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GUIDANCE FOR THE SUBMISSION OF RESEARCH AND MARKETING APPLICATIONS FOR INTERVENTIONAL CARDIOLOGY DEVICES:

PTCA CATHETERS
ATHERECTOMY CATHETERS
LASERS
INTRAVASCULAR STENTS

Draft Document

Office of Device Evaluation
Division of Cardiovascular, Respiratory and Neurological Devices
Interventional Cardiology Devices Group

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Devices and Radiological Health

GUIDANCE FOR THE SUBMISSION OF RESEARCH AND MARKETING APPLICATIONS FOR INTERVENTIONAL CARDIOLOGY DEVICES:

PTCA CATHETERS
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LASERS
INTRAVASCULAR STENTS

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OFFICE OF DEVICE EVALUATION

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PREFACE

The development of a guidance document for interventional cardiology devices, including percutaneous transluminal coronary angioplasty (PTCA) balloon catheters, coronary guidewires, atherectomy catheters, lasers and intravascular stents, is based on the Division of Cardiovascular, Respiratory and Neurological Devices (DCRND) evaluation of numerous device applications, and the establishment of certain criteria necessary to conduct such evaluations. The purpose of the guidance is to recommend the important preclinical tests and clinical design considerations that should be incorporated in the overall evaluation of interventional cardiology devices in order to collect data that will document the devices' safety, effectiveness and clinical utility. Suggestions and recommendations contained in this guidance are not mandatory requirements, but are nonetheless considered appropriate requirements to generate valid scientific evidence. Furthermore, this is a dynamic document which will be reviewed periodically by the Interventional Cardiology Devices Branch (ICDB), DCRND, and by panel members as device materials, designs and indications for use change and technology improves. Assistance in the preparation of this guidance document was sought from staff members of the ICDB[1], members of the Circulatory Systems Devices Panel[2], the National Heart, Lung and Blood Institute (NHLBI)[3], clinical researchers[4] and representatives of industry[5]. All comments have been considered and, where appropriate, were incorporated into the guidance document.

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NONCLINICAL STUDIES REQUIREMENTS

Most interventional cardiology devices, including PTCA balloon catheters, coronary atherectomy devices, lasers and intravascular stents, are post-amendment class III devices (post-amendment refers to marketing after the enactment of the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act on May 28, 1976). As such, they require approval of a premarket approval (PMA) application, prior to commercial distribution or marketing. Additionally, clinical data is required to support the determination of safety and effectiveness. Thus, an investigational device exemptions (IDE) application as a significant risk device study is required to be approved by FDA and the reviewing institutional review board (IRB) prior to initiation of a clinical trial. This document describes the general framework to be followed in testing interventional cardiology devices and outlines the type of data that is considered necessary and appropriate for submission in an IDE application and in a subsequent PMA application. This document specifically addresses the requirements for material biocompatibility and toxicity, in vitro physical testing, animal studies and clinical trials, as well as the content and format of the IDE and PMA.

I. GENERAL CONSIDERATIONS FOR ANIMAL STUDIES

The common mode of action of all vascular interventional devices is to remove atheromatous material or to split it open while stretching the remaining soft parts of the vascular and perivascular tissue.[1,3a,10a,19,19a] Thus, such devices achieve their goal by creating a controlled but substantial injury to the vessel wall. Although the ultimate aim of these procedures is to increase vascular lumen size, the actual pathological changes take place in the vessel wall itself. Therefore, thorough morphological studies in suitable animal models are essential for proving the safety and effectiveness of coronary artery interventional devices.

The end result of injury caused by interventional devices in *normal* vessels is self-limited.[1] The healing process in normal vessels, subsequent to induced injury, restores the original lumen despite doubling the wall thickness. Therefore, studies should be performed on atherosclerotic models which may be more appropriate for assessing certain cardiovascular devices, rather than normal animals. However, other models may be utilized with adequate justification.

In vivo animal studies should be designed to closely approximate the intended use of the device in humans in order to demonstrate the safety of the procedure, to evaluate the functional characteristics of the device design and to validate the performance of interventional cardiovascular devices. The term "procedure" as used hereinafter refers to interventions including angioplasty, atherectomy, lasers, and stents. The studies should be conducted using models of spontaneous or diet-induced atherosclerosis and the selected treatment sites should have diameters similar to those of human coronary arteries. Other models may be used with adequate justification.

Considerations for the selection of atherosclerosis animal models:

1. a. The susceptibility of a selected species to develop spontaneous or diet induced atherosclerosis must be established.

   b. The animal model chosen should reflect the type of lesion to be evaluated in the clinical study. For example, the coronary arteries in the rabbit model are too small to reflect the diameter of the human coronaries. The iliac artery would be more the size of a human coronary artery. Hence, the pig model may be more appropriate for evaluating interventional devices for treating coronary atherosclerosis.

   c. Although one would prefer lesions in animals that morphologically resemble those in humans, currently accepted animal models of atherosclerosis may suffice.[2]

d. Certain special considerations may favor one animal model over another. For instance, the pig model may be more appropriate than the dog and rabbit models in evaluating intravascular stents.[3]

2. Optimal dimension of induced lesion - extent of luminal narrowing to be demonstrated pre-procedure:

   In order to show the effectiveness of the interventional cardiovascular devices, atherosclerotic lesions produced in study animals should result in 40% to 70% luminal diameter narrowing, as noted by pre-procedure angiography. Lesions of less than 40% narrowing of luminal diameter pre-procedure should be excluded from the study.

Based on the above, the suggested guidelines are:

1. The studies should be conducted in animal models of spontaneous or diet induced atherosclerosis. However, other animal models may be used with adequate justification.

2. Based on a review of the literature we would recommend the swine model (normal swine, miniswine or microswine may be used).

3. If a rabbit model is used, the treatment site (artery) selected should be the diameter of human coronary artery, e.g. the iliac arteries. However, caution should be exercised when extrapolating conclusions from rabbit peripheral vessel studies to human coronary arteries.

4. The procedure should be performed on atherosclerotic lesions which produce 40% to 70% reduction in luminal diameter, as determined by angiography pre-procedure. **Lesions producing less than 40% luminal diameter narrowing pre-procedure should be excluded from the studies.**

5. Post-procedure studies:

   a. Affect of the device on the treated vessel must be demonstrated by post-procedure angiographic studies.

   b. Pathological studies:

      Pathological studies should be aimed at determining:

      i. affect of the device in increasing the arterial lumen;

ii. the safety of the procedure by demonstrating the lack of damage to the vessel wall; and

iii. the presence or absence of distal embolization (where applicable).

Number of observations: Pathological studies should be performed 24 hours post-procedure (acute) in one group of animals, 8 weeks post-procedure in another group of animals and at 6 months for permanent implants such as stents, in a third group of animals. A minimum of 6 animals with effective luminal dilatation of at least one lesion each should be included in each group.

At sacrifice the segment of artery subjected to the procedure along with adjacent proximal and distal normal segments should be carefully dissected out. The artery should be cross sectioned at three to four millimeter intervals and gross photographs should be obtained. In the case of stents, longitudinal sections should be taken to demonstrate reendothelialization. The segments should be processed for routine histology, sectioned and stained. In addition to Hematoxylin and Eosin stain, elastic and connective tissue stain(s) should be performed on the sections. Transmission and scanning electron microscopy should be used to complement light microscopy evaluation.

