**Statistical Analysis Plan**

**for**

**The InterGraft Study (IDE G140221)**

# Clinical Evaluation of a Vascular Venous Anastomotic Connector for Minimally Invasive Connection of an Arteriovenous Graft for Hemodialysis [InterGraft Study]

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## DOCUMENT HISTORY

| Revision | Description | Date |
|---|---|---|
| 1.0 | Original Version | January 30, 2015 |
| 2.0 | VIG InterGraft Study Version | May 29, 2019 |
| 3.0 | Changed: Total roll-in subjects from 12 to 15, study sites participating from 20 to 23 and maximum total of enrolled subjects (including roll-ins) from 170 to 173. | July 24, 2020 |

**SIGNATURE PAGE**

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Table of Contents

## LIST OF ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AIG | Arterial InterGraft Connector |
| AV | Arteriovenous |
| AVG | Arteriovenous graft |
| CEC | Clinical Events Committee |
| CRF | Case Report Form |
| DCC | Data Coordination Center |
| DSMB | Data Safety and Monitoring Board |
| EDC | Electronic Data Capture |
| ESRD | End Stage Renal Disease |
| GCP | Good Clinical Practice |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| KDOQI | Kidney Disease Outcome Quality Initiative (National Kidney Foundation) |
| MM | Medical Monitor |
| ePTFE | expanded Polytetrafluoroethylene |
| SAP | Statistical Analysis Plan |
| UADE | Unanticipated Adverse Device Effect |
| VIG | Venous InterGraft Connector |

## 1.0 OVERVIEW

This document outlines the statistical analysis plan (SAP) for the InterGraft Study described in the current Investigational Plan (revision 8). It is intended to outline the statistical procedures and methods used to design the study and to analyze the resulting clinical data, in conformance with the recommended practices contained in *ICH E9 Statistical Principles for Clinical Trials*. The statistical procedures that are described in this document are consistent with those contained in the associated *Investigational Plan for the InterGraft Study (IDE G140221)*, but contain additional details on their implementation.

Data collected from subjects during the initial phase of this IDE study, e.g., prior to the interim analysis under Version 1.0 of the SAP for the original InterGraft™ System (VIG + AIG) assessment, will not be included in the evaluation of the primary analysis study results in the InterGraft Study. Results for the initial phase (total of 52 subjects) will be analyzed and reported separately.

The current InterGraft study does not contain an interim analysis. The value for the expected cumulative patency rate used in the current sample size estimate has been updated, based on the interim analysis results from the initial phase for subjects in which the VIG was used. The planned statistical analyses in this Version 3 of the SAP are otherwise identical to those outlined in the original Version 1 and Version 2.

### 1.1 Name and Intended Use of the Device

The InterGraft™ Venous Anastomotic Connector provides a minimally invasive, sutureless method for attachment of an arteriovenous graft to a vein in the upper extremity. The InterGraft™ Venous Anastomotic Connector facilitates creation of the arteriovenous graft connection to a vein in support of hemodialysis in subjects with End Stage Renal Disease. The InterGraft™ Venous Anastomotic Connector is used together with conventional suturing of the arterial anastomosis to facilitate creation of an arteriovenous graft in support of hemodialysis in subjects with End Stage Renal Disease.

### 1.2 Background

The InterGraft™ Venous Anastomotic Connector was developed for minimally invasive venous anastomoses of a standard hemodialysis graft. The current study will evaluate the safety and performance of the InterGraft™ Venous Anastomotic Connector for a venous anastomosis of a commercially available, 6 mm diameter, ePTFE hemodialysis graft. While recognizing that a native fistula is the recommended access for hemodialysis, AV grafts remain a frequently used access type. This study focuses on subjects who have a failed fistula, cannot have a fistula or are better suited for an AV graft, as determined by the physician. The graft implant procedural outcomes, the number and type of major adverse events, and patency throughout a six (6) month follow-up period will be evaluated. The 6-month patency rate will be compared with a pre-specified patency performance goal that is drawn from prior surgical AV graft literature and published performance standards.[10, 14-20 in the Investigational Plan]

