axis views, and VRTs. Calcifications can in general be described and graded with increasing severity using the following terms:

- Spotty
- Confluent
- Horse-shoe and circumferential

In particular horse-shoe and circumferential calcifications are of relevance if vessel dimensions are borderline.

The location and degree of calcifications at the level of the puncture site of the common femoral artery should be assessed. Anteriorly located calcification may interfere with suture systems commonly used for a totally percutaneous, transfemoral approach.



Figure 34 – Nearly circumferential calcification



Figure 35 – Axial image at the level of the common femoral arteries (white arrows). Calcifications are located posteriorly on the right and anteriorly on the left.

Transfemoral



Figure 36 – Volume rendered image in AP (middle), LAO (right) and RAO (left) projection for assessment of iliofemoral tortuosity.

Tortuosity

Vascular tortuosity can be best assessed on VRTs given the three-dimensional nature of this technique. Quantification of tortuosity is not standardized. For documentation, AP and oblique views of the iliac vasculature should be obtained.

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2. Submitting CT Images

- 2.1. All images should be uploaded to the image transfer portal (Moving Pictures) at the time of the visit window. Before submitting the CT, ensure the study contains complete systolic and diastolic volume sets and that the Subject ID is available.
- 2.2. The sponsor has provided access to an Electronic Data Transmittal Form (see example 2.4-1) on the Moving Pictures website <https://mddximage.com>. This form should be filled out completely and accurately by the study coordinator in order to avoid queries.
- 2.3. If there are questions about completing the Electronic Echo Data Transmittal form, refer to the Moving Pictures "Quick Start Guide", or contact a support team member for assistance (support contact information on Moving Pictures website: <https://mddximage.com>).
- 2.4. CT images requiring independent review should be uploaded 72 hours prior to the case being presented.

CT Data Transmittal Form Example 2-1

The screenshot shows a web-based form titled "De-Identify and Upload". It contains several sections:

- STEP 1:** Fields for "Case ID", "Subject ID", "Date of Imaging" (18 Aug 2015), "Reason for upload" (New Case), "Language of CT Tech Name" (Latin), "Value Size" (2000), "Scan Protocol at Time of Scan (Shortname)", "Scan Protocol at Time of Scan (Shortname)", "Weight (cm)", "Weight (kg)", and "Comments" (Test Case).
- STEP 2: SELECT WHAT:** A table with columns for "Electronic Transmittal", "Echocardiography", "Echocardiography 90 Day (see study for Echocardiography 90 Day)", and "30 Day". Each column has a "Not Updated" button.
- Time Points:** A grid of buttons for "4 Month", "1 Year", "3 Year", "5 Year", "7 Year", "9 Year", and "Unbooked". Each button has a "Not Updated" label.
- Image:** A small thumbnail of a CT scan image showing a cross-section of the heart.

Bibliography

3. System-Specific CT Acquisition and Reconstruction Techniques

CT Acquisition and Reconstruction Techniques for Transcatheter Aortic Valve Procedure Planning Utilizing GE Healthcare CT Scanners

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INTRODUCTION

Transcatheter aortic valve procedures have proven to be an effective alternative in the treatment of aortic stenosis in high-risk and inoperable patients. Contrast-enhanced computed tomography (CT) has become an integral part of transcatheter aortic valve procedure planning by allowing for anatomical assessment of the aortic root and the aorto-iliofemoral vasculature within a single examination. It is critical that artifact free image data is obtained to allow for reliable anatomical measurements. Data acquisition strategies and scanning protocols may vary depending on scanner manufacturer, system, and institutional preferences. This document provides some recommendations for reliable CT image acquisition for transcatheter aortic valve procedures.

This paper is presented as a service to medical personnel by Edwards Lifesciences and GE Healthcare. The information in this white paper has been compiled from available literature. Although every effort has been made to report faithfully the information, the editors and publisher cannot be held responsible for the correctness. This paper is not intended to be, and should not be construed as, medical advice. For any use, the product information guides, inserts, and operation manuals of the various drugs and devices should be consulted. Edwards Lifesciences and the editors disclaim any liability arising directly or indirectly from the use of drugs, devices, techniques, or procedures described in this paper.

WARNING: Any reference to x-ray exposure, intravenous contrast dosage, and other medication is intended as a reference guideline only. The guidelines in this document do not substitute for the judgment of a healthcare provider. Each scan requires medical judgment by the healthcare provider about exposing the patient to ionizing radiation. Use the As Low As Reasonably Achievable (ALARA) radiation dose principle to balance factors such as the patient's condition, size and age; region to be imaged; and diagnostic task.

NOTE: Algorithms/protocols included in this paper are for educational reference only. Edwards does not endorse or support any one specific algorithm/protocol. It is up to each individual clinician and institution to select the treatment that is most appropriate.

Philipp Blanke, MD is a paid consultant to Edwards Lifesciences.

WORK-FLOW RATIONALE

The key component of all approaches is an ECG-assisted data acquisition which covers at least the aortic root, while the remainder of the data acquisition may be performed without ECG-assistance. If employed properly, ECG-assistance allows for artifact-free depiction of the aortic root. The sequence of patient preparation and the relevant principles of CT data acquisition will be explained in brief below.

PATIENT PREPARATION

- Positioning of the patient on the scanner table, typically supine, should closely resemble positioning on the cath lab table.
 - This is important for the prediction of c-arm angulation from the CT dataset.
 - Placement of ECG-electrodes and IV access should follow institutional policies.
- Patient instruction on breath-holding prior to scanning may improve compliance with the breath-holding instructions during the scan.
 - Due to the advanced age and frailty of this patient population, additional time may be needed for patient instruction.

Providing time for the patient to practice the breath hold prior to scan acquisition may drastically improve patient compliance and thereby scan quality.

CT SCAN - SCAN LENGTH AND SCAN STRATEGY

In general, there are two different approaches on how to combine the ECG-assisted data acquisition of the aortic root structures and the non-ECG assisted computed tomography angiography (CTA) of the aorta-iliofemoral vasculature for evaluation of the transfemoral access route:

- 1) ECG-assisted data acquisition of the heart and aortic root followed by a non-ECG assisted CTA of the thorax, abdomen and pelvis. Although this approach results in repeat data acquisition of the aortic root and cardiac structures, the time-intensive ECG-assisted data acquisition (in particular when using retrospective ECG-gating) is kept to a minimum which aids in limiting the contrast dose. Furthermore, limiting the ECG-assisted data acquisition also limits the radiation dose intensive component of the examination; although the cardiac scan range is covered twice.

The proposed protocols for all GE scanner Families use this approach. In 40mm detector coverage systems, cardiac data acquisition is performed with retrospective ECG-gating. With the Revolution CT system, with 160mm detector coverage, a one beat, gated whole heart volume scan is performed.

- 2) ECG-gated data acquisition of the thorax followed by a non-ECG gated CTA of the abdomen and pelvis. The disadvantage of this approach, when using 40 mm detector systems, is the relatively long acquisition time required for the entire thorax (depending on scanner model this will vary but in some cases it may exceed 15 seconds, in particular when using retrospective ECG-gating), which increases the risk of breathing artifacts at the level of the cardiac structures.

GE REVOLUTION™ CT

1. Scout		
General <ul style="list-style-type: none"> • Lateral and AP scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> • Start: Superior 60 • End: Inferior 800 • Tube current 10 mA • Tube voltage: 120 kV • ECG trace: On • Scout Plane: 90 and 0 degrees • Auto Voice (Breath hold command): Inspiration 	Comment Take note of the iso-center indicator line on the first scout to ensure that the patient is positioned within 2 cm of isocenter to allow for best image quality. Adjust table height to indicated iso-center location if more than 2 cm off before acquiring the 2 nd scout.
2. ECG-gated axial data acquisition of the aortic root/heart (Group 1) followed by non-gated CTA of the thorax, abdomen, and pelvis (Group 2).		
Smart Prep		
General <ul style="list-style-type: none"> • Bolus tracking to automatically trigger the diagnostic scan acquisition based on the HU reading in the ROI reaching the prescribed enhancement threshold • Slice location: approx 2 cm below the carina • ROI location: Ascending aorta 	Data acquisition <ul style="list-style-type: none"> • Monitoring Delay: 12 sec • Monitoring Inter Scan Delay: 1 sec • Tube voltage: 120 kV • Tube current: 100 mA • Diagnostic Delay: Auto Minimum • Enhancement Threshold: 200 HU 	Comment The effective ("diagnostic") delay between reaching the threshold and the start of the subsequent data acquisition (Group 1) is the combined time comprising the length of the breath hold command (auto voice), the time needed for table movement and the subsequent pre-scan delay (pre-set delay time in Group 1)
Group 1 scan parameters - ECG-gated axial data acquisition of the aortic root/heart		
General <ul style="list-style-type: none"> • ECG-gated axial data acquisition of the aortic root and heart • Scan range beginning 2 cm below the carina to the base of the heart • Dose modulation is not recommended to ensure optimal image quality throughout the entire cardiac cycle • Smart mA automatically sets the tube current to achieve the targeted Noise Index within the range defined by the min and max values 	Data acquisition <ul style="list-style-type: none"> • Auto voice (Breath hold command): On (#1 – Suspension) • Pre-set Delay Time: 2 seconds (Together with the auto voice command and table movement, this results in a diagnostic delay of 4-5sec) • Scan Type: Cardiac • Rotation Speed: 0.28 seconds • SFOV: Cardiac Large • DFOV: 25 cm • Slice thickness: 0.625 mm • Collimation: 160 mm (Smart Collimation will automatically select the appropriate collimation for the planned scan range) • Tube voltage: 120 kV • Tube current: Smart mA: Min: 50 mA Max: 600 mA 	Data reconstruction <ul style="list-style-type: none"> • Axial multiphase reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm • Slice Thickness: 0.625 mm • Increment: 0.625 mm • Iterative Reconstruction ASiR-V: 50% • Recon: Std • Use ECG editing if necessary

REVOLUTION CT (CONT)

<ul style="list-style-type: none"> Repeat acquisition is an additional option which can be used when covering the gated acquisition within a single volume. It may be useful in patients with atrial fibrillation, frequent premature contractions or extremely variable heart rates. See section on ECG Editing to learn how to select the desired heart beat for reconstruction. 	<ul style="list-style-type: none"> Noise Index: 30 Widen for SSF: On Auto Gating: Off (Dose modulation is not recommended, alternatively ensure max mA during systole) Targeted Phase reconstruction: 5-95% HR Variation Allowance: 4 bpm 	
Group 2 scan parameters - non-gated CTA of the thorax, abdomen, and pelvis		
<p>General</p> <ul style="list-style-type: none"> Helical, non-gated acquisition Scan range: lung apices to the lesser trochanters of the femoral bone The Prep/Group Delay is needed to allow for the contrast opacified blood to reach the iliofemoral arteries 	<p>Data acquisition</p> <ul style="list-style-type: none"> Prep/Group Delay 10.0s Auto voice (Breath hold command): On (#1 - Suspension) Scan type: Helical SFOV: Large Body Detector coverage: 80 mm Pitch: 0.992 Table Speed: 158.75 mm/sec Rotation Speed: 0.5 seconds Slice Thickness: 0.625 mm Tube voltage: <ul style="list-style-type: none"> 80 kV for BMI <23 kg/m² 100 kV for BMI 23 - 27 kg/m² 120 kV for BMI >27 kg/m² Tube current: Smart mA: <ul style="list-style-type: none"> Min: 10 mA Max: 530 mA Noise Index: 18 Scan direction: cranio-caudal 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Slice Thickness: 0.625 mm Increment: 0.625 mm Iterative Reconstruction ASiR-V: 50% Recon: Std

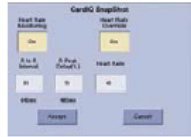
REVOLUTION CT (CONT)

Contrast application protocol	
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the ECG-gated axial CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Triphasic administration protocol with pure contrast, followed by a contrast/saline mixture, followed by a saline chaser Placement of IV access per hospital protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> For normal weighted patients and an iodinated contrast agent with 300 mg/ml apply 30 ml contrast at 3.5 ml/sec, followed by 60 ml of 70% contrast/30% saline at 3.5 ml/sec, followed by 30 ml saline at 3.5 ml/sec; this results in a total amount of 72 ml total contrast agent (adjust for contrast agents with differing iodine concentrations) For large patients and an iodinated contrast agent with 300 mg/ml apply 40 ml contrast at 4.0 ml/sec, followed by 80 ml of 70% contrast/30% saline at 4.0 ml/sec, followed by 30 ml saline at 4.0 ml/sec; this results in a total amount of 96 ml total contrast agent (adjust for contrast agents with differing iodine concentrations) Please move this bullet to bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the ascending aorta with a region of interest placed within the ascending aorta; threshold set at 200 HU.

REVOLUTION DISCOVERY CT (REVOLUTION HD, REVOLUTION GSI), DISCOVERY CT750 HD, DISCOVERY CT, OPTIMA CT660, REVOLUTION EVO AND LIGHTSPEED VCT SCANNER PLATFORMS:

1. Scout		
General <ul style="list-style-type: none"> Lateral and AP scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> Start: Superior 60 End: Inferior 800 mA: 10 mA ECG trace: On Scout Plane: 90 and 0 degrees Auto Voice (Breath hold command): Inspiration 	
2. Retrospectively ECG-gated data acquisition of the aortic root/heart (Group 1) followed by non-gated CTA of the thorax, abdomen, and pelvis (Group 2).		
Smart Prep		
General <ul style="list-style-type: none"> Bolus tracking to automatically trigger the diagnostic scan acquisition based on the HU reading in the ROI reaching the prescribed enhancement threshold. Slice location: approximately 2 cm below the carina ROI location: Ascending aorta 	Data acquisition <ul style="list-style-type: none"> Monitoring Delay: 7 sec Tube current: 60 mA Tube voltage: system sets it to be same as Group 1 Slice/Collimation: 5 mm ISD: 1.4 Diagnostic Delay: Auto Minimum Pre-set delay time: 3 seconds (this results in a 'diagnostic delay' of approximately 5-6sec, if rotation time is kept identical between both groups, i.e. 0.4sec) Enhancement Threshold: 150 HU 	Comment <p>The effective ('diagnostic') delay between reaching the threshold and the start of the subsequent data acquisition (Group 1) is the combined time comprising the length of the breath hold command, (auto voice), the time needed for table movement and the subsequent pre-scan delay.</p>

REVOLUTION DISCOVERY CT (REVOLUTION HD, REVOLUTION GSI), DISCOVERY CT750 HD, DISCOVERY CT, OPTIMA CT660, REVOLUTION EVO AND LIGHTSPEED VCT SCANNER PLATFORMS: (CONT)

Group 1 scan parameters - Retrospectively ECG-gated data acquisition of the aortic root/heart		
General <ul style="list-style-type: none"> ECG-gated data acquisition of the aortic root and heart Scan range: beginning 2 cm below the carina to the base of the heart Irregular heart rates (HRs) are frequent within the TAVR population. Using the HR override capability with manually setting the HR to a lower value yields a lower pitch value which results in redundant CT data acquisition and thus provides the greatest fill in image reconstruction (e.g. utilization of SnapShot Segment, SnapShot Burst or SnapShot Burst Plus) 	Data acquisition <ul style="list-style-type: none"> Scan Mode: Cardiac Helical Scan Parameter: <ul style="list-style-type: none"> < 80 bpm: SnapShot Segment > 80 bpm: SnapShot Burst DFOV: 25 cm HR Override: On (manually enter min HR present on the ECG trace) Rotation speed: <ul style="list-style-type: none"> HR < 80 bpm: 0.40 seconds HR > 80 bpm: 0.35 seconds Tube voltage: <ul style="list-style-type: none"> 120 kVp for BMI > 25 kg/m² 100 kVp for BMI < 25 kg/m² Tube current (manual): 450/600/700 mA for small, average and large patients ECG Dose modulation is not recommended, alternatively ensure maximum mA in systole (e.g. 25 to 45%, R-peak delay 35%) TargetPhase reconstruction: 5-95% Slice/Collimation: 0.625mm Scan direction: cranio-caudal Pitch: Autopitch (determined by HR) Auto voice (Breath hold command): Inspiration only 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Slice Thickness: 0.625 mm Increment: 0.62 mm Recon: Std Iterative reconstruction: ASiR (if available) 50%
		
<ul style="list-style-type: none"> Keeping as many parameters the same in Group 1 and Group 2 will result in a faster transition between the gated and non-gated groups In particular the rotation time needs to be consistent. The non-gated Group 2 is limited to a rotation speed of 0.40 seconds. Thus for heart rates < 80 bpm, both groups should employ 0.40 seconds. For heart rates > 80 bpm, a rotation speed of 0.35 seconds should be used, however this leads to a longer transition time 		

Group 2 scan parameter – non-gated CTA of the thorax, abdomen, and pelvis		
<p>General</p> <ul style="list-style-type: none"> Scan range: Lung apices/upper thoracic inlet to the proximal femoral (lesser trochanter) Max mA values will vary between scanner models 	<p>Data acquisition</p> <ul style="list-style-type: none"> Scan type: Helical Pitch: 0.984 Table Speed: 39.76 mm Rotation Speed: 0.4 seconds Slice Thickness: 1.25 mm Collimation: 40 mm Tube Voltage: <ul style="list-style-type: none"> 100 kV for BMI < 25 kg/m² 120 kV for BMI > 25 kg/m², Tube current: Smart mA <ul style="list-style-type: none"> Min: 10 mA Max: 700 mA (may vary among scanner systems) Noise Index: 18.4 Scan direction: cranio-caudal No additional automated breath hold command (no AutoVoice); alternatively manually instruct patient to slowly exhale 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Slice Thickness: 1.25 mm Increment: 0.8 mm Recon: Std Iterative reconstruction: ASiR (if available) 50%

Contrast application protocol	
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per hospital protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Recommended contrast media application: 90 cc iodinated contrast medium at 3.5 to 4 cc/sec (300mg/ml iodine contrast agent) Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the ascending aorta with a region of interest placed within the ascending aorta; threshold set at 150 HU.

