Study Title: IntravaScular Ultrasound (IVUS) Imaging During Transvenous LEad Extraction (ISEE)

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PROTOCOL TITLE: IntravaScular Ultrasound (IVUS) Imaging During Transvenous LEad Extraction (ISEE)

PI: Hemal M. Nayak, MD

CO-I(S): Andrew Beaser, MD

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SPONSOR: Investigator-Sponsor

TYPE OF RESEARCH: Clinical Trial

INTERVENTION: Intravascular ultrasound (IVUS) imaging conducted during transvenous lead extraction (TLE)

MANUFACTURER OF INTERVENTION (if applicable):

Volcano Corporation
2870 Kilgore Road
Rancho Cordova, CA 95670 USA

STUDY SUMMARY

TITLE	IntravaScular Ultrasound (IVUS) Imaging During Transvenous LEad Extraction (ISEE)
SHORT TITLE	ISEE
PROTOCOL NUMBER	IRB18-1600
METHODOLOGY	Clinical Trial
SAMPLE SIZE	100 consecutive patients that have been recommended for lead extraction, with at least one lead over 1 year dwell time
STUDY DURATION	1 year
STUDY CENTER(S)	University of Chicago Medicine, Penn Medicine, University of Michigan, Allina Health
OBJECTIVES	The purpose of this study is to evaluate IVUS as a tool for grading the presence of fibrotic adhesions to cardiac pacemaker/defibrillator leads during transvenous lead extraction (TLE).
DIAGNOSIS AND MAIN INCLUSION CRITERIA	Subjects that have been recommended for TLE with at least one transvenous lead over 1 year dwell time.
STUDY PRODUCT	IVUS catheter (Visions® PV.035)
DURATION OF ADMINISTRATION	For the duration of the TLE procedure
STATISTICAL METHODOLOGY	Traditional statistical methods will be employed. The student's T-test will be used for continuous comparisons. Fisher's exact or the Chi-square test will be applied for dichotomous variables. Spearman correlation coefficients will be calculated.

LIST OF ABBREVIATIONS

CIED	Cardiovascular implantable electronic device
CXR	Chest x-ray
ICD	Implantable cardioverter-defibrillator
ILA	Intravascular lead adherence
INNV	Innominate vein
IVUS	Intravascular ultrasound
PA	Postero-anterior
RA	Right Atrium
SVC	Superior vena cava
TV	Tricuspid valve
TEE	Transesophageal echocardiography
TLE	Transvenous lead extraction

INTRODUCTION

BACKGROUND AND RATIONALE

Increased indications for permanent cardiac pacing with biventricular pacing systems and the success of implantable cardioverter-defibrillators (ICD) in improving mortality in patients with ventricular arrhythmias and chronic systolic heart failure, has resulted in a significant increase in the rate of implantation of cardiovascular implantable electronic devices (CIEDs) [1,2]. Unfortunately, there has also been a parallel rise in the rate of CIED infection and lead failure or malfunction with subsequent increase in the need for transvenous lead extraction (TLE) [1,3]. As outlined in the 2017 Heart Rhythm Society (HRS) consensus statement on lead management and extraction, CIED leads should be fully removed in the case of system infection (class I indication), and lead removal is suggested in the case of lead malfunction, fracture, or recall [4]. Some CIED leads can be removed without locking stylets or powered cutting sheaths, and therefore, TLE poses little risk to the patient. However, due to the development of fibrosis on the majority of CIED leads especially within sensitive venous and cardiac structures, more complex procedures are often necessary, requiring the use of laser sheaths or powered cutters to break the lead free from tissue and vascular adhesions. During this procedure, major adverse events can occur that can lead to patient morbidity and mortality. The most common mechanical injury during TLE is a tear in the superior vena cava (SVC) [5]. Though rare, this complication is often devastating and associated with significant morbidity and mortality and almost always requires emergent surgical intervention [4]. A common variable associated with this major complication is the presence of significant intravascular lead adhesion (ILA) or fibrosis [5].

Currently it is difficult to predict the locations and severity of ILA within the SVC or right atrium (RA) giving physicians a significant disadvantage when entering these procedures. Pre-procedure imaging with CXR, CT scan and fluoroscopy have limited utility [6]. While clinical risk factors such as female gender, longer lead dwell time, presence of high voltage coil or existence of multiple leads in the vascular space,

low body mass index (BMI) and younger patient age have all been associated with a greater likelihood of ILA, they are not reliable predictors due to the inherent inter-patient variability in the vascular biology dictating the development of ILA [7,8,9,10].

Phased-array intracardiac echocardiography (ICE) and/or radial-ICE, also known as IVUS, have become important imaging tools in electrophysiology (EP) [11]. It is standard of care to use ICE in many EP procedures [11]. It helps in performing safe trans-septal puncture, aids in identifying important cardiac structures (papillary muscles, pulmonary veins, aortic cusps), and is utilized to monitor for complications (pericardial effusion, clot development, steam pops) [11].

Radial-ICE or IVUS has been utilized during TLE and was found to be a feasible and safe tool to visualize leads in a small study of 25 patients. The authors concluded that radial-ICE evaluation "is safe and feasible in patients with pacing and defibrillating leads before and during transvenous lead removal, offering an excellent visualization of cardiac leads and related areas of adherence. ICE can assist pacing and ICD lead removal and could improve procedure efficacy and safety" [12]. Sadek and colleagues evaluated phased array ICE in 50 patients undergoing TLE. The authors concluded that while phased-array ICE was able to identify areas of binding it was not able to identify binding sites that are high versus low risk of requiring complex extraction techniques. In this study, there were no adverse events noted with using ICE [13]. Radial ICE or IVUS has a number of advantages over phase- array ICE because it can provide a 360° cross-sectional image, allowing better visualization and assessment of ILA.

