Optimize PRO Study

NCT: 04091048

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Medtronic

Clinical Investigation Plan Addendum

Clinical Investigation Plan/Addendum Title	Optimize PRO TAVR Post Market Study – FX Addendum
Study Product Name	Medtronic Evolut™ FX System
Sponsor/Local Sponsor	Medtronic, Inc. Structural Heart Clinical [redacted]
Document Version	3.0, 15 December 2022
Co-Principal Investigators	Dr. Kendra Grubb Emory University Hospital [redacted] Dr. Steven Yakubov Riverside Methodist Hospital / Ohio Health Research Institute [redacted]

Confidentiality Statement

1. Investigator Agreement and Signature Page

Study product Name	Medtronic Evolut™ FX System
Sponsor	Medtronic Structural Heart Clinical
Version Number/Date	3.0, 15 December 2022

I have read the Optimize PRO Clinical Investigation Plan – FX Addendum and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with local and internal institutional requirements including the Optimize PRO Study Protocol, Optimize PRO – FX Addendum, GCP, and ethical principles that have their origin in the Declaration of Helsinki.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical study without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol addendum and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study addendum.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Refer to the Optimize PRO parent protocol for a glossary of terms.

3. Synopsis

Title	Optimize PRO – FX Addendum
Devices	Medtronic Evolut™ FX TAV System
Sponsor	Medtronic Structural Heart Clinical Research
FX Addendum Principal Investigator	Dr. Hemal Gada
Product Status	Only commercially approved product will be used.
Study Objective	The purpose of this addendum is to collect post-market clinical evidence on valve performance and procedural outcomes associated with the Evolut FX Device.
Primary Endpoint	Rate of all-cause mortality or all-stroke at 30 days
Secondary Endpoints	• Median days from index procedure to discharge • Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge • Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days • Percentage of subjects with a Non-Coronary Cusp (NCC) depth of implant between 1.0 and 5.0 mm • Percentage of subjects with a canting absolute value |NCC — Left Coronary Cusp (LCC)| of ≤ 2.0 mm
Additional Exploratory Endpoints	• 30-day and 1-year hospital re-admission rates • 1-year composite of all-cause mortality or all-stroke • Percent of patients with a major vascular complication • Percent of patients that require a recapture or resheath of the TAV • Percent of patients in which the target depth of implant was achieved • Orientation of valve relative to native anatomy
Study Design	Post-market, multi-center, prospective, non-randomized
Sample Size	Approximately 10 sites in the United States with approximately 150 subjects

Patient Population	Subjects with severe, symptomatic aortic stenosis (AS) necessitating valve replacement
Duration	Total addendum duration is estimated to be 24 months (time from first subject implanted to one-year follow-up on last subject implanted)
Key Inclusion Criteria	• Acceptable candidate for treatment with the Evolut FX system in accordance with the Instructions for Use and local regulations • Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater • Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits • Anatomically suitable for transfemoral TAVR with the Medtronic TAVR system • Subject meets the legal minimum age to provide Informed Consent based on local regulatory requirements

Key Exclusion Criteria	• Contraindicated for treatment with the Evolut™ FX system in accordance with the Instructions for Use
	• Anatomically not suitable for the Evolut™ FX system
	• Previous aortic valve replacement
	• Reduced ventricular function with left ventricular ejection fraction (LVEF) < 35% as measured by resting echocardiogram
	• Frailty assessments identify:
	  ○ Subject is <80 years of age and three or more of the following apply; OR subject is ≥ 80 years of age and two or more of the following apply
	  ▪ Wheelchair bound
	  ▪ Resides in an institutional care facility (e.g., nursing home, skilled care center)
	  ▪ Body Mass Index <20kg/m^2
	  ▪ Grip strength <16kg
	  ▪ Katz Index score ≤4
	  ▪ Albumin <3.5 g/dL
	• Bicuspid valve verified
	• Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70°
	• Implanted with pacemaker or ICD
	• Prohibitive left ventricular outflow tract calcification

	• Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions • Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent, adherence to the protocol required follow-up exams • Currently participating in an investigational drug or another device trial (excluding registries) • Need for emergency surgery for any reason • Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable
Study Procedures and Assessments	• Clinical assessment at baseline, discharge, 30 days, and 1 year • Transthoracic echo at baseline, discharge, and 1 year • Multi-Detector Computed Tomography at baseline and anytime post-procedure through the 30-day visit (contrast required for post-procedure CT) • Quality of Life pre- and post-procedure, 30 days, and 1 year • 12-lead ECG at pre- and post-procedure, discharge, 30 days, and 1 year

4. Introduction

4.1. Parent Study

The Optimize PRO Clinical Investigation Plan (Parent protocol or Parent CIP) is the governing document for this addendum. Always refer to the most recent version of the parent protocol for details not described within this addendum. The purpose of this addendum is to provide details and requirements unique to participation in the FX addendum portion of the study.