LOW CONTRAST DOSE PROTOCOL FOR 64 SLICE FAMILY OF SCANNERS –

Options for consideration to optimize scan parameters when contrast volumes need to be minimized.

- Same scanner settings as listed above, except reduce threshold setting for bolus tracking (e.g. 80 HU)
- Reduce scan length of the retrospectively ECG-gated CTA to a minimum to cover only the aortic root as opposed to the entire heart, as this is the time-expensive part in regard to data acquisition
- Reduce total amount of contrast to 50-60 cc
- Injection rate should be lowered, but should at least be 3.5 cc/sec
- Threshold to trigger initiation of the retrospective ECG-gated spiral data acquisition can be lowered to 80 HU
- Use a lower kV such as 80 kV in thin patients
- These alterations should allow for a sufficiently contrast enhanced CT dataset of the aortic root. Contrast attenuation of the iliofemoral acquisition may be variable. Lowering kVp may help to maintain adequate opacification of the peripheral vessels

RECONSTRUCTION OF MULTIPHASIC DATA SET

Multiphase data should be reconstructed to enable evaluation of the aortic valve and aortic root throughout the entire cardiac cycle (e.g. in 10% intervals throughout the cardiac cycle). Although aortic root measurements are recommended in systole multiphase data sets allow for interrogation of other phases if systolic phases have degraded image quality (e.g. motion artifacts). Multiphase reconstruction: From the Prescription (Rx) screen, select the prescription type from the menu. Enter the Start phase/msec, End phase/msec, and Interval to reconstruct.



ABSOLUTE RECONSTRUCTIONS

Millisecond prescription for data reconstruction, i.e. reconstruction windows in fixed msec distances from the R-peak, may improve image quality in patients with irregular heart rates. An end-systolic target millisecond reconstruction range is +250 to +300 milliseconds at 25 msec intervals. Hovering the mouse on the ECG trace will indicate phase % and +/- millisecond location.

REVIEW OF DATA RECONSTRUCTION AND ECG-EDITING

- Image reconstructions of the aortic root and heart should be reviewed immediately after the scan when the raw data is still available
- The ECG-gating should be reviewed to ensure that the automated algorithms correctly identifies the R-peaks

ECG EDITING ON **REVOLUTION CT**

It may be helpful to insert, remove, or move a trigger to normalize a heart cycle when a trigger occurs at an incorrect location. This may occur when abnormal ECG waveform patterns or excessive background noise are present during scan acquisition.

- Open the ECG-gated scan series in the Reconstruction and Image Processing area on the image monitor
- To [insert] a trigger, place the cursor at the intended position on the ECG trace (right-click to "Insert R-peak Trigger"). An additional trigger will display on the ECG trace
- To [delete] a trigger point on the ECG trace, place the cursor on the trigger and right-click "Delete R-peak Trigger".
- To [move] a trigger, place the cursor over the trigger and click and drag it to the new location
- To switch to a second heart beat when repeat acquisition is used, place the cursor in the ECG Editor, right-click and select "Switch Scan". The reconstruction window toggles to the other scan

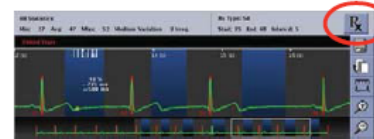


ECG EDITING ON **REVOLUTION DISCOVERY CT** (REVOLUTION HD, REVOLUTION GSI), DISCOVERY CT750 HD, DISCOVERY CT, OPTIMA CT660, REVOLUTION EVO AND LIGHTSPEED VCT SCANNER PLATFORMS:

Cardiac Helical exams allow for image reconstruction at any point in the RR-interval as image data was acquired throughout the entire cardiac cycle using retrospective ECG-gating. The ECG editor provides the ability to move or reposition the reconstruction window.

In the ECG Editor click the "Rx" icon for the global phase prescription method, i.e. the entered phase values are applied to all available heart cycles.

Global phase prescription allows selecting the phases of the cardiac cycle from which images are created. The blue highlighted areas represent the recon windows for each available RR-interval. The example below displays a reconstruction window ranging from 35 to 60% of the RR-interval. Gray areas represent x-ray exposure/available image data within the exam.



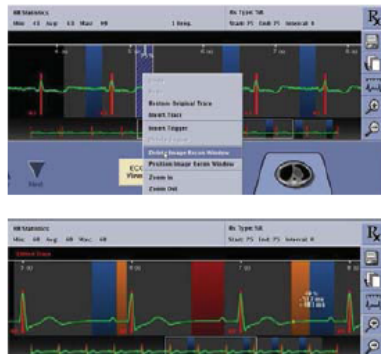
ECG-editing: If R-peaks of the ECG trace were not correctly identified by the trigger points, the trigger points need to be corrected along the ECG trace: Insert, remove, or move a trigger to normalize a heart cycle when a trigger occurs at an undesirable location.



- To [insert] a trigger, place the cursor at the intended location along the ECG trace (right-click "Insert Trigger"). An additional trigger point (red line) appears on the ECG trace
- Following insertion of a trigger point, a recon window needs to be added (right-click "Add Recon Window"). Confirm that the recon window is in the desired location before confirming image reconstruction
- To [delete] a trigger point on the ECG trace, place the cursor on the trigger (red line), right-click "Delete Trigger"
- To [move] a trigger, place the cursor over the trigger and click and drag it to the desired location

Deleting a trigger affects the position of reconstruction windows in adjacent RR-intervals, when relative reconstructions (%) are employed. In contrast "Delete Image Recon Window" retains the trigger point while image data following the selected trigger point does not contribute to image reconstruction, thus not affecting adjacent RR-intervals. This approach may be employed to improve image quality, e.g. in cases of premature contractions or atrial fi with extremely variable heart rates.

- Place the cursor in the blue image reconstruction window in the ECG editor, right click "Delete Image Recon Window"



- An orange (relaxed phase) or red (ungated) area appears on the trace if reconstruction window removal results in insufficient z-axis overlap to create gated images in order to compensate for the removed recon window. Relaxed phase reconstruction windows indicate where relaxed phase reconstruction images will be created. The images are reconstructed as close to the requested phase as possible, with a maximum of a 20% phase offset

In contrast to the global phase prescription across all RR-intervals, reconstruction windows can also be moved manually. Manually move or adjust recon window of one or more heart cycles, e.g. in setting of varying heart rates. Always review the images created from the edit ECG Trace process. Editing the trace changes the reconstruction using the original scan data.

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CT Acquisition and Reconstruction Techniques for Transcatheter Aortic Valve Procedure Planning Utilizing Philips Hardware

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PARTNER 3
December 2015, Version 1.0

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NOTE: Algorithms/protocols included in this paper are for educational reference only. Edwards does not endorse or support any one specific algorithm/protocol. It is up to each individual clinician and institution to select the treatment that is most appropriate.

Philipp Blanke, MD is a paid consultant to Edwards Lifesciences.

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K1-62

INTRODUCTION

Transcatheter aortic valve procedures have proven to be an effective alternative in the treatment of aortic stenosis in high-risk and inoperable patients. Contrast-enhanced computed tomography (CT) has become an integral part of transcatheter aortic valve procedure planning by allowing for anatomical assessment of the aortic root and the aorto-iliofemoral vasculature within a single examination. It is critical that artifact free image data is obtained to allow for reliable anatomical measurements. Data acquisition strategies and scanning protocols may vary depending on scanner manufacturer, system, and institutional preferences. This document provides some recommendations for reliable CT image acquisition for transcatheter aortic valve procedures.

WORK-FLOW RATIONALE

The key component of all approaches is an ECG-assisted data acquisition which covers at least the aortic root, while the remainder of the data acquisition may be performed without ECG assistance. If employed properly, ECG assistance allows for artifact-free depiction of the aortic root. The sequence of patient preparation and the relevant principles of CT data acquisition will be explained in brief below.

PATIENT PREPARATION

- Positioning of the patient on the scanner table, typically supine, should closely resemble positioning on the cath lab table.
 - This is important for the prediction of c-arm angulation from the CT dataset.
 - Placement of ECG-electrodes and IV access should follow institutional policies.
- Patient instruction on breath-holding prior to scanning may improve compliance with the breath-holding instructions during the scan.
 - Due to the advanced age and frailty of this patient population, additional time may be needed for patient instruction.

Providing time for the patient to practice the breath hold prior to scan acquisition may drastically improve patient compliance and thereby scan quality.

CT SCAN - SCAN LENGTH AND SCAN STRATEGY

In general, there are two different approaches on how to combine the ECG-assisted data acquisition of the aortic root structures and the non-ECG assisted computed tomography angiography (CTA) of the aorto/iliofemoral vasculature for evaluation of the transfemoral access route:

- 1) Cardiac ECG-assisted data acquisition of the heart and aortic root (usually beginning 2cm below the carina) followed by a non-ECG assisted CTA of the thorax, abdomen and pelvis. Although this approach results in repeat data acquisition of the aortic root and cardiac structures, the time-intensive ECG-assisted data acquisition is kept to a minimum which aids in limiting the contrast dose. Furthermore, limiting the ECG-assisted data acquisition also limits the radiation dose intensive component of the examination; although the cardiac scan range is covered twice. *The proposed protocols below all use this approach.*
- 2) ECG-assisted data acquisition of the thorax followed by a non-ECG assisted CTA of the abdomen and pelvis. The disadvantage of this approach is the relatively long acquisition time required for the entire thorax (may exceed 15 seconds), which increases the risk of breathing artifacts at the level of the cardiac structures.

NOTE: *The following protocols are fully editable by the user (in particular tube current and tube voltage settings may be changed). Customized protocols can be saved as alternate protocols.*

PHILIPS BRILLIANCE iCT, INGENUITY, IQon, BRILLIANCE 64

1. Surview (Topogram/Scout)		
General <ul style="list-style-type: none"> AP topogram/scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Length: 750 mm Tube voltage: 120 kV Tube current: 30 mA Field of View: 500 mm 	
2. Non-enhanced scan (optional)		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode: Prospective ECG-gating, axial Pulsing window: 75% of RR-interval Tube voltage: 120 kV Tube current: 55 mAs Anatomical dose modulation: No Slice/Collimation: AUTO Scan direction cranio-caudal Rotation time: 0.4 sec 	Data reconstruction <ul style="list-style-type: none"> Axial reconstruction within the pulsing window: 75% phase Field of View limited to the heart: 220 mm Slice thickness (thin): 2.5 mm Increment (thin): 2.5 mm Filter: CB
3. Locator		
General <ul style="list-style-type: none"> Plan location of Locator on Surview: 2 cm below carina Place region of interest (ROI) within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: None Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	
4. Bolus Tracking		
General <ul style="list-style-type: none"> Same location as #3 Threshold: change/difference of 110 HU in the ROI within the ascending aorta to trigger cardiac contrast enhanced data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	

PHILIPS BRILLIANCE iCT, INGENUITY, IQon, BRILLIANCE 64 (CONT)

5. Retrospectively ECG-gated cardiac data acquisition - Contrast enhanced		
General <ul style="list-style-type: none"> Retrospectively ECG-gated data acquisition of the aortic root and heart Plan data acquisition on Surview: Scan range beginning 2 cm below the carina to the base of the heart Use unenhanced CaSc CT data for planning if available 	Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 sec Breath hold command: Inspiration only Tube voltage: 120 kV Tube current: 800 mAs (1000 mAs for large patients) Anatomical dose modulation: NO Dose modulation throughout the cardiac cycle: full exposure throughout is preferred, alternatively dose modulation with peak dose in systole Slice/Collimation: AUTO Scan direction cranio-caudal Pitch: Auto Pitch Rotation time: 0.4 sec 	Data reconstruction <ul style="list-style-type: none"> Axial multiphase reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart: 220 mm Slice thickness: 0.9 mm Increment: 0.45 mm Filter: XCB Iterative reconstruction: iDose⁴ or IMR
6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
General <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	Data acquisition <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 120 kV Tube current: 251 mAs Anatomical dose modulation: Z-Modulation: 3-D Modulation Slice/Collimation: AUTO Scan direction: cranio-caudal DoseRight: YES DoseRight Index: 26 Pitch: MAX per DRI Rotation time: MIN per DRI FOV: 350 mm 	Data reconstruction <ul style="list-style-type: none"> Axial reconstructions Slice thickness thin: 1.5 mm Increment: Contiguous or Overlap Filter: B for ST Recon, YB for Lung Recon Iterative reconstruction: iDose⁴ or IMR

PHILIPS INGENUITY CT SP/CORE/ELITE

NOTE: SP and Core, 64 row detector; collimation 64 x 0.625 mm; 40 mm z-axis coverage; Elite, 128 slice, 64 x 0.625 mm detector row system with dual focal spot positions to double the number of slices within the 40 mm z-axis gantry coverage.