Any information gained from ex vivo studies may complement the information obtained in the in vivo studies, e.g., tests performed on isolated segments of atherosclerotic human arteries obtained at autopsy which could be used to demonstrate, (a) the affect of the device in increasing the arterial lumen, (b) the safety of the procedure by demonstrating the lack of damage to the vessel wall, and (c) the presence or absence of distal embolization.

The test protocol (including objectives and methods), identification of the lesion being treated (vessel size, percent stenosis, lesion location, number of lesions treated and type of lesions), results (including the investigator's comments) and the study conclusions should be provided. Histological studies should include morphometric analysis of the lesions. Detailed descriptions of changes in vessel walls should be included, e.g., complications such as dissection, perforation etc.

Finally, all testing must be conducted using the final sterilized product and should be performed in accordance with the Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies regulation (21 CFR, Part 58). All deviations from the GLP regulation should be described fully, including a justification for accepting the results of these tests.

I. BIOCOMPATIBILITY TESTING FOR ALL INTERVENTIONAL CARDIOLOGY DEVICES

The overall safety evaluation of an investigational device begins with an assessment of its biocompatibility. Biocompatibility evaluation depends, in part, on the full characterization of all device materials after sterilization. To ensure identity, the material specifications from the manufacturer, and qualitative and quantitative information concerning all constituent materials used in the manufacturing of a device, especially long-term blood contact must be provided. Furthermore, all protocols, test results and the identification of control materials should be provided in order that an independent evaluation of the study conclusions can be made. Protocols do not need to be submitted if standard methods are utilized (e.g., USP methods) and complete references for the methods are provided.

Biocompatibility testing may not be necessary if a material has a long history of use in currently marketed interventional cardiology devices. If there is sufficient knowledge about the biocompatibility/toxicity of every constituent of a human blood contact device or implant, then the new blood contact device and implant need not be subjected to further biocompatibility tests. It is incumbent upon the device sponsor to provide sufficient evidence to prove that biocompatibility testing is not necessary. A sponsor may submit information and data available in publications or other legitimate sources which show that the material is non-toxic in tests identical or equivalent to the biological tests required in the Tripartite Biocompatibility Guidance or ISO Guidance for Medical Devices.

While the Tripartite Guidance is comprehensive for testing of polymers, not all tests in the Guidance are considered necessary for interventional cardiology devices. According to the ISO Guidance, only the first 7 of the 10 tests listed below are considered necessary for the interventional cardiology devices such as PTCA catheters, laser catheters, and atherectomy devices which are not implanted. Intravascular stents are implanted devices, therefore when appropriate, biocompatibility testing for these devices also includes mutagenicity and carcinogenicity testing.

The following toxicity tests, for an interventional cardiology device, are considered the necessary and appropriate tests for its use and mode of contact with the body. A manufacturer, however, may substitute or omit tests with adequate justification. In addition to providing results from the tests, the sponsor should also provide a discussion of what the results mean.

1. Sensitization Assay - To estimate the potential for sensitization of a test material and/or the extracts of a material using an animal and/or human (e.g., Guinea Pig Maximization Test or human patch test).

2. Irritation Tests - To estimate the irritation potential of test materials and their extracts, using appropriate site or implant tissue such as skin and mucous membrane in an animal model and/or human. (e.g., USP Intracutaneous Test)

3. Cytotoxicity - To determine the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by materials and/or extracts from the materials using cell culture techniques (e.g., USP Biological Reactivity Tests, In Vitro; MEM Elution or Agarose Overlay).

4. Systemic Toxicity (acute) - To estimate potential adverse effects involving the entire organism and occurring after administration of a single dose of a test sample given within 24 hours.

5. Hemocompatibility or Hemolysis - To evaluate the effects of blood contacting materials on hemolysis (i.e., the degree of red cell lysis and the separation of hemoglobin caused by test materials and/or in vitro extracts), thrombosis, plasma proteins, enzymes, and the formed elements of the blood using an animal model, with particular attention to the acceleration of the processes of intravascular thromboses.

6. Pyrogenicity - To evaluate the material mediated pyrogenicity of the test materials and/or extracts (e.g., USP Rabbit Pyrogenicity Test).

7. Implantation Tests - To evaluate the local toxic effects on living tissue, at both the gross level and microscopic level, from a sample material that is surgically implanted into appropriate animal implant site or tissue, e.g., muscle, for 7 - 90 days (e.g., USP Implantation Test). Actual length of implant duration should be decided with discretion, case by case, by the sponsor and ICDB/FDA according to the indication of the device involved and the length of the clinical use.

8. Mutagenicity or Genotoxicity - To determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by materials and/or extracts from the materials using mammalian and non-mammalian cell culture techniques. A battery of tests commonly accepted by the scientific community should be used (e.g., Gene Mutation in Salmonella typhimurium (AMES Test), Gene Mutation in Mammalian cells In Vitro, Cytogenetic Damage in Mammalian Cells (micronuclei or chromosomal aberrations), In Vitro Mammalian Cell Transformation, and Unscheduled DNA Synthesis).

9. Subchronic Toxicity - To determine the potential toxic effects from multiple exposures to test materials and/or extracts during a period of 1 day to approximately 10% of the total life of the test animal (e.g., 90 days for rats).

10. Carcinogenicity or combined Chronic Toxicity/Carcinogenicity - To assess the material mediated carcinogenicity over a period of the animal's total life and long term toxicity of the test material and/or extract in an appropriate animal model. An appropriate animal model should be one which is not prone to production of fibrosarcomas at the implant site regardless of the material implanted. Data on the animal's hematology blood chemistry, gross and histopathology should be collected. For this guidance, carcinogenicity testing when necessary, is only required for implants. In addition, if the mutagenicity, genotoxicity test battery has negative results then the carcinogenicity assay can be run concurrent with the clinical study.

All materials (e.g., polymers, metals, radiopaque material, adhesives, color additives and other leachable additives) in each component of the device must be non-toxic to human tissues. All new materials must pass the tests pursuant to the Tripartite Biocompatibility Guidance for Medical Devices to assure their safe use in an interventional cardiology device. Color additive petitions are generally not necessary for color additives used in interventional cardiology devices since colors used in these devices are not in contact with the body for a significant period of time. Thus, the routine biocompatibility testing of the color is sufficient to assess its potential toxicity.

The effects of sterilization on device materials and potential leachables, as well as toxic by-products resulting from sterilization, should be considered when conducting biocompatibility tests. Therefore, testing should be performed on the sterilized final product and any leachable material from the sterilized final product or representative samples. All test articles must be sterilized using the same procedure that is to be actually used in the manufacturing and sterilization of the final device. The exact chemical analysis of device extracts (eluant or leachable) may not be required while the extracts are subject to toxicity testing. But, as stated above, the qualitative and quantitative information of all constituent materials in the device before extraction must be provided, and the material specifications for the device must be comprehensive.

If any toxic leachables, by-products, or metabolites exist in the extracts from a sterilized device, the results of the toxicity tests on the extracts should represent the cumulative toxicities from the extracts. To ensure that the toxicity test results observed from the extracts of a device can represent the probable real toxicity of the device in actual human use, the extraction conditions and procedures must be rigorous, and the efficiency of the extractions must provide a safety factor which extends beyond that possibly attainable by the natural extraction in blood and other human tissues. The method of extraction from the device must be described in detail. If toxic responses are obtained from the extracts, then, chemical analysis of the extract must be performed to identify its toxic compound. If a device or its materials are found to be toxic, the sponsor should attempt to find an alternate material that is non-toxic.