At the University of Chicago, IVUS is routinely used during TLE. At first, we used it to monitor for complications like the development of pericardial effusion or clots. We quickly realized that it had other uses. Under the following IRB protocol #16-0272 titled "Safety and Outcomes of Electrophysiology Procedures in the Electrophysiology Laboratory at the University of Chicago: A Prospective Registry for Arrhythmia Care". Dr. Beaser and I reviewed and collected data on 56 patients who had undergone TLE where IVUS imaging was performed and ILA was identified and quantified. We correlated the degree of ILA seen on IVUS to metrics reflecting the difficulty of TLE (pulses of laser energy delivered and time required to traverse an area of fibrosis or ILA). We found that (1) ILA can be readily visualized, accurately quantified using IVUS, (2) The degree of ILA correlates highly with difficulty of extraction as measured by the time required to traverse and the amount of laser pulses delivered in each vascular segment and (3) IVUS has potential to identify patients who may be at low risk for vascular complications in the SVC-RA region during TLE. No additional complications were found by routinely using IVUS and we noted that there was an added incremental value to clinical predictors of fibrosis. For example, a patient with a low body mass index, a high lead dwell time and a dual coil ICD lead would be expected to have a higher amount of ILA based on clinical factors. We found that these factors were not reliable. In many cases, IVUS was able to demonstrate minimal ILA, This finding helped guide laser sheath use and the need for placing the Philips rescue balloon. In contrast, a patient with risk factors predicting low ILA may have IVUS findings indicating the opposite. This type of finding would help in determining whether the extraction should be approached from below (femoral work station) or not performed using laser (e.g. refer to surgery). Our work was presented in the Philips Imaging Symposium in July 2018 in Philadelphia. Our data was very well received by our EP colleagues, and this led us to initiating a larger multi-center study to validate our findings.

Therefore, the purpose of this study is to prospectively evaluate intravascular ultrasound (IVUS) imaging as a tool for grading the presence and characterization of ILA to cardiovascular implantable electronic device (CIED) leads during transvenous lead extraction (TLE) procedures in a multi-center study. IVUS should identify the location and severity of these adhesions, which we will then correlate to difficulty of the extraction procedure using metrics like pulses of laser energy delivered and time required to traverse an area of fibrosis or ILA. We will be focusing primarily on the section from innominate vein (INNV) down through the superior vena cava (SVC) to the right atrium.

Currently, the Visions® PV.035 IVUS catheter is designed for use in the evaluation of vascular morphology in blood vessels of the peripheral vasculature [Appendix A]. It is commonly used during interventional cardiology and radiology procedures and has a solid safety profile [14-19]. In a large study of 227 patients, the Visions® PV.035 IVUS catheter was used to assess pelvic vein insufficiency. There were no adverse events related to IVUS imaging [14]. Two other studies of 117 and 104 patients respectively, found that imaging with the Visions® PV.035 IVUS catheter was safe and not associated with any adverse events [15,16]. Three other studies using the Visions® PV.035 IVUS catheter found similar results [17,18,19]. In all of these studies, the Visions® PV.035 IVUS catheter was used to image peripheral veins. In our proposed study, we wish to use IVUS to image leads in venous structures (SVC, INNV) and the SVC-RA junction. The IVUS catheter will need to be inserted through a sheath inserted in the right or left femoral vein and pass through the RA to reach the regions of interest which constitutes an "off-label" use of the product. This "off-label" use of the IVUS catheter is standard clinical practice in the University of Chicago EP cath lab. There were no adverse events seen with use of IVUS in our cohort of 56 patients that Drs. Beaser and I studied from the EP registry data. Based on the published literature supporting the safety of the Visions® PV.035 IVUS catheter and our own experience, we believe that using IVUS for this purpose provides a non-significant risk to patients.

OBJECTIVES

We hypothesize that:

IVUS imaging will provide incremental value beyond clinical factors in identifying vascular adherence

Specific Aims:

Aim 1: Experienced operators at 5 major lead management medical centers will be able to image ILA using IVUS during TLE

Aim 2: ILA will be correlated to metrics of TLE difficulty

Aim 3: The incremental value of IVUS will be assessed systematically in identifying patients at low risk of developing a vascular tear in the SVC-RA region

PRIMARY ENDPOINTS

1. Ability of IVUS to image ILA

SECONDARY ENDPOINTS:

1. Correlate ILA grade to metrics reflecting the difficulty of TLE
2. Fluoroscopy time of the procedure, number and type of extraction sheaths used, and changes in tooling type during the procedure.

Primary safety endpoints:

1. Major complications during lead extraction as defined by the 2017 HRS expert consensus statement on cardiovascular implantable electronic lead management and extraction 4]. These include death, cardiac avulsion, vascular laceration, and pericardial effusion, requiring intervention during the extraction procedure.

STUDY DESIGN

OVERALL STUDY DESIGN:

This study will be conducted at 4 major institutions (University of Chicago Medicine, Penn Medicine, University of Michigan, Allina Health) that specialize in TLE. The investigators in this study are electrophysiologists with expertise in TLE and imaging using ICE. All adult patients over the age of 21 years scheduled to undergo lead TLE for any indication will be eligible to participate as long as the lead dwell time is greater than 1 year.

Duration of study: 1 year

SUBJECT SELECTION AND WITHDRAWAL

SITES:

Subjects selected for study will be recruited from 4 sites: University of Chicago Medicine, Chicago, IL; Penn Medicine, Philadelphia, PA; University of Michigan, Ann Arbor, MI; Allina Health, St.Paul, MN

Eligibility: Patients that have been recommended for lead extraction are eligible for enrollment.

A total of 100 eligible patients will be enrolled in the study. Twenty-five patients will be enrolled at each site which will allow 2 things: (1) the operator will first become comfortable with interpreting the images obtained from IVUS (5 patients) and (2) imaging from the remaining 20 patients will help reinforce understanding of the grading scale [25 patients x 4 sites = 100 patients]. Assuming a Pearson correlation sample size calculation:

- Power: 80%
- Alpha Value: 5%
- Baseline Ho Correlation: 0.50
- Alternative Correlation: 0.70
- Drop-Out Rate: 20%
- Sample Size Calculation: 100 patients

See Appendix D for further information.