1. Survey (Topogram/Scout)		
General <ul style="list-style-type: none"> AP topogram/scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Length: 750 mm Tube voltage: 120 kV Tube current: 30 mA Field of View: 500 mm 	
2. Non-enhanced scan (optional)		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode: Prospective ECG-gating, axial Pulsing window: 75% of RR-interval Tube voltage: 120 kV Tube current: 55 mAs Anatomical dose modulation: No Slice/Collimation: AUTO Scan direction cranio-caudal Rotation time: Core/Elite: 0.4 sec SP: 0.33 sec 	Data reconstruction <ul style="list-style-type: none"> Axial reconstruction within the pulsing window: 75% phase Field of View limited to the heart: 220 mm Slice thickness (thin): 2.5 mm Increment (thin): 2.5 mm Filter: CB
3. Locator		
General <ul style="list-style-type: none"> Plan location of Locator on Survey: 2 cm below carina Place region of interest (ROI) within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: None Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	

4. Bolus tracking		
General <ul style="list-style-type: none"> Same location as #3 Threshold: change/difference of 110 HU in the ROI within the ascending aorta to trigger cardiac contrast enhanced data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	
5. Retrospectively ECG-gated cardiac data acquisition - Contrast enhanced		
General <ul style="list-style-type: none"> ECG-assisted data acquisition of the aortic root and heart Plan data acquisition on Survey: Scan range beginning 2 cm below the carina to the base of the heart Use unenhanced CaSc CT data for planning if available 	Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage: 120 kV Tube current: 800 mAs (1000 mAs for large patients) Anatomical dose modulation: No Dose modulation throughout the cardiac cycle: full exposure throughout is preferred, alternatively dose modulation with peak dose in systole Slice/Collimation: AUTO Scan direction: cranio-caudal Pitch (if helical): Auto Pitch (based on heart rate) Rotation time: Core/Elite: 0.3 sec SP: 0.27 sec 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart: 220 mm Slice thickness: 0.9 mm Increment: 0.45 mm Filter: XCB Iterative reconstruction: iDose⁴ or IMR.
6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
General <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	Data acquisition <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 120 kV Tube current: 251 mAs Anatomical dose modulation Z-Modulation, 3-D Modulation Slice/Collimation: AUTO Scan direction: cranio-caudal Pitch: MAX per DRI Rotation time: MIN per DRI FOV: 350 mm 	Data reconstruction <ul style="list-style-type: none"> Axial reconstructions Slice thickness thin: 3 mm Increment: 3 mm Filter: B for ST Recon, YB for Lung Recon Iterative reconstruction: iDose⁴ or IMR

PHILIPS BRILLIANCE iCT ELITE

1. Surview (Topogram/Scout)		
General <ul style="list-style-type: none"> AP topogram/scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Length: 750 mm Tube voltage: 120 kV Tube current: 30 mA Field of View: 500 mm 	
2. Non-enhanced scan (optional)		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode: Prospective ECG-gating, axial Pulsing window: 75% of RR-interval Tube voltage: 120 kV Tube current: 55 mAs Anatomical dose modulation: NO Slice/Collimation: AUTO Scan direction cranio-caudal Rotation time: 400 msec Scan time: 16 sec Scan length: 14 cm 	Data reconstruction <ul style="list-style-type: none"> Axial reconstruction within the pulsing window: 75% phase Field of View limited to the heart: 220 mm Slice thickness (thin): 2.5 mm Increment (thin): 2.5 mm Filter: CB
3. Locator		
General <ul style="list-style-type: none"> Plan location of Locator on Surview: 2 cm below carina Place region of interest (ROI) within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: None Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Cycle time: Automatically populated and is set to 16 x 0.625 mm 	

4. Bolus tracking		
General <ul style="list-style-type: none"> Same location as #3 Threshold: change/difference of 150 HU to trigger cardiac contrast enhanced data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	
5. Retrospectively ECG-gated cardiac data acquisition - Contrast enhanced		
General <ul style="list-style-type: none"> ECG-assisted data acquisition of the aortic root and heart Plan data acquisition on Surview: Scan range beginning 2 cm below the carina to the base of the heart Use unenhanced CaSc CT data for planning if available 	Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage: 120 kV Tube current: 800 mAs (1000 for large patients) Anatomical dose modulation: No Dose modulation throughout the cardiac cycle: full exposure throughout is preferred, alternatively dose modulation with peak dose in systole Slice/Collimation: AUTO Scan direction cranio-caudal Pitch (if helical): Auto pitch Rotation time: 0.27 sec 	Data reconstruction <ul style="list-style-type: none"> Axial multiphase reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart: 220 mm Slice thickness: 0.9 mm Increment: 0.45 mm Filter: XCB Iterative reconstruction: iDose⁴ or IMR

6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
General <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	Data acquisition <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 120 kV Tube current: 251 mAs Anatomical dose modulation: Z-Modulation, 3-D Modulation Slice/Collimation: AUTO Scan direction: cranio-caudal DoseRight: YES DoseRight Index: 26 Pitch: MAX per DRI Rotation time: MIN per DRI FOV: 350 mm 	Data reconstruction <ul style="list-style-type: none"> Axial reconstructions Slice thickness (thin): 3 mm Increment: 3 mm Filter: B for ST Recon, YB for Lung Iterative reconstruction: iDose⁴ or IMR

PHILIPS IQon SPECTRAL CT

1. Surview (Topogram/Scout)		
General <ul style="list-style-type: none"> AP topogram/scout covering the thorax, abdomen and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Length: 750 mm Tube voltage: 120 kV Tube current: 30 mA Field of View: 500 mm 	
2. Non-enhanced scan (optional)		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode: Prospective ECG-gating, axial Pulsing window: 75% of RR-interval Tube voltage: 120 kV Tube current: 42 mAs Anatomical dose modulation: NO Slice/Collimation: AUTO Scan direction: cranio-caudal Rotation time: 0.33 sec 	Data reconstruction <ul style="list-style-type: none"> Axial reconstruction within the pulsing window: 75% Field of View limited to the heart: 220 mm Slice thickness (thin): 2.5 mm Increment (thin): 2.5 mm Filter: CB
3. Locator		
General <ul style="list-style-type: none"> Plan location of Locator on Surview: 2 cm below carina Place region of interest (ROI) within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: None Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	
4. Bolus tracking		
General <ul style="list-style-type: none"> Same location as #3 Threshold: change/difference of 110 HU to trigger cardiac contrast enhanced data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) Tube current: Automatically populated and is set to 30 mAs Tube voltage: Automatically populated and is set to 120 kVp Slice/Collimation: Automatically populated and is set to 16 x 0.625 mm 	

5. Retrospectively ECG-gated cardiac data acquisition - Contrast enhanced

<p>General</p> <ul style="list-style-type: none"> ECG-assisted data acquisition of the aortic root and heart Plan data acquisition on Survey: Scan range beginning 2 cm below the carina to the base of the heart Use unenhanced CaSc CT data for planning if available 	<p>Data acquisition</p> <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage: 120 kV Tube current: 620 mAs (775 mAs for large patients) Anatomical dose modulation: No Dose modulation throughout the cardiac cycle: full exposure throughout is preferred, alternatively dose modulation with peak dose in systole Slice/Collimation: AUTO Scan direction cranio-caudal Pitch (if helical): AutoPitch Rotation time: 0.27 sec 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart: 220 mm Slice thickness: 0.9 mm Increment: 0.45 mm Filter: XCB Iterative reconstruction: iDose⁴ or IMR Conventional and Spectral results
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6. CTA of the thorax/abdomen/pelvis - Contrast enhanced

<p>General</p> <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	<p>Data acquisition</p> <ul style="list-style-type: none"> Delay: Variable (use minimum delay possible) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 120 kV Tube current: 193 mAs Anatomical dose modulation: Z-Modulation, 3-D Modulation Slice/Collimation: AUTO Scan direction: cranio-caudal DoseRight: YES DoseRight Index: 26 Pitch: MAX per DRI Rotation time: MIN per DRI FOV: 350 mm 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial reconstructions Slice thickness thin: 3 mm Increment: 3 mm Filter: B for ST Recon, YB for Lung Iterative reconstruction: iDose⁴ or IMR Conventional or Spectral results
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Contrast application protocol

<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/ heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per hospital protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Recommended contrast media application: Site specific and scan protocol driven Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the ascending aorta with a region of interest placed within the ascending aorta; threshold set at 110 HU above baseline, delay to start of data acquisition after reaching threshold 5 sec
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LOW-CONTRAST DOSE PROTOCOL - RATIONAL FOR ALL SCANNER TYPES

- Reduce scan length of the retrospectively ECG-gated CTA to a minimum to cover only the aortic root as opposed to the entire heart, as this is the time-intensive part in regard to data acquisition
- Injection rate and total amount of contrast may be lowered
- Threshold to trigger initiation of the retrospective ECG-gated spiral data acquisition can be lowered to 80 HU
- Reduce tube voltage to increase contrast attenuation

These alterations should allow for a sufficiently contrast enhanced CT dataset of the aortic root. Contrast attenuation of the iliofemoral acquisition may be variable.

RECONSTRUCTION OF MULTIPHASIC DATA SET

The image data of the aortic root and heart should be reconstructed as multiphasic data set throughout the entire cardiac cycle in 5% or 10% intervals, allowing for cine review of the anatomy.

REVIEW OF DATA RECONSTRUCTION AND ECG-EDITING

- Image reconstructions of the aortic root and heart should be reviewed immediately after the scan when raw data is still available
- The ECG-gating should be reviewed to ensure that the automated algorithms correctly identifies the R-peaks
- If any R points were not correctly identified, manual correction should be performed. This can enhance the quality of cardiac images in the presence of heart rate irregularities
- To activate the editing tools, click the pencil icon. If the icon is grayed out, editing has been disabled





- Right-click on an arrhythmia to Accept or Reject



- Double-click on the wave to add a new R point
- Move an existing R point by drag and drop
- Double click on a R point to delete it



- Move phase points by drag and drop



- Additional options are available in the right-click menu



- The undo option functions with the editing tools. Click this to delete your edit



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CT Acquisition and Reconstruction Techniques for Transcatheter Aortic Valve Procedure Planning Utilizing Siemens Hardware

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WARNING: Any reference to X-ray exposure, intravenous contrast dosage, and other medication is intended as a reference guideline only. The guidelines in this document do not substitute for the judgment of a health care provider. Each scan requires medical judgment by the health care provider about exposing the patient to ionizing radiation. Use the As Low As Reasonably Achievable (ALARA) radiation dose principle to balance factors such as the patient's condition, size, and age; region to be imaged; and diagnostic task.

NOTE: Algorithms/protocols included in this book are for educational reference only. Edwards does not endorse or support any one specific algorithm/protocol. It is up to each individual clinician and institution to select the treatment that is most appropriate.

Philipp Blanke, MD is a paid consultant to Edwards Lifesciences.

INTRODUCTION

Transcatheter aortic valve procedures have proven to be an effective alternative in the treatment of aortic stenosis in high-risk and inoperable patients. Contrast-enhanced computed tomography (CT) has become an integral part of transcatheter aortic valve procedure planning by allowing for anatomical assessment of the aortic root and the aorto-iliofemoral vasculature within a single examination. It is critical that artifact-free image data is obtained to allow for reliable anatomical measurements. Data acquisition strategies and scanning protocols may vary depending on scanner manufacturer, system, and institutional preferences. This document provides recommendations for reliable CT image acquisition for transcatheter aortic valve procedures.

WORK-FLOW RATIONALE

The key component of all approaches is an ECG-assisted data acquisition that covers at least the aortic root, while the remainder of the data acquisition may be performed without ECG assistance. If employed properly, ECG assistance allows for artifact-free depiction of the aortic root. The sequence of patient preparation and the relevant principles of CT data acquisition will be explained in brief below.

PATIENT PREPARATION

- Position the patient, typically supine, on the scanner table to closely resemble cath lab table positioning. This is important for the prediction of C-arm angulation from the CT dataset.
- Place ECG-electrodes and IV access in accordance with institutional policies.
- Provide time for the patient to practice the breath hold prior to scan acquisition to improve patient compliance and thereby scan quality.
- Allow additional scanning and instruction time as needed due to the advanced age and frailty of this patient population.

CT SCAN - SCAN LENGTH AND SCAN STRATEGY

In general, two different approaches are used to combine the ECG-assisted data acquisition of the aortic root structures and the non-ECG-assisted computed tomography angiography (CTA) of the aorto/ilio/femoral vasculature for evaluation of the transfemoral access route:

- 1) Cardiac ECG-assisted data acquisition of the heart and aortic root (usually beginning 2cm below the carina) followed by a non-ECG-assisted CTA of the thorax, abdomen, and pelvis. Although this approach results in repeat data acquisition of the aortic root and cardiac structures, the time-intensive ECG-assisted data acquisition is kept to a minimum that aids in limiting the contrast dose. Furthermore, by limiting the ECG-assisted data acquisition this decreased the radiation dose-intensive portion of the examination, although the cardiac scan range is covered twice. The proposed protocols for all Siemens scanner families use this approach.
- 2) ECG-assisted data acquisition of the thorax followed by a non-ECG-assisted CTA of the abdomen and pelvis. The disadvantage of this approach is the relatively long acquisition time required for the entire thorax (may exceed 15 seconds), which increases the risk of breathing artifacts at the level of the cardiac structures.

SIEMENS SOMATOM DEFINITION FLASH AND SOMATOM FORCE

Siemens SOMATOM Flash and Siemens SOMATOM Force systems are dual-source CT systems allowing for a heart rate independent temporal resolution of 75 msec and 66 msec, respectively, when rotation times of 285 msec and 250 msec are employed.

1. Topogram		
General <ul style="list-style-type: none"> • AP topogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> • Manufacturers' default setting 	
2. CaSc (optional)		
General <ul style="list-style-type: none"> • Can be used for visualization of annular calcification • Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> • Prospective ECG-triggering • CARE KV: Off • Ref. kVp: 120 kVp • CARE dose 4D: On • Ref. mAs: 80 mAs/rot • Default trigger in end-systole • Slice/Collimation: <ul style="list-style-type: none"> 2 x 128 x 0.6 mm (Flash) 2 x 192 x 0.6 mm (Force) • Scan direction cranio-caudal • Rotation time: <ul style="list-style-type: none"> 285 msec (Flash) 250 msec (Force) 	Data reconstruction <ul style="list-style-type: none"> • Axial reconstruction within the pulsing window, commonly BestDiast • Field of view limited to the heart • Slice thickness: 0.75 mm • Increment: 0.5 mm • Convolution kernel: <ul style="list-style-type: none"> Heart View medium CaSc B35f (Flash) Qt36 (Force)
3. Premonitoring for Bolus tracking (CARE Bolus)		
General <ul style="list-style-type: none"> • Plan location of pre-monitoring on topogram: 2 cm below carina • Alternatively plan pre-monitoring using the CaSc CT data • Pre-monitoring should transect through ascending aorta • Place region of interest (ROI) within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> • Delay: 2s • Effective (eff.) mAs: 120 mAs • Effective (eff.) kVp: 120 kVp • Slice/Collimation: <ul style="list-style-type: none"> Acq. 1 x 10.0 mm • Cycle time: 1.57s 	
4. Monitoring for Bolus tracking (CARE Bolus)		
General <ul style="list-style-type: none"> • Same location as pre-monitoring • Threshold: Change of 100HU to trigger retrospective ECG-gated spiral data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> • Delay: 2s • Effective (eff.) mAs: 20 mAs • Effective (eff.) kVp: 120 kVp • Slice/Collimation: <ul style="list-style-type: none"> Acq. 1 x 10.0 mm • Cycle time: 1.57s 	

SIEMENS SOMATOM DEFINITION FLASH AND SOMATOM FORCE (CONT)

5. Retrospective ECG-gated spiral data acquisition – Contrast enhanced		
<p>General</p> <ul style="list-style-type: none"> ECG-gated dual source data acquisition of the aortic root and heart Plan data acquisition on topogram: Scan range beginning 2 cm below the carina to the apex of the heart Use unenhanced CaSc CT data for planning if available 	<p>Data acquisition</p> <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 4 seconds Breath hold command: Inspiration only CARE KV: On (Dose saving optimized for "vasculature") Ref. kVp: 120 kVp Reference tube current: 250 mAs/rot Anatomical dose modulation: CARE Dose 4D on Pulsing (dose modulation throughout cardiac cycle): Off Slice/Collimation: 2 x 128 x 0.6 mm (Flash) 2 x 192 x 0.6 mm (Force) Scan direction: Cranio-caudal Pitch: automatic (adaption to heart rate) Rotation time: 285 msec (Flash) 250 msec (Force) 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5 or 10% intervals in sinus rhythm, 50 msec intervals in atrial fibrillation Use ECG editing if necessary Field of view limited to the heart Slice thickness: 0.75 mm Increment: 0.5 mm Medium smooth convolution kernel with either filtered back projection B26f (Flash) Bv40 (Force) or iterative reconstruction (e.g SAFIRE, strength 3, I26f)
6. High-pitch CTA of the thorax, abdomen, pelvis – Contrast enhanced		
<p>General</p> <ul style="list-style-type: none"> High-pitch ("Flash") dual source data acquisition of the thorax, abdomen, and pelvis Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	<p>Data acquisition</p> <ul style="list-style-type: none"> Delay 5s (minimum delay; needed for repositioning the patient table and adjusting the tube-detector system) No additional automated breath hold command; alternatively manual instruction to slowly exhale. CARE KV: On (Dose saving optimized for "vasculature") Ref. kVp: 100 kVp Reference tube current: 200 mAs/rot Anatomical dose modulation: CARE Dose 4D on Slice/Collimation: 2 x 128 x 0.6 mm (Flash) 2 x 192 x 0.6 mm (Force) Pitch: 3.4 (Flash) 3.2 (Force) Rotation time: 285 msec (Flash) 250 msec (Force) 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial reconstructions Slice thickness: 0.75 mm Increment: 0.5 mm Medium smooth convolution kernel with either filtered back projection B26f (Flash) Bv40 (Force) or iterative reconstruction (e.g SAFIRE/ADMIRE, strength 3, I26f)

Contrast application protocol	
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of an IV access in an antecubital vein (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the ascending aorta with an ROI placed within the ascending aorta; threshold set at 100 HU above baseline, delay to start of data acquisition after reaching threshold 6 sec The proposed delay can be considered a default setting and may be increased in patients with poor ejection fraction. This may help prevent the high-pitch spiral acquisition from outrunning the bolus.