### 1.3 Device Description

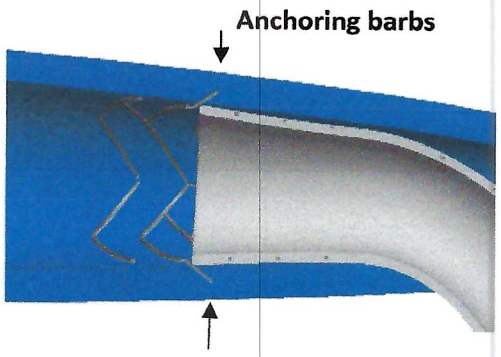
The InterGraft™ Venous Anastomotic Connector (VIG) is designed for transcatheter delivery within a vein and connection to a graft that has been tunneled under the skin in a standard manner. The connections are made via small skin incisions.

The InterGraft™ VIG is constructed with a nitinol framework encapsulated with ePTFE in the midsection and uncoated at the ends (**Figure 1**). The InterGraft™ VIG is delivered and deployed within the target vessels using customized transcatheter delivery systems. The VIG is a flexible, flared, self-expanding endoprosthesis designed for coaxial placement in peripheral veins up to 10 mm in diameter. The distal flared end is configured as a nitinol scaffold with anchoring barbs that extend into the vein wall. The 'graft end' of the VIG is configured as a stent-like framework for anchoring within the ePTFE graft. The

materials used in constructing the VIG are all medical-grade with well-established biocompatibility profiles.

The VIG is supplied pre-mounted in customized percutaneous delivery systems for over-the-wire delivery via a 11F sheath. The VIG is intended as a permanent implant. The delivery systems is a sterile, single use, disposable item.

**Figure 1- InterGraft Venous Anastomotic Connector (VIG).** Note barbs that anchor VIG within the vein (arrows).




## 2.0 STUDY DESIGN

This is a multicenter, prospective, non-randomized design study. The planned study enrollment is 146 evaluable subjects who require AV graft placement for hemodialysis and who meet the entry criteria.

The current study will allow for a maximum enrollment of 173 subjects, including a provision for 12 subjects lost to follow-up and up to 15 roll-in cases. Data from roll-in subjects will not be included in the primary analysis but will be analyzed separately.

The study will include up to 23 participating clinical centers. Study site investigators will be physicians skilled in AVG placement and interventional techniques. Study data will be collected up to the point at which each subject has completed the 6-month endpoint or experienced a terminal study endpoint.

No single clinical site may contribute more than 25% of the total enrollment (excluding roll-in subjects).

### 2.1 Study Objectives

The study has the following primary objective:

Primary: To demonstrate that the 6-month cumulative patency of grafts connected with the InterGraft™ VIG is similar to that of grafts connected using standard sutured anastomoses.

### 2.2 Study Endpoints and Hypotheses

#### 2.2.1 Primary Endpoint

The primary endpoint is cumulative patency at 6 months, defined as the percentage of subjects free from loss of access of the study graft for hemodialysis, assessed at 6 months.

The primary study endpoint of the cumulative patency rate at 6 months will be evaluated in the following testable hypotheses:

$H_0$: $(\text{Cumulative Patency Rate})_{6\ \text{Months}} \leq PG$

$H_1$: $(\text{Cumulative Patency Rate})_{6\ \text{Months}} > PG$

Where, PG = Performance Goal, here equal to 75%.

#### 2.2.1.1 Choice of Performance Goal

Based on a review of the literature and prior studies of similar AVGs cleared for commercial distribution, the observed cumulative patency rate at 6 months for standard AV graft implants ranged from 65% to 98%. Based on the proposed sample size for the current study (see below) and an expected cumulative patency rate of 84.6% seen for AVGs placed using the VIG in the initial phase, the exact, lower two-sided 95% confidence bound for cumulative patency is estimated to be 79.9%. A comparison to a target Performance Goal (PG) of 75% has been chosen for the evaluation.