4.2. Purpose

The purpose of this addendum is to collect post-market clinical evidence on valve performance and procedural outcomes associated with the Evolut FX Device.

5. Objective and Endpoints

5.1. Objective

The purpose of this addendum is to collect post-market clinical evidence in the United States, on valve performance and procedural outcomes associated with the Evolut FX Device.

5.2. Endpoints

The following endpoints will be used to evaluate valve performance and procedural outcomes associated with the Evolut™ FX System.

5.2.1. Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all stroke at 30 days.

5.2.2. Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days
- Percentage of subjects with an NCC depth of implant between 1.0 and 5.0 mm
- Percentage of subjects with an absolute canting value |NCC-LCC| of ≤ 2.0 mm

5.2.3. Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates
- 1-year composite of all-cause mortality or all-stroke
- Percent of patients with a major vascular complication
- Percent of patients that require a recapture or resheath of the TAV
- Percent of patients in which the target depth of implant was achieved
- Orientation of valve relative to native anatomy

5.2.4. Rationale

The basis for the selection of these study endpoints include:

- Clinically relevant outcomes of the Evolut™ FX System

- Objectively defined and measurable in the majority of subjects
- Consistent with current recommendations for endpoints in TAVR clinical studies[1]

6. Study Design

This is a post market, multi-center, prospective, non-randomized study. The study methods include the following measures to minimize potential sources of bias:

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- Core labs will evaluate all echocardiograms; echocardiographic trial endpoint results will be based on Core Lab assessments.
- Subjects will be screened to confirm eligibility for enrollment with pre-defined inclusion and exclusion criteria.

6.1. Duration

The enrollment period is estimated to be approximately 12 months and subjects will be followed for one year post index procedure; therefore, the estimated total duration of the addendum (first subject enrolled to last subject completing his/her last follow-up exam) is estimated to be approximately 24 months.

6.2. Study Oversight

Refer to the Optimize PRO Parent Protocol for details of study oversight.

6.3. Trial Organization

Refer to the Optimize PRO parent protocol for details on participating site requirements, site principal investigators (PIs), site heart teams, the publications committee, and trial training.

7 Product Description

7.1 Description of Devices

7.1.1 Medtronic Evolut FX System

The Medtronic Evolut FX System is a TAVR implantation system comprised of the following 3 components (Table 1):

- Medtronic Evolut FX TAV
- Medtronic Evolut FX DCS
- Medtronic Evolut FX LS

The system components for the Evolut FX System are shown in Table 1 and detailed descriptions provided in Sections 7.1.2.1, 7.1.2.2 and 7.1.2.3. A summary of features unique to the Evolut FX System is shown in Figure 1.

Table 1. Evolut™ FX System Components

Component	US Model Number	Size (mm)	Aortic Annulus Diameter (range in mm)
Medtronic Evolut FX TAV	EVOLUTFX-23	23	18 – 20
	EVOLUTFX-26	26	20 – 23
	EVOLUTFX-29	29	23 – 26
	EVOLUTFX-34	34	26 - 30
Evolut FX DCS (18 Fr/14eFr)	D-EVOLUTFX-2329	Used with 23, 26, and 29 mm TAVs	Not applicable
Evolut FX DCS (22 Fr/18eFr)	D-EVOLUTFX-34	Used with 34 mm TAVs	Not applicable
Evolut FX LS	L-EVOLUTFX-2329	Used with 23, 26, and 29 mm TAVs	Not applicable
	L-EVOLUTFX-34	Used with 34 mm TAVs	Not applicable