SIEMENS SOMATOM DEFINITION AS64 AND AS+

Siemens SOMATOM Definition AS64 and AS+ are dual-source CT systems for a heart rate independent temporal resolution of 150 msec and 142 msec, respectively, when rotation times of 300 msec and 285 msec are employed.

1. Topogram		
General <ul style="list-style-type: none"> AP topogram view covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> Manufacturers' default setting 	
2. CaSc (optional)		
General <ul style="list-style-type: none"> Can be used for visualization of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Prospective ECG-triggering CARE KV: Off Ref. kVp: 120 kVp CARE dose 4D: On Ref. mAs: 80 mAs/rot Default trigger in end-systole Slice/Collimation: 64 x 0.6 mm (AS64) 128 x 0.6 mm (AS+) Scan direction: Cranio-caudal Rotation time: 300 msec (AS64) 285 msec (AS+) 	Data reconstruction <ul style="list-style-type: none"> Axial reconstruction within the pulsing window, commonly BestDiast Field of view limited to the heart Slice thickness: 0.75 mm Increment: 0.5 mm Convolution kernel: B35f Heart View medium CaSc
3. Pre-monitoring for Bolus tracking (CARE Bolus)		
General <ul style="list-style-type: none"> Plan location of pre-monitoring on topogram: 2 cm below carina Alternatively plan pre-monitoring using the CaSc CT data. Pre-monitoring should transect through ascending aorta. Place ROI within the ascending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 2s Effective (eff.) mAs: 20 mAs Effective (eff.) kVp: 120 kVp Slice/Collimation: Acq. 1 x 10.0 mm Cycle time: 1.16s 	
4. Monitoring for Bolus tracking (CARE Bolus)		
General <ul style="list-style-type: none"> Same location as pre-monitoring Threshold: Change of 100HU to trigger retrospective ECG-gated spiral data acquisition (#5) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 10s Effective (eff.) mAs: 20 mAs Effective (eff.) kVp: 120 kVp Slice/Collimation: Acq. 1 x 10.0 mm Cycle time: 1.16s 	

5. Retrospective ECG-gated spiral data acquisition - Contrast enhanced		
General <ul style="list-style-type: none"> ECG-gated data acquisition of the aortic root and heart Plan data acquisition on topogram: Scan range beginning 2 cm below the carina to the apex of the heart Use unenhanced CaSc CT data for planning if available 	Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 7 seconds Breath hold command: Inspiration only CARE KV: On (Dose saving optimized for "vasculature") Ref. kVp: 120 kVp Reference tube current: 250 mAs/rot Anatomical dose modulation: CARE Dose 4D on Pulsing (dose modulation throughout cardiac cycle): Off Slice/Collimation: 64 x 0.6 mm (AS64) 128 x 0.6 mm (AS+) Scan direction: Cranio-caudal Pitch: Automatic (adaption to heart rate) Rotation time: 300 msec (AS64) 280 msec (AS+) 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5 or 10% intervals in sinus rhythm, 50 msec intervals in atrial fibrillation Use ECG editing if necessary Field of view limited to the heart Slice thickness: 0.75 mm Increment: 0.5 mm Medium smooth convolution kernel with either filtered back projection (B26f) or iterative reconstruction (e.g SAFIRE, strength 3, I26f)
6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
General <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay 5s (minimum delay; needed for repositioning of the patient table and adjusting the tube-detector system) No additional automated breath hold command; alternatively manual instruction to slowly exhale. CARE KV: On (Dose saving optimized for "vasculature") Ref. kVp: 100 kVp Reference tube current: 200 mAs/rot Anatomical dose modulation: CARE Dose 4D on Slice/Collimation: 64 x 0.6 mm (AS64) 128 x 0.6 mm (AS+) Scan direction: Cranio-caudal Pitch: 1.45 Rotation time: 300 msec (AS64) 285 msec (AS+) 	Data reconstruction <ul style="list-style-type: none"> Axial reconstructions Slice thickness: 0.75 mm Increment: 0.5 mm Medium smooth convolution kernel with either filtered back projection (B26f) or iterative reconstruction (e.g SAFIRE, strength 3, I26f)

Contrast application protocol	
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of IV access in an antecubital vein (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the ascending aorta with a ROI placed within the ascending aorta; threshold set at 100 HU above baseline, delay to start of data acquisition after reaching threshold 7 sec

LOW-CONTRAST DOSE PROTOCOL - RATIONALE FOR ALL SCANNER TYPES

- Same scanner settings as listed above, except the threshold setting for bolus tracking
- Reduce scan length of the retrospectively ECG-gated CTA (#5) to a minimum to cover only the aortic root as opposed to the entire heart, as this is the time-intensive part in regard to data acquisition
- Injection rate might be lowered
- Threshold to trigger initiation of the retrospective ECG-gated spiral data acquisition can be lowered to 80 HU
- Systems with the capability of low kV data acquisition (70kV - 90kV, Force) may allow for reduced iodine delivery rates as low kV data acquisition increases iodine attenuation; CARE KV settings need to be adjusted (setting 4-7).

These alterations should allow for a sufficiently contrast-enhanced CT dataset of the aortic root. Contrast attenuation of the iliofemoral acquisition may be variable.

DOSE MODULATION FOR RETROSPECTIVE ECG-GATED SPIRAL DATA ACQUISITION

The protocols listed above do not employ dose modulation for the retrospective ECG-gated spiral data acquisition, allowing for image reconstructions throughout the entire cardiac cycle at a constant image noise level. This allows for identifying the reconstruction phase with largest annular dimensions and optimal image quality. If dose modulation is employed, peak dose should be applied during systole with a pulsing window set to 5 - 35%. MinDOSE should not be used, as this renders images non-interpretable outside of the pulsing window.

RECONSTRUCTION OF MULTIPHASIC DATA SET

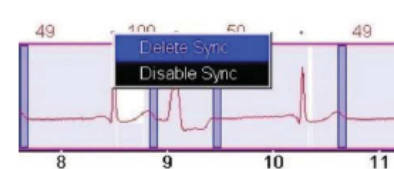
Multiphasic ("dynamic", "cine") data sets can be reconstructed using a relative approach (percentage intervals [%] between two R-peaks) or an absolute approach (fixed distance of the reconstruction window from the R-peak, reported as [msec]).

The relative approach (e.g. 5 or 10% intervals) performs well in regular sinus rhythm. In case of increased heart rate variability, atrial fibrillation, or ectopic beats, absolute reconstruction should be employed (e.g. 50 msec) in combination with ECG-editing if necessary.

CAVEAT: "Best Diastole" and "Best Systole" are algorithms which aim at automated identification of optimal reconstruction phases with the least coronary artery motion in Diastole or Systole. However, these algorithms are intended for coronary CTA and not aortic root imaging.

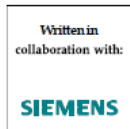
REVIEW OF DATA RECONSTRUCTION AND ECG-EDITING

- Image reconstructions of the aortic root and heart should be reviewed immediately after the scan when raw data is still available
- The ECG-gating should be reviewed to ensure that the automated algorithms correctly identified the R-peaks (dots, also known as "Syncs" should be aligned with R-peaks)
- If R-peaks were not correctly identified, manual correction should be performed (e.g. "Insert Sync" if an R-peak was not identified, or "Delete Sync" if a Sync was placed on anything other than the R-peak; alternatively Syncs can also be shifted manually)
- In case of ectopic contractions, absolute reconstruction should be used and the Sync of the ectopic beat should be deleted



- If mis-registration or stair-step artifacts are present, ECG-editing should be employed with either modification of trigger-points (if they were initially incorrectly identified by the algorithm) or deletion of trigger-points (in premature contraction or atrial fibrillation).

CT Acquisition and Reconstruction Techniques for Transcatheter Aortic Valve Procedure Planning Utilizing Toshiba Hardware



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INTRODUCTION

Transcatheter aortic valve procedures have proven to be an effective alternative in the treatment of aortic stenosis in high-risk and inoperable patients. Contrast-enhanced computed tomography (CT) has become an integral part of transcatheter aortic valve procedure planning by allowing for anatomical assessment of the aortic root and the aorto-iliofemoral vasculature within a single examination. It is critical that artifact-free image data is obtained to allow for reliable anatomical measurements. Data acquisition strategies and scanning protocols may vary depending on scanner manufacturer, system, and institutional preferences. This document provides recommendations for reliable CT image acquisition for transcatheter aortic valve procedures.

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WARNING: Any reference to X-ray exposure, intravenous contrast dosage, and other medication is intended as a reference guideline only. The guidelines in this document do not substitute for the judgment of a health care provider. Each scan requires medical judgment by the health care provider about exposing the patient to ionizing radiation. Use the As Low As Reasonably Achievable (ALARA) radiation dose principle to balance factors such as the patient's condition, size, and age; region to be imaged; and diagnostic task.

NOTE: Algorithms/protocols included in this paper are for educational reference only. Edwards does not endorse or support any one specific algorithm/protocol. It is up to each individual clinician and institution to select the treatment that is most appropriate.

Phillip Blanke, MD is a paid consultant for Edwards Lifesciences.

WORK-FLOW RATIONALE

The key component of all approaches is an ECG-assisted data acquisition that covers at least the aortic root, while the remainder of the data acquisition may be performed without ECG assistance. If employed properly, ECG assistance allows for artifact-free depiction of the aortic root. The sequence of patient preparation and the relevant principles of CT data acquisition will be explained in brief below.

PATIENT PREPARATION

- Position the patient, typically supine, on the scanner table to closely resemble catheterization table positioning. This is important for the prediction of C-arm angulation from the CT dataset.
- Place ECG-electrodes and IV access in accordance with institutional policies.
- Provide time for the patient to practice the breath hold prior to scan acquisition, as it may significantly improve patient compliance and thereby scan quality.
- Plan additional scanning and instruction time as needed, due to the advanced age and frailty of this patient population.

CT SCAN - SCAN LENGTH AND SCAN STRATEGY

In general, two different approaches are used to combine the ECG-assisted data acquisition of the aortic root structures and the non-ECG-assisted computed tomography angiography (CTA) of the aorto/ilio/femoral vasculature for evaluation of the transfemoral access route:

- 1) Cardiac ECG-assisted data acquisition of the heart and aortic root (usually beginning 2 cm below the carina) followed by a non-ECG-assisted CTA of the thorax, abdomen, and pelvis. Although this approach results in repeat data acquisition of the aortic root and cardiac structures, the time-intensive ECG-assisted data acquisition is kept to a minimum that aids in limiting the contrast dose. Furthermore, limiting the ECG-assisted data acquisition also limits the radiation dose intensive component of the examination, although the cardiac scan range is covered twice. *The proposed protocols for the Aquilion ONE Family and the Aquilion PRIME and Aquilion 64/VeloCT 128 Families without variable helical pitch (vHP) use this approach.*
- 2) ECG-assisted data acquisition of the thorax followed by a non-ECG assisted CTA of the abdomen and pelvis. The disadvantage of this approach is the relatively long acquisition time required for the entire thorax (may exceed 15 seconds), increases the risk of breathing artifacts at the level of the cardiac structures. *The proposed protocols for the Aquilion PRIME Family and Aquilion 64/VeloCT 128 Family utilizing vHP (variable helical pitch) use this approach.*

TOSHIBA - AQUILION ONE 64/AQUILION ONE VISION

1. Scanogram		
General <ul style="list-style-type: none"> • AP/LAT Scanogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> • AP Scanogram: 120 kVp/50 mA • LAT Scanogram: 120 kVp/100 mA 	
2. Non-enhanced scan (optional) - Calcium Score		
General <ul style="list-style-type: none"> • Can be used for quantification of annular calcification • Can be used for planning of subsequent contrast-enhanced data acquisition • Volume data can be acquired as a single-beat/one rotation scan 	Data acquisition <ul style="list-style-type: none"> • Acquisition mode: Ca Score Volume Mode • Tube voltage: 120 kVp • Tube current: ^{SURE}Exposure • R-R Scanning Window: HR < 71 bpm (75%); HR > 71 bpm (40%) (determined by scanner) • Slice/Collimation: 0.5/240 (120 mm) • Rotation time: Aquilion ONE 640: 350 msec Aquilion ONE VISION: 275 msec 	Data reconstruction <ul style="list-style-type: none"> • Field of View limited to the heart (220 mm) • Slice thickness 0.5 mm • Increment 0.25 mm • ^{SURE}IQ: Ca Score (FC 12)
3. S&V Scan and View		
General <ul style="list-style-type: none"> • Plan location of ^{SURE}Start on AP Scanogram view: Center of volume • Place region of interest (ROI) within the descending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> • Delay: 0 seconds • Tube current: 50 mA • Tube voltage: 120 kVp • Slice/Collimation: 0.5 mm x4 • Rotation Time: Aquilion ONE 640: 350 msec Aquilion ONE VISION: 275 msec 	
4. Bolus tracking - ^{SURE} Start		
General <ul style="list-style-type: none"> • Same location as #3 • Threshold: 300 HU 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> • Delay: 10 seconds • Tube current: 50 mA • Tube voltage: 100 kVp • Slice/Collimation: 0.5 mm x4 • Rotation Time: Aquilion ONE 640: 350 msec Aquilion ONE VISION: 275 msec • Cycle time/repetition: 2 second intermittent interval • Voice timing: 14 seconds 	

TOSHIBA - AQUILION ONE 640/AQUILION ONE VISION (CONT)

5. ECG-assisted cardiac data acquisition - Contrast enhanced		
<p>General</p> <ul style="list-style-type: none"> ECG-assisted data acquisition of the aortic root and heart as a single beat/one rotation scan Plan volume acquisition on scanogram view: Scan range beginning 1 cm below the carina to the apex of the heart Use unenhanced CaSc CT data for planning if available Set medium FOV (320 mm) – Must match helical CTA 	<p>Data acquisition</p> <ul style="list-style-type: none"> No delay after monitoring has reached threshold (system starts immediately with data acquisition) Breath hold command: Inspiration only (Breath command set in ^{START} at 14 seconds after beginning of contrast injection) Tube voltage: 100 kVp Tube current: ^{START} Exposure (automatically selects the tube current based on the patient size) Target mode set to 50% and exposure window set to 1000 msec will ensure full R-R scan. The exposure time can be adjusted based upon HR. This is a single beat/one rotation scan Slice/Collimation: Configured based upon desired scan length (0.5x240/0.5x280/0.5x320) Rotation time: Aquilion ONE 640: 350 msec Aquilion ONE VISION: 275 msec 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial multiphase reconstruction covering the entire cardiac cycle in 5% or 10% intervals Use ECG editing if necessary Field of View limited to the heart (220 mm) Slice thickness: 0.5 mm Increment: 0.25 mm ^{START} IQ: Cardiac CTA (FC 03) Iterative reconstruction: AIDR 3D
6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
<p>General</p> <ul style="list-style-type: none"> Scan range: Upper thoracic aperture to the proximal femoral (lesser trochanter) Set medium FOV (320 mm) – Must match volume scan 	<p>Data acquisition</p> <ul style="list-style-type: none"> Delay: 6 seconds (minimum delay needed to reposition scanner and continue with non-gated acquisition) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 100 kVp Tube current: ^{START} Exposure (automatically selects the tube current based on the patient size) Slice/Collimation: 0.5 mmx80 Scan direction: Cranio-caudal Pitch: Fast Rotation time: Aquilion ONE 640: 350 msec Aquilion ONE VISION: 275 msec 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Slice thickness: 1.0 mm Increment: 0.8 mm ^{START} IQ: CTA Body FC 08 Iterative reconstruction: AIDR 3D

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Contrast application protocol	
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the ECG-assisted as a single beat/one rotation scan of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per institutional protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Recommended contrast media application: 50 - 90 cc iodinated contrast medium at 4 cc/sec Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the descending aorta with an ROI placed within the descending aorta; threshold set at 250 HU

RECOMMENDATIONS FOR A LOW-CONTRAST PROTOCOL

- Use lower range of total amount of contrast (50 cc)
- Place ROI for bolus tracking (^{START} in ascending aorta as this decreases the delay between contrast administration/arrival to the start of the data acquisition
- A threshold of 250 HU ensures a contrast attenuation of at least 250 HU in the aortic root, however with 50 cc of contrast, attenuation of the non-gated scan may be variable

TOSHIBA - AQUILION PRIME WITH VARIABLE HELICAL PITCH (vHP OPTIONAL)