Inclusion:

- Patients at least 21 years of age
- Patients with at least one lead over 1 year dwell time requiring extraction

Exclusion:

- Inability of patient capacity to provide consent for themselves either due to medical or psychiatric comorbidity
- Venous occlusion to the extent that the IVUS catheter cannot pass
- Leads < 1 year dwell time requiring extraction

STUDY DEVICE

Visions® PV.035 IVUS catheter (Volcano, San Diego, CA) [Appendix B]

STUDY PROCEDURES

SCREENING VISIT

Patients will be screened for the study using inclusion and exclusion criteria outlined in Section 3. Informed consent will be obtained as detailed in Section 0. The following data will be collected at screening once informed consent is obtained:

Demographics to Record:

1. Baseline characteristics:

a. Age
b. Gender
c. Body mass index
d. Height
e. Race

2. Medical Co-morbidities
    a. Diabetes
    b. Creatinine clearance rate (ESRD)
    c. Hypertension
    d. Coronary artery disease
    e. Prior open chest surgery
    f. Left ventricular ejection fraction (%)
    g. NYHA functional class
3. Lead Data
    a. Reason for extraction (indication per HRS Consensus Guidelines)
    b. Type of leads
        i. Location
        ii. Fixation type
        iii. Function
        iv. SVC Coil (Y/N, single or dual)
    c. Number of leads
    d. Lead dwell times
4. Routine laboratory data including blood culture or wound culture results if applicable.
5. Chest x-ray findings
6. Transesophageal echocardiography (TEE) or transthoracic echocardiogram (if performed)

PROCEDURE

Transvenous lead extraction (TLE) should be performed in an EP lab, cardiac OR or hybrid lab as is customary based on the operator's preference. A PA and lateral CXR is recommended any time prior to TLE to confirm the number, type and location of all implanted leads and hardware. The following tests are recommended but left to the discretion of the operator: (1) transesophageal echocardiography (TEE) or transthoracic echocardiogram to look for vegetations (thrombus w/ infection indication) and tricuspid valve (TV) regurgitation, and (2) right or left subclavian vein venogram to evaluate patency of venous structures. If performed, reports of these tests will be collected. Prior to the start of the procedure, the operator will need to perform the following assessment:

1. Assessment of risk and /or difficulty of extraction based on clinical variables alone
    a. Based on the following clinical variables, what is your assessment of risk or difficulty of extraction? (LOW (L) = 1 point, MODERATE (M) = 2 points, HIGH (H) = 3 points)
        i. Lead dwell time LOW MODERATE HIGH
        ii. Number of leads in vascular space LOW MODERATE HIGH

iii. Type of lead LOW MODERATE HIGH
iv. BMI of patient LOW MODERATE HIGH
v. Patient age LOW MODERATE HIGH
vi. Gender (male=1 point, female=2 points)

TOTAL: 6-8 points = overall LOW risk , 9-11 = MODERATE risk, 12-17 = HIGH risk

b. Are you planning on inserting the Philips Rescue Balloon guidewire (PRB-G) during this case?
    i. If Yes, why?
    ii. If No, why not?
    iii. If you are going to use the PRB-G, are you planning on inserting the Rescue Balloon up front? YES or NO

Two or more large (7F – 12F) venous sheaths will be inserted in the right and left femoral veins as per standard of care as part of the TLE procedure. A 8.5F SRO or other long sheath can help direct the IVUS (Visions® PV.035) catheter and may be used as one of the two standard of care access sheaths. If a long sheath is not used, an 8.5 F short sheath is the minimum size required to use the IVUS catheter.

Prior to pocket access, the IVUS catheter is inserted through a right or left femoral venous approach and advanced under fluoroscopic guidance to the RA. If the pacemaker lead entry is in left pectoral region, imaging will begin from the innominate vein using the medial end of left clavicle as the origin, registered under fluoroscopy. If the pacemaker leads start from right pectoral region, then imaging begins in the cranial portion of SVC, using the medial end of the right clavicle as origin, registered under fluoroscopy. A 0.32 guidewire can help with IVUS catheter manipulation if necessary.

Based on fluoroscopy alone, in left sided device implants, the chest will be divided into 3 zones: Zone 1includes the area between the head of the clavicle and the innominate vein; zone 2 includes the area between the innominate vein to SVC-RA junction and zone 3 includes the area between the SVC-RA junction through to the mid RA. In right sided device implants, zone 1 includes the area between the head of clavicle to the SVC-RA junction; zone 2 includes SVC-RA junction through to the mid RA.

From there the physician retracts the IVUS catheter through the SVC to the RA in a “survey” run, looking for areas of ILA between the lead and the SVC wall in the previously outlined zones. He/she will also note the presence of lead-on-lead binding. At least one representative image from each zone will be recorded, labelled and saved on the IVUS console. Fluoroscopic images of IVUS catheter position at each site of image recording will be saved and labelled. Using the following scale, grading of ILA in each zone of interest, based on relative motion of lead will be performed:

i. Grade 1: Freely mobile, Rarely adjacent to vasculature
ii. Grade 2: Restricted mobility, Frequently adjacent to vasculature
iii. Grade 3: Immobile, Always adjacent to vasculature
iv. Grade L, added to number: Lead-to-lead binding

If no ILA is seen, the extraction procedure commences.

If physician identifies locations of adhesions, he/she returns the IVUS catheter to those locations to evaluate severity of adhesion and quantify adhesions based on standardized grading scale which is outlined above. Once all adhesions are evaluated, the extraction procedure commences and the physician gains pocket access and prepares the lead for extraction. The subjective amount (small, moderate, large) of pocket calcification needs to be noted.

The physician begins the extraction until the leads are free through the subclavicular space. At this point, a second run of IVUS imaging is done focusing on areas of highest adhesion seen in the initial imaging. These IVUS images will be collected and saved. When adhesion areas are located, traction is applied to lead of interest to watch the dynamic response of lead movement, then regraded accordingly. Both grades, initial and secondary, should be recorded. The highest grade of adhesion seen in the zone of interest is recorded for that lead. Once this is done, the IVUS catheter may or may not be removed during the extraction procedure. It may left in the low RA to monitor for pericardial effusion development. Added imaging protocol should add 10 minutes to the overall procedure.

During the extraction, the following information needs to be recorded: Laser pulse number of lasing per zone, number of handle pulls for mechanical sheath and time of progression through zone of interest.