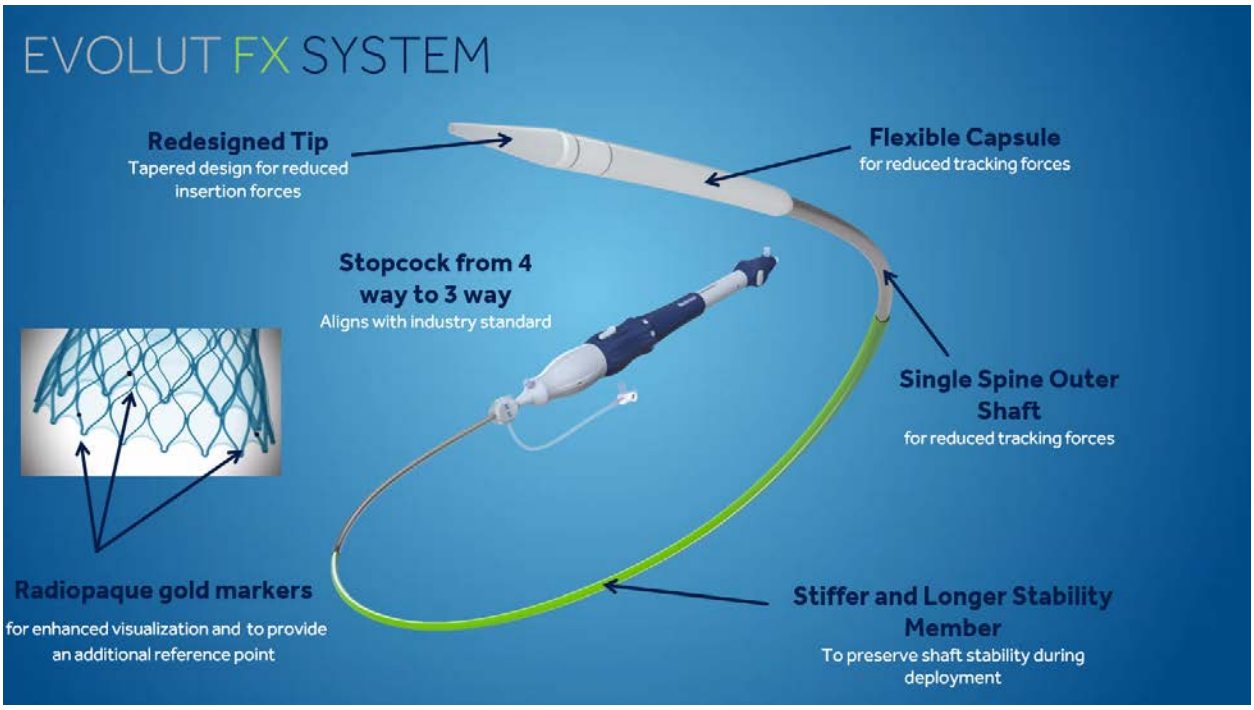

Figure 1. Evolut FX System – changes from Evolut PRO+ include radiopaque gold markers for enhanced visualization, a single spine outer shaft, longer and stiffer stability member, flexible capsule, 3 way stopcock, and redesigned tip.

7.1.2.1 Medtronic Evolut FX Transcatheter Aortic Valve

The Medtronic Evolut FX TAV is available in 4 sizes (23, 26, 29, & 34mm), covering an aortic annulus diameter of 18 to 30 mm. For the 26mm and 29mm bioprostheses: If the patient's annulus diameter is within 0.5 mm of the upper or lower bound of the range, use of the larger valve size can be considered, provided additional dimensional criteria as outlined in the Clinical Investigation Plan (CIP) are met. The TAV is comprised of 3 leaflets, a sealing skirt, and outer tissue wrap constructed from glutaraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame, as well as 3 gold radiopaque markers located approximately 3 mm from the inflow of the frame. These radiopaque markers are aligned below the 3 tissue commissure pads, between the inner tissue skirt and the outer tissue wrap, and serve to enhance visualization during implant. The TAV is processed with an anti-mineralization treatment of AOA, a compound derived from oleic acid, a naturally occurring long-chain fatty acid. With the exception of the markers added to the frame, there are no changes to the frame compared to the Evolut PRO+ TAV.