### 2.2.2 Secondary Endpoints

Secondary endpoints for the study include:

1. Acute device success, defined as AV graft flow at the end of the procedure (determined by palpable graft thrill and audible bruit), without significant bleeding or emergent surgery
2. Primary Unassisted Patency at 6 Months, defined as the percentage of subjects free from the first occurrence of either access thrombosis or an access procedure performed to maintain access patency.
3. Time to First Cannulation, defined as the time from initial access placement to the first graft cannulation.
4. Number and type of interventions required to maintain secondary patency
5. Number and type of serious adverse events (SAEs) through 6 months. SAEs include the following: death, emergent surgery, infection requiring treatment (e.g., prolonged or intravenous antibiotic therapy), significant bleeding (defined as bleeding requiring treatment), and pseudoaneurysm.

### 2.2.3 Safety Considerations

All AEs and SAEs will be documented and reported.

#### 2.2.3.1 Clinical Events

**Adverse Event (AE)** is defined as any undesirable sign, symptom or medical or psychological condition even if the event is not considered to be related or possibly related to the study device or study procedure/intervention. Medical condition/diseases present before starting the study will be considered adverse events only if they worsen after starting study treatment. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of a study device that adversely affects the rights, safety or welfare of subjects.

**Serious Adverse Event (SAE)** is defined as any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs in-patient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

**Unanticipated Adverse Event (UAE)** is defined as any event or experience that meets all three criteria below:

- Is unexpected in terms of nature, severity or frequency, given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studied
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the patient or others at greater risk of harm than was previously known or recognized OR results in actual harm to the patient or others

The occurrence of AEs, including SAEs and UAEs, will be monitored throughout the study duration. Adverse event information will be collected and reported on designated AE forms, assessed and classified by the principal investigator as serious/not serious. The investigator will also determine the relatedness of the AE to the study device and study procedure according to the following definitions:

- Related (AE is clearly related to the device/procedure);
- Possibly related (AE may be related to the device/procedure);
- Unrelated (AE is clearly not related to the device/procedure).

Review of Adverse Events. SAEs should be reported to the sponsor within 24 hours of occurrence, and to national and local regulatory authorities, in accordance with national and local policies and procedures. In addition, all unanticipated adverse device effects will be evaluated at the time of occurrence and reported to the sponsor within 24 hours.

### 2.2.3.2 Clinical Events Committee

A Clinical Events Committee (CEC) will provide medical review of SAEs, UAEs, and any deaths that may occur throughout the study. The CEC will be compromised of the Medical Monitor, and the Sponsor's Chief Science Officer, Chief Technology Officer and Director of Clinical Affairs. Details of CEC operations will be defined in a CEC Charter document.

The principal investigator/institution will permit study-related monitoring, audits of IRB/Ethics committee reviews, and regulatory inspections by providing direct access to source data and documents. On-site data monitoring will be performed by Sponsor's study monitors. Any data discrepancies will be resolved and documented by a standardized data query process.

#### 2.2.3.3 Data and Safety Monitoring Board

An independent DSMB is established and has responsibility for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The DSMB is an independent group advisory to the Sponsor, and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the Sponsor about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety, and
- Notification of and referral for abnormal findings

Details of DSMB operations are defined in the DSMB Charter document.

### 2.3 Sample Size Justification

The required sample size for the study was estimated using the following assumptions:

- Test basis: Kaplan-Meier estimate of cumulative patency rate at 6 months, with exact binomial estimation for purposes of sample size
- Type I error (alpha): 0.025 (one-sided)
- Statistical power: 80%
- Performance Goal (PG): 75%
- Expected cumulative patency for InterGraft at 6 months: 84.6%.

Based on the above assumptions, a total of 146 evaluable subjects would be required to compare observed cumulative patency to a PG of 75%. With an expected loss-to-follow-up rate of 8% over 6 months, a total of 158 subjects would need to be enrolled in the evaluation phase.

### 2.4 Study Duration and Termination

Enrollment is expected to occur over a 24-month period. With a minimum of 6-month follow-up and 2-month period of data analysis and regulatory submission preparation, the total duration of the study is expected to be 32 months.

