Statistical Analysis Plan: Post-market, prospective evaluation of PHOTO-oxidized decellularized bovine pericardium used as a patch in Vascular repair and reconstruction surgery: PHOTO-V

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PHOTO-V Study
Statistical Analysis Plan

PhotoFix® Decellularized Bovine Pericardium

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SIGNATURE PAGE

The signatures below constitute the approval of this plan and the attachments.

Erin Hurley, Project Manager — Date: 07/27/2018

Karen Sylvester, Senior Project Manager — Date: 07/27/2018

Revision History

Version Date	File Name	Summary of Changes
07/27/2018	*PHOTO-V* Study Statistical Analysis Plan V1.0	Initial Version

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1. INTRODUCTION

1.1. Scope

This document contains detailed information to aid in the production of the Interim Analysis Report and the Final Study Report for the PHOTO-V Study. The contents of this document were written and reviewed by the sponsor, CryoLife, Inc.

1.2. Study Overview

This study is a post-market, prospective, multicenter study designed to evaluate the clinical outcomes of patients receiving PhotoFix® Decellularized Bovine Pericardium (PhotoFix) as a patch within a vascular repair or reconstruction procedure. A goal of 100 patients will be enrolled at approximately 10 sites.

The primary study endpoint for patients with carotid artery stenosis (CAS) undergoing carotid endarterectomies (CEA) will be rate of ipsilateral central neurologic events; the primary endpoint for all other vascular procedures will be primary patency. The secondary endpoints include overall survival, all-cause reoperation rate, device-related reoperation rate, explant rate, restenosis rate, adverse event rate, and secondary patency (hemodialysis access repair (HAR) only). Data will be collected at 5-time points: baseline (pre-operatively), intra-operatively, 1 month post-operatively, 3 months post-operatively, and 6 months post-operatively.

The investigation will be conducted for a period of time required to collect all follow-up, as needed on each patient, but no longer than 7 months after the patient's operation.

1.3. Study Objective

The objective of this post-market clinical follow-up study is to evaluate the clinical outcomes of patients receiving PhotoFix as a patch within a vascular repair or reconstruction procedure.

2. DETAILED STATISTICAL METHODS

2.1. General Statistical Methods

All measured variables and derived parameters will be listed individually in an Excel spreadsheet listing and, if appropriate, tabulated by descriptive statistics. For descriptive statistics, summary tables will be provided. Sample size, frequency, and percentages will be presented for categorical variables. Sample size, arithmetic mean, standard deviation, median, minimum and maximum will be presented for continuous variables.

2.2. Study Population

All consented patients will be included in the basic patient demographics summary; this section will include data collected on the Demographics Electronic Case Report Form (eCRF). All patients who receive PhotoFix as part of their vascular repair or reconstruction surgery will be considered enrolled and included in all additional summaries and analyses.

2.3. Patient Indication, Disposition and Characteristics

The number of patients with each surgical indication will be summarized. Subgroup summaries will be included, as deemed necessary, and based on the sample sizes and apparent differences between the patients.

Change in patient status, including, withdrawals, discontinuations, and screen failures, will be summarized in a disposition table for all subjects. Reasons for any discontinuation will also be categorized and summarized appropriately.

2.4. Demographics and Patient Baseline Characteristics

Patient demography will be presented using summary statistics (sample size, mean, standard deviation, median, minimum and maximum) for continuous measurements, or frequency tables (numbers and percentages) for categorical measurements.

2.5. PhotoFix Patches

The number of PhotoFix patches implanted during each surgery will be presented as frequency counts. Also, the average number of PhotoFix patches implanted will be summarized as a continuous outcome. The size of PhotoFix patches implanted, as indicated on the box, will be included as a summary table. The size of implanted PhotoFix patches will be described using summary statistics for continuous measurements (sample size, mean, standard deviation, median, minimum and maximum).

2.6. Operative Characteristics

Operative details, including surgical description, concomitant procedure description, ability to detect patch sidedness, and patch implant technique, will be presented using frequency tables. Surgery descriptions will be manually categorized, as deemed appropriate. Concomitant surgical procedures will also be manually categorized, as deemed appropriate.