7.1.2.2 Medtronic Evolut FX Delivery System

The Evolut FX DCS is available in two sizes: 18 Fr and 22 Fr. The 18 Fr FX DCS (hereafter 23-29 mm Evolut FX DCS) is compatible with the Evolut FX 23-29 mm TAVs and the 22 Fr FX DCS is compatible with the Evolut FX 34 mm TAV. The delivery catheter systems are designed to be compatible with commercial 0.035" intravascular wires, and 18 Fr and 22 Fr introducers. The DCS Fr size / TAV compatibility and the compatibility with commercial intravascular wires and introducers is identical to Evolut PRO+. Changes have been made to the tip, capsule, stability member, outer shaft, ILS stopcock and to the handle in order to improve overall ease of use through reduced insertion forces tracking forces of the DCS in tortuous anatomies while preserving stability during deployment.

The DCS consists of a catheter with an integrated handle to assist the user with accurate and controlled deployment. The handle features a gray front grip used to stabilize the system. The deployment knob turns to deploy the bioprosthesis. Arrows on the deployment knob indicate the direction of rotation required to deploy the bioprosthesis. If desired, the deployment knob can be turned in the opposite direction to partially or fully recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the radiopaque paddle attachment. Once the radiopaque capsule marker band reaches the distal end of the radiopaque paddle attachment, it is at the point of no recapture. The deployment knob also features a trigger, which can be engaged to make macro adjustments to the capsule position. The end of the handle features a tip-retrieval mechanism, which can be used to withdraw the catheter tip to meet the capsule after the device has been fully deployed.

7.1.2.3 Evolut FX Loading System

The Evolut FX compresses the bioprosthesis into the catheter. There have been no changes made between the Evolut PRO+ and FX loading systems. This loading system is designed for compatibility with this specific TAV and delivery system.

7.2 Manufacturer

The legal manufacturer and design site of the Evolut FX system is as follows:

Medtronic CoreValve LLC
[redacted]

7.3 Intended Population

The study population includes patients with symptomatic native aortic valve stenosis necessitating valve replacement. Patients who undergo an emergency procedure should not be included in this study.

7.4 Product Training Requirements

The Evolut FX system will be used within the commercially approved indication in the United States, with exception to any inclusion and exclusion criteria in this protocol, and obtained by the study sites according to standard hospital procedures for commercial products. Local existing approved procedures for commercial product regarding training, distribution, shipment, storage, and handling will be followed. In the event of a device malfunction or explant, refer to the Optimize PRO parent protocol.

7.5 Product Labeling, Tracking, and Accountability

Refer to the Optimize PRO parent protocol for product tracking, labeling, and accountability.

7.6 Product Storage

Sites will follow their institutional standard practice for storing commercial TAVR product.

8 Study Site Requirements

8.1 FX Addendum Site Activation

All sites should be activated to the parent protocol prior to, or concurrent with, FX Addendum activation. Full Ethics Committee (EC) or Institutional Review Board (IRB) approval/acknowledgement should be received prior to beginning study activities.

Prior to activation to the addendum, Medtronic will train study site personnel on this clinical investigation plan addendum, and any corresponding changes to the informed consent or data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study addendum related activities.

9 Selection of Subjects

9.1 Study Population

The study population includes patients with symptomatic native aortic valve stenosis that necessitates valve replacement who meet the criteria for on-label use of the Evolut™ FX system in accordance with the Instructions for Use and local regulations.

9.2 Subject Enrollment

This addendum will involve approximately 150 subjects in the US, based on the number of subjects with an attempted TAVR procedure among all active sites. To ensure a widespread distribution of data and to minimize bias in the study results, no site will implant more than 40 subjects without prior authorization from Medtronic. Subjects who exit from the study after implantation will not be replaced.

9.3 Inclusion Criteria

Prospective subjects must meet all of the following inclusion criteria to be eligible for participation:

1. Acceptable candidate for treatment with the Evolut™ FX system in accordance with the commercial Instructions for Use and local regulations
2. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater
3. Subject and the treating physician agree that the subject will return for all required post procedure follow-up visits
4. Anatomically suitable for transfemoral TAVR with the Medtronic TAVR system
5. Subject meets the legal minimum age to provide Informed Consent based on local regulatory requirements

9.4 Exclusion Criteria

Subjects are not eligible for study participation if they meet ANY of the following exclusion criteria:

1. Contraindicated for treatment with the Evolut™ FX system in accordance with the commercial Instructions for Use
2. Anatomically not suitable for the Evolut™ FX system
3. Previous aortic valve replacement
4. Reduced ventricular function with left ventricular ejection fraction (LVEF) < 35% as measured by resting echocardiogram
5. Frailty assessments identify:

