VQI-DELTA Paclitaxel Device Safety Analysis – Phase I Study Protocol

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1.0 Background:

In December 2018, a meta-analysis published by Katsanos and colleagues identified an association between the use of paclitaxel drug coated balloons (DCB) or drug eluting stents (DES) in the treatment of peripheral arterial disease (PAD) and increased mortality at two and five years after treatment, when compared to patients treated with non paclitaxel-coated or eluting devices[1]. After further investigation of the available data, the FDA advised physicians to inform patients of this reported risk and consider alternatives to paclitaxel devices in the treatment of PAD. The FDA has initiated additional review of the mortality signal and convened an Advisory Panel.

Since 2004, the Society of Vascular Surgeons has collected detailed clinical data regarding the treatment of PAD through the Vascular Quality Initiative (VQI). Today, VQI collects data from over 550 hospitals in North America, and contains over 575,000 individual patient records. The VQI Peripheral Vascular Intervention Registry (PVI) module was launched in 2010 and began capturing device identifier information in the fall of 2016 with linkage to the Global Unique Device Identification Database (GUDID). The PVI registry has established a linkage to the Social Security Death Index file in order to ascertain vital status in a longitudinal manner. As such, the VQI-PVI registry may serve as a unique and representative data source for assessing the long-term safety of Paclitaxel DCB and DES.

The Data Extraction and Longitudinal Trend Analysis (DELTA) surveillance system was developed to monitor ongoing clinical datasets in an effort improve the efficiency of identifying potential medical device safety concerns. DELTA has been previously validated for prospective monitoring of clinical registries and clinical data sets and is available as an open source software tool with associated technical documentation [2-5].

The VQI-DELTA Paclitaxel Device Safety Analysis seeks to assess the comparative safety of paclitaxel coated balloons and stents in the treatment of PAD through analysis of the Vascular Quality Initiative (VQI) Peripheral Vascular Intervention (PVI) registry module using the DELTA system.

As a National Evaluation System for health Technology (NEST) demonstration project the Registry Assessment of Peripheral Devices (RAPID) is a private public partnership of academia, industry and governmental regulatory agencies dedicated to the improving the national evaluation of peripheral arterial devices throughout the total product lifecycle. RAPID has convened the RAPID Pathways Working Group to address issues related to paclitaxel in a framework that will improve future device evaluation. The VQI DELTA Paclitaxel Device Safety Analysis will be conducted in communication with the RAPID Pathways initiative.

2.0 Study Objectives:

1. The objective of the VQI – DELTA Paclitaxel Study is to evaluate the relative safety of Paclitaxel used as an antiproliferative agent in the treatment of symptomatic PAD. We will analyze Paclitaxel Drug Coated Balloons (DCB) and Paclitaxel Drug Eluting Stents (DES), both together and as unique exposures using propensity score matched survival analysis.
2. If a mortality signal is detected we will then analyze factors associated with mortality.

3.0 Active Surveillance System: All proposed analyses will be performed using DELTA v3.65 which has the capability to prospectively monitor clinical data repositories for safety signals, and is designed to support risk-adjusted prospective safety surveillance analyses of complex clinical datasets.

4.0 Data Source and Limitations: All proposed analyses will be performed using VQI PVI dataset to maximize consistency of outcome and clinical covariate definitions[6]. Limitations include incomplete linkage to the SSDI because social security numbers are not universally available to the VQI PVI registry. This limitation is partly mitigated by the ability to ascertain survival status through VQI center reporting directly to the registry. While capture of patient, lesion and treatment variables is generally complete for the index procedure some covariates may have missing data. While the VQI mandates consecutive procedure capture there is obligate time lag for centers to perform audits against their claims data.

5.0 Scientific Oversight Committee: At the initiation of the project, a study oversight committee will be established including two representatives from VQI (Drs. Eldrup-Jorgensen and Bertges) and two representatives from the DELTA data analysis center (Drs. Resnic and Matheny), two representatives from FDA (Misti Malone, PhD, Danica Marinac-Dabic, MD, PhD) and two representatives from the peripheral vascular device manufacturer industry (Joshua Smale, BS, Aaron Lottes, PhD, MBA). The study oversight committee will be responsible for the approval of the study protocol, will have oversight of the overall performance and execution of the study, will propose any additional exploratory (post-hoc) analyses, and approve any proposed publications resulting from the project.