Once the extraction is completed, the following data will be collected:

Procedural Data to Record:

1. Length of Procedure (Patient-on-table to wheel-out)
2. Order of leads extracted
3. IVUS Procedure
    a. Length of imaging time
    b. Location of adhesions (images will be captured and collected for the study)
    c. Grading of adhesion in zone of interest, based on relative motion of lead:
        i. Grade 1: Freely mobile, Rarely adjacent to vasculature
        ii. Grade 2: Restricted mobility, Frequently adjacent to vasculature
        iii. Grade 3: Immobile, Always adjacent to vasculature
        iv. Grade L, added to number: Lead-to-lead binding
4. Length of Extraction (Opening pocket to start of re-implantation, if applicable)
5. Extraction tools
    a. Laser, Mechanical, Dilating Sheath
    b. Starting sheath size
    c. Change of sheath size, settings (40 v. 80Hz), and type
    d. Use of Outer Sheath
    e. Switching of leads to extract
6. Location of adhesions felt by extractor
7. Operator rating about ease of sheath advancement in each zone (zones 1-3):
    a. None – removed without sheaths
    b. 0 – advanced without power assistance
    c. 1 – Power assistance but easily advanced
    d. 2 – Power assistance with effort

8. Laser pulse number of lasing per segment
9. Number of handle pulls for mechanical sheath
10. Time of progression through zone of interest
11. Pocket calcification (Y/N)
12. Clinical Outcome Data:
    a. Extraction procedural success, as defined above
    b. Major/minor complications, as defined by 2017 HRS consensus guidelines
    c. Complications from IVUS catheters (if any)

PREDISCHARGE

The patient will be assessed at pre-discharge for the occurrence of any major adverse events including: death, need for open heart surgery, cardiac tamponade, or need for re-operation.

STATISTICAL PLAN AND CONSIDERATIONS

Using Stata statistical software (StataCorp LP, College Station, Texas), ILA grades will be correlated to the time required and amount of laser pulsations delivered to traverse each vascular segment. Spearman correlation coefficients will be calculated. The student's T-test will be used for continuous comparisons. Fisher's exact or the Chi-square test will be applied for dichotomous variables.

RISKS AND BENEFITS

RISKS

It is standard of care to insert 2 or more large (7F – 12F) venous sheaths in the right and left femoral veins during TLE. This is done to provide access for large volume resuscitation and a conduit for temporary peripheral bypass in the event of a major vascular complication like SVC or RV tear [4]. In many centers ICE is already being utilized during TLE to monitor for complications. This study will require the operator to manipulate the IVUS catheter in the RA, SVC and IV. Potential risks of the overall procedure include venous perforation leading to cardiac tamponade. Based on published data, the risk of this event occurring is very low [11-13]. Specifically, in a recent review of ICE/IVUS in EP procedures that was published in 2018, ICE/IVUS use was not associated with any major complications. Additionally, there were no adverse events seen with use of IVUS in our cohort of 56 patients that Drs. Beaser and I studied. Please refer to IFU's for potential risks associated with IVUS catheter. [Appendix B] While we believe there are little to no added risks for using IVUS, procedure time may be increased by 10 minutes in order to capture images via IVUS. In our experience though, the acquisition of IVUS images can be done simultaneously with other parts of the procedure thereby not adding any additional time to the procedure.

BENEFITS

IVUS shows promise as a tool to evaluate the presence of ILA in the SVC and other cardiac structures. This could potentially allow operators to risk-stratify the allowing them to better select the resources, tools and approach to the procedure.

SAFETY AND ADVERSE EVENTS

Monitoring of Adverse Events

During the procedure, participants will be monitored by physicians (including anesthesiology), nurses, and technicians in accordance with standard operating procedures for routine catheter ablation procedures. Real-time hemodynamic monitoring during the procedure will be measured using arterial access. Real-time cardiac visualization will occur with the use of intracardiac echocardiography.

Post-operative monitoring will follow standard care for clinical ablation procedures, which includes overnight admission for observation with monitored telemetry and measurement of heart rate, blood pressure, oxygen saturation, and respiratory rate.

Table 1 Adverse Event Definitions and Grading

Term	Definition
Adverse Event (AE) Ref: ISO 14155-2011 Ref: MEDDEV 2.7/3 12/2010	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the procedures involved (any procedure in the clinical investigation plan).
Adverse Device Effect (ADE) Ref: ISO 14155-2011 Ref: MEDDEV 2.7/3 12/2010	Adverse event related to the use of an investigational medical device This definition includes any adverse event resulting from insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) Ref: ISO 14155-2011 Ref: MEDDEV 2.7/3 12/2010	Adverse event that led to: • Death • Serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or

Term	Definition
	○ a permanent impairment of a body structure or a body function, or ○ in-patient or prolonged hospitalization of existing hospitalization, or ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Fetal distress, fetal death, or a congenital abnormality or birth defect. NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) Ref: ISO 14155-2011 Ref: MEDDEV 2.7/3 12/2010	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) Ref: 21 CFR Part 812	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Device Deficiency Ref: ISO 14155-2011 Ref: MEDDEV 2.7/3 12/2010	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation.

A. Assessing Relationship to Study Device

The site investigator will be responsible for assessing the relationship of the AE to the study device as related or unrelated, and for reporting the event to UChicago according to criteria in Appendix C.

Table 2 Adverse Event Relatedness Criteria

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

B. Adverse Event Reporting

Adverse events should be reported to the UChicago study team according to the table in Appendix C.

The site investigator is responsible for expeditiously evaluating adverse events for severity and causality designation according to details in Tables 1 and 2. The site investigator is responsible for providing supporting documentation to UChicago. All AEs that are considered related to the study or the device must be followed to resolution.

The UChicago study team will report adverse events to the FDA, UChicago IRB, and Phillips according to details in Appendix C.

All SAEs reported from participating sites will be reviewed by the Lead Principal Investigator or his/her physician designee. Only those determined to be serious and unexpected by the Lead Principal Investigator will be distributed to participating sites. If Phillips informs the Lead PI of new device information that impacts the safety of subjects, the UChicago study team will be responsible for distributing this information to sites.

A safety monitor (a physician who is not part of the study and does not perform TLE) will be designated. His/her role will be to evaluate and adjudicate any potential IVUS related adverse events. The study will be halted upon the discovery of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.