II. PTCA BALLOON CATHETERS

Percutaneous transluminal coronary angioplasty (PTCA) balloon catheters are devices intended for dilatation of stenosed coronary arteries in order to improve perfusion. Dilatation is accomplished by inflation of a balloon, which is mounted onto the distal end of a catheter, to a specified diameter within the diseased segment of the artery.

In order to assess the functionality and safety of a balloon catheter in traversing the coronary vasculature and dilating stenoses, a preclinical evaluation of catheter performance is necessary. The preclinical requirements for a PTCA catheter include in vitro physical testing of the device and an assessment of its performance in animals. The preclinical evaluation required for a given device will depend on its specific design characteristics and indications for use. This information, in addition to complete biocompatibility data, must be submitted in order to establish the preliminary safety of a PTCA catheter and subsequently gain approval to conduct clinical studies.

A. PHYSICAL TESTING REQUIREMENTS

The PTCA catheter should be tested to ensure that its design and construction are suitable for its intended use. The physical tests in the following section should be conducted on completed catheters or suitable subassemblies, which have been exposed to a validated sterilization cycle or to a cycle validated to be equivalent. Additionally, where appropriate, testing involving the balloon catheter should be conducted in an environment which simulates in vivo conditions (e.g., 37°C water bath).

A complete report for each test conducted must be provided for review by FDA. Each test report should include the protocol (purpose, procedures, and equipment set-up), results, conclusions and a justification for the test specification in light of the clinical requirements of the device. Proper justification must be provided for any omission, substitution or combination of the tests outlined below. Note that additional tests may be required to examine new design features of a device.

1. Balloon Minimum Burst Strength - Determine the rated burst pressure for each balloon size (i.e., each balloon diameter and length combination). This test should be conducted on complete catheters or subassemblies in which the balloon is mounted on the catheter shaft. Any loss of pressure, whether due to failure of the balloon, shaft or proximal or distal seals, should be considered a failure in this test. The pressure at which the failure occurred and the failure mode should be recorded. The rated burst pressure is based on the results of the balloon burst testing, which shows statistically with at least 95% confidence that 99.9% of the balloons will not burst at or below the minimum burst

pressure. Attachment A describes one method of determining rated burst pressure. The rated burst pressure should be specified in the device labeling.

2. Balloon Compliance (Distensibility) - Evaluate the change in balloon diameter versus inflation pressure. This test should be conducted on complete catheters or subassemblies in which the balloon is mounted on the catheter shaft. Provide a chart which shows balloon compliance up to the mean burst pressure for each balloon size. The chart, which also should be included in the labeling, should clearly indicate the rated burst pressure and the pressure at which the labeled (nominal) balloon diameter is attained.

3. Balloon Inflation/Deflation Performance - Show that the inflation and deflation of the balloon for each catheter model can be accomplished within clinically acceptable time limits. Techniques recommended in the instructions for use should be used to inflate and deflate the balloon. This test should be conducted on complete catheters in an environment which simulates use of the device in a coronary artery. Observe and describe any interference with complete balloon deflation.

4. Balloon Fatigue (Repeated Balloon Inflation) - Determine the repeatability (40 inflations) of successful balloon inflation to the rated burst pressure for each size balloon. This test should be conducted on complete catheters or subassemblies in which the balloon is mounted on the catheter shaft. Any loss of pressure, whether due to failure of the balloon, shaft or proximal or distal seals, should be considered a failure in this test. The mode of any failure should be recorded. The results should demonstrate statistically with at least 95% confidence that 90% of the balloons will sustain 40 repeated inflations to the rated burst pressure.

5. Bond Strength - Determine the pull strength of all bonds in the catheter. The bonds may include adhesive joints, heat seals, laser welds, and solvent bonds.

6. Catheter Diameter and Balloon Profile - Determine the outside diameter of the catheter shaft and the profile of the deflated balloon. The location of the largest balloon profile along the distal half of the working length of the balloon and at the catheter tip (including the inner member or wire) should be identified and used for the measurement of deflated balloon profile. Identify the methods used to obtain the measurements.

7. Tip Pull Test - For fixed wire catheters or other catheters with one or more joints in the distal tip (e.g., spring or nose-cone tips), determine the pull force necessary to separate the distal tip from the catheter.

8. Over-the-Arch Torque Strength Test - Determine the torque strength of the catheter when its distal tip is not free to rotate. The catheter should be inserted into a test fixture which consists of a simulated aortic arch and coronary artery. While fixing the distal tip, rotate the proximal end of the catheter until failure occurs. Report the number of rotations to

failure and the mode of failure for each sample tested. Device labeling should specify the maximum number of rotations recommended based on the test results.

9. Over-the-Arch Torque Response Test - Evaluate the torque response characteristics of the catheter. Report the degree of distal rotation with respect to rotation of the proximal end of the catheter. The test should be conducted with the catheter inserted into the test fixture described in #8 above.

10. Balloon Preparation - Test the ease of balloon preparation by filling the balloon with contrast medium and expelling air from the balloon.

11. Catheter Body Burst Pressure - If the catheter is intended for injection of contrast medium or other fluids, determine the maximum pressure that the catheter body can withstand during injection. This test should simulate actual use conditions.

12. Contrast Medium Flow Rate - If the catheter is intended for injection of contrast medium, determine the flow rate of contrast at the catheter body burst pressure and at pressures utilized during actual clinical use.

13. Pressure Monitoring - If the catheter is intended for measurement of pressure, determine whether the catheter can reproduce patient waveforms without distortion. The natural frequency and damping coefficient for the catheter must be reported.

B. ANIMAL STUDIES

Specific considerations for PTCA Balloon Catheters (also refer to the General Considerations section for suggested animal model, pathological studies and reporting) are as follows:

Animal studies of PTCA catheters are only necessary if the design of the catheter or mode of angioplasty differs from that of "standard" balloon catheters that are presently approved for marketing by FDA. "Standard" balloon catheters comprise angioplasty systems which operate on the principle of hydraulic pressurization applied through an inflatable balloon attached to the distal end of a catheter and may include fixed wire, over-the-wire, and rapid exchange systems. New balloon catheter designs which would require prior animal studies include for example, devices with heated balloons or balloons with cutting edges. Animal studies of standard balloon catheters are not required to support an IDE unless specifically requested by FDA.

The following studies should be conducted in at least six animals:

1. Maneuverability - Test maneuverability of the catheter in reaching the stenotic portion of

the artery. Ease of catheter movement through arteries should also be assessed. The test should ensure the physical integrity of the catheter while in use.

2. Performance - Determine the ease, completeness, and balloon inflation and deflation times. Assess whether radiopaque markers are adequate for fluoroscopic visualization. If the catheter is intended for pressure measurement, measure the distal tip arterial pressure.