1. Scanogram		
<p>General</p> <ul style="list-style-type: none"> AP/LAT Scanogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	<p>Data acquisition</p> <ul style="list-style-type: none"> AP Scanogram: 120 kVp/50 mA LAT Scanogram: 120 kVp/100 mA 	
2. Non-enhanced scan (optional) - Calcium Score		
<p>General</p> <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition Sequential scan using step and shoot mode 	<p>Data acquisition</p> <ul style="list-style-type: none"> Acquisition mode: Scan & Scan (sequential mode) Tube voltage: 120 kVp Tube current: ^{START} Exposure R-R Scanning Window: HR < 71 bpm (75%); HR > 71 bpm (40%) Slice/Collimation: 3.0 mmx4 Rotation time: 350 msec 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Field of View limited to the heart (220 mm) Slice thickness: 0.5 mm Increment: 0.25 mm ^{START} IQ: Ca Score (FC 12)
3. S&V Scan and View		
<p>General</p> <ul style="list-style-type: none"> Plan location of ^{START} on AP Scanogram view: 1 cm below carina Place region of interest (ROI) within the descending aorta 	<p>Data acquisition (manufacturers' default settings)</p> <ul style="list-style-type: none"> Delay: 0 seconds Tube current: 50 mA Tube voltage: 120 kVp Slice: 0.5 mmx4 Rotation Time: 350 msec 	

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TOSHIBA – AQUILION PRIME WITH VARIABLE HELICAL PITCH (vHP, OPTIONAL) (CONT)

4. Bolus tracking – ^{SURE} Start		
General <ul style="list-style-type: none"> Same location as #3 Threshold: 180 HU 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 10 seconds Tube current: 50 mA Tube voltage: 100 kVp Slice/Collimation: 0.5 mmx4 Rotation Time: 350 msec Cycle time/repetition: 2 second intermittent interval 	
5. ECG-gated thoracic data acquisition and non-gated data acquisition of the abdomen and pelvis- Contrast enhanced		
General <ul style="list-style-type: none"> Utilize vHP (optional scan mode on Aquilion PRIME family of CT scanners) Allows for one helical scan/ one breath hold combining gated thoracic and non-gated abdominal/pelvic data acquisition Plan helical scan from above apices of the proximal femoral to the lesser trochanter The retrospectively ECG-gated helical acquisition should be set to start above lung apices to below apex of the heart 	Thoracic Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage: 100 kVp Tube current and anatomical dose modulation: ^{SURE}Exposure XYZ Modulation Helical retrospectively ECG gated mode using vHP Slice/Collimation: 0.5 mmx80 Rotation time: 350 msec Pitch: Cardiac (automatically set by ^{SURE}Cardio) 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle in 5% or 10% intervals Use ECG editing if necessary Field of View limited to the heart (220 mm) Slice thickness: 0.5 mm Increment: 0.25 mm ^{SURE}IQ: Cardiac CTA (FC 03) Iterative reconstruction: AIDR 3D
	Abdominal/Pelvic Data acquisition <ul style="list-style-type: none"> Tube voltage: 100 kVp Tube current and anatomical dose modulation: ^{SURE}Exposure XYZ Modulation Slice/Collimation: 0.5 mmx80 Scan direction: Cranio-caudal Pitch: Standard Rotation time: 350 msec 	Data reconstruction <ul style="list-style-type: none"> Slice thickness: 1.0 mm Increment: 0.8mm ^{SURE}IQ: CTA Body (FC 08) Iterative reconstruction: AIDR 3D
Contrast application protocol		
General <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/ heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per institutional protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	Specific <ul style="list-style-type: none"> Recommended contrast media application: 90 cc iodinated contrast medium at 4 cc/sec Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the descending aorta with an ROI placed within the descending aorta; threshold set at 180 HU 	

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TOSHIBA – AQUILION PRIME WITHOUT VARIABLE HELICAL PITCH (vHP)

1. Scanogram		
General <ul style="list-style-type: none"> AP/LAT Scanogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> AP Scanogram: 120 kVp/50 mA LAT Scanogram: 120 kVp/100 mA 	
2. Non-enhanced scan (optional) – Calcium Score		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode: Scan & Scan (sequential mode) Tube voltage: 120 kVp Tube current: ^{SURE}Exposure R-R Scanning Window: HR < 71 bpm (75%); HR > 71 bpm (40%) Slice/Collimation: 3.0 mmx4 Rotation time: 350 msec 	Data reconstruction <ul style="list-style-type: none"> Field of View limited to the heart (220 mm) Slice thickness: 0.5 mm Increment: 0.25 mm ^{SURE}IQ: Ca Score (FC12)
3. S&V Scan and View		
General <ul style="list-style-type: none"> Plan location of ^{SURE}Start on AP Scanogram view: 1cm below carina Place ROI within the descending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 0 seconds Tube current: 50 mA Tube voltage: 120 kVp Slice/Collimation: 0.5 mmx4 Rotation Time: 350 msec 	
4. Bolus tracking – ^{SURE} Start		
General <ul style="list-style-type: none"> Same location as #3 Threshold: 180 HU 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 10 seconds Tube current: 50 mA Tube voltage: 100 kVp Slice/Collimation: 0.5 mmx4 Rotation Time: 350 msec Cycle time/repetition: 2 second intermittent interval 	

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TOSHIBA - AQUILION PRIME WITHOUT VARIABLE HELICAL PITCH (vHP) (CONT)

5. ECG-gated data acquisition of the aortic root/heart		
General <ul style="list-style-type: none"> Retrospectively ECG-gated helical acquisition of the aortic root and heart. 	ECG-gated Data acquisition of the aortic root and heart <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage: 100 kVp Tube current and anatomical dose modulation: ^{SURR}Exposure XYZ Modulation Helical retrospective ECG Gated mode Slice/Collimation: 0.5 mmx80 Rotation time: 350 msec Pitch: Cardiac (set by ^{SURR}Cardio) 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart (220 mm) Slice thickness: 0.5 mm Increment: 0.25 mm ^{SURR}IQ: Cardiac CTA (FC 03) Iterative reconstruction: AIDR 3D
6. CTA of the thorax/abdomen/pelvis - Contrast enhanced		
<ul style="list-style-type: none"> Non-gated data acquisition of the thorax, abdomen, and pelvis immediately following the prior data acquisition 	Thorax/Abdominal/Pelvic Data acquisition <ul style="list-style-type: none"> Delay prior to scan scans: 7 seconds (minimum delay needed to reposition scanner and continue with non-gated acquisition) No additional automated breath hold command; alternatively manual instruction to slowly exhale Tube voltage: 100 kVp Tube current and Anatomical dose modulation: ^{SURR}Exposure XYZ Modulation Slice/Collimation: 0.5 mmx80 Scan direction: Cranio-caudal Pitch: Standard Rotation time: 350 msec 	Data reconstruction <ul style="list-style-type: none"> Slice thickness: 1.0mm Increment: 0.8 mm ^{SURR}IQ: CTA Body (FC 08) Iterative reconstruction: AIDR 3D
Contrast application protocol		
General <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per institutional protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	Specific <ul style="list-style-type: none"> Recommended contrast media application: 80 - 100 cc iodinated contrast medium at 4 cc/sec Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the descending aorta with an ROI placed within the descending aorta; threshold set at 180 HU 	

TOSHIBA - AQUILION 64 AND AQUILION VELOCT 128 WITH vHP

1. Scanogram		
General <ul style="list-style-type: none"> AP/LAT Scanogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	Data acquisition <ul style="list-style-type: none"> AP Scanogram: 120 kVp/50 mA LAT Scanogram: 120 kVp/100 mA 	
2. Non-enhanced scan (optional) - Calcium Score		
General <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	Data acquisition <ul style="list-style-type: none"> Acquisition mode - Scan & Scan (sequential mode) Tube voltage: 120kVp Tube current: 300mA (Aquilion 64), ^{SURR}Exposure (Velo CT 128) R-R Scanning Window: HR < 71 bpm (75%); HR > 71 bpm (40%) Slice/Collimation: 3.0 mmx4 Rotation time: 400 msec, 350 msec (optional) 	Data reconstruction <ul style="list-style-type: none"> Field of View limited to the heart (220mm) Slice thickness: 0.5mm Increment: 0.25mm ^{SURR}IQ: Ca Score (FC12)
3. S&V Scan and View		
General <ul style="list-style-type: none"> Plan location of ^{SURR}Start on AP Scanogram view: 1 cm below carina Place region of interest (ROI) within the descending aorta 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 0 seconds Tube current: 50 mA Tube voltage: 120 kVp Slice/Collimation: 0.5 mm x4 Rotation time: 400 msec (350 msec optional) 	
4. Bolus tracking - ^{SURR} Start		
General <ul style="list-style-type: none"> Same location as #3 Threshold: 180 HU 	Data acquisition (manufacturers' default settings) <ul style="list-style-type: none"> Delay: 10 seconds Tube current: 50 mA Tube voltage: 100 kVp Slice/Collimation: 0.5 mmx4 Rotation time: 400 msec (350 msec optional) Cycle time/repetition: 2 second intermittent interval 	

TOSHIBA - AQUILION 64 AND AQUILION VELOCT 128 WITH vHP (CONT)

5. ECG-gated thoracic data acquisition and non-gated data acquisition of the abdomen and pelvis - Contrast enhanced		
<p>General</p> <ul style="list-style-type: none"> Utilize Variable Helical Pitch (vHP) vHP is an optional scan mode on Aquilion 64 and Aquilion VeloCT 128 CT scanners. Allows for one helical scan/one breath hold combining gated/ non-gated data acquisition. Plan helical scan from above apices to below ischium. The retrospectively ECG-gated helical acquisition should be set to start above lung apices to below apex of the heart 	<p>Thoracic Data acquisition</p> <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds. Breath hold command: Inspiration only Tube voltage: 100 kVp Tube current: fixed tube current adjusted to BMI, e.g. 400mA (Aquilion 64), ^{SURE}ExposureXYZ Modulation (Velo CT 128) Helical retrospective ECG Gated mode using vHP Slice/Collimation: 0.5x64 Rotation time: 400 msec, 350msec (optional) Pitch: Cardiac (Set by ^{SURE}Cardio) 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart Slice thickness: 0.5 mm Increment - 0.25 mm ^{SURE}IQ: Cardiac CTA FC 03 (Velo CT 128), FC 43 (Aquilion 64) Quantum De-noising Software (QDS+) (Aquilion 64) Boost 3D (Aquilion 64) Iterative reconstruction - AIDR 3D (Velo CT 128)
<p>General</p> <ul style="list-style-type: none"> Non-gated data acquisition of the thorax, abdomen, and pelvis. 	<p>Abdominal/Pelvic Data acquisition</p> <ul style="list-style-type: none"> Tube voltage: 100 kVp Tube current and Anatomical dose modulation: ^{SURE}Exposure XYZ Modulation Slice/Collimation: 0.5x64 Scan direction: cranio-caudal Pitch: Standard Rotation time: 350 msec 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Axial reconstructions - 3mmx3mm Slice thickness thin - 1.0mm Increment - 0.8mm ^{SURE}IQ: CTA Body FC 08 Quantum De-noising Software (QDS+) (Aquilion 64) Boost 3D (Aquilion 64) Iterative reconstruction - AIDR 3D (Velo CT 128)
Contrast application protocol		
<p>General</p> <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/ heart and the CTA of the thorax/abdomen/pelvis placement of IV access per hospital protocol (an 18-gauge IV typically provides the highest safety) automated contrast injection using a dual-cylinder injector 	<p>Specific</p> <ul style="list-style-type: none"> Recommended contrast media application: 90 cc iodinated contrast medium at 4 cc/sec Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the descending aorta with a region of interest placed within the descending aorta; threshold set at 180 HU. 	

TOSHIBA - AQUILION 64 AND AQUILION VELOCT 128 WITHOUT vHP

1. Scanogram		
<p>General</p> <ul style="list-style-type: none"> AP/LAT Scanogram covering the thorax, abdomen, and pelvis including the proximal femoral to the lesser trochanter 	<p>Data acquisition</p> <ul style="list-style-type: none"> AP Scanogram: 120 kVp/50 mA LAT Scanogram: 120 kVp/100 mA 	
2. Non-enhanced scan (optional) - Calcium Score		
<p>General</p> <ul style="list-style-type: none"> Can be used for quantification of annular calcification Can be used for planning of subsequent contrast-enhanced data acquisition 	<p>Data acquisition</p> <ul style="list-style-type: none"> Acquisition mode - Scan & Scan (sequential mode) Tube voltage: 120 kVp Tube current: 300mA (Aquilion 64), ^{SURE}Exposure (Velo CT 128) R-R Scanning Window: HR < 71 bpm (75%); HR > 71 bpm (40%) Slice/Collimation: 3.0 mm x4 Rotation time: 400 msec (350 msec optional) 	<p>Data reconstruction</p> <ul style="list-style-type: none"> Field of View limited to the heart (220 mm) Slice thickness 0.5 mm Increment 0.25 mm ^{SURE}IQ: Ca Score (FC 12)
3. S&V Scan and View		
<p>General</p> <ul style="list-style-type: none"> Plan location of ^{SURE}Start on AP Scanogram view: 1 cm below carina Place ROI within the descending aorta 	<p>Data acquisition (manufacturers' default settings)</p> <ul style="list-style-type: none"> Delay: 0 seconds Tube current: 50 mA Tube voltage: 120 kVp Slice/Collimation: 0.5 mm x4 Rotation time: 400 msec (350 msec optional) 	
4. Bolus tracking - ^{SURE} Start		
<p>General</p> <ul style="list-style-type: none"> Same location as #3 Threshold: 180 HU 	<p>Data acquisition (manufacturers' default settings)</p> <ul style="list-style-type: none"> Delay: 10 seconds Tube current: 50 mA Tube voltage: 100 kVp Slice/Collimation: 0.5 mm x4 Rotation time: 400 msec (350 msec optional) 	

TOSHIBA - AQUILION 64 AND AQUILION VELOCT 128 WITHOUT vHP (CONT)

5. ECG-gated data acquisition of the aortic root/heart - Contrast enhanced		
General <ul style="list-style-type: none"> Retrospectively ECG-gated helical acquisition of the aortic root and heart 	Thoracic Data acquisition <ul style="list-style-type: none"> Delay after monitoring has reached threshold: 5 seconds Breath hold command: Inspiration only Tube voltage 100 kVp Tube current: fixed tube current adjusted to BMI, e.g. 400mA (Aquilion 64), ^{Siemens}Exposure XYZ Modulation (Velo CT 128) Helical retrospective ECG Gated mode Slice/Collimation: 0.5 mm x64 Rotation time: 400 msec (350 msec optional) Pitch: Cardiac (set by ^{Siemens}Cardio) 	Data reconstruction <ul style="list-style-type: none"> Axial multiphasic reconstruction covering the entire cardiac cycle, 5% or 10% intervals in sinus rhythm Use ECG editing if necessary Field of View limited to the heart Slice thickness: 0.5 mm Increment: 0.5 mm ^{Siemens}IQ: Cardiac CTA FC 43 (Aquilion 64), FC 03 (VeloCT 128) Quantum De-Noising Software (QDS+) (VeloCT 128) Boost 3D (VeloCT 128) Iterative reconstruction – AIDR 3D (VeloCT 128)
6. Contrast enhanced ECG-assisted cardiac data acquisition		
General <ul style="list-style-type: none"> Non-gated data acquisition of the thorax, abdomen, and pelvis. 	Abdominal/Pelvic Data acquisition <ul style="list-style-type: none"> Delay between scans: 7 seconds Tube voltage 100 kVp Tube current and Anatomical dose modulation: ^{Siemens}Exposure XYZ Modulation Slice/Collimation: 0.5 mm x64 Scan direction: Cranio-caudal Pitch: Standard Rotation time: 400 msec (350 msec optional) 	Data reconstruction <ul style="list-style-type: none"> Axial reconstructions: 3 mm x 3 mm Slice thickness: 1.0mm Increment: 0.8mm ^{Siemens}IQ: CTA Body FC 08 Quantum De-Noising Software (QDS+) Boost 3D Iterative reconstruction – AIDR 3D (VeloCT 128)

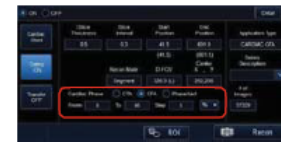
Contrast application protocol	
General <ul style="list-style-type: none"> Single contrast application for both the retrospectively ECG-gated CTA of the aortic root/heart and the CTA of the thorax/abdomen/pelvis Placement of IV access per institutional protocol (an 18-gauge IV typically provides the highest safety) Automated contrast injection using a dual-cylinder injector 	Specific <ul style="list-style-type: none"> Recommended contrast media application: 80 - 100 cc iodinated contrast medium at 4 cc/sec Contrast bolus monitoring and timing of data acquisition by means of bolus tracking at the level of the descending aorta with an ROI placed within the descending aorta; threshold set at 180 HU

RECOMMENDATIONS FOR A LOW-CONTRAST PROTOCOL

- Use reduced amount of contrast material (e.g. 50 - 60 cc)
- Place ROI for bolus tracking (^{Siemens}Start) in ascending aorta as this decreases the delay between contrast administration/arrival to the start of the data acquisition
- Reduce threshold for bolus tracking to 160 HU
- Limit the Z-axis coverage of the ECG-gated data acquisition to the aortic root, as this is the Time-intensive part of the examination (due to the low pitch value for ECG-gated data acquisition)
- This approach should allow for sufficient contrast attenuation of the aortic root, however contrast attenuation of the non-gated scan may be variable

RECONSTRUCTION OF MULTIPHASIC DATA SET

Multiphasic ('dynamic', 'cine') data sets can be reconstructed using a relative approach (percentage intervals [%] between two R-peaks) or an absolute approach (fixed distance of the reconstruction window from the R-peak, reported as [msec]).