6.0 Devices of Interest: The proposed safety analyses will evaluate two classes of paclitaxel coated interventional devices used to treat PAD and compare patient outcomes with propensity score matched patients of similar risk who receive alternative devices within the same calendar quarter of the case implant. The primary outcome will be freedom from death using a propensity matched survival analysis approach. Three principle analyses are planned:

a) Paclitaxel DCB (including the Bard Lutonix, Medtronic In.Pact and Philips Spectranetics Stellarex DCB's) as compared with propensity matched patients treated with plain balloons.

b) Paclitaxel delivering DES (including the Cook Zilver PTX and Boston Scientific Eluvia DES) as compared with propensity matched cases using bare metal stents (BMS).

c) Patients treated with either Paclitaxel DCB or Paclitaxel DES compared with propensity matched controls (with DCB patients matched to patients treated with plain balloons, and DES patients matched to patients treated with BMS. Matches will be retained from the individual device cohort analyses).

Note that this analysis is planned at the device class level and is not intended to compare early or late mortality between specific devices or brands.

7.0 Missing Data: Based on previous data quality audits of VQI Registry , it is anticipated that less than 3% of all data to be used in the VQI- DELTA Paclitaxel study will be missing from the limited dataset. If missing data represents less than 3% of the total dataset, simple imputation methods will be used, substituting missing data with median gender-specific values for continuous variables, and assuming "negative" results for dichotomous variables. If missing data represents >3.0% of any covariate used in the propensity score match model (see below), the Study Oversight Committee will determine the most appropriate manner to handle missing data, including consideration of multivariate imputation methods or case-wise deletion.

8.0 Patient Inclusion and Exclusion Criteria: All patients, age 18 or older, who underwent endovascular interventional treatment of the femoral or popliteal arteries for symptomatic PAD between 1/1/17 and 4/1/2020 will be candidates for inclusion in the analyses. See Figure 1 for case inclusion diagram.

In an effort to focus this safety evaluation on those patients being treated in accordance with accepted 'best practice' endovascular intervention strategies and 'on-label' use of devices, patients will be excluded if they received a balloon expandable stent or a balloon expandable stent graft in the treatment of femoral or popliteal disease. Balloon expandable stents will be excluded because current best practice favors placement of self-expanding nitinol stents which were engineered for the femoral popliteal segment and tested in multiple trials for this indication [7-9].

Patients will also be excluded (as either potential cases or controls) if their index procedure was performed for acute limb ischemia as compared with chronic conditions as they have different treatment strategies and higher major amputation and mortality rates as compared with conventional use of PVI for chronic ischemic conditions[10-14]. In addition, patients with prior angioplasty or stenting of the SFA-popliteal segment will be excluded in order to avoid the possibility of improperly assigning paclitaxel exposure to the control group.

Control patients for each of exposure groups will be selected as follows. For the DCB, control patients will be selected from patients treated with "plain balloon" therapies, and will exclude those patients treated with any form of stent (including non-Paclitaxel DES, self-expanding or covered stents). Control patients for the Paclitaxel DES analyses will

be selected from those patients receiving bare metal self-expanding stents (BSES) with or without concomitant plain balloon angioplasty.

Second and later procedures

The primary analysis will consider the first procedure recorded in the VQI PVI registry as the qualifying index procedure. Should patients with a first treatment that is not paclitaxel and has a subsequent paclitaxel device treatment, the paclitaxel case will be considered the index case for that patient.

9.0 Endpoint Definitions: The primary safety outcome of interest is survival (freedom from death from any cause) at 2 years post intervention in three cohorts of patients:

a) Patients treated with paclitaxel DCB,

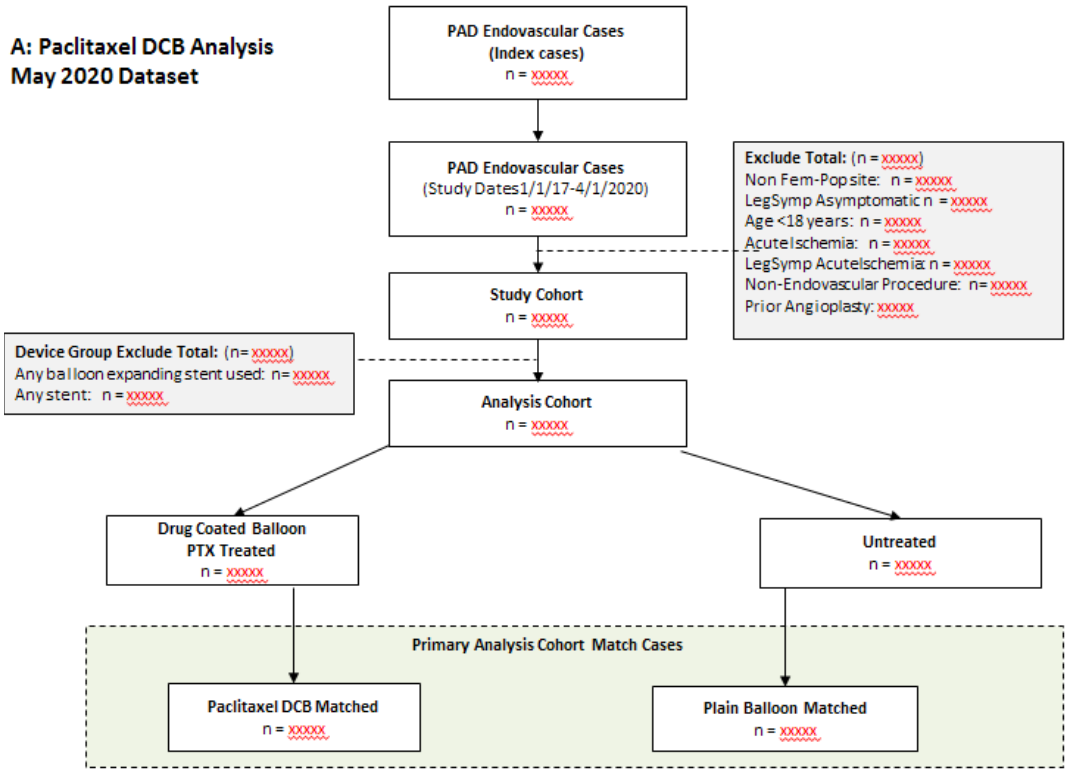
b) Patients treated with paclitaxel DES and

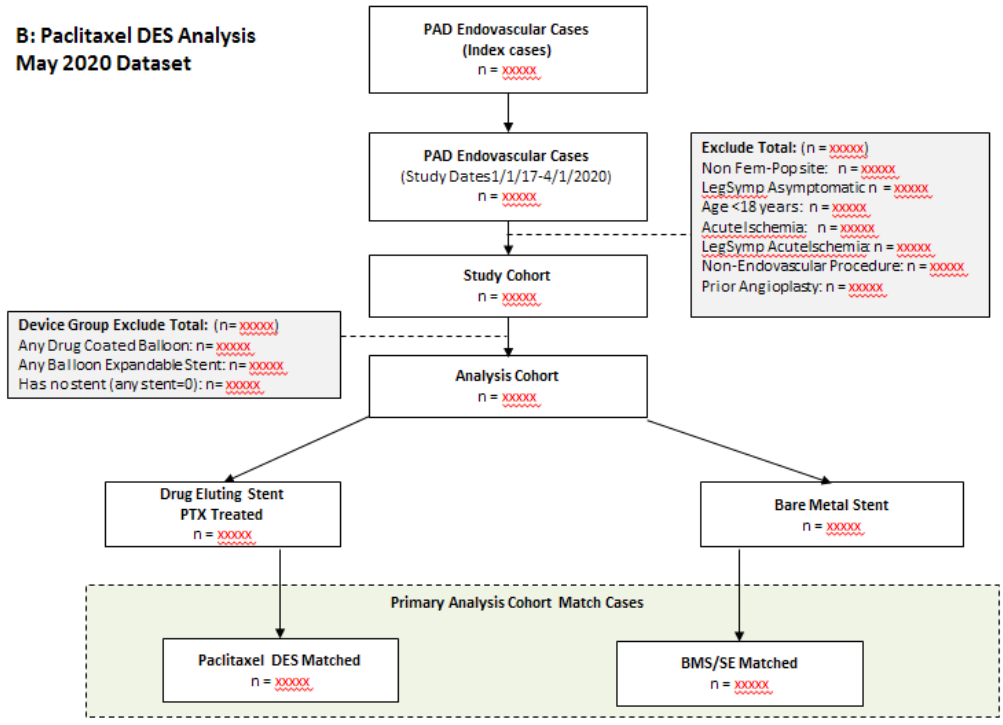
c) Patients treated with either paclitaxel DCB ***or*** DES analyzed together.