3. Pathology - Detailed gross and microscopic studies of normal and affected segments of the arteries involved should be performed in separate animals at 24 hours and at 8 weeks. (See page 3 for details)

III. CORONARY ATHERECTOMY DEVICES

Atherectomy devices are percutaneous transluminal catheter-type devices that mechanically remove diseased tissue, such as atherosclerotic plaque or thrombus, from coronary arteries by utilizing various cutting/ablating methods. Although safety and effectiveness is ultimately determined by the device's performance in the clinical setting, in vitro bench testing of the device assists in determining the reasonable safety of the device. Additionally, bench testing is used to help show how well the device can be navigated to the target lesion(s) to remove diseased tissue while minimizing damage to the treatment site and all potentially related areas of concern. Since tissue removal can be carried out in many ways through many different device designs, providing specific bench tests is difficult. It is incumbent upon the manufacturer to clearly define the operational parameters and specifications for the device. Tests must then be developed to examine the adequacy of these parameters/characteristics to safely and reliably remove diseased tissue. A general overview of the types of concerns that need to be addressed is provided below. It is in no way intended to be all inclusive, as this area is constantly changing and presenting new challenges. It is the sponsor's responsibility to conduct testing which adequately addresses the concerns outlined below as well as any others which may arise due to the unique design of the given device.

A. PHYSICAL TESTING REQUIREMENTS

All testing must be performed on the final sterilized product, or with proper justification, on an unsterilized product. A thorough discussion of the design elements aimed at minimizing treatment site damage must be provided. The operational parameters must be clearly defined and the potential failure modes should be identified. The tests conducted should validate the safety of the device design and the method for avoiding or limiting the adverse consequences of failures. In order to conduct an independent evaluation of the adequacy of these tests, the objectives, procedures, test set-up, results and conclusions must be clearly defined for each bench test performed. The test conclusions must be based on clinically relevant performance specifications.

1. STRENGTH TESTS - Based upon the mode of operation and the intended use of the device, a Failure Modes Effects Analysis should be utilized to identify the appropriate strength tests to be performed. The strength of all appropriate joints under the various loading conditions which could be encountered during use (e.g., tensile and torsional, compressional and/or bending loads) should be tested.

2. CATHETER TESTS - If the device uses a standard catheter design, determine the physical integrity of the device based on the tests outlined under the PTCA section of this guidance.

3. BALLOON TESTS - If the device contains a component which can be inflated, then the balloon related testing outlined in the PTCA section of this guidance should be considered and the pertinent balloon qualification testing performed. In choosing the appropriate tests, the manufacturer must consider the intended function of the balloon in the device's design.

4. TORQUE TESTS - Determine the torque necessary to operate the device within the coronary anatomy in accordance with the design constraints of the system; determine the maximum torque required for the actual cutting of material; and determine the torque transmission and failure characteristics of all rotating components.

5. FLOW RATE TEST - Determine the flow rate of contrast medium through, or around, the device to demonstrate that the flow rate is sufficient to achieve the desired effect (e.g., flow rate of contrast agent allows adequate fluoroscopic visualization).

6. FLEXIBILITY TESTS - Demonstrate that the device has sufficient flexibility to negotiate the coronary anatomy without compromising the functionality of the device or causing it to kink. The likelihood of material fractures in a clinical setting should also be addressed.

7. HEAT GENERATION - With all rotational devices, the possibility of excessive heat generation within the treated vessel exists. Testing should be conducted which examines the heat generated by the device and its affects on device components and the treatment area.

8. LIFE TESTS - Demonstrate the dependability and longevity of the power source. Also, establish the fatigue life of the device in order to demonstrate the proper functioning of the device under fully loaded conditions over extended periods of time.

9. ELECTRICAL TESTS - Demonstrate the electrical safety of the device, in accordance with ANSI/AAMI ES 1 "American National Standard, Safe Current Limits for Electromedical Apparatus:. and applicable sections of UL 544, "Medical and Dental Equipment." In lieu of providing the actual test data, a statement certifying conformance with these standards and any other applicable standards must be provided.

B. ANIMAL STUDIES

Specific considerations for Coronary Atherectomy Devices (also refer to the General Considerations section for suggested animal model, pathological studies and reporting) are as follows:

FDA recommends that the study consist of a minimum of six animals per group, (6 acute and 6 long term), in which the lesions have a $\geq$ 40 percent luminal diameter narrowing pre-atherectomy. Where appropriate, more than one site per animal should be treated to maximize the information gained from the study.

1. SAFETY - Assess the safety of the procedure by analyzing the damage to the vessel wall, the complications resulting from device use both acutely and long term, and device malfunctions. All complications occurring during the procedure and postoperatively must be fully documented. Pathological and histological evaluations must be performed at 24 hours and 8 weeks postprocedure. For the pathological studies, the segment of artery subjected to atherectomy along with the adjacent proximal and distal normal segments should be excised at the time of sacrifice and the gross photographs obtained from cross sections of the artery cut at three to four millimeter intervals. For histological examination, routine histology sectioning and staining should be obtained with the Hematoxylin and Eosin stains, and at least one elastic tissue stain must be performed on the sections. Histological studies should also include a morphometric analysis of the lesions, including detailed descriptions of changes in the vessel wall (e.g., complications such as dissection, perforation, and irregularities causing flow disturbances resulting in thrombus formation).

   In the case of atherectomy devices, evaluation of the safety of such devices must include studies aimed at identifying the potential for particulate emboli (dimensions and quantity of). These studies may be performed in animals to detect such things as ischemia/infarction distal to the procedure and histologic evidence of thromboemboli in the microvasculature. Segments of atherosclerotic vessels at autopsy in humans may also provide useful information by collecting effluent distally and analyzing it.

2. FUNCTIONALITY - Evaluate the functional characteristics of the device as established in the in vitro bench testing. All device modifications or corrective actions implemented as a result of these in vivo studies must also be discussed in detail.

3. PERFORMANCE - Evaluate the devices's performance in vivo consistent with the intended use (i.e., to remove atheromatous material from various target lesions). The performance evaluation should assess the following areas of concern:

   a. introduction into vasculature;
   b. navigating tortuous segments;
   c. reaching diseased sites;
   d. visualization;
   e. cutting and/or removal of atheromatous tissue;
   f. effectiveness of the removal/retrieval mechanism;
   g. removal of device from vasculature; and
   h. compatibility with ancillary equipment.

IV. CARDIOVASCULAR LASERS

Cardiovascular lasers are transluminal catheter-type devices that use a laser energy source, such as an excimer laser, to ablate atherosclerotic plaque from the coronary or peripheral arteries. These devices are post-amendment Class III devices which require the approval of a PMA application prior to commercial marketing.

A. GENERAL CHARACTERISTICS

In order to demonstrate that the proposed use of the laser system is safe for clinical use, appropriate in vitro and in vivo studies must be conducted to ensure that the use of the laser at its selected operating parameters will not perforate the vessel or cause excessive tissue damage. Therefore, the choice of laser output parameters should be derived from consideration of the following:

- mode of tissue interaction
- absorption characteristics of the target tissue
- thermal effects on tissue
- tissue healing characteristics

Furthermore, the laser output parameters that characterize the laser must be completely described as follows:

- wavelength
- temporal characteristics
  - continuous or pulsed
  - pulsewidth
  - repetition rate
- beam profile
- energy density (mJ/mm^2)
- power density (W/mm^2)
- fiberoptic tip temperature profile
- transmission medium (direct contact, saline/contrast field, blood field)

Statements made regarding the ability of the laser device to perform its intended function must be substantiated by appropriate data from bench and animal testing, including all theoretical considerations, laboratory tests, results of animal and cadaver studies. Additionally, data is needed to justify the laser wavelength and energy characteristics being proposed for clinical use. The data must show that the laser device can successfully be used as it is intended (e.g., in a dry/wet field, intraoperatively, percutaneously, with manual guidance, using a foot pedal, or a flushing mechanism for debris) and that the laser at its selected operating parameters will

not perforate the vessel or cause excessive tissue damage for each type of tissue to be treated or encountered in the treatment procedure (i.e., thrombotic or fibrotic clot or calcified plaque).