Relative Reconstruction settings in 5% intervals

For retrospectively ECG-gated CT data, the relative approach (e.g. 5% or 10% intervals) performs well in regular sinus rhythm. In case of increased heart rate variability, atrial fibrillation, or ectopic beats, absolute reconstruction should be employed in combination with ECG-editing if necessary.



Absolute Reconstruction settings in 50 ms intervals

REVIEW OF DATA RECONSTRUCTION AND ECG-EDITING

- Image reconstructions of the aortic root and heart should be reviewed immediately after the scan when raw data is still available
- The ECG-gating should be reviewed to ensure that the automated algorithms correctly identify the R-peaks
- If R-peaks were not correctly identified, manual correction should be performed (e.g. add an R-peak if an R-peak was not identified or delete an R-peak if an R-peak was placed on anything other than the R-peak; alternatively R-peaks can be shifted manually)
- In case of ectopic contractions, absolute reconstruction should be used and the R-peak of the ectopic beat should be deleted



ECG-editing screen showing correctly identified R-peaks.

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Appendix K-2 Sub-Study CT

CT Substudy Manual of Operations

Edwards Lifesciences LLC
Protocol US IDE Trial #2015-08

Edwards Lifesciences LLC

One Edwards Way

Irvine, CA 92614

Document Title: CT Substudy Manual of Operations

Trial Sponsor: Edwards Lifesciences





Protocol Title: A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients who have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement.

Protocol Identifier: US IDE Trial #2015-08

CT Substudy Manual of Operations

Edwards Lifesciences LLC
 Protocol US IDE Trial #2015-08

Document Approval: St. Paul's Cardiac CT Core Lab, Edwards Lifesciences, LLC
Document title: CT Procedure Manual
Document version: Version 3.0; Nov 2017
Study number: 2015-08

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CT Substudy Manual of Operations

Edwards Lifesciences LLC
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CT Substudy Manual of Operations

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DOCUMENT REVISION HISTORY

Document Revision History begins with the first revision after the initial approved version.

Section updated in version FINAL_v 2.0, May 2016	Changes resulting in version FINAL_v 3.0, Nov 2017	Reason for change
Headers and throughout document <i>Sub-study</i>	Headers <i>Substudy</i>	Removed the “-” to align with the protocol and other trial resources
Section 2 a. All sites will be required to submit to the Imaging Core Lab, a de- identified sample of a CT performed per section 3 via Moving Pictures WebSend at https://www.mddximage.com	Section 2 b. All sites will be required to submit to the Imaging Core Lab, a de-identified sample of a CT performed per section 3 via Bioclinica Smart Submit at https://smartsubmit.bioclinica.com .	Updating with new url and image vendor name.
Section 3 <i>Single-source 64-row scanners are not sufficient</i>	Section 3 <i>Single-source 64-row scanners are sufficient if heart rate is adequately controlled</i>	Per the CT core lab, adequate imaging may be obtained in 64-slice scanners when the heart rate is appropriately controlled
Section 3, Heart Rate Control	Section 3, Heart Rate Control Heart rate for single-source 64-slice scanners must be <80 bpm to ensure adequate image quality.	Adding upper parameter for appropriate heart rate control in single-source 64-slice scanners

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CT Substudy Manual of Operations

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Section updated in version FINAL_v 2.0, May 2016	Changes resulting in version FINAL_v 3.0, Nov 2017	Reason for change												
<p>Table 2</p> <table border="1"> <thead> <tr> <th data-bbox="293 401 509 432">Scanner</th> <th data-bbox="509 401 683 462">Acquisition mode</th> </tr> </thead> <tbody> <tr> <td data-bbox="293 462 509 772"> Single-source volume scanner <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Philips iCT 256 (8cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) </td> <td data-bbox="509 462 683 772">ECG-gated, 'one-beat, one-slab' volume acquisition</td> </tr> <tr> <td data-bbox="293 772 509 1050"> Dual-Source scanner <ul style="list-style-type: none"> • Siemens Somatom Definition, Flash, Force </td> <td data-bbox="509 772 683 1050">Helical/spiral acquisition with retrospective ECG-gating (do not use high-helical pitch acquisition or step-and shoot mode)</td> </tr> </tbody> </table>	Scanner	Acquisition mode	Single-source volume scanner <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Philips iCT 256 (8cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) 	ECG-gated, 'one-beat, one-slab' volume acquisition	Dual-Source scanner <ul style="list-style-type: none"> • Siemens Somatom Definition, Flash, Force 	Helical/spiral acquisition with retrospective ECG-gating (do not use high-helical pitch acquisition or step-and shoot mode)	<p>Table 2</p> <table border="1"> <thead> <tr> <th data-bbox="693 401 930 432">Scanner</th> <th data-bbox="930 401 1125 432">Acquisition mode</th> </tr> </thead> <tbody> <tr> <td data-bbox="693 432 930 758"> Single-source volume scanner with extended z-axis coverage <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) • Philips iCT 256 (8cm coverage)¹ </td> <td data-bbox="930 432 1125 758">ECG-gated, 'one-beat, one-slab' volume acquisition</td> </tr> <tr> <td data-bbox="693 758 930 1119"> Sing-Source scanner with limited z-axis coverage and Dual-Source scanner <ul style="list-style-type: none"> • All GE systems except for GE Revolution • All Philips systems¹ • All Siemens systems² • All Toshiba systems except for Aquilion One/Vision </td> <td data-bbox="930 758 1125 1119">Helical/spiral acquisition with retrospective ECG-gating</td> </tr> </tbody> </table>	Scanner	Acquisition mode	Single-source volume scanner with extended z-axis coverage <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) • Philips iCT 256 (8cm coverage)¹ 	ECG-gated, 'one-beat, one-slab' volume acquisition	Sing-Source scanner with limited z-axis coverage and Dual-Source scanner <ul style="list-style-type: none"> • All GE systems except for GE Revolution • All Philips systems¹ • All Siemens systems² • All Toshiba systems except for Aquilion One/Vision 	Helical/spiral acquisition with retrospective ECG-gating	Adding acquisition modes for additional scanners to be used in the substudy
Scanner	Acquisition mode													
Single-source volume scanner <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Philips iCT 256 (8cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) 	ECG-gated, 'one-beat, one-slab' volume acquisition													
Dual-Source scanner <ul style="list-style-type: none"> • Siemens Somatom Definition, Flash, Force 	Helical/spiral acquisition with retrospective ECG-gating (do not use high-helical pitch acquisition or step-and shoot mode)													
Scanner	Acquisition mode													
Single-source volume scanner with extended z-axis coverage <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) • Philips iCT 256 (8cm coverage)¹ 	ECG-gated, 'one-beat, one-slab' volume acquisition													
Sing-Source scanner with limited z-axis coverage and Dual-Source scanner <ul style="list-style-type: none"> • All GE systems except for GE Revolution • All Philips systems¹ • All Siemens systems² • All Toshiba systems except for Aquilion One/Vision 	Helical/spiral acquisition with retrospective ECG-gating													
<p>Table 2 footnote Note – For Dual-Source CT scanner, the use of high-pitch helical data acquisition should be avoided.</p>	<p>Table 2 footnote Note – ¹ Philips iCT 256 can be operated with either ECG-gated, 'one-beat, one-slab' volume acquisition or Helical/spiral acquisition with retrospective ECG-gating; ² For Dual-Source CT scanner, the use of high-pitch helical data acquisition should be avoided.</p>													

1. Site-preparation

In order to reach the highest rate of diagnostic scans possible, and to salvage potentially non-diagnostic data by means of ECG-editing etc., all sites participating in the CT substudy will be responsible for completing all required training and ensuring their institution's scanner and protocols are compatible with the scanning protocol outlined in section 3 of this document.

2. Site Validation

The purpose of the Site CT Qualification Process is to ensure adherence to the imaging protocol as well as ensure compatibility between site CT acquisition, upload process and the Core Lab analysis tools.

Site will be validated upon successful completion of the following items:

1. Completing and returning a follow-up survey (will be sent to site by Edwards Lifesciences).
2. The first submission of a CT of an enrolled substudy patient to the Imaging Core Lab.
 - c. All sites will be required to submit to the Imaging Core Lab, a de-identified sample of a CT performed per section 3 via Bioclinica Smart Submit at <https://smartssubmit.bioclinica.com>.
 - d. A critique of the CT qualification scan will be emailed or faxed to the site and study sponsor as notification of the qualification status
 - e. If the site does not qualify with the first submission, the Imaging Core Lab will use the critique to recommend changes for resubmission of another CT study.

3. CT Data Acquisition

Contrast-enhanced computed tomography (CT) allows for assessment of the Transcatheter Heart Valve (THV) in regard to positioning, expansion, and leaflet morphology and function. Similarly, it allows evaluation of Surgical Aortic Valves (SAVs) and their leaflets. However, image interpretation, particularly in regard to leaflet assessment, can be significantly limited by motion and mis-registration artifacts as well as beam-hardening artifact or poor contrast attenuation.

This section provides recommendations and requirements for scanner selection and data acquisition techniques. Adherence to these guidelines is essential to provide sufficient image data sampling while minimizing potential artifacts; thereby optimizing the diagnostic yield.

Data acquisition strategies and scanning protocols vary based on scanner systems. For the purpose of this substudy, an ECG-assisted data acquisition which covers at least the aortic root throughout the entire cardiac cycle is required.

The relevant principles of CT data acquisition will be explained in brief below.

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NOTE: Only cardiac CT imaging is required for the post-TAVR CT scan at 30 days and at one year for the purpose of the substudy. A CTA of the thorax, abdomen and pelvis is NOT required at 30 days and one year.

Scanner selection

It is required that post-TAVR CT scans are performed with either

- Dual-source systems or
- Single-source volume scanners.

Single-source 64-row scanners are sufficient if heart rate is adequately controlled.

Note: The scanner employed ideally shall remain the same for the 30 day and one year CT examination.

Heart rate control

CT data acquisition at lower heart rates is preferred as this minimizes motion artifacts. Administration of heart rate controlling medications (e.g. beta blockers) should be considered in patients with accelerated heart rates (e.g., >65 bpm), in particular when using single-source volume scanners. Heart rate for single-source 64-slice scanners must be <80 bpm to ensure adequate image quality.

Note: Administration should follow institutional protocols such as those commonly used for coronary CTA. Contraindications for Beta-Blockers need to be considered

Contrast enhancement

Contrast administration protocols should be adopted from institutional protocols for coronary CTA. For recommendations see Table 1.

Table 1: Recommendations for contrast administration:

Parameter	Recommendation
Iodine concentration	Iodinated contrast agent as per institutional standards
Flow rate	4-6ml/sec
Volume	As per institutional standard for routine coronary cardiac CT, commonly 50-80cc
IV-access	Antecubital vein is recommended
Timing	Bolus tracking to allow for peak contrast in the ascending aorta

Data Acquisition Mode

The ECG-assisted, contrast enhanced image acquisition of the aortic root constitutes the main and most important part of the post-TAVR CT scan at 30 days and one year. To allow for evaluation of potential leaflet restriction, and to ensure abundant image data in case of artifacts, it is required that the entire cardiac cycle is covered, independent of the acquisition mode employed. Table 2 provides an overview of acquisition modes stratified by scanner type to meet imaging requirements.

Table 2: Required acquisition modes stratified by CT system

Scanner	Acquisition mode
Single-source volume scanner with extended z-axis coverage <ul style="list-style-type: none"> • GE Revolution (16cm coverage) • Toshiba Aquilion One/Vision or Aquilion Premium (16cm coverage) • Philips iCT 256 (8cm coverage)¹ 	ECG-gated, 'one-beat, one-slab' volume acquisition
Sing-Source scanner with limited z-axis coverage and Dual-Source scanner <ul style="list-style-type: none"> • All GE systems except for GE Revolution • All Philips systems¹ • All Siemens systems² • All Toshiba systems except for Aquilion One/Vision 	Helical/spiral acquisition with retrospective ECG-gating

Note – ¹ Philips iCT 256 can be operated with either ECG-gated, 'one-beat, one-slab' volume acquisition or Helical/spiral acquisition with retrospective ECG-gating; ² For Dual-Source CT scanner, the use of high-pitch helical data acquisition should be avoided.

Dose modulation

In order to achieve constant, diagnostic image quality throughout the cardiac cycle, we recommend maintaining peak tube current throughout the cardiac cycle and to avoid dose modulation (Figure 1 and 2).

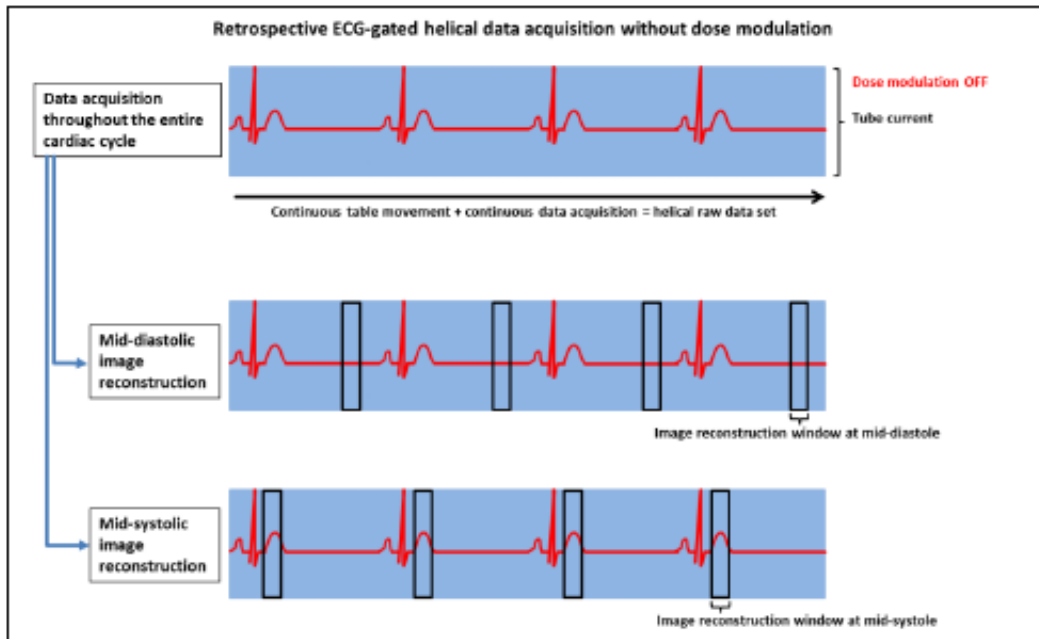


Figure 1 – Retrospective ECG-gated helical data acquisition without dose modulation. The tube current (blue bar) is set at its peak during the entire cardiac cycle. The black boxes indicate the time point of image reconstruction within the cardiac cycle.