The study may be terminated at any time for reasons of safety, based on a recommendation by the DSMB, an IRB/Ethics Committee, or based on other considerations by the sponsor. Serious, device related or possibly related adverse events that are unexpected in either frequency or type may prompt a review by the principal investigator, Medical Monitor and Sponsor, and may lead to consideration of stopping the study. Such a review and discussion will be documented and included with the study records.

## 3.0 PROTOCOL

Enrollment in the study is determined at the time of surgery, after the physician has confirmed that inclusion criteria have been met, subjects have no exclusion criteria, and the final inclusion criterion has been met (e.g., target vessels are suitable for connection to a graft using the Venous InterGraft™ Connector and a sutured arterial anastomosis.) Enrolled subjects will be assigned a unique study subject identification number.

### 3.1 Study Population

The following inclusion and exclusion criteria must be met for enrollment in the study:

**Initial Inclusion Criteria** (All must be answered YES for study eligibility.)

1. Subject is ≥ 18 years of age.
2. Subject requires the creation of a vascular access graft for hemodialysis, secondary to a diagnosis of End Stage Renal Disease.
3. Subject is able to have the vascular access graft placed in an upper extremity.
4. Baseline imaging shows suitable vascular anatomy/ vessel size for the InterGraft™ Venous Connector and an artery at least 3.5 mm in diameter that is suitable for creating the arterial anastomosis.
5. Subject has a reasonable expectation of remaining on hemodialysis for at least 6 months.
6. Subject or his/her legal guardian understands the study and is willing and able to comply with the dialysis schedule and follow-up requirements.
7. Subject or his/her legal guardian provides written informed consent. NOTE: In accordance with the requirements of some Institutional Review Boards (IRB), where applicable, only those subjects with capacity to consent for themselves will be included. Thus, where required by the IRB, adult individuals who lack capacity to consent for themselves will be excluded from the study.

**Final Inclusion Criterion to be applied at the time of surgery** (Must be answered YES for enrollment into the study.)

Physician's examination at time of surgery shows no significant vessel lesions, calcification(s), anatomic structures or abnormalities that may limit ability to safely deploy the InterGraft™ Venous Connector or create a sutured arterial anastomosis.

**Exclusion Criteria** (All must be answered NO for study eligibility.)

1. Subject has a documented and unsuccessfully treated ipsilateral central venous stenosis as determined by imaging.
2. Subject currently has a known or suspected bacterial, fungal, or HIV infection. NOTE: Subjects with hepatitis B or C may be included in the study. .
3. Subject has a known hypercoagulable or bleeding disorder or requires treatment with warfarin or heparin

4. Subject has had a previous instance of Heparin Induced Thrombocytopenia type 2 (HIT-2) or has known sensitivity to heparin.
5. Subject has co-morbid conditions that may limit their ability to comply with study and follow-up requirements.
6. The patient has had >2 previous arteriovenous accesses in treatment arm.
7. Subject is currently taking Aggrenox®.
8. Subject is in need of, or is scheduled for any major surgery within 30 days of the study procedure.
9. Subject is currently taking maintenance immunosuppressant medication such as rapamycin, mycophenolate or mycophenolic acid, prednisone (>10 mg), cyclosporine, tacrolimus or cyclophosphamide.
10. Life expectancy is less than 12 months.
11. Subject is pregnant.
12. Subject is a poor compliance risk (i.e. history of IV or oral drug abuse).
13. The subject is enrolled in another dialysis or vascular investigational study.

### 3.2 Study Procedures

The study procedure will be performed in accordance with the Instructions for Use (IFU) provided with the study device. A commercially available 6mm diameter synthetic graft will be used. Such grafts may include conventional ePTFE grafts or grafts designed for early cannulation (within 24-48 hours). The study procedure will be performed in an operating room that has fluoroscopic imaging capability for guiding placement of the VIG. The anesthesia regimen will be determined at the physician's discretion; there are no study-specific anesthesia requirements. A regional nerve block is typically performed for placement of an AVG. Standard, routine hemodynamic monitoring will be performed to assess cardiovascular status throughout the procedure. Heparin anticoagulation may be provided at the physician's discretion.