- Subject is <80 years of age and three or more of the following apply; OR subject is ≥ 80 years of age and two or more of the following apply
  - Wheelchair bound
  - Resides in an institutional care facility (e.g., nursing home, skilled care center)
  - Body Mass Index <20kg/m^2
  - Grip strength <16kg
  - Katz Index score ≤4
  - Albumin <3.5 g/dL

6. Bicuspid valve verified
7. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70°
8. Implanted with pacemaker or ICD
9. Prohibitive left ventricular outflow tract calcification
10. Estimated life expectancy of less than 12 months due to associated non-cardiac co-morbid conditions
11. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams
12. Currently participating in an investigational drug or another device trial (excluding registries)
13. Need for emergency surgery for any reason
14. Subject is less than legal age of consent, legally incompetent, or otherwise vulnerable*.

** Notes: Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.* [(2)]

10 Study Procedures

10.1 Schedule of Events

Protocol required follow-up evaluations should be performed at the trial site. Remote visits via phone contact are permitted, if necessary. The protocol required evaluations for each trial interval are listed as follows and summarized in Table 2.

10.1.1 Screening and Enrollment Procedures

Refer to the Optimize PRO parent protocol for screening and enrollment procedures. Training specific to implanting the Evolut FX TAV will be required prior to enrolling in the addendum.

10.1.2 Implant Procedure (TAVR) and peri-procedural data collection

Refer to the Optimize PRO parent protocol for details pertaining to the implant procedure, pre- and peri-procedural data collection, including 12-lead ECG timepoints, required laboratory tests, and procedural angiograms confirming cusp overlap view. In addition to the views specified in the Optimize PRO parent protocol, fluoroscopy images in the **LAO view** are required to be saved at the following two time points:

- Prior to crossing the aortic arch
- In the ascending aorta prior to switching to RAO view, ideally immediately prior to crossing the annulus

If the aortic arch is recrossed for the purpose of aligning the commissures, a second set of the two images listed above will be required.

A post-procedure MSCT with contrast has been added for the purpose of assessing coronary-commissure overlap, and can be collected anytime post-procedure through the 30 day follow-up visit.

Procedural aspects specific to the Medtronic TAVR system should be performed according to the Instructions for Use.

The valve deployment will be completed in accordance to the cusp overlap technique via procedural angiogram, and the standard procedures of the implanting physicians and the TAVR clinical pathway protocol requirements noted in the Optimize PRO parent protocol. This described TAVR clinical pathway should serve as a guide for accelerated discharge. Institutional clinical TAVR pathways can be followed as long as the modifications are consistent with an accelerated discharge.

10.1.2.1 External ECG Monitors

The conduction disturbance pathway indicates in some circumstances that the subject should be discharged home with an external ECG monitor (Holter monitor). Holter monitors will be provided to participating sites for the FX addendum.

10.1.3 Follow-Up Evaluations

Refer to the Optimize PRO parent protocol for requirements for 30-day and 12-month follow-up visits. Note a Modified Rankin Score assessment should be conducted at 1 and 3 months following any stroke event.

10.1.3.1 Visit Windows

Day 0 = day of index procedure

- 30 Day (30 + 14 days)
- 12 months (365 ± 30 days)

Table 2. Summary of Visit Schedule and Required Evaluations

	Screening	TAVR Procedure	Discharge	30 Days	12 Months
Informed Consent and HIPAA Authorization	X				
Clinical Assessment (Physical Assessment and Concomitant Medications)	X		X	X	X
NYHA Classification	X		X	X	X
TTE	X		X[6]		X
MSCT Angiogram	X		X[7]		
Procedural Angiogram		X			
Laboratory Test	X		X		
12-Lead ECG[1]		X[5]	X	X	X
Modified Rankin Score[2]	X				
Quality of Life Questionnaires[3]	X			X	X
STS Risks Assessment	X				
Katz Index of Independence in Activities of Daily Living	X				
5-Meter Gait Speed	X				
Grip Strength	X				
Pacemaker Interrogation[4]				X	X
Adverse Event Review		X	X	X	X

[1] Refer to Appendix 18.1 of the Optimize PRO parent protocol - Conduction Disturbance Management for discharge 12-lead ECG requirements.