2.7. Concomitant Statins and Blood Thinners

Medications will not be coded. Concomitant medications will be defined as any medication that stops on or after the day of consent. All medications will be presented in a data listing. Summary statistics of patients on statins and blood thinners will be presented individually, as numbers and percentages.

2.8. Study Evaluations

All summaries will be presented in aggregate; subgroup summaries, by indication, will be included, as deemed appropriate.

2.9. Definition of Analyses

All analyses will focus on outcomes reported during the follow-up period, after PhotoFix implant. Analyses will summarize data collected through the end of follow-up; analyses at each time point are not planned, unless otherwise indicated.

2.9.1 Primary Analysis

- (Carotid Endarterectomy Only)
  Incidence of Central Neurologic Events:
  - Percent of patients who experienced at least one transient ischemic attack
  - Percent of patients who experienced at least one case of amaurosis fugax
  - Percent of patients who experienced at least one stroke
  - Percent of patients who experienced symptomatic carotid occlusion at least once
  - Percent of patients who experienced any of the central neurologic events of interest at least once
- (All Non-Carotid Indications)
  Primary Patency:
  - Time from PhotoFix implantation to the time when patency in the vessel is documented as lost
    - Loss of patency includes loss of previously palpable pulses, presentation of recurrent symptoms, a drop in ABI>0.15 in the case of lower limb artery repair, Doppler ultrasound findings of occlusion, angiography of the affected vessel or a combination of these.

Loss of patency will also be considered if an intervention to restore or maintain patency is documented. In the event that loss of patency is documented as "no" on the Follow-up eCRFs and evidence of an intervention involving patency restoration is reported on the Adverse Event eCRF, a query will be issued and resolved appropriately.

2.9.2 Secondary Analysis

- **Overall Survival:**
  - Percent of patients surviving
    - *Early mortality*: Death < 30 days following PhotoFix implantation
    - *Late mortality*: Death ≥ 30 days following PhotoFix implantation
- **All-Cause Reoperation Rate:**
  - Percent of patients requiring reoperations
    - Reoperation includes the repair or alteration of the surgical area around the patch.

- **Device-Related Reoperation Rate:**
  - Percent of patients requiring unplanned reoperations that are documented as possibly, probably or definitely, device-related
- **Explant Rate:**
  - Percent of patients requiring device explants
    - Explants will include the removal of PhotoFix for any reason after implantation.
- **Adverse Event Rate**:
  - Percent of patients who experienced at least one adverse event
  - Percent of patients who experienced at least one device-related adverse event
- **Restenosis Rate:**
  - Percent of patients who develop stenosis
    - Stenosis is considered as the recurrence of abnormal narrowing of an artery or vein after corrective surgery.
    - Categorization of stenosis ≥ 50% will occur if data is available.
- (Hemodialysis Access Repair only)
  Secondary Patency:
  - Time from implantation to the point where the access is abandoned.

2.10. Incidence of Central Neurologic Events

Frequency counts and percentages will be presented in a table for enrolled patients who received PhotoFix during carotid endarterectomy (CEA).

2.11. Primary Patency

A Kaplan-Meier (KM) survival curve for primary patency will be estimated for enrolled patients who received PhotoFix for any non-CEA procedure. Additional KM plots for primary patency may be estimated by surgical indication but will be determined by the sample size of each subgroup; sample sizes of 20 patients or more will be considered to estimate meaningful plots.

2.12. Overall Survival

Frequency counts and percentages will be presented in a table for enrolled patients. A KM survival curve for overall survival will be estimated for all enrolled patients. Additional KM plots for survival may be estimated by mortality category (all-cause mortality, vascular-related mortality, and device-related mortality) but will be determined by the sample size of each subgroup; however, it is unlikely that the sample size will be large enough for subgroup analysis.