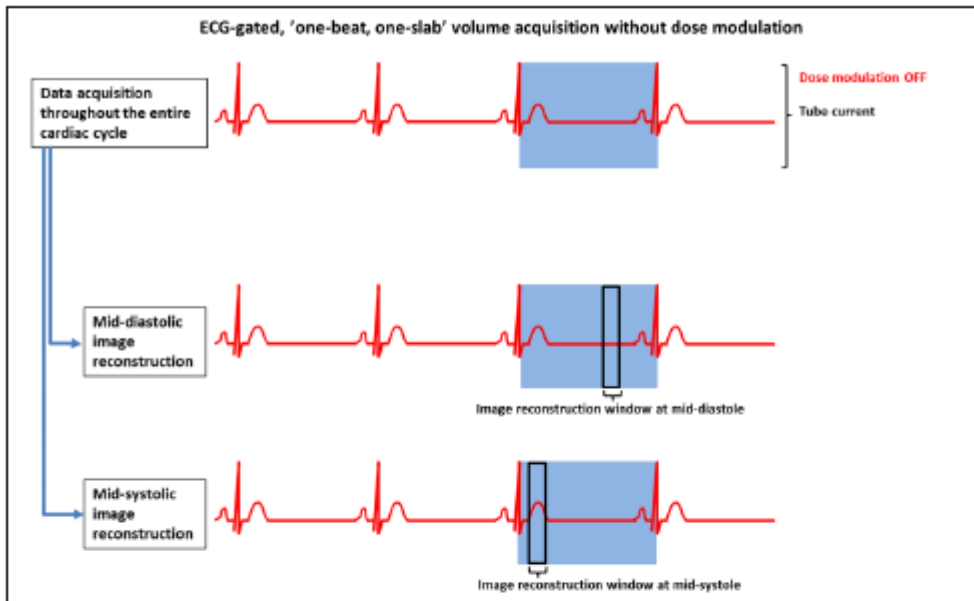


Figure 2 - ECG-gated, 'one-beat, one-slab' volume acquisition without dose modulation. The tube current (blue bar) is set at its peak during the entire cardiac cycle. The black boxes indicate the time point of image reconstruction within the cardiac cycle.

Scan coverage

The ECG-assisted data acquisition has to at least cover the entire SAV/THV (Figure 3). Scan coverage can be extended to include the entire heart, however this will increase the radiation burden to the patient.

CAVEAT: Please consider that the aortic root changes position during the cardiac cycle, with the potential of only partially covering the SAV/THV during certain parts of the cardiac cycle. Ensure that the anticipated scan range covers the SAV/THV throughout the entire cardiac and accommodates for changes in position.

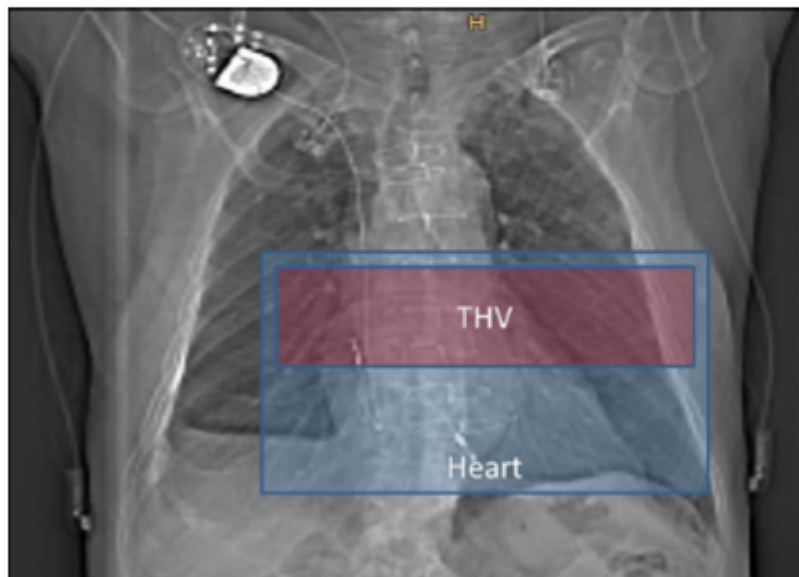


Figure 3 – Scout views. Scan coverage can be limited to the THV/SAV as opposed to the entire heart, but should include the entire THV/SAV.

Scan settings

- **Peak tube current:** Scan settings should follow the institutional standard. Lower tube current can be used if anticipated increase in image noise is compensated by iterative image reconstruction.
- **Tube voltage:** Data acquisition with low tube voltage (e.g. 70-100kVp) should be avoided, as this increases beam hardening and streak artifacts of the metal components of the SAVs and THVs. Instead, data acquisition should be performed at 120kVp, alternatively at 140kVp. The latter however can significantly reduce the attenuation of the iodinated contrast media. Scan settings should be reviewed and care should be taken to avoid use of automated tube voltage selection algorithms in favour of manual selection of tube voltage.

Dose modulation should be avoided. If however dose-modulation is used, tube current should only be lowered to a level to still allow for diagnostic image quality.

Note - When using Siemens scanners (Siemens Healthcare, Forchheim, Germany), the use of MinDOSE (algorithm to lower tube current to 4% of peak current) should be avoided.

Table 3: Recommendations for scan parameters

Parameter	Recommendation
Tube current	Absolute or reference tube current settings similar to institutional settings for routine coronary cardiac CT
Dose modulation	Dose modulation is not recommended in order to allow for images of equal, diagnostic image quality throughout the entire cardiac cycle
Tube voltage	120kVp, alternatively 140kVp to reduce beam hardening artifacts of stent frame (in particular with volume-scanners); use of 100kVp or 80kVp is not recommended; automated algorithms for tube voltage selection may need to be overridden
Collimation	Thinnest possible, e.g. 0.625 with GE and Philips hardware, 0.6mm with Siemens Hardware, 0.5mm/0.25mm with Toshiba hardware

4. CT Data Reconstructions

Raw data protection

In order to allow for further image reconstruction if primary reconstructions are artifact impaired or insufficient, raw data should be protected from automated deletion on the scanner console. Raw data protection should occur immediately after data acquisition.

Data Reconstructions

Image data should be reconstructed as follows:

- Thin sliced axial reconstructions
- These should cover the entire cardiac cycle as multiphase/multiphasic reconstructions (AKA 4D-CT, cine)
- Reconstruction field of view should be limited to the heart, using a 512 x 512 matrix.
- Thin sliced reconstruction can be reconstructed in an overlapping fashion (increment < slice thickness)

Multiphasic reconstructions are typically reconstructed in an interval fashion, either using a relative (percentage) approach, or an absolute approach (msec).

1. For Single-Source Volume scanner (GE Revolution, Philips iCT256, Toshiba Aquilion One/Vision):
 - 5% or 10% increments
2. For Dual-Source systems (Siemens Somatom Definition, Flash, Force):
 - 5% or 10% increments (relative reconstruction)
 - or 50ms increments (absolute reconstruction)

As opposed to relative reconstruction, absolute reconstruction is less susceptible to stair-step and double contour artifacts in the setting of atrial fibrillation or premature contractions. In absolute reconstruction, the distance of the reconstruction window to the preceding R-peak remains constant independent of the length of the RR-interval. When using retrospective ECG-gating, absolute reconstructions are favorable in particular for systolic/end-systolic image reconstruction.

Table 4: Recommendations for image reconstruction parameters

Parameter	Recommendation
Reconstruction Technique	Either filtered back projection or iterative reconstruction are acceptable. If iterative reconstruction is used, the strength/weighting should be intermediate (e.g. ADMIRE/SAPHIRE/IRIS strength 3, ASIR 40%)
Slice thickness	Thinnest possible, e.g. 0.625 with GE and Philips hardware, 0.6mm with Siemens Hardware, 0.5mm/0.25mm with Toshiba hardware
Slice overlap	Slice overlap is recommended to improve MPR quality; e.g. 0.4 mm increment with 0.6 mm slice thickness when using Siemens equipment
Reconstruction field of view and matrix	Small field of view (FOV) limited to the heart; 512 x 512 matrix
Reconstruction kernel	Same kernel as used for coronary CTA per institutional standard; alternatively use edge-pronounced kernel ('stent' kernel, e.g. l46f) in particular with pronounced blooming,
Multiphasic reconstruction	Coverage of the entire cardiac cycle: Volume scanner (GE Revolution, Philips iCT256, Toshiba Aquilion One/Vision): <ul style="list-style-type: none"> • 5% or 10% increments Other scanner: <ul style="list-style-type: none"> • 5% or 10% increments (relative reconstruction), • 50ms increments (absolute reconstruction)

R-peak recognition

Prior to image reconstruction, the ECG-stripe should be reviewed to ensure that the scanner correctly sensed the R-peaks for timing of image reconstructions. Commonly, if R-peak recognition was incorrect, such as in the case of weak ECG-signal or artifacts, R-peak recognition and thus image synchronization can be manually corrected. This applies for both ECG-gated, 'one-beat, one-slab' volume acquisition as well as helical acquisition with retrospective ECG-gating.

ECG-editing with retrospective ECG-gating

Due to low pitch values, and thus redundant image data sampling, helical acquisition with retrospective ECG-gating allows for ECG-editing to improve the quality of image reconstructions. ECG-editing is particularly useful in the setting of

- Atrial fibrillation
- Premature atrial and ventricular contractions (PACs and PVCs)

Atrial fibrillation and ectopic heart beats result in RR-intervals of significantly different length, leading to stair-step and double-contour artifacts.

In case of premature contractions, ECG-editing aims at avoiding image reconstruction which uses image data from RR-intervals which are affected by the premature contractions. Importantly, these may differ in regard to diastolic or systolic image reconstruction. It is important to understand how and which RR-intervals are affected by premature contractions.

- Preceding RR-Interval which is terminated by PVC/PAC: Shortening of diastole of the preceding RR-interval (e.g. missing mid/end-diastolic image data in case of diastolic image reconstruction)
- RR-Interval beginning with PVC/PAC: Relative shift of cardiac phases within the ectopic RR-interval due to reduced LV loading within the shortened preceding RR-interval.
- Subsequent RR-Interval (only with PVC): Due to increased LV filling during compensatory pause, LV ejection increases in the subsequent RR-interval.

In particular, in coronary CTA, end-systole has been proven to be the cardiac phase yielding most reliable image quality, in particular when using high temporal resolution systems such as dual-source scanners. This is because end-systole can be considered the most stable phase within the cardiac cycle in regard to impact of increased heart rate variability with varying length of the RR-intervals. While the position of end-systole in the cardiac cycle is directly related to the length of the LV ejection time, it remains fairly constant with regard the absolute distance from the R-peak in msec.

The length of the preceding RR-interval determines the LV filling state, and thus the length of the LV ejection time and position of end-systole (Figure 4).

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- If the preceding RR-interval is shorter, LV filling is reduced and the subsequent LV ejection time is shorter, i.e. end-systole is closer to the R-peak.
- If the preceding RR-interval is longer, LV filling is increased and the LV ejection time is longer, i.e. end-systole is closer to the R-peak.

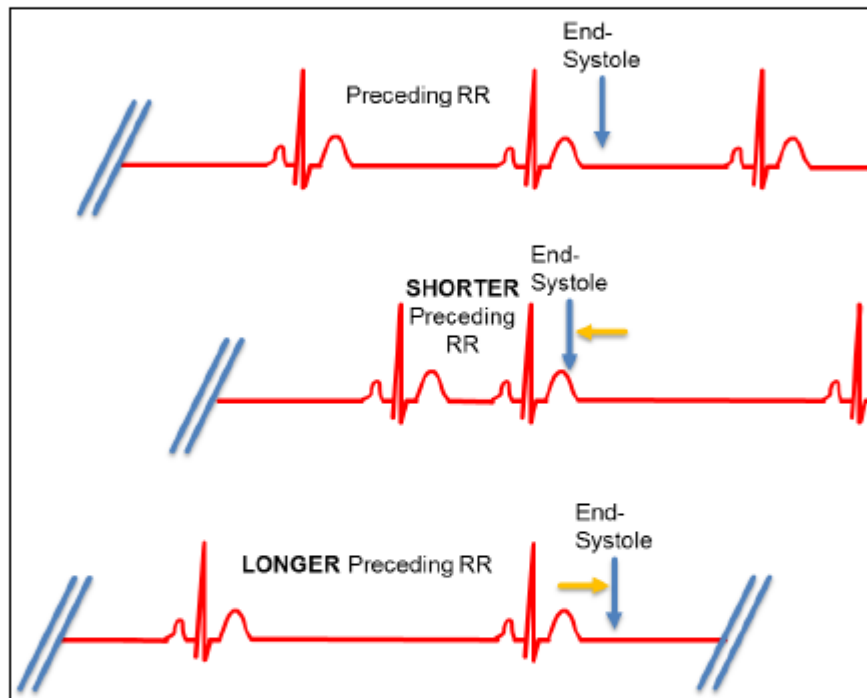


Figure 4 – Dependency of the position of end-systole on the length of the preceding RR-interval. The length of the preceding RR-interval determines the LV filling state, and thus the length of the LV ejection time and position of end-systole.

The above stated relationship is important to understand its influence on end-systole timing in premature contractions and atrial fibrillation. Importantly, there are differences between PACs and PVCs with regard to the subsequent RR-interval following the RR-interval beginning with the PAC/PVC (Figure 5).

Premature atrial contraction:

1. The RR-interval prior to the PAC is shortened, often missing mid-/end-diastole.
2. The RR-interval beginning with the PAC, end-systole shifts towards the R-peak.
3. The subsequent RR-interval is not affected.

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Premature ventricular contraction:

1. The RR-interval prior to the PVC is shortened, often missing mid-/end-diastole.
2. The RR-interval beginning with the PVC, end-systole shifts towards the R-peak.
3. The subsequent RR-interval is affected, as the RR-interval beginning with the PVC is elongated due to the compensatory pause, leading to increased LV filling and shift of end-systole in the subsequent RR-interval.

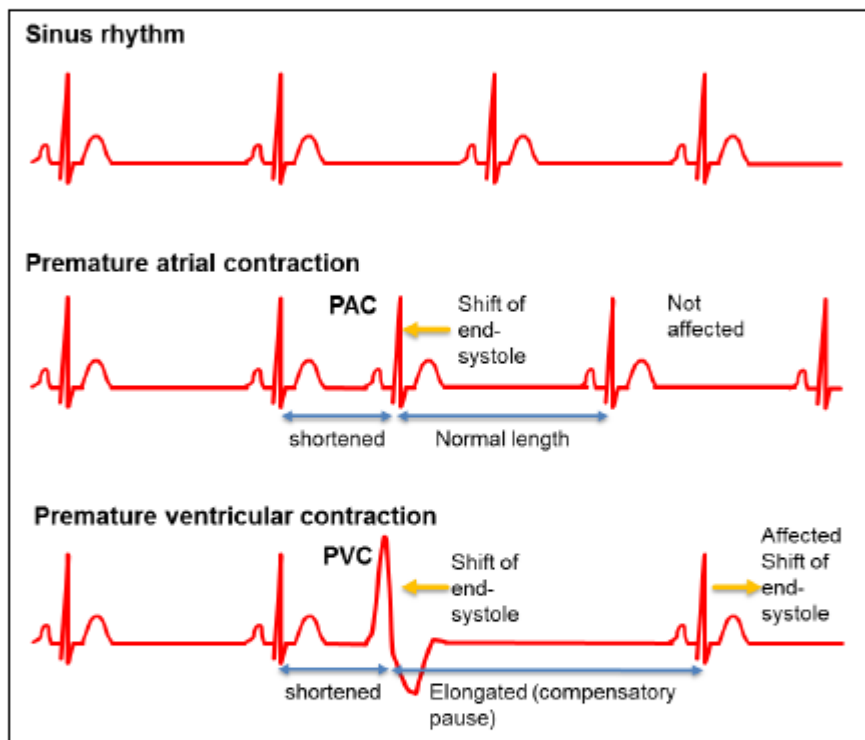


Figure 5 – Influence of PACs/PVCs on the position of end-systole.

Helical acquisition with retrospective ECG-gating and its inherent low pitch values with redundant image data sampling, allows for ECG editing to help eliminate the negative impact of premature ventricular contractions. This is performed by manually deselecting specific RR-intervals that contain extra-systoles.

In the setting of PACs or PVCs, the following approach is recommended when performing end-systolic image reconstruction using an absolute [msec] reconstruction technique (Figure 6):

1. Keep reconstruction window in shortened RR-interval which is terminated by PAC/PVC, as position of end-systole is not affected.
2. Eliminate reconstruction window in RR-interval beginning with PAC/PVC, as position of end-systole is altered, being closer to the R-peak.
3. Only in PVCs the subsequent RR-interval is affected, given the compensatory pause with increased LV filling. If possible without resulting in a data gap, the reconstruction window in the subsequent should be deleted/deactivated.