Subjects will be followed at 2 weeks and monthly thereafter through 6 months to assess graft patency and complications. Measurement of access flow rate is part of standard care. Data from routine AV access flow monitoring performed as part of usual care will also be collected. The required schedule for subject treatment and evaluation is shown in **Table 1**.

**Table 1: Schedule of Subject Treatment and Evaluation**

| Timeframe (window) | Test/Procedure |
|---|---|
| Pre-procedure (within 30 days) | Baseline imaging of target AVG site (performed as part of standard care)<br>Baseline labs: Hgb, Hct, WBC, platelets |
| Pre-procedure (within 24 hours) | Urine pregnancy test for female subjects with reproductive potential |
| Immediately following end of AVG implant procedure (before leaving surgery suite) | Confirmation of AVG flow (palpable thrill, audible bruit; In addition, angiogram may be performed at physician's discretion, if warranted.) |
| Post- procedure (within 48 hours) | Post procedure labs: Hgb, Hct |
| At discharge | Confirmation of AVG flow (palpable thrill, audible bruit) |
| 2 weeks following the procedure (14 +4/-7 days) | Clinical follow- up with AVG evaluation (includes collection of information regarding subsequent hospitalization and AEs) |
| 30, 60, 90, 120, 150,180 days following the procedure<br>(± 14 days) | Clinical follow- up with AVG evaluation (includes collection of information regarding subsequent hospitalization, AEs, and AVG interventions)<br><br>AVG flow rate evaluation (ultrasound or similar) is performed at the 90-day and 180-day follow-up visits |

The following final events will justify cessation of study follow-up: death, AVG abandonment, lost to follow up (at least 3 attempts to contact the subject should be made and documented), or completion of study follow-up.

### 3.3 Patient Withdrawal

Patients may withdraw consent from the study at any time. Study data collected prior to withdrawal will be analyzed and included with the final study results. The investigator may withdraw the patient from the study at any time if assessed to be in the best interest of the patient.

### 3.4 Protocol Violations

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of the research project that is not approved by the IRB and study sponsor prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), national or local regulations. Protocol violations may or may not be under the control of the research team or hospital staff.

### Major Protocol Violations

All major protocol violations must be reported to the IRB, as applicable and in accordance with local IRB policy, AND to the study sponsor, immediately upon discovering them, and no later than seven (7) calendar days from the time the study team receives knowledge of the event.

A major violation is a protocol violation that meets the following criteria:

- Represent a serious or continuing failure on the part of the study team to comply with the protocol, standard operating procedures, GCPs, federal, state or local regulations;
- Impacts patient safety or substantially alter risks to patients. May or may not result in actual harm (clinical, emotional, social, financial, etc.);
- Significantly damages the completeness, accuracy and reliability of the data collected for the study;
- Is under control of the investigator/research team/hospital staff

## 4.0 DATA ANALYSIS

The following sections describe statistical analysis procedures and considerations.

### 4.1 General Statistical Considerations

a. Descriptive statistics will be used to summarize subject baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimums and maximums. Categorical variables will be summarized in frequency distributions.
b. Statistical analyses will be performed by validated software (e.g., SAS, SPSS, or Cytel Software)
c. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
d. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the case report form (CRF) will be provided for all key baseline, demographic and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

A one-sided p-value of 0.025 will be considered evidence of statistical significance for the primary study endpoint.

### 4.2 Analysis Populations

All subjects who meet the enrollment criteria and in whom the VIG InterGraft™ Connector is attempted will be included in the ITT primary analysis population. Roll-in cases will not be included in the main study analyses.

### 4.3 Primary Endpoint

Cumulative patency at 6 months will be evaluated using the estimated patency from a Kaplan Meier survival analysis. The test statistic will take the following form:

$$\text{Z-test statistic} = \frac{(P - 0.75)}{SE(P)}$$

Where, (P) represents the Kaplan Meier estimate of cumulative patency at 6 months, and the standard error SE (P) is estimated using the method of Peto *et al* (1977).

Subjects who withdrawn for reasons other than loss of cumulative patency will be included in the analysis up until the time of withdrawal, and be considered censored in the analysis, according to usual convention, after withdrawal.