B. PHYSICAL TESTING REQUIREMENTS

These testing requirements are similar to those for Coronary Atherectomy Devices.

All testing must be performed on the final sterilized catheter delivery system or, with proper justification, on subassemblies which have been sterilized using the same sterilization method as the final product. The protocol (including purpose, procedures and test set-up), test results and study conclusions based on clinically relevant performance specifications should be provided in order to allow an independent evaluation of the study conclusions.

1. STRENGTH TESTS - Determine the strength of all joints and materials for the different loads which could be encountered during use (e.g., tensile and torsional, compressional and/or bending loads). Justification for the test specifications must be based on clinically relevant requirements including, for example, information obtained from published articles.

2. FLEXIBILITY TESTS - Demonstrate that the catheter has sufficient flexibility to negotiate the coronary anatomy without compromising the catheter functionality. A minimum bending radius should be determined from this testing.

3. TRANSMISSION TESTS - Determine the transmission efficiency and beam profile exiting the delivery system during and after simulated use, at the maximum recommended power levels and number of pulses.

4. FLOW RATE TEST - Determine the flow rate of contrast medium or saline through, or around, the catheter under simulated conditions (i.e., guidewire in place, tortuous arterial segment) to demonstrate that the flow rate is sufficient to achieve the desired effect (e.g., adequate fluoroscopic visualization, cooling or flushing).

Other tests outlined in the Coronary Atheretomy Devices and/or PTCA Catheters sections of this guidance should be performed, where appropriate for the specific delivery system.

C. ADDITIONAL STUDIES

The following testing requirements must be fulfilled in order to justify the safe use of the laser in a clinical investigation:

1. Protocols for each prior study must be provided and must give a clear, concise description of the purpose of the study, how the protocol effectively addressed the purpose, and how the results support the purpose.

2. The data must identify the animal species, site, type and size of lesion, reference diameter of blood vessel, method of approach to the lesion, fate of debris, and the conditions of the recanalized vessel in terms of initial state versus post-treatment state. In addition, the data must include the specific laser treatment parameters used such as diameter of laser beam or fiber tip, laser power, treatment procedures followed including exposure times, number of exposures and time between exposures, fiber tip temperature, the dosimetric procedures followed which validate these laser parameters, fiber position in relation to tissue and fiber contact with transmission medium(saline/blood).

3. Data from the work of others may be used if it is shown that the target tissue, and other operative and output parameters of the laser device used in these studies, are equivalent to those in the proposed study. Careful correlations must be made by extracting the appropriate data from the studies. Simply providing summaries or copies of the publications from these studies is not sufficient.

4. The bibliography should contain sufficient documentation to demonstrate the effective use of similar devices. Copies of the cited references, abstracts, personal communications and unpublished reports must be provided.

5. In vivo animal data must include sufficient follow-up to demonstrate the healing characteristics of the laser-treated vessel. The work of others may be used here if proper correlations are made.

6. If the laser device has the potential to produce toxic or mutagenic effects on tissue, it is then necessary to evaluate this risk versus benefit of removing atherosclerotic plaque to the patient. Studies must be initiated to investigate the potential of toxicity or mutagenicity for the wavelength(s) in question and the results of these studies should be submitted to the IDE application prior to FDA granting IDE approval.

7. The method of laser excitation frequency should be specified. Data must be presented to demonstrate that emissions from the laser will not cause interference, or other problems, with pacemakers, electronic circuits used in monitoring, or computer instrumentation. If

the laser is radiofrequency (RF)-excited, information must be provided to show that the electromagnetic interference (EMI) from a laser device will not be sensed by a pacemaker's sensing circuitry and thus inhibit the pacemaker, leading to temporary cessation of pacing. FDA's concern in this instance is not one of EMI induced damage to the pacemaker itself, but one of possible adverse effect on a patient, or others exposed, due to pacemaker inhibition cause by the temporal pattern of the laser-burst cycles during the surgical procedure. Results of testing must be submitted with the laser held as close to the equipment as it is likely to be in the surgical suite. Comparisons must be made between the RF emissions from the laser device to those from other RF emitting medical devices commonly used in the surgical suite. The RF emission compliance with American National Standards Institute (ANSI) specifications must describe the means for ensuring that the E-fields reported are actually maximum; estimates of uncertainty and antenna-device distance for the various positions at which the RF data were obtained, must be provided.

8. If a direct viewing capability during lasing is possible, an analysis, data, and information to document that the surgeon will not be exposed to hazardous levels of laser energy must be provided as required by the Federal Laser Standard (21 CFR Part 1040).

D. ANIMAL STUDIES

Specific considerations for Cardiovascular Lasers (also refer to the General Considerations section for suggested animal model, pathological studies and reporting) are as follows:

The data must include the animal species, site, type and size of lesion, diameter of blood vessel, method of approach to the lesion, fate of debris, and the conditions of the recanalized vessel in terms of initial state versus post-treatment state. In addition, the data must include the specific laser treatment parameters used such as diameter of laser beam or fiber tip, laser power, treatment procedures followed including exposure times, number of exposures and time between exposures, fiber tip temperature, the dosimetric procedures followed which validate these laser parameters, fiber position in relation to tissue and fiber contact with transmission medium (saline/blood).

In vivo animal data must include sufficient follow-up to demonstrate the healing characteristics of the laser-treated vessel. Pathological studies should be performed on blood vessels treated with lasers on groups of animals sacrificed at 24 hours and at 8 weeks (follow up beyond this time interval may not be necessary).

V. INTRAVASCULAR STENTS

Intravascular stents are implantable devices that are placed percutaneously in peripheral and coronary arteries to maintain vessel patency. These devices are post-amendment Class III devices which require the approval of a PMA application prior to commercial marketing. Clinical data is required to support the determination of the stent's safety and effectiveness. Therefore, an IDE application as a significant risk device study is required to be approved by FDA and the reviewing IRB prior to initiation of a clinical trial. The following sections describe the in vitro and animal study requirements considered to be necessary to support the approval of an IDE application for a clinical investigation and in a subsequent PMA application. All currently available stents are metallic. For this reason, the guidance focuses on testing applicable to metallic stents.

A. IN VITRO TESTING

In vitro studies of intravascular stents includes both bench testing and non-human biologic testing. The data generated during this phase of testing should be conducted according to a consistent and established protocol. The results of these tests should be reported in a statistically meaningful format, i.e., specifications of the number of samples, range of values, mean, standard deviation and lower tolerance limits at a 95 percent probability. For any comparative test, a p-value (or similar measure) indicating statistical significance of the comparison should be provided. Test samples must have undergone sterilization by the process to be used for production purposes and, where appropriate, subjected to the recommended maximum number of re-sterilization cycles using the worst-case method and/or conditions specified. Consideration of worst-case, within tolerance conditions for geometries, blood pressure, etc. must be included.