[2] A Modified Rankin Score assessment should be conducted at 1 and 3 months following any stroke event.

[3] Quality of Life Questionnaires include EQ-5D and KCCQ.

[4] In-office pacemaker interrogations at pacemaker implant, 30-days, and 12 months and CareLink™ Transmissions at 3, 6, and 9 months required for subjects implanted with pacemakers post index TAVR procedure.

[5] ECGs are required within 48 hours pre-procedure and then again within 2 hours post-procedure. Depending on the Conduction Disturbance pathway the subject is in post-procedure, additional ECGs may be required at 24 hours and 48 hours post-procedure.

[6] Discharge TTE should be done between 12 hours and 7 days post TAVR

[7] Post-procedure CT may be conducted anytime post-procedure through the 30 day follow-up visit. This CT must be conducted with contrast to allow for proper assessment of anulus location relative to implanted TAV.

10.1.4 Additional Evaluations for Pacemaker Implants

Refer to the Optimize PRO parent protocol for requirements for interrogation of implanted permanent pacemakers.

10.1.5 Missed Follow-Up Visits

Refer to the Optimize PRO parent protocol for instructions on the handling of missed follow-up visits.

10.1.6 Core Labs

Refer to the Optimize PRO parent protocol for details on Core Labs utilized for this study. The ECG Core Lab will not be utilized for the FX Addendum.

10.1.7 Subject Consent

A separate subject consent form will be provided for this addendum. Refer to the Optimize PRO parent protocol for instructions pertaining to obtaining subject consent and revisions to informed consent forms.

10.2 Assessment of Efficacy

Refer to the Optimize PRO parent protocol for assessments of efficacy.

10.3 Assessment of Safety

Refer to the Optimize PRO parent protocol for assessments of safety including adverse events and device deficiencies.

10.4 Device Malfunction or Explant

Refer to the Optimize PRO parent protocol for instructions pertaining to device malfunction or explant.

10.5 Data Collection

Refer to the Optimize PRO parent protocol for details pertaining to data collection.

10.5.1 Source Documents

Refer to the Optimize PRO parent protocol for source documentation requirements.

10.6 Deviation Handling

Refer to the Optimize PRO parent protocol for details on deviation handling.

10.7 Subject Exit, Withdrawal or Discontinuation

Refer to the Optimize PRO parent protocol for details on subject exit, withdrawal or discontinuation.

11 Risks and Benefits

11.1 Potential Risks

There are possible risks and side effects connected to the Evolut™ FX TAV implant, but the risks are the same as those for an implant of the Evolut FX™ TAV without participation in this study, with the exception of the incremental risks associated with the post-procedure CT scan. Standard risks associated with use of the Evolut™ FX system in the study are provided in the Instructions for Use.

Risks and events will be continuously monitored, assessed, and documented by the investigator.

11.2 Potential Benefits

Participation in this clinical study will not result in any direct benefit to the patient. Trial subjects implanted with an Evolut™ FX device receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to expansion of the knowledge base with respect to the use of the Evolut™ FX system in a routine hospital setting.

11.3 Risk-Benefit Rationale

Refer to the Optimize PRO parent protocol for discussion on risk minimization, alternative therapies, and results from the risk analysis and justification for this study.

12 Adverse Events and Device Deficiencies

Refer to the Optimize PRO parent protocol for requirements pertaining to Adverse Events and Device Deficiencies.

12.1 Emergency Contact Details for Reporting AEs and Device Deficiencies

Investigators should contact their Medtronic clinical trial monitor or site manager if they have any questions regarding reportable AEs. Medtronic will provide and maintain a listing of current contact details for each site.

13 Statistical Design and Methods

13.1 General Aspects of Analysis

13.1.1 Enrolled Population

Within the enrolled population the following analysis sets are distinguished:

- **The attempted implant set:** The attempted implant set consists of all enrolled subjects with an attempted TAVR implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia or conscious sedation administered, vascular line placed, TEE placed, or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure. Enrolled subjects that do not receive an attempted TAVR implant are to be exited from the study.
- **The implanted set:** The implanted set consists of all the attempted implant subjects who are actually implanted with the TAV. Subjects with an attempted implant that do not actually receive a TAV are to be exited from the study following discharge from the index hospitalization.
- **Per protocol (PP) set 1 for TAVR care pathway:** This per protocol set consists of all implanted subjects with percutaneous and transfemoral access only and no concomitant procedures including percutaneous coronary intervention (PCI). This per protocol set 1 will be used for the secondary endpoint median days from index procedure to discharge. Time zero begins on the date of the first attempted implant procedure.
- **Per protocol (PP) set 2 for conduction disturbance pathway:** This per protocol set consists of all attempted implant subjects whose peri and post TAVR index procedure follows the conduction disturbance pathway management and cusp overlap technique. This per protocol set 2 will be used for the secondary endpoint rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days.