See Figure 1 for case/control identification and association with mortality.

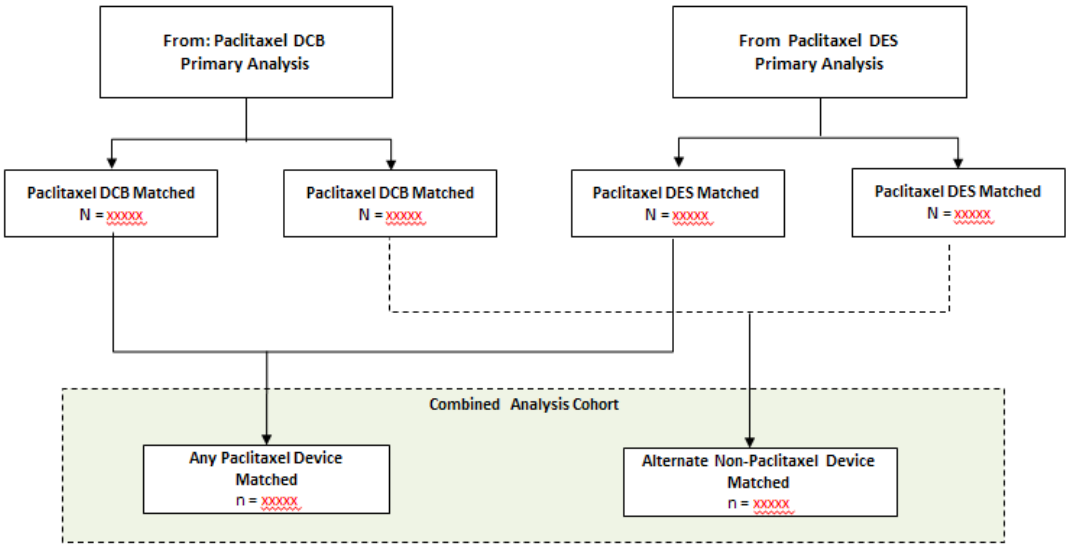
The secondary efficacy endpoint is the composite endpoint of Intervention Success at 2 years defined as the freedom from death (from any cause), retreatment of the target limb or major amputation at 2 years. An additional secondary efficacy endpoint will be successful ambulation at 1 year post treatment.

Figure 1: Case Inclusion of exposures and controls. Panel A: Paclitaxel drug coated balloon analysis, Panel B: Paclitaxel drug eluting stent analysis and Panel C: Any Paclitaxel Device.





C: Paclitaxel Combined Analysis
May 2020 Dataset



10.0 Statistical Methodology:

10.1 Propensity Score Model Development: Patients receiving a device of interest (either DCB or DES) will be matched with control patients (those receiving any traditional balloon or BMS respectively) who had undergone an interventional procedure during the same calendar quarter, in a 1:1 ratio based on propensity score matching using a non-parsimonious propensity model as described below.

A propensity score (i.e. probability of receiving the interventional device of interest) for each patient will be calculated using the propensity score model via logit estimation. The propensity score model itself will be recalibrated with each new cumulative analysis performed. Ordering of patients will be randomized before each match procedure, control patients will not be allowed to match to more than 1 exposure (no replacement) and no common-support will be imposed during matching.

10.2 Variable Selection for Propensity Score Matching: Covariates will be included in the propensity score model if they were available to the treating physician at the time the index intervention, are considered to be associated with the outcomes of interest based on prior published research, or plausibly related to the selection of the interventional device (based on expert opinion).

Proposed variables to be considered for inclusion in the propensity score match model include:

- Age
- Male Gender
- Current smoker
- BMI
- History of hypertension
- History of diabetes
- History of Coronary artery disease
- Positive Pre-procedural Cardiac Stress Test
- History of heart failure
- History of COPD
- Renal Insufficiency (defined as creatinine > 2.0mg/dL)
- Dialysis dependent
- Poor pre-operative functional status
- Poor pre-operative ambulation
- Procedural indication for critical limb ischemia
    - Claudication
    - Critical Limb Ischemia – Rest Pain
    - Critical Limb Ischemia – Tissue Loss
- Presence of active infection in treated limb
- Emergent procedural status

- Treatment length
- Treatment for chronic occlusion

Variables will be excluded if they are found to be co-linear with covariates already included in the propensity score model. To guard against the possibility of the model being unable to converge due to quasi-complete (or complete) separation, we will calculate linear Variance Inflation Factor (VIF) for each candidate covariate, excluding from the model any covariate with VIF>8, and further assessing any covariate with a VIF >4.[15] For this latter group, we will review the correlation to identify those covariates that were highly correlated (with correlation coefficient > 0.80) and eliminate one of the two highly correlated covariates.