1. Specification Conformance Testing: The following testing should be conducted on clean and processed material samples, i.e., metal wire:

   a. Material analysis - Samples should be chemically analyzed and impurities quantified to ppm accuracy. In addition, scanning electron microscopy (SEM) testing should be performed to detect any evidence of surface contamination or impurities.

   b. Mechanical properties - Samples should be measured for tensile strength and elongation. The minimum requirements of any applicable American Society for Testing and Materials (ASTM) specification should be met.

   c. Corrosion - Samples should be analyzed for resistance to corrosion.

2. Stent Integrity - The following testing should be conducted on finished, sterilized stents after deployment with the proposed delivery system, except where noted.

   a. Stent free-area percentage and dimensional changes - The percentage change in free or open area and decrease in length as a function of stent diameter should be determined and a graphical representation of such submitted.

   b. Stent uniformity testing - The uniformity of the expanded stent should be determined by quantitative documentation after expansion in a tube and should be consistent with the labeled expanded diameter.

   c. Radial (hoop) strength - The change in stent diameter as a function of circumferential pressure should be determined. The pressure at which deformation is no longer completely reversible should be recorded.

   d. Fatigue testing - An in-depth analysis of the stent's fatigue resistance is required to assure that the arterial/venous implant conditions to which the stent will be subjected will not result in fatigue and corrosion despite millions of cycles of stress. The following data is required:

      (1) A finite element or other stress analysis that identifies the peak stresses in the stent when subjected to a worst-case physiological load. The amount of residual stress must be determined and accounted for when calculating safety factors. This analysis should demonstrate that fatigue failure of the stent will not occur during the implant life of the stent. (The use of finished, sterilized stents is not necessary for finite element analysis.)

      (2) Accelerated in vitro testing of approximately 10 years equivalent real time should be conducted on a statistically significant sample of stents expanded to their largest intended diameter and dynamically cycled over simulated vessel conditions. A complete description of the test protocol and sample preparation used in this study should be provided.

   e. Stent recoil - Quantify the amount of elastic recoil (spring-back) for each sized stent and correlate this parameter to the recommended placement (sizing) procedure.

   f. Magnetic resonance imaging - Determine whether the stent will cause artifacts with magnetic resonance scans due to distortion of the magnetic field. Literature references may substitute for actual data with adequate justification.

   g. Stent expansion - Determine whether the plastic deformation experienced by the stent in going from its initial to final position could give rise to crack initiation. An examination of expanded stents, using the proposed delivery system, should be

performed under an appropriate magnification. In addition, specify the smallest flaw size (length, width and depth) that can be detected by quality control inspectors on the surface of the stent.

h. Dimensional Verification - Measure and visually inspect the stent to document that all dimensional specifications do not deviate from the design specifications.

3. Stent/Catheter System Testing: Testing is needed to demonstrate that the delivery catheter can safely and reliably deliver the stent to the intended location and that the stent is not adversely affected by the catheter. Unless otherwise noted, all testing should be conducted on complete sterilized assemblies with stents mounted. Testing involving the balloon should be conducted after the device has been soaked in a 37°C saline bath.

a. Maximum Pressure - Conduct this test on balloons/stents of each balloon and length. The test results must show statistically that, with 95% confidence, 99.9% of the catheters will not experience balloon, shaft, proximal adaption or proximal/distal seal loss of integrity at or below the maximum recommended pressure, i.e., the pressure required to expand the stent to its labeled diameter.

b. Stent Diameter vs. Balloon Inflation Pressure - Conduct this test on balloons/stents of each diameter and plot/graph the stent diameter versus inflation pressure. This graph, or a tabular representation, should be provided in the Instructions for Use and/or the outside package labeling.

c. Bond Strength - Test the bond strength at locations where adhesives or other junction bonding methods are used for bonding between parts of the catheter.

d. Diameter and Profile - Determine the diameter of the catheter shaft, profile of the balloons and inflated diameter of the balloons to ensure that the actual diameter matches the labeled diameters. Stent mounting is not required.

e. Balloon Deflatability - Show that the balloon can be completely deflated by the recommended procedure following stent expansion when it is in an environment simulating a stenosed vessel. Observe and describe any interference with balloon deflation. In addition, observe and describe any interference in withdrawing the deflated balloon from the deployed stent.

f. Balloon Inflation and Deflation Time - Show that inflation and deflation of the balloons using the recommended procedure in the labeling can be accomplished within a specified time.

g. Catheter Body Maximum Pressure (if applicable) - Determine the maximum pressure that the catheter body can withstand when one of the lumens is used for power

injection of contrast media.

h. Contrast Media Flow Rate (if applicable) - Determine the contrast media flow rate through the inner lumen at or below the maximum recommended injection pressure. Stent mounting is not required.

i. Pressure Waveform (if applicable) - Determine the natural frequency and damping ratio of the lumen recommended for pressure monitoring. Damping of the pressure waveform must be appropriate and provide accurate measurement; otherwise, the Instructions for Use must clearly state that the catheter is not intended for distal pressure monitoring. Stent mounting is not required.

j. Tip Pulling and Torquing - Show that the force required to break the joints and/or materials in the distal end of the catheter is sufficiently large to assure the integrity of the tip during pulling, pushing or torquing maneuvers.

k. Stent Crimping - If the stent is not provided pre-mounted on the delivery catheter, testing must be conducted to show the functionality of all crimping devices and that the crimping procedure will not damage the stent or catheter.

l. Crossing Profile - Determine the crossing profile of the stent/delivery system and discuss its clinical acceptability.

B. ANIMAL STUDIES

Specific considerations for Intravascular Stents (also refer to the General Considerations section for suggested animal model, pathological studies and reporting) are as follows:

The purpose of animal studies is to evaluate the early and late patency rates of the stent, the biologic reaction of the vessel and the performance of the delivery catheter. A minimum of 25 stents should be evaluated; however, sponsors should be aware of the risks involved in too carefully limiting the number of animals/stents studied. More than one stent can be implanted in an animal. The vessels selected for testing must have diameters similar to those proposed for stent placement in the clinical trial. The smallest and largest diameter stents must be included in the animal studies. Although normal vessels can be stented, it does not necessarily follow that the stent will perform similarly in atherosclerotic vessels. If an atherosclerotic model is not evaluated, additional justification for the device's intended use must be provided. The majority of stents must remain implanted for a minimum of 6 months, and some stents should be explanted at periodic intervals in order to completely characterize the reendothelialization process.

The testing protocol(s), test results and study conclusions should be fully described in the IDE application in order that an independent evaluation of the conclusions can be made. In addition to documenting all complications occurring during the procedure and follow-up, the following is required:

1. Study Parameters

    a. Provide a clear description of the pre-stenting vessel characteristics, i.e., lumen diameter, versus post-stenting and follow-up lumen diameter as obtained from arteriography.

    b. Described the anti-coagulation therapy utilized in the animal studies with respect to its similarity to that proposed in the clinical trial.

    c. Document the exact specifications of the stents used, i.e., unexpanded diameter, length, expanded diameter and inflation pressure.

    d. Document the use of multiple stents at one lesion location, if this will be permitted in the clinical trial.