### 4.4 Secondary Endpoints

The following secondary endpoints will be evaluated in the study, but there are no formal hypotheses that are tested or associated significance levels assigned to results. Nominal confidence intervals may be calculated in summarizing clinical results for secondary endpoints but not for purposes of product labeling.

1. Acute device success will be summarized by the success rate and associated 95% confidence interval.

2. Primary Unassisted Patency at 6 Months will be summarized by the patency rate and associated 95% confidence interval.

3. Time-to-First-Cannulation will be summarized by the median time and frequency distribution.

4. Number and type of interventions required to maintain secondary patency will be summarized by the frequency distributions of numbers and types of interventions.

5. Number and type of serious adverse events (SAEs) will be summarized by frequency distributions of the numbers and types of SAEs, the subject rates of SAEs by type, and the proportion of subjects with at least one SAE.

### 4.5 Additional Safety Data

In addition to summarizing and reporting SAEs (Secondary Endpoint 6), the number and type of non-serious adverse events (AEs) will be summarized by frequency distributions of the numbers and types of AEs and the subject rates of AEs by type.

### 4.6 Interim Analysis

No interim analysis is planned for the current InterGraft VIG study.

### 4.7 Gender Analysis

Cumulative patency rates between genders will be compared by gender using a log rank test statistic to compare their respective Kaplan-Meier survival curves. The heterogeneity of cumulative patency rates will also be examined using the test statistic used for the primary endpoint analysis. Gender specific summary statistics will also be provided for study primary and secondary endpoints.

### 4.8 Pooling of Sites

Cumulative patency rates will be compared between study sites using a Chi-square test to evaluate the association between rates and sites. A p-value of 0.15 or less would be considered evidence of a possible site interaction, requiring a further evaluation of subject baseline factors to determine if site differences can be explained by these factors.

### 4.9 Sensitivity Analyses

The primary endpoint is cumulative patency at 6 months, defined as the percentage of subjects free from loss of access of the study graft for hemodialysis, assessed at 6 months. Loss of access, including graft abandonment, and the associated time of occurrence will be considered events for purposes of the primary endpoint analysis.

Subjects who have died for reasons unrelated to the study device will be considered as censored with regard to the primary endpoint analysis at the time of death, and their last known status will be used.

Subjects who have become lost to follow-up or who have withdrawn consent for participation in the study prior to 6 months will be considered to have missing primary endpoint outcomes. In the primary analysis, these subjects will be considered to have been censored at the last documented determination of their status prior to study exit. Sensitivity analyses will also be performed to determine the potential impact of these missing data on the primary analysis results, including a tipping point analysis where their status at the time of study exit is assumed to be loss of patency.

### 4.10 Protocol Violations

All protocol violations will be summarized and reported by type of violation and classification as major or non-major violation.

### 4.11 Data Collection and Management

#### 4.11.1 Data Collection

Primary data collection based on source documented medical records will be performed by study coordinators or other designated research staff at each site. Electronic data capture will be used. Site training (web-based) will be provided by the Data Coordinating Center (DCC). All EDC training will be documented in the Investigator site file. Throughout the study, a help desk at the DCC will be available for any questions that arise from sites concerning the EDC.

#### 4.11.2 Data Management

The DCC will use a validated clinical data management system consisting of a relational database and a web application to capture the study data through single-pass data entry. Automated edit checks for missing, discrepant, and out of range data will be programmed into the data entry forms, and manual edits will be conducted by the DCC Managers on an ongoing basis. The Sponsor will provide a list of edit checks to the DCC.

Any data discrepancies identified during data monitoring will be communicated to study sites for resolution or justification. Once all discrepancies and queries have been resolved, the site principal Investigator will confirm the data accuracy with his/her signature on a Verification CRF. Once the study is completed, all data have been entered into the clinical database, and all discrepancies have been resolved, an audit will be conducted to verify that all requirements for database lock have been met. After database lock, the DCC will export the data into SAS datasets and provide them to the project statistician.

CRF submission status will be tracked by the DCC.

## 5.0 REFERENCES

Peto R, Pike MC, Armitage P et al. Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of each Patient. *British J of Cancer* 1977; 35:1-39