The primary analysis for the primary objective and secondary safety and effectiveness objectives will use the attempted implant set.

13.2 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for the attempted implant, implanted, and per protocol sets. Continuous variables will be summarized as means, medians, standard deviations, first and third quartiles, minima and maxima and categorical variables will be summarized as frequencies and percentages.

13.3 Primary Analysis

The study objective and endpoints are descriptive, and no statistical hypothesis testing will be performed. The primary endpoint analysis will be conducted after the last subject has had the opportunity to be followed through 30 days post procedure.

13.3.1 Primary Endpoint

The primary endpoint is the rate of all-cause mortality or all-stroke at 30 days. A Kaplan-Meier survival analysis will be performed with results summarized at 30 days and 12 months. This endpoint is descriptive, and no statistical hypothesis test will be performed.

13.4 Sample Size

This study is not hypothesis driven; therefore, the sample size for the attempted implant population is not guided by statistical principals and is fixed at approximately 150 subjects at approximately 10 sites in the US.

13.5 Secondary Endpoints

The following are the secondary endpoints:

- Median days from index procedure to discharge
- Percentage of subjects with ≥ moderate aortic regurgitation (AR) at discharge
- Rate of pacemaker implant for new onset or worsening conduction disturbance at 30 days
- Percentage of subjects with an NCC depth of implant between 1.0 and 5.0 mm
- Percentage of subjects with a canting absolute value |NCC-LCC| of ≤ 2.0 mm

13.6 Additional Exploratory Endpoints

The following are additional exploratory endpoints:

- 30-day and 1-year hospital re-admission rates
- 1-year composite of all-cause mortality or all-stroke
- Percentage of subjects with a major vascular complication at 30 days
- Percentage of subjects that require a recapture or resheath of the TAV
- Percentage of subjects in which the target depth of implant was achieved
- Orientation of valve relative to native anatomy

13.7 Missing Data

Refer to the Optimize PRO parent protocol for details pertaining to missing data.

14 Ethics

14.1 Statement of Compliance

Refer to the Optimize PRO parent protocol for a statement of compliance.

15 Study Administration

15.1. Monitoring

Refer to the Optimize PRO parent protocol for details pertaining to monitoring.

15.2. Data Management

Refer to the Optimize PRO parent protocol for details pertaining to data management.

15.3. Direct Access to Source Data/Documents

Refer to the Optimize PRO parent protocol for details pertaining to direct access to source data and documents.

15.4. Confidentiality

Refer to the Optimize PRO parent protocol for confidentiality information.

15.5. Liability

Refer to the Optimize PRO parent protocol for liability information.

15.6. CIP Amendments

Refer to the Optimize PRO parent protocol for information on CIP Amendments.

15.7. Record Retention

Refer to the Optimize PRO parent protocol for details pertaining to record retention.

15.8. Publication and Use of Information

Refer to the Optimize PRO parent protocol for details pertaining to publication and the use of study information.

15.9. Suspension or Early Termination

Refer to the Optimize PRO parent protocol for details pertaining to suspension or early termination of the study or individual study sites.

16 Other Institutions and Professional Services

Refer to the Optimize PRO parent protocol for details pertaining to Core Labs and any other professional services provided for this study.

17 References

1. Gilard M et al. Registry of Transcatheter Aortic-Valve Implantation in High-Risk Patients. New England Journal of Medicine 2012:1705-1715.

2. International Standard ISO 14155:2011(E). Clinical investigation of medical devices for human subjects - Good Clinical Practice

18 Appendices

The Post-Procedure CT Requirements are listed below. Refer to the Optimize PRO parent protocol for all other Appendices.