STUDY MONITORING, AUDITING AND INSPECTING

The University of Chicago responsibility as the clinical sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation. The University of Chicago requires IRB review and a subject Informed Consent Form for all research. Monitoring may be conducted remotely by The University of Chicago Research Office.

Through centralized monitoring, The University of Chicago will assess the site's performance in the following areas:

- Verification that informed consent was obtained and documented properly
- Adherence to protocol eligibility criteria and requirements
- Conduct and documentation of procedures and assessments related to:
- Study endpoints
- Protocol required safety assessments
- Evaluating, documenting, and reporting unanticipated adverse device effects, subject deaths, and withdrawals, especially when a withdrawal may be related to an adverse event.
- Investigator oversight and delegation of authority to study personnel
- Verification of study-specific required documentation
- Conduct and documentation of procedures essential to trial integrity

As the investigator, the physician is responsible for conducting the study in accordance with the signed agreement, the investigational plan (protocol), applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB/EC. The principal investigator must also accept responsibility for all aspects of the study including the actions of any sub-investigators participating in the study at the investigational site.

Data Monitoring

The responsibility of The University of Chicago as sponsor is to ensure protocol and regulatory compliance through proper monitoring of the clinical investigation in U.S. sites. The University of Chicago is also required to ensure that the device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the clinical investigation in accordance with the signed study agreement, the study protocol, and applicable laws. The primary investigator must also accept responsibility for all aspects of the clinical investigation including the actions of any co-investigators participating in the clinical investigation at the investigational site.

Study data will be reviewed and source verified at The University of Chicago to ensure that the investigator and the clinical investigation team conducts the clinical investigation in accordance with the clinical investigation protocol and applicable FDA and local laws and regulations to ensure adequate protection of the rights, safety and wellbeing of subjects and the quality and integrity of the resulting data.

PATIENT INFORMED CONSENT

All study subjects must provide written informed consent using the applicable IRB informed consent form. Each patient will receive a copy of his/her signed consent form. The original signed consent document must be kept on file at the investigative site.

The study must be explained in a language that is understandable to the patient and s/he must be allowed sufficient time to decide whether to participate in this study. All subjects will be assured that they have

the right to withdraw from the study at any time during the course of the protocol and this decision will not influence his/her relationship with the lead investigator, the treating physician and/or the study staff.

DATA HANDLING, AND RECORD KEEPING, AND CONFIDENTIALITY

University of Chicago will receive coded study data from participating sites for study analysis.

Data will be collected on paper by study coordinators at the respective participating sites and transcribed into an electronic RedCap database which will be maintained on-campus locations at the University of Chicago. Data will be managed by the PIs and study coordinators. Access to the data will be limited to site PIs and research coordinators only during the study enrollment period.

All patient specific identifiers will be kept separate from the primary research database. The research database will be organized by a unique patient identifier.

DEVICE TRACKING

The Industry-Sponsor may ship investigational devices only to qualified investigators participating in the clinical investigation. A tracking system will be used to maintain complete and accurate record of shipment and disposition of the investigational devices. Records of shipment shall include the name and address of the consignee, type and quantity of device, and date of shipment.

Device Tracking By Investigator

Investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them. Under no circumstances may the investigational device be used/made available to any person who has not been pre-approved by the Sponsor as an investigator for use.

Each site will record lot and model numbers of each device received onto a device tracking log. When a device is used, the subject identification along with the model and lot number of the device used will be recorded. Any device returned to the Industry-Sponsor, due to malfunction, expiration, etc. will also be documented on the device tracking log. Contaminated devices will be returned to Industry-Sponsor in the appropriate biohazard packaging.

Upon completion or termination of a clinical investigation an investigator is required to return to the Industry-Sponsor any remaining supply of devices.

FINANCIAL CONSIDERATIONS

No remuneration will be provided to subjects. Funding for this study will be provided by the industry sponsor: Philips. The industry sponsor will be providing the Visions® PV.035 IVUS catheter and accompanying console to the sites for use in this study.

REFERENCES

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Appendix A

SCHEDULE OF EVENTS

	Screening	Procedure (Day 0)	Pre-discharge
Informed consent	X		
Medical Records Review	X		
Clinical Evaluation	X		
Chest X-ray report	X		
Transesophageal echocardiography (TEE) or Transthoracic echocardiogram	X [a]		
Transvensous Lead Extraction Data		X	
Venogram results		X	
IVUS images and Fluoroscopy Pictures		X	
Adverse Events	X	X	X

[a] Discretion of operator

Appendix B

Instructions For Use

Visions® PV .035

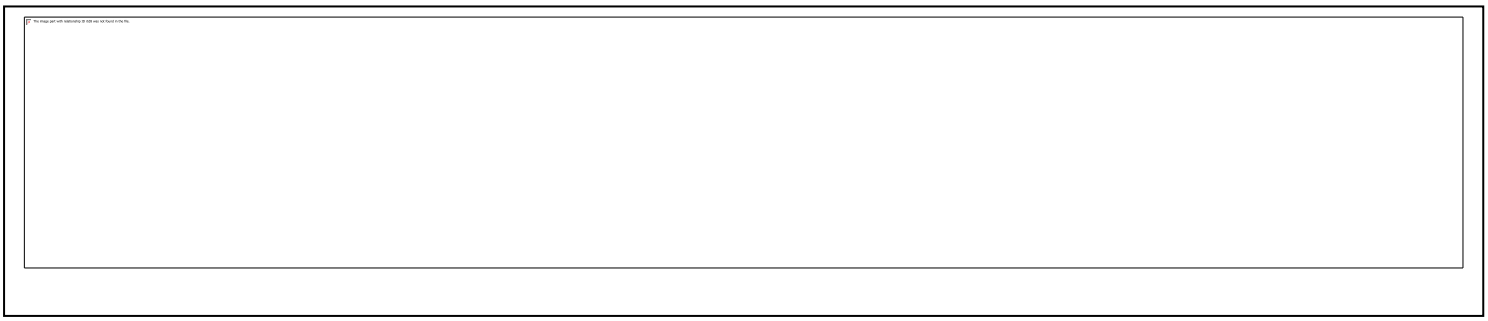
DIGITAL IVUS cATHETER

CAUTION – Investigational Device Limited by Federal law to investigational use

English Page 1

English

DIGITAL IVUS Catheter



CAUTION:

1. U.S. Federal Law restricts this device to sale by or on the order of a physician.

2. Prior to use, read this entire package insert.

INTENDED USE:

The Visions® PV .035 catheters are designed for use in the evaluation of vascular morphology in blood vessels of the peripheral vasculature by providing a cross-sectional image of such vessels.