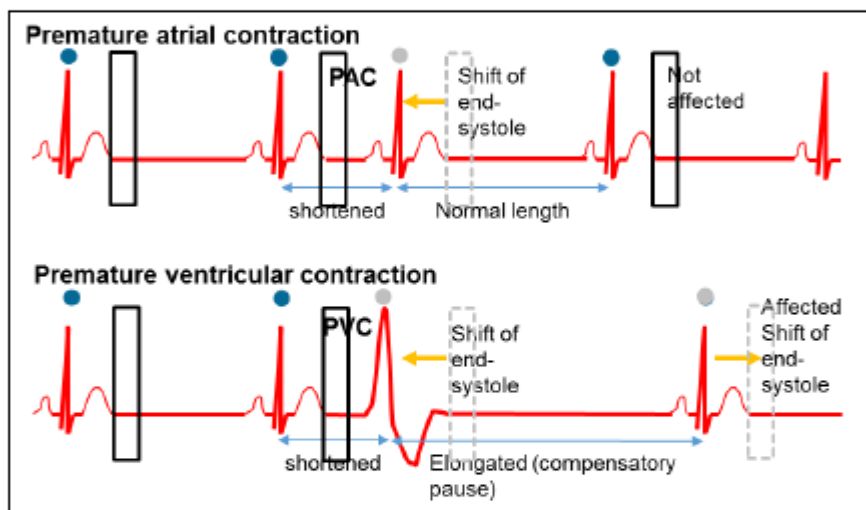


Figure 6 – Approach to end-systolic data reconstruction in PACs/PVCs using ECG-editing and absolute (msec) reconstruction.

The situation is very different, when diastolic images are being reconstructed. In the setting of PACs or PVCs, the following approach is recommended when performing diastolic image reconstructions (commonly with relative [%] reconstruction) (Figure 7):

1. Eliminate reconstruction window in the RR-interval which is terminated by the PAC/PVC, if this RR-interval is shortened (most commonly). Note: Shortening of the RR-interval impacts the absolute position of the reconstruction window when using a percentage/relative reconstruction. Furthermore, lack of mid-/late-diastolic data would also interfere with absolute reconstruction.
2. If possible, also eliminate reconstruction window in RR-interval beginning with PAC/PVC.
3. In PVC, the subsequent RR-interval may be affected, but data gap may not allow for deletion.

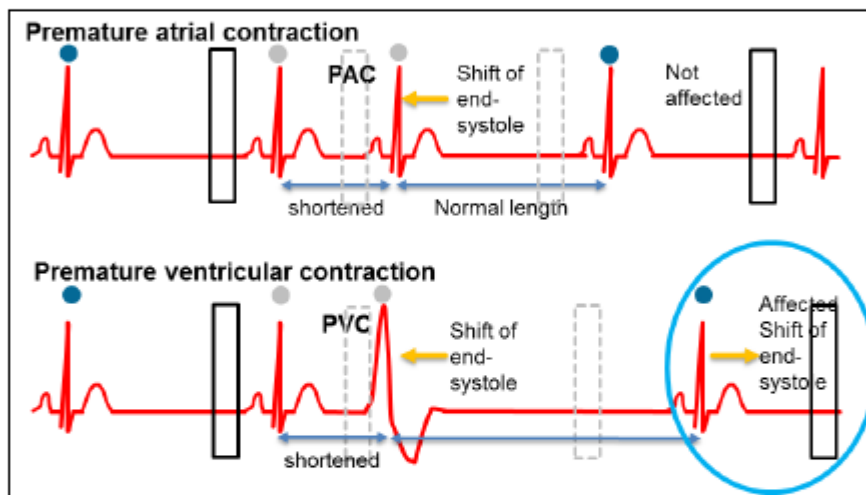


Figure 7 -- Approach to diastolic data reconstruction in PACs/PVCs using ECG-editing and relative (%) reconstruction.

5. Submitting CT Images

Refer to Appendix K-1 for CT submission instructions.

Appendix L Histopathology

1.0 Purpose

The purpose of the following protocol is to provide the Investigator (clinical site) with procedures for handling and assessing the study valve after explantation. The assessment should include gross examination, identification of the primary failure mode and contributory factors leading to the explant (if possible), photographs and other documentation, and preparation of the explanted valve for shipment to the Sponsor or designated Histopathology Laboratory for further analysis. Also, included is an overview of the procedures to be followed by the Sponsor and/or designated Histopathology Laboratory for gross analysis, as well as macro and micro histopathology analysis. Investigational valves that are removed at any time an allegation of device malfunction should be returned to the Sponsor for evaluation. All other explants (those not with an allegation of device malfunction) should be sent to the Histopathology Core Lab. Refer to section 6.0 for tissue shipment information.

2.0 Valve Explanation Procedure

Upon autopsy (only), prior to removal of the valve from the heart, obtain *in situ* photographs of the inflow and outflow tracts, valve leaflets, and conduit tissue. Using care, the valve should be excised in a fashion so as to keep the valve and surrounding structure as intact as possible.

For all explants (those obtained at autopsy as described above or through valve replacement surgery following standard surgical practice), once removed the valve should be rinsed of all residual blood by gently agitating in sterile Lactated Ringers solution.

Prior to shipment of the valve to the Sponsor or designated Histopathology Laboratory for further dissection and pathologic analysis, grossly examine the explanted tissue *in toto* and record observations on the explanted valve CRF. Gross photographs will be taken of both inflow and outflow tracts. Observations of stent frame apposition and neointimal incorporation will be documented.

Swab cultures of possibly infected areas should be taken, sent to the appropriate laboratory and documented in the pathology report. If no infection is obvious, then no culture swab is necessary.

3.0 Tissue Dissection Procedure

Once the valve has been explanted, grossly examined, and photographed, the tissue should be sent to the Sponsor or designated Histopathology Laboratory for histological analysis. Place the sample into a specimen cup or equivalent container. The specimen cup should contain 10% buffered formalin solution. On the outside of the container, label the study patient number, valve serial number, site number, and date of explant. The tissues will be examined at the Sponsor or designated histopathology laboratory to determine the morphology of the tissue/valve, as well as to assess leaflet calcification, and general histopathology. The valve tissues will be stained with H&E, Von Kossa, or other relevant stains and will be reviewed by a certified pathologist.

4.0 Fixation

Explanted study valve samples shall be submitted in 10% formalin.

5.0 Documentation

Please provide the following supporting documents to enable complete explant assessment. The documents should enable the Sponsor to determine explant date, duration of implant, surgical pathology, mediating study patient history, reason for reoperation, gross description, and pathology notes. The documents may be returned with the shipped tissue.

- Operative report dictated at the explant
- Sponsor Case Report Forms
- Pathology report (once available)
- Blood study results (once available)
- Preoperative Echocardiographic Report (Just Prior to Explant)

6.0 Tissue Shipment

Investigational valves that are removed at any time with an allegation of device malfunction should be returned to the Sponsor for evaluation. Contact your sponsor representative for assistance with the return which will include a Compliant Report (completed by the Sponsor) and biohazard packaging.

Shipping Address:

Edwards Lifesciences LLC
1212 Alton Pkwy
Irvine, CA 92606
Attention: Returned Goods
CER/RGA#: _____

Investigational valves that are removed for any reason other than an allegation of device malfunction should be sent to the Histopathology Laboratory. Place the specimen container within two, separately sealed biohazard plastic bags. Place the sealed sample in a small non-crushable box. Ship the tissue to the Sponsor's designated Histopathology Laboratory by Federal Express PRIORITY (Sponsor billing number 0900-2768-9) or equivalent shipping service:

Histology Core Laboratory: Renu Virmani, MD
CV Path Institute, Inc.
19 Firstfield Road
Gaithersburg, MD 20878
Phone: 301-208-3745 Ext. 105

7.0 Procedure for Evaluation at Sponsor or Designated Histopathology Laboratory

Gross Examination and Photographs:

If possible, photographs should be taken at each stage of dissection to better document observations. Assessment of the valve leaflets and commissures will include presence of leaflet fenestrations, tears, thrombus formations and calcified nodules. Photographs will be taken of all suspected abnormalities. The gross examination should include macroscopic assessment of the following:

Mobility and shape of leaflets;
Host tissue overgrowth;
Leaflet wear or degeneration;
Leaflet thickness;
Leaflet fenestrations;
Fibrosis sheathing;

Calcification (leaflet and conduit);
Evidence of infection;
Aneurysm formation;
Valve thrombosis;
Tissue rejection;
Inflammation.

8.0 Radiographic Analysis

Additionally, X-rays will be taken of all valve/devices to assess placement and apposition of the stent frame to the host vessel and to identify leaflet calcification. X-rays will be in both transverse and longitudinal planes.

9.0 Dissection and Sampling

A portion of each valve assembly, to include one commissure and one half of each adjacent valve leaflet, will be removed from the assembly and submitted for scanning electron microscopic examination. The portion will be removed by making two longitudinal cuts through the length of the host vessel and metal stent frame. The remaining valve leaflets will be excised away at the point of attachment to the assembly.

Scanning Electron Microscopy

Scanning electron microscopy will be employed to assess degree of intimal incorporation of the metal stent frame, endothelial coverage of the host vessel neointima and valve leaflets. Leaflet surface topology will be assessed and any defects in the surface identified.

10.0 Histopathology Evaluation

Paraffin:

Valve leaflets will be inked on the outflow surfaces to maintain orientation. Serial slices of the leaflets will be made from base to free edge and flat embedded for cross-sectional examination. Hematoxylin and eosin, trichrome, Movat pentachrome, Von Kossa calcium, and Phosphotungstic acid-hematoxylin stains will be performed on all sections.

Plastic:

The remaining valve assembly (minus the portion removed for SEM) will be processed and embedded in methylmethacrylate plastic. Transverse sections will be sawed and ground from the area of the superior tip of the first stent strut (proximal end), from the mid portion near the proximal end of the short bar assembly (not to include PET skirt) and from the distal end through the short bar assembly and commissures.

Transmission electron microscopy (TEM)

One half of each valve leaflet from the mid-portion will be reserved for transmission electron microscopy. The section will be of full leaflet thickness, flat embedded in epoxy resin and cross-sectioned. TEM will be employed to assess collagen integrity and calcium deposition.

Explant Shipping Form

Please enter the following information and fax the form to CV Path at (301) 208-3745 24 hours prior to shipment.

Ship to:
TBD

Protocol #: <u>SAPIEN 3 Expanded Indication</u>	Subject ID: _____
Sponsor: <u>Edwards Lifesciences</u>	Device Type: <u>SAPIEN 3™ THV</u>
Study Site: _____	Site Principal Investigator: _____

Item Shipped (Serial Number)	Sender: Print Name / Signature	Date Harvested (If available)	Shipping Tracking Number	Date Sent

Comments:

Please keep a copy of this form in the subject study file. If possible, please include a copy of this form in the package

Appendix M EQ-5D-5L



Health Questionnaire

English version for the UK

Sample

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

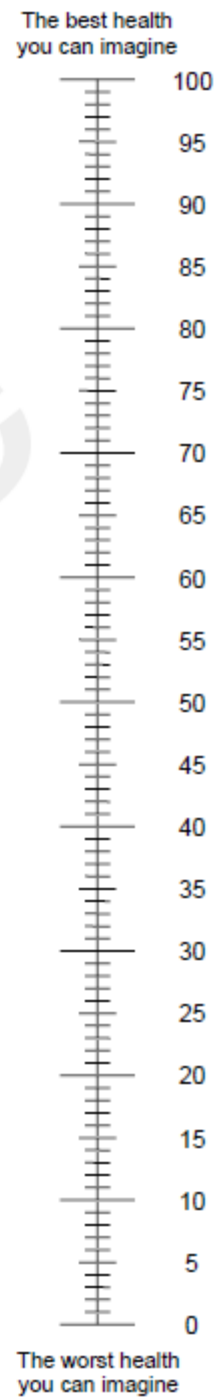
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Appendix N Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

- Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Showering/Bathing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking 1 block on level ground	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Doing yardwork, housework or carrying groceries	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climbing a flight of stairs without stopping	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hurrying or jogging (as if to catch a bus)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become...

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

- | | | | | |
|--------------------------|---|--------------------------|--------------------------|-----------------------------|
| Every morning | 3 or more times a week, but not every day | 1-2 times a week | Less than once a week | Never over the past 2 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

- | | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not at all bothersome | I've had no swelling |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

- | | | | | | | |
|--------------------------|--------------------------|--------------------------|--|--------------------------|--------------------------|-----------------------------|
| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1-2 times per week | Less than once a week | Never over the past 2 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

- | | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Extremely bothersome | Quite a bit bothersome | Moderately bothersome | Slightly bothersome | Not at all bothersome | I've had no fatigue |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

- | | | | | | | |
|--------------------------|--------------------------|--------------------------|--|--------------------------|--------------------------|-----------------------------|
| All of the time | Several times per day | At least once a day | 3 or more times per week but not every day | 1-2 times per week | Less than once a week | Never over the past 2 weeks |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

- | | | | | |
|---|--|--|---------------------------|--------------------------|
| I felt that way
all of the time | I felt that way
most of the time | I occasionally
felt that way | I rarely felt that
way | I never felt that
way |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an X in one box on each line

Activity	Severely limited	Limited quite a bit	Moderately limited	Slightly limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Working or doing household chores	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Visiting family or friends out of your home	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intimate relationships with loved ones	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix O SF-36

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot ▼	Yes, limited a little ▼	No, not limited at all ▼
a <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d Climbing <u>several</u> flights of stairs.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e Climbing <u>one</u> flight of stairs.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f Bending, kneeling, or stooping.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h Walking <u>several hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i Walking <u>one hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j Bathing or dressing yourself.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

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4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Were limited in the kind of work or other activities 1..... 2..... 3..... 4..... 5
- d. Had difficulty performing the work or other activities (for example, it took extra effort) 1..... 2..... 3..... 4..... 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... 1..... 2..... 3..... 4..... 5
- b. Accomplished less than you would like 1..... 2..... 3..... 4..... 5
- c. Did work or other activities less carefully than usual..... 1..... 2..... 3..... 4..... 5

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6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a. Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e. Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f. Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g. Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h. Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i. Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. I am as healthy as anybody I know.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

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Appendix Q Actigraphy/QOL Sub-Study QOL measures [Enrollment Closed]

Visual Analogue Scale (VAS) ¹

A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain. From the patient's perspective this spectrum appears continuous \pm their pain does not take discrete jumps, as a categorization of none, mild, moderate and severe would suggest. It was to capture this idea of an underlying continuum that the VAS was devised.

Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, as illustrated in Fig. 1. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks. There are many other ways in which VAS have been presented, including vertical lines and lines with extra descriptors. As such an assessment is clearly highly subjective, these scales are of most value when looking at change within individuals.

Figure 1 VAS example

How severe is your pain today? Place a vertical mark on the line below to indicate how bad you feel your pain is today.

No pain | _____ | Very severe pain

PF-10 Health Survey²

The Optum™ PF-10 Health Survey is a Health Survey that uses just 10 questions to measure physical health and well-being from the patient's point of view.

Taking only two to three minutes to complete, the PF-10 is a practical, reliable and valid measure of physical health and is particularly useful in large population health surveys or for applications that combine a generic and disease-specific health survey.

As the survey uses norm-based scoring, comparisons can be made among the other generic health surveys (SF-36v2® and SF-8™). It is a widely used tool for monitoring population health, comparing and analyzing disease burden and predicting medical expenses.

The PF-10 is available in multiple modes of administration and in both standard four-week and acute one-week recall periods.

KCCQ-12³

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, self-administered instrument that quantifies physical function, symptoms (frequency,

severity and recent change), social function, self-efficacy and knowledge, and quality of life.

In the KCCQ, an overall summary score can be derived from the physical function, symptom (frequency and severity), and social function and quality of life domains. For each domain, the validity, reproducibility, responsiveness and interpretability have been independently established. Scores are transformed to a range of 0-100, in which higher scores reflect better health status.

The KCCQ-12 reduces the **KCCQ's** 23 items to 12. This short version significantly increase the speed and ease of questionnaire administration while preserving the sensitivity, specificity, and reliability of the original instruments.

¹ VAS source: <http://buderimosteopathy.com.au/wp-content/uploads/2012/02/VAS.pdf>

¹ <https://www.optum.com/optum-outcomes/what-we-do/health-surveys/sf-12v2-health-survey.html>

¹ <http://cvoutcomes.org/pages/3214>