18.1 Appendix I: Post-Procedure MSCT Requirements

18.1.1 General Requirements

- Multi-detector CT scanner (64-slice minimum) with ECG-gating capability.
- ECG-gated contrast enhanced aortic root (slice thickness of ≤1.0 mm).
- Temporal resolution should be optimized to reduce motion artifact.

- Spatial resolution should be as high as possible (goal is smallest isotropic voxel size).

18.1.2 ECG-gated Contrast Enhanced Scan of Aortic Root

Retrospective ECG-gated scans are recommended, which allows for reconstruction in various phases of the cardiac cycle and optimal evaluation of anatomic dimensions and valve morphology. Recommended scan parameters are listed in Table 3.

Prospective ECG-gated sequential scans (step-and-shoot) and high-pitch spiral scans with ECG-gating (flash spiral) are also acceptable. The following parameters are important to the optimum scan:

- Detector collimation 0.4-0.625 mm.
- Slice thickness ≤1.0 mm.
- The recommended coverage area is from superior to the aortic arch to inferior to the cardiac apex. The minimum required coverage area is from 50 mm above the aortic annulus to 10 mm below the aortic annulus.
- The recommended slice overlap is 0.4 mm (will result in isotropic voxels with a 20 cm field of view).

18.1.3 Post-processing

- Retrospective ECG-gated scans
  - Verify heart rate ECG triggers are at consistent place in cardiac cycle, edit if necessary. Additional editing/removal of arrhythmias may be performed.
  - Reconstruct at multiple phases (10 increments of 10%), with ≤1.0 mm slice thickness. If the system has the capability, also reconstruct a “best systolic” and “best diastolic” phase.
- Prospective ECG-gated scans (including flash spiral)
  - Reconstruct with medium soft kernel and slice thickness ≤1.0 mm (slice overlap of 0.4 mm recommended).

Table 3: Recommended Parameters for Post-Procedure MSCT

Parameter	Recommendation
IV injection with iodine contrast	80-100 (320mg/ml or higher), modify per patient as appropriate
Injection rate	4-6 mL/sec
Bolus tracking, delay	Delay time calculated using protocol for current scanner (bolus tracking or similar) with peak of contrast concentration in the ascending aorta during acquisition.
ECG-gating	Retrospective

Scan direction	Cranial-caudal
Scan coverage	From above the aortic arch to past the cardiac apex
Detector collimation	0.4 – 0.625 mm
Pitch	0.2–0.43 adapted to the heart rate
Dose modulation	Modulation and full current between 30 and 80% of the cardiac cycle
Slice thickness	0.8 mm
Slice overlap	0.4 mm
Reconstruction kernel	Medium Smooth
Post-processing	Retrospective ECG gating reconstruction algorithm that minimizes motion artifact. Reconstruct at multiple phases (10 minimum). Reconstructed slice thickness ≤0.8 mm.

19 Version History

Version	Summary of Changes	Author(s)/Title
1.0	New Document	[redacted]
2.0	• Updated wording of objective to reference "FX Device" instead of "FX TAV" • Updated total number of subjects to approximately 150 subjects at approximately 10 sites, with a limit of 40 subjects per site • Updated Moderate AR Secondary Endpoint to be at Discharge instead of 30 Days • Removed statement that FX Valve system will be market released prior to study enrollment as FDA approval has been received. • Updated the duration of the enrollment period and overall study based on increase in sample size • Specified that training specific to implanting the Evolut FX TAV will be required prior to enrolling in the addendum	[redacted]

	• Specified additional fluoroscopy images required prior to crossing aortic arch and immediately before crossing the annulus • Clarified Discharge CT will need to be with contrast • Updated that External ECG (Holter) monitors will be provided to the sites for the FX addendum • Stated ECG Core Lab will not be utilized for FX • Changed primary endpoint timing to after the last subject is followed for 30 days post-procedure • Added appendix with Discharge CT requirements	
3.0	• Expanded window for post-procedure CT to be anytime between TAVR implant and 30 day follow-up visit • Corrected reference 2 to cite International Standard ISO 14155:2011(E) • Added footnote to Table 2 clarifying that discharge TTE should be done between 12 hours and 7 days post TAVR • Corrected interquartile range to first and third quartiles in description of baseline variables • Clarified the Primary Endpoint to occur after the last subject has had the opportunity to be followed through 30 days • Clarified that this study is not hypothesis driven, and that sample size is not determined by statistical principles.	[redacted]