2.13. All-Cause Reoperation Rate

Frequency counts and percentages will be presented in a table for enrolled patients. A KM survival curve for freedom from reoperation will be estimated for all enrolled patients. Additional KM plots for freedom from reoperation may be estimated by surgical indication but will be determined by the sample size of each subgroup; however, it is unlikely that the sample size will be large enough for subgroup analysis.

2.14. Device-Related Reoperation Rate

Frequency counts and percentages will be presented in a table for enrolled patients. A KM survival curve for freedom from device-related reoperation will be estimated for all enrolled patients. Additional KM plots for freedom from device-related reoperation may be estimated by surgical indication but will be determined by the sample size of each subgroup; however, it is unlikely that the sample size will be large enough for subgroup analysis.

2.15. Explant Rate

Frequency counts and percentages will be presented in a table for enrolled patients. A KM survival curve for freedom from explant will be estimated for all enrolled patients. Additional KM plots for freedom from explant may be estimated by surgical indication but will be determined by the sample size of each subgroup; however, it is unlikely that the sample size will be large enough for subgroup analysis.

2.16. Restenosis Rate

Frequency counts and percentages will be presented in a table for enrolled patients. A KM survival curve for freedom from restenosis (≥50%) will be estimated for all enrolled patients. Additional KM plots for freedom from restenosis (≥50%) may be estimated by surgical indication but will be determined by the sample size of each subgroup; however, it is unlikely that the sample size will be large enough for subgroup analysis.

2.17. Adverse Events

Adverse events will not be coded. The incidence of adverse events will be summarized for the aggregate sample. Adverse events will be considered as any event happening during or after PhotoFix implant. Any adverse event that occurs prior to surgery will not be included in the summary or analysis.

Adverse events will be summarized based on timing, in relation to surgery. Events will be categorized as early if the event occurs <30 days after surgery, while late post-operative events will be considered as events occurring ≥30 days after surgery.

Adverse events will be summarized by pre-specified category; events classified as other will be manually classified, as deemed appropriate. The following will be included in the summary of adverse events: consequence of event, required drug treatment or intervention, severity, relation to surgery, relation to PhotoFix, and status of event at end of study. Events deemed to be related to PhotoFix, with any definitive assessment, will be summarized in a frequency table; additional information discovered during event investigation will be described, as deemed necessary.

Adverse event rate will be presented as frequency counts and percentages in a table for enrolled patients. Adverse events will be presented in aggregate and by surgical indication.

2.18. Secondary Patency

A Kaplan-Meier (KM) survival curve for secondary patency will be estimated for enrolled patients who received PhotoFix for hemodialysis access repair (HAR).

2.19. Interim Analysis

There is an interim analysis planned for January of 2019. This analysis will be used to assess the interim performance and safety of PhotoFix. The interim analysis report will focus on the summary statistics of all primary and secondary endpoints. Sample size, frequency, and percentages will be presented for categorical variables. Sample size, arithmetic mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Summaries will be presented in tables. The creation of KM plots and sub-analyses by surgical indication, device relation or timing of event are not planned.

2.20. Sample Size and Power Considerations

Sample size determination was not based on rigorous statistical considerations. It was determined that the inclusion of approximately 100 patients at up to 10 sites, in different geographic areas, would provide an acceptable opportunity to assess clinical use in a variety of settings and patients.

2.21. Handling Missing Data

Listings will be provided for all data. Descriptive statistics will be provided for all planned visits as provided on the eCRFs.

Data may be entered as unknown and therefore will appear in the data listings as such.

2.22. Protocol Deviations

Protocol deviations will be displayed in a data listing as provided by the CryoLife clinical team.

2.23. Computer Systems and Packages Used for Statistical Analyses

IBM SPSS Statistics, Version 19 (SPSS, Inc., Chicago IL, USA) Statistical Software Package will be used for analyses and computations. SigmaPlot (Systat Software, San Jose, CA) and R 3.5.1 for Windows (R Foundation for Statistical Computing, Vienna, Austria (URL: http://www.R-project.org/)) may be used to supplement analyses, as deemed necessary.