The Visions® PV .035 ultrasound imaging catheters are designed for use as an adjunct to conventional angiographic procedures to provide an image of the vessel lumen and wall structures and dimensional measurements from the image.

DESCRIPTION:

The Visions PV .035 catheter is an over-the-wire intravascular imaging catheter with a digital ultrasound transducer at the distal end. The transducer utilizes a 64-element cylindrical array that radiates acoustic energy into the surrounding tissue and detects the subsequent echoes. The information from the echoes is used to generate real-time images of the peripheral vessels.

The Visions PV .035 catheter is introduced percutaneously or via surgical cutdown into the vascular system, and is designed to track over 0.035”-0.038” (0.89-0.97mm) guide wires.

The catheter body has markers 1 cm apart along the working length. There are 25 radiopaque markers on the distal end of the catheter, starting 1 cm from the imaging plane, with the 25th RO marker overlapping the distal-most wide inked marker. Inked markers (non-radiopaque) continue along the shaft, spaced 1 cm apart, middle-to-middle, with wider marks indicating 5 cm intervals.

A lubricious GlyDx® hydrophilic coating is applied externally to a distal portion of the catheter.

The Visions PV .035 catheters may only be used with Volcano s5™ Series and CORE™ Series of Systems.

CONTRAINDICATIONS:

- Use in cerebral vasculature
- Situations presenting a reasonable probability of tissue or organ damage
- Vessel spasm
- Severe calcification
- Angiographic evidence of thrombus
- Severe vessel tortuosity

ADVERSE EFFECTS:

As with all catheterization procedures, complications may be encountered with the use of the Visions PV .035 digital IVUS catheter. Possible adverse effects include, but are not limited to, the following: occlusion; vessel spasm; vessel dissection; perforation, rupture or injury; restenosis; hemorrhage or hematoma; drug reactions; allergic reaction to contrast medium; hypo/hypertension; infection; arteriovenous fistula; embolism; entry puncture site bleeding; vascular wall injury; vessel thrombosis; pseudoaneurysm (at site of catheter insertion); renal failure; aneurysm; vessel trauma requiring surgical repair or intervention; death.

WARNINGS:

- Use of the Visions PV .035 catheters should be restricted to specialists who are familiar with, and have been trained to perform, the procedures for which this device is intended.

- The product is supplied sterile; if the pouch is opened or damaged compromising the sterile barrier, please discard the product. This product cannot be re-sterilized or re-used.

- The Visions PV .035 catheter is designed for single use only. VOLCANO Corporation ("VOLCANO"), makes no warranty, representation or condition of any kind, whether expressed or implied (including any warranty of merchantability, suitability or fitness for a particular purpose) respecting the re-use of the catheter.

- In addition, VOLCANO assumes no responsibility or liability for incidental or consequential damages which may result from such re-use. Re-use including resterilization of unused product may result in, but is not limited, to the following:

- Potential critical harm to patient due to Device Separation, Material Deformation or Infection/Sepsis

- Failure to Image or other device malfunctions

- The catheter transducer is a delicate electronic assembly. Deliberate misuse by bending, twisting or any other severe physical manipulation will void the warranty.

- Do not use the Visions PV .035 device for purposes other than those indicated.

PRECAUTIONS:

The Visions PV .035 device is a delicate scientific instrument and should be treated as such. Always observe the following precautions:

- Protect the catheter tip from impact and excessive force.

- Do not cut, crease, knot, or otherwise damage the catheter.

- Protect the electrical connections from exposure to fluid.

- Do not handle the transducer.

- The outside diameter along the entire length of the guide wire should not exceed the maximum specified.

- During use, ensure that the placement of the catheter does not preclude blood flow through the vessel.

- Clean guide wire and flush catheter thoroughly with sterile heparinized normal saline before and after each insertion.

- Keep the exterior of the catheter wiped down with sterile heparinized normal saline during prolonged use.

- When inserting the guide wire both catheter and wire must be straight with no bends or kinks, or damage to inner lumen may occur.

- Do not advance the guide wire against significant resistance. If binding occurs between the catheter and the guide wire while inside the patient, CAREFULLY REMOVE BOTH the wire and catheter and do not use. If binding occurs outside of the patient, remove the catheter and do not use.

- When advancing or re-advancing the catheter over a guide wire and through a stented vessel, in the event that the stent is not fully apposed against the vessel wall, the guide wire / and or catheter may become entangled in the stent between the junction of the catheter and guide wire or within one or more stent struts. This may result in entrapment of catheter/guide wire, catheter tip separation, and/or stent dislocation. Never use force to advance the catheter.

- Use caution when re-advancing a catheter over a guide wire and into a stented vessel, in the event that the catheter may come in contact with one or more stent struts. Subsequent advancement of the IVUS catheter could cause entanglement between the catheter and the stent(s) resulting in entrapment of catheter/guide wire, catheter tip separation, and/or stent dislocation.

- Use caution when removing the catheter over the guide wire from a stented vessel to minimize patient risk.

- The catheter should never be forcibly inserted into lumens narrower than the catheter body or forced through a tight stenosis.

- If resistance is encountered during pullback, remove the entire system (guide wire, IVUS catheter, sheath/guide catheter) at the same time.

INSTRUCTIONS FOR USE:

The Visions PV .035 catheter may be introduced into the vascular system percutaneously or surgically and advanced to the desired location. The frequency and duration of administration is subject to the discretion of the physician and depends upon the procedure and information required.