2. Performance of the Stent/Delivery System

    a. Preparation - the ease by which the device can be prepared for use.

    b. Introduction - the ability of the device to be loaded onto the guidewire or into a guiding catheter.

    c. Pushability - the ability of the system to transmit sufficient, even force proximally allowing for equal and smooth movement distally.

    d. Trackability - the ability of the system to advance distally over a guidewire, following the guidewire tip, along the path of the vessel, including in narrow, tortuous vessels.

    e. Flexibility - the ability of the stent/delivery system to bend in order to accommodate a turn or angle it is required to negotiate, and the flexibility of the stent to conform with the vessel after the stent is deployed.

    f. Radiopacity - the visibility of the stent and delivery system under fluoroscopy.

    g. Inspection - a post-evaluation inspection to document any evidence of damage to the delivery system.

    h. Accessories - a description of the performance of all accessories recommended in the

labeling such as guiding catheters, hemostasis valves, sheaths, etc.

i. Investigator Preference - a complete summary of comments made by investigators regarding stent performance.

3. Angiographic, Hemodynamic and Histological Results

a. Angiographic - determine flow characteristics of the stented vessel immediately following stent deployment and immediately prior to explantation. In addition, note the angiographic presence of acute thrombus and rate the amount on a scale of 1 to 5.

b. hemodynamic - determine if EKG or blood pressure changes were noted during the implantation period. Document any cases of distal embolization.

c. Histological

(1) Measure the neointimal thickness at each follow-up period throughout the stented length, including at stent/artery junctures.

(2) Document any occurrences of intravascular trauma induced by stent placement in the vessel of interest.

(3) Provide a pathology report including gross findings and microscopic studies involving both conventional and scanning electron microscopic techniques. The explanted vessel should be evaluated for outer diameter enlargement, lumen narrowing, filling defects, patency of side branches, protrusions of the stent into the vessel lumen and medial thinning.

(4) Conduct a detailed examination of explanted stents to document integrity.

CLINICAL STUDY REQUIREMENTS

I. FEATURES OF CLINICAL STUDIES

The success of a clinical trial is based on the overall coordination of three features: the design of the study; the conduct of the study; and the analysis of the results. While FDA has limited control over the sponsor's comprehensive efforts to conduct a successful clinical trial, the sponsor must carefully consider and execute each step of the trial according to the initial overall study plan.

The clinical study must be ultimately capable of demonstrating the safety and effectiveness of the device in terms of (1) the patient population for which use of the device is intended; (2) the conditions of use for the device, including conditions of use prescribed, recommended or suggested in the labeling or advertising, and other conditions of use; (3) the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) the reliability of the device (see 21 CFR 860.7(b)). To determine that there is reasonable evidence of the device's safety and effectiveness, FDA must rely on valid scientific evidence to determine that the probable benefits to health from the use of the device for its intended use and conditions of use outweigh any probable risks and that the use of the device for its intended use and conditions of use will provide clinically significant results. Assurance that the use of the device will provide clinically significant results is further defined in 21 CFR 860.7(e)(1) and in the ODE Blue Book Memorandum #P91-1.*

A. CLINICAL STUDY DESIGN

The basic study design should be based on a well-defined, clear question (hypothesis) or set of questions that are to be answered about the device by the clinical study. The study purpose determines the type of study that needs to be conducted with the objectives allowing the goals to be achieved. Furthermore, the design of a prospective trial should be able to answer the question(s) with a defined degree of precision. There are fundamental features in designing a clinical trial in order that valid evidence can be obtained. All standard texts on the design of clinical trials attest to the importance of the combination of all these features since these features will demonstrate the validity and scientific soundness of the proposed clinical trial.[4,5,8,15] These seven fundamental features to be incorporated into a clinical protocol include: clear statement of objective(s), protocol development implementing the study design, sample size determination, patient recruitment procedures, baseline and follow-up assessments, outcome variables or endpoints, and definitions of success and failure.

* This document can be obtained from CDRH's Division of Small Manufacturer's Assistance by calling (800) 638-2041 or (301) 443-6597.

1. Statement of the Study Objective

The objective of the study must be focused and clearly stated, and must be consistent with the research question(s) to be answered or with the intended labeling claims for the device. It is not sufficient to state that the objective is to determine the device's safety and effectiveness since the study must be capable of answering the objective and must be scientifically and medically relevant. The specific question will depend on the criteria for effectiveness, i.e., is the investigational device treatment better than other standard treatments, or is it similar in effectiveness (or at least no worse than a predetermined specific difference) to the standard treatment for the medical disease or condition being treated. Investigators and study sponsors may prefer to state the objective in statistical terms by developing a hypothesis, i.e., the research question is restated in numerical terms concerning the endpoint variables and the anticipated difference between groups resulting in a null and alternate hypothesis. At a minimum, the objectives of the study should address the purpose of the study (e.g., to determine safety and effectiveness), the disease to be treated, the device to be evaluated, the treatment schedule, the subjects to be enrolled, and the parameters to be measured. Once stated, the protocol should be written describing how the study design will be implemented.

At times it may be necessary to conduct a small feasibility study (also known as a pilot or limited study) in order to confirm the device design and operating specifications, and to refine both the indications for its use and hypothesis to be studied. A feasibility study does not need to be a separate trial if it is intended for physicians to gain experience with the use of the device. In this situation, it can be integrated into the multicenter trial, provided it is intended as such, and the feasibility study is well-designed using consistent protocols.

More than one objective may be studied during the course of a clinical trial. However, these objectives should be appropriate and reflect the goals to be achieved; these objectives may also be reasonably similar so that one objective refines those that are more broadly stated. While this may give some flexibility to outcome of results and for future labeling claims, broadly stated objectives often lead to poorly designed protocols and the collection of questionable data. Thus, it is extremely important that study objectives be well defined.

2. Protocol Development Implementing the Study Design

The design for the clinical study will be a direct function of the study objective, and takes into consideration other factors such as comparability of treatment groups with a control group, selection of clinically relevant outcome variables, and procedures to control potential sources of bias. The study design is implemented by the development of a written protocol. It is prudent that the study design minimize all potential sources of bias by incorporating the following features: random assignment of patients to treatment and

control; use of standard patient inclusion/exclusion criteria; use of standardized methods of assessment for baseline and outcome variables; quantitative methods for measurement(s) of variables; blinding of investigators and subjects, when appropriate; and maximizing patient follow-up for the duration of the study.

The comparability of the treatment group to an appropriate control group can be demonstrated by use of standardized inclusion and exclusion criteria and the assignment of treatment based on predetermined, random methods. Not only are controls necessary to measure treatment effects that are solely due to the investigational device, they are also necessary to reduce biases due to concomitant therapies, the natural course of the disease being studied and observer interpretation of results. Without a control, it may not be possible to distinguish the response due to the investigational device and the response due to the natural course of disease, by chance, or by the inability to reduce any biases that are inadvertently introduced into a clinical trial (e.g., investigator bias).