In addition to guarding against co-linearity, the number of variables will be limited to prevent potential instability in the propensity score model through the inclusion of "too many" covariates. We will therefore estimate the number of maximum candidate covariates to include by calculating the total number of composite outcomes during the first 12 months of accumulating data, and dividing this total by 4[16].

10.3 Propensity Score Matching and Survival Analysis: Matched controls will be selected as the nearest-neighbor in a 1:1 ratio from all patients who underwent endovascular treatment of PAD during the calendar quarter as the interventional treatment of interest (either DCB or DES), using a fixed caliper width of 0.2 SD of the logit of propensity score[4, 17, 18] using a greedy matching algorithm. Separate propensity score (and matches) will be developed for the DCB and DES analyses.

The adequacy of the propensity score match model will be assessed by analyzing the distribution of risk factors between cohorts. A propensity score match will be considered adequate for all post-match percent standardized differences less than a 0.10 threshold.

10.4 DELTA Alerts: To determine whether any (potentially) observed difference in the survival is meaningful we will prospectively establish ***both*** a requirement for demonstration of statistical significance in the estimated survival function as well as the requirement that the magnitude of difference between the performance of the propensity score matched controls. Any deviation will be considered meaningful enough to possibly warrant further review.

DELTA alerts will be triggered if the Kaplan-Meier survival probability curve for the device of interest ("case") demonstrates a "clinically meaningful" increased risk of mortality, as defined by **an *increased mortality at 2 years ≥ 50% than the survival rate of the alternative*** ("control") population, with a final survival analysis Log Rank test significant at the p=0.05 level[19].

10.5 Sample Size Expectation and Estimated Statistical Power: Based on case counts (without further exploration of the VQI dataset), annual mortality following femoral-popliteal endovascular intervention was observed to be 12.1%. We anticipate a total sample of 5,700 paclitaxel DES and 25,200 paclitaxel DCB treated patients would be captured by 4/1/2020, with 1,865 PTX-DES and 8,250 PTX-DCB patients having been followed for a minimum of 2 years. Further conservatively assuming 90% match with non-paclitaxel treated patients, the statistical power to detect a 50% increase in mortality at 5 years, given α=0.05, exceeds 99% for each of the three primary analyses.

10.6 Pre-specified subgroups:: Pre-specified subgroups will be explored through independent propensity score match analyses for any evidence of uniquely increased risk of mortality. These subgroups will include: age <70yr versus ≥70yrs, female gender, patients on dialysis, and patients with cardiac history (including CAD, CHF or a positive stress test). Similarly, the three primary analyses will be further explored through analysis of the subgroup of patients treated for critical limb ischemia will be analyzed separately from those patients treated for intermittent claudication.

Additionally, the association between discharge statin medications and treatment with Paclitaxel devices will be explored, as well as the potential relationship between treatment with optimal medical therapy (discharge medications including statin, aspirin +/- P2Y12 inhibitor agent) and mortality.

10.7 Falsification Hypothesis Analysis: A pre-specified falsification-hypothesis analysis will performed to assess the extent of residual confounding after propensity score matching. For each of the exposures of interest, we will evaluate matched patient cohorts for the documentation of resuming smoking on follow up evaluation. Continued active smoking is anticipated to be independent of the selection of the specific interventional device, and is therefore an appropriate Falsification Hypothesis candidate outcome. If the falsification hypothesis demonstrates no evidence for residual confounding through finding similar rates of smoking in follow up, we will conclude that the propensity score match was robust in minimizing residual confounding.

11.0 Study Analysis and Final Report: It is anticipated that the final report will serve as the basis for at least one manuscript that will be prepared within 6 months of the completion of the analysis and submitted for publication in peer reviewed journal. Members of the committee will be invited to participate in the writing and review of each of the proposed manuscripts. Additional, post-hoc and exploratory analyses may be deemed suitable for inclusion in additional manuscripts, on the approval of the study steering committee.

12.0 Human Subjects Institutional Review: All study related materials will be submitted for IRB review and approval per the institutional requirements of VQI and Lahey Clinic.

13.0 References

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