- Review the Volcano Imaging System Operator's Manual thoroughly prior to use of this device. Check system operation prior to the use.
- Open the Visions PV .035 catheter packaging using sterile technique and place the hoop in the sterile field.
- Prepare the catheter by flushing the guide wire lumen through the port at the catheter's Y-connector, and then wipe down the entire working length with sterile heparinized normal saline.
- Remove the clear/white cap from the PIM connector.
- Connect the PIM connector of the Visions PV .035 catheter to the Patient Interface Module as described in the imaging system Operator's Manual. Verify that the device is imaging.

- Place the Visions PV .035 catheter onto the intravascular guide wire. A guide wire of 0.035” (0.89 mm)-0.038" (0.97 mm) can be used.
- Activate the hydrophilic coating using sterile heparinized normal saline.
- Advance the Visions PV .035 catheter over the guide wire to the site of the vasculature to be imaged. The guide wire should always be advanced ahead of the IVUS catheter.
- Check the Monitor for an image. Once the image has been obtained, the catheter can be advanced over the guide wire to image additional segments of vasculature.
- If an image is not obtained or is not satisfactory, consult the Volcano Imaging System Operator’s Manual.
- Once imaging has been completed, remove the Visions PV .035 catheter and flush thoroughly with sterile heparinized normal saline.
- For subsequent imaging, clean guide wire and flush catheter thoroughly with sterile heparinized normal saline before re-insertion.
- When the procedure is completed, remove and discard the catheter in accordance with local regulations.

STORAGE AND HANDLING:

Products should be stored in a dry, dark, cool place in their original packaging.

PRODUCT SPECIFICATIONS:

Model Visions PV .035

Maximum shaft outer diameter 7.0F (0.092", 2.33 mm)

Maximum scanner diameter 8.2F (0.108", 2.73 mm)

Maximum guide wire 0.038" (0.97 mm)

Minimum Introducer sheath 8.5F (0.111”, 2.83 mm)

Usable length 90 cm

Acoustic Output Parameter	**B-Mode**
$I_{SPTA.3}$ (mW/cm^2)	0.0534
$I_{SPPA.3}$ (W/cm^2)	0.0680
Pr.3 (MPa)	0.0482
PD (μs)	0.333
PRF (Hz)	2.09×10^4
Center Freq (MHz)	9.00
MI*	0.0162
TI*	6.18×10^{-5}

Maximum overall uncertainty ±20.4%

* As estimated in tissue

TI: Thermal Index defined as TI = $W_{01x1} f_c$

210

W_{01x1}: Bounded-square Output (mW)

f_c: Center Frequency (MHz)

MI: Mechanical Index defined as MI= $Pr.3/(f_c^{1/2})$

$I_{SPPA.3}$: Derated Intensity, Spatial Peak Pulse Average (W/cm^2)

$I_{SPTA.3}$: Derated Intensity, Spatial Peak Temporal Average (mW/cm^2)

Pr.3: Derated Peak Negative Pressure at a location of the maximum derated pulse intensity integral (MPa)

PD: Pulse Duration (μs)

PRF: Pulse Repetition Frequency (Hz)

LIMITED WARRANTY:

Subject to the conditions and limitations on liability stated herein, Volcano Corporation ("VOLCANO") warrants that the Visions PV .035 catheter (the "Catheter"), as so delivered, shall materially conform to VOLCANO's then current specification for the Catheter upon receipt for a period of one year from the date of delivery. ANY LIABILITY OF VOLCANO WITH RESPECT TO THE CATHETER OR THE PERFORMANCE THEREOF UNDER ANY WARRANTY, NEGLIGENCE, STRICT LIABILITY OR OTHER THEORY WILL BE LIMITED EXCLUSIVELY TO CATHETER REPLACEMENT OR, IF REPLACEMENT IS INADEQUATE AS A REMEDY OR, IN VOLCANO'S OPINION, IMPRACTICAL, TO REFUND OF THE FEE PAID FOR THE CATHETER. EXCEPT FOR THE FOREGOING, THE CATHETER IS PROVIDED "AS IS" WITHOUT WARRANTY OF ANY KIND, EXPRESSED OR IMPLIED, INCLUDING WITHOUT LIMITATION, ANY WARRANTY OF FITNESS, MERCHANTABILITY, AND FITNESS FOR A PARTICULAR PURPOSE OF NONINFRINGEMENT. FURTHER, VOLCANO DOES NOT WARRANT, GUARANTEE, OR MAKE ANY REPRESENTATIONS REGARDING THE USE, OR THE RESULTS OF THE USE, OF THE CATHETER OR WRITTEN MATERIALS IN TERMS OF CORRECTNESS, ACCURACY, RELIABILTY, OR OTHERWISE. Licensee understands that VOLCANO is not responsible for and will have no liability for any items or any services provided by any persons other than VOLCANO. VOLCANO shall have no liability for delays or failures beyond its reasonable control.

Additionally, this warranty does not apply if:

1. The Catheter is used in a manner other than described by VOLCANO in the Instructions For Use supplied with the Catheter.

2. The Catheter is used in a manner that is not in conformance with purchase specifications or specifications contained in the Instructions For Use.
3. The Catheter is re-used or re-sterilized.
4. The Catheter is repaired, altered, or modified by other than VOLCANO authorized personnel or without VOLCANO authorization.

If claims under this warranty become necessary, contact VOLCANO for instructions and issuance of a Return Material Authorization number if the Catheter is to be returned. Equipment will not be accepted for warranty purposes unless the return has been authorized by VOLCANO.

PATENT www.volcanocorp.com/patents.php

This product is licensed to the customer for single use only.

Visions is a registered trademark of Volcano Corporation and is registered in the United States and other countries.

Volcano and the Volcano logo are registered trademarks of Volcano Corporation in the United States and other countries.

ADDITIONAL QUESTIONS REGARDING THIS PRODUCT SHOULD BE DIRECTED TO:

Legal Manufacturer: 

Volcano Corporation

2870 Kilgore Road

Rancho Cordova, CA 95670
USA

Telephone: 800.228.4728

(916) 638-8008

Fax: 916.638.8112

Authorized European Representative: 

Volcano Europe BVBA/SPRL

Excelsiorlaan 41

B-1930 Zaventem, Belgium

Telephone: +32.2.679.1076

Fax: +32.2.679.1079

Manufacturing Sites:

Volcano Corporation

2870 Kilgore Road

Rancho Cordova, CA 95670 USA

Or

Volcarica S.R.L.

Coyol Free Zone and Business Park

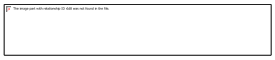
Building B37

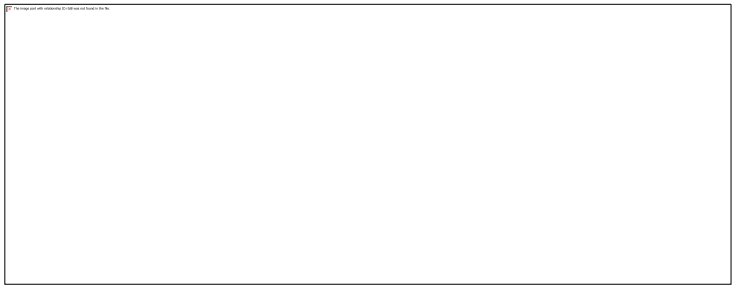
Coyol, Alajuela, Costa Rica

Telephone: (800) 228-4728

(916) 638-8008

Fax: (916) 638-8112





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501-0100.12/007 Revision Date: 10/2015

Appendix C: Adverse Event Reporting Requirements

Table 3 Adverse Event Reporting to University of Chicago

University of Chicago study team contact information: Tiffany Hart, Lead CRA and Hemal Nayak, MD
Phone #(773)702-0535 and Fax#(773)834-2109

Event Classification	Event Reporting to University of Chicago (UChicago)
Adverse Event	Event recorded and tracked at site.
Serious Adverse Event and Serious Adverse Device Effects	Event recorded using study provided reporting forms and reported within 48 hours of PI knowledge and required source documentation provided
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	• Reported as soon as possible, but within 48 hours of site PI knowledge • Site should call or UChicago CRA (contact above) to report event and email thart@medicine.bsd.uchicago.edu • Event recorded using study provided reporting forms and reported within 48 hours of PI knowledge and required source documentation provided
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) NOTE: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	• If the defect lead to a serious event, this should be reported as soon as possible, but within 48 hours of site PI's knowledge. Otherwise, report within 48 hours of site PI's knowledge. • Event recorded using study provided reporting forms and reported within 48 hours of PI knowledge and required source documentation provided

Table 4 Adverse Event Reporting by University of Chicago

Event Classification	**UChicago Communication to FDA**	**UChicago Communication to UChicago IRB**	**Reporting to Phillips**
Adverse Event	NA	Details provided at time of annual review, per IRB policy.	None, as these are expected events.
Serious Adverse Event Serious Adverse Device Effects	NA	Details provided at time of annual review, per IRB policy, as these are not unanticipated events.	None, as these are expected events.
Unanticipated Adverse Device Effect Unanticipated Serious Adverse Device Effect	Reported as soon as possible, but within 48 hours of Lead PI knowledge. These would be unexpected and would be reported to the FDA regardless of IDE status for this study.	UADE reported within 10 days of PI knowledge USADE reported directly to IRB Chairman upon PI knowledge, followed by formal reporting to the IRB within 48 hours. Study will be halted if event presents a significant or unreasonable risk to subjects enrolled in the study	Reported as soon as possible, but within 48 hours of Lead PI knowledge, including a copy of any notification provided to the FDA.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) NOTE: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Investigational Device Deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event and will be reported to the FDA within 48 hours of Lead PI knowledge. All other device deficiencies will be reported within 10 days.	Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event will be reported to the IRB within 10 days of PI knowledge.	Investigational Device Deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event and will be reported within 48 hours of Lead PI knowledge, including a copy of any information provided to the FDA. All other device deficiencies will be reported within 10 days.

Appendix D

Pearson's Correlation Tests

Numeric Results when H1: ρ0 ≠ ρ1

Power	N	Alpha	Beta	ρ0	ρ1
0.80092	80	0.05000	0.19908	0.50000	0.70000

References

Graybill, Franklin. 1961. An Introduction to Linear Statistical Models. McGraw-Hill. New York, New York.
Guenther, William C. 1977. 'Desk Calculation of Probabilities for the Distribution of the Sample Correlation
Coefficient', The American Statistician, Volume 31, Number 1, pages 45-48.
Zar, Jerrold H. 1984. Biostatistical Analysis. Second Edition. Prentice-Hall. Englewood Cliffs, New Jersey.

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one.
N is the size of the sample drawn from the population. To conserve resources, it should be small.
Alpha is the probability of rejecting a true null hypothesis. It should be small.
Beta is the probability of accepting a false null hypothesis. It should be small.
ρ0 is the value of the population correlation under the null hypothesis.
ρ1 is the value of the population correlation under the alternative hypothesis.

Summary Statements

A sample size of 80 achieves 80% power to detect a difference of -0.20000 between the null hypothesis correlation of 0.50000 and the alternative hypothesis correlation of 0.70000 using a two-sided hypothesis test with a significance level of 0.05000.

Dropout-Inflated Sample Size

Dropout Rate	Sample Size N	Dropout-Inflated Enrollment Sample Size N'	Expected Number of Dropouts D
20%	80	100	20

Definitions

Dropout Rate (DR) is the percentage of subjects (or items) that are expected to be lost at random during the
course of the study and for whom no response data will be collected (i.e. will be treated as "missing").
N is the evaluable sample size at which power is computed. If N subjects are evaluated out of the N' subjects
that are enrolled in the study, the design will achieve the stated power.
N' is the total number of subjects that should be enrolled in the study in order to end up with N evaluable
subjects, based on the assumed dropout rate. After solving for N, N' is calculated by inflating N using the
formula N' = N / (1 - DR), with N' always rounded up. (See Julious, S.A. (2010) pages 52-53, or Chow, S.C.,
Shao, J., and Wang, H. (2008) pages 39-40.)
D is the expected number of dropouts. D = N' - N.

Procedure Input Settings

Autosaved Template File
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Design Tab

Solve For:	Sample Size
Alternative Hypothesis:	H1: ρ0 ≠ ρ1
Power:	0.80
Alpha:	0.05
ρ0 (Baseline Correlation):	0.50
ρ1 (Alternative Correlation):	0.70