Selection of an appropriate control is a difficult process; one must consider such issues as the intended use of the device, the natural history of disease, potential adverse effects, alternative therapies and the subjective or objective nature of the outcome variables that need to be evaluated. Overall, there are two types of controls - concurrent and historical. A concurrent control is one where the data is collected over the same period of time as that used to generate the data by the investigational device. Concurrent controls are utilized differently depending on how the comparative data is obtained. Such methods include, for example, randomized, non-randomized, and matched. A historical control is one in which the data were collected in a period of time previous to that used for the generation of data for the investigational device.

a. Randomized Control Group

Randomization is considered the most appropriate method for evaluating the safety and effectiveness of a new treatment. It is clear that the major advantage of using a randomized control group is to minimize the introduction of biases into the study. A randomized control group is a good choice for studies when the disease being studied is variable, the baseline and outcome variables are subjectively assessed and when the baseline characteristics may influence the outcome. It also facilitates the creation of comparable and homogenous patient groups, and permits use of statistical methods for data analysis. Randomization in a clinical trial refers to the allocation of treatments by the act of chance. By assuring that the treatment assignment cannot be predicted, the treatment is independent of patient characteristics and any uncontrolled variables are randomly distributed. Although the random assignment is unpredictable, the process must be based on a predetermined randomization method. Even though randomization may be considered the best method for clinical study design, it must be consistent with the ethical principles for protecting the subject's rights, safety and welfare. There are all too many recent instances in medicine where prior to a

randomized trial investigators have touted their new treatment as a "dramatic lifesaving breakthrough". Yet, when a properly performed randomized trial has been subsequently conducted results have often been quite different from those that were expected.

Implementation of proper randomization involves consideration of stratification, blocking, and the use of random number tables for patient assignment. Stratification is used to avoid over-representation of a specific subgroup of patients in the study and to balance the study subgroup(s). The typical strata include age, sex, race, disease risk. This approach is very useful when foreign countries participate in the study. The stratified randomization method is useful when confounding variables are known to affect the outcome; thus, each stratified patient group uses a randomization procedure. The sequence of random assignment of patients to the treatment and control group should be prepared before their enrollment and strictly followed.

FDA encourages, when possible, that randomization be blocked by site. This method has several advantages. For example, a site that has poor follow-up can be removed from the study without affecting the overall randomization scheme. In addition, blocking by site reduces the chance that a particular site could unevenly affect the results, as could happen if all of a site's patients happen (by chance) to be randomized to only one of the treatments.

b. Non-randomized Concurrent Control Group

The major disadvantage of using a non-randomized concurrent control is the potential for patient selection bias on the part of the investigators. This is especially important to control when the investigators believe that the investigational treatment is undoubtedly better than the standard treatment, or when the investigator selects subjects for investigational treatment based on criteria other than that specified in the inclusion and exclusion criteria.

c. Historical Controls

Historical controls are useful when the study endpoints are objectively measured, the disease is predictable and consistent, and the influence of baseline characteristics are minimal compared to the treatment effect (i.e, the baseline is well-defined and predictable about the course of the disease). The selection of historical data, either from published literature, medical records or other databases and registries, should ensure consistent use of critical study variables between groups, including inclusion/exclusion criteria, indications, baseline characteristics, standard evaluations or outcome variables, and identical definitions of outcome. These controls should also be as recent as possible in order to ensure that the available methods for the diagnosis and treatment are consistent with the disease being treated in the study.

Sponsors should try to directly obtain the relevant data analyses rather than relying on published reports. Published reports often do not take into account the specific patient subset a certain device may be designed for. Literature controls are usually poor since it is almost impossible to have all relevant information and they fail to contain the rigors of establishing clear parameters in defining the group, i.e., inclusion and exclusion criteria are frequently poorly specified. This approach can be useful, however, in generating a hypothesis rather than testing a hypothesis.

3. Sample Size Determination

The number of subjects to be enrolled in a clinical trial should be based on statistical calculations at a pre-defined level of statistical significance consistent with the study objective and ensuring that an adequate number of patients complete the protocol. The number of subjects should be established or fixed before a study begins and is usually expressed as a minimum number of treatment and control patients. Although infrequently used, sample size can be based on a sequential method where the final number of subjects is based on continual analysis of data throughout the entire clinical trial and the observed difference between the treatment and control unequivocally exceeds pre-defined values. The assumptions and statistical methods used to estimate the required population size should be completely described. For example, if a sequential method is used the procedure by which P values are adjusted so that the overall Type I error remains at a prespecified value should be reviewed.

Study population size is primarily a function of the pre-determined level of significance (i.e, α - the probability of a Type I error) and the power of the study to detect a treatment effect of a pre-determined magnitude (i.e., power equals 1 - β where β is the probability of a Type II error). There is some variability in selecting the probability of Type I and II errors. As a general rule, α should not be greater than .05 and β should not be greater than .20. Any deviation from this range of values would need to be clearly justified. The greater the difference to be detected between treatment and control groups in the study, the less number of subjects are needed provided the α and β remain unchanged. Other factors that need to be considered in calculating the study sample size include, for example, the expected lost to follow-up rate, length of follow-up period and allocation ratio to the treatment groups. It is imperative that the sponsor seek the assistance of a statistician familiar in clinical trial methodology in order to develop the protocol and determine the appropriate number of subjects to be enrolled in the study.

4. Patient Screening and Recruitment Procedures

Patients should be enrolled in a manner which eliminates selection bias. The protocol should detail the procedure by which consecutive patients meeting the inclusion criteria for the study are selected for possible enrollment. All situations in which a patient is a candidate for enrollment in the study by virtue of meeting the inclusion and exclusion

criteria but is not offered a chance by the investigator for enrollment, or the patient declines enrollment in the study, should be documented and the reason recorded. It may be desirable to establish a separate registry for these patients.

5. Baseline and Follow-Up Assessments

Relevant variables must be assessed for each subject prior to treatment in order to establish the baseline characteristics of the patient population. These parameters should be consistent with the study objectives, should be clinically relevant to the disease being studied, should be comparable to parameters of alternative therapies in the treatment of the disease, should be clearly and concisely defined and should be measured by objective and standardized methods.

6. Outcome Variables or Endpoints

As with baseline assessments, outcome variables or clinically relevant endpoints must be objective and clinically informative about the disease and device being studied, and must be concisely defined. Outcome variables are best assessed using blinded techniques in order to reduce or eliminate biases. It is recognized that while performing a blinded core lab analysis may be possible for some interventional devices, it is clearly impossible for others such as radiopaque stents. However, even in this case the automated edge detection algorithm available with quantitative systems would be expected to correctly define vessel contour in a certain percentage of angiograms. If manual selection is chosen to define vessel contours in an unexpected number of cases, an explanation for this type of deviation would need to be provided. All report forms should have sufficient space to record the variables at each patient examination period, including preprocedure, during treatment and postprocedure.

7. Definitions of Success, Failure and Complications

The conclusions drawn from the study will be determined, in part, by the criteria used to assess the effectiveness of the treatment. Therefore, the study should be evaluated on the basis of carefully defined criteria which should be accurate and fit the goal(s) of the trial. Standard definitions of success, failure and complications (major and minor) must be established prior to initiating the study, and be used, without change, during patient enrollment and during data analysis.

B. CONDUCTING THE STUDY

The sponsor of the clinical trial must ensure that all study investigators, monitors, and subjects are adhering to the same written protocol. A monitoring plan should be in place to ensure the consistent execution of the study before, during and after subject treatment. Follow-up of all subjects and compliance with the protocol is imperative. Violations of the

protocol may invalidate the study results. Ensuring subject follow-up at all assessment periods for the duration of the study will minimize bias caused by subjects lost-to-followup, or study dropouts.

Utilization of a separate data or safety monitoring team ensures that physicians will not prematurely conclude a favorable study result, and then bias the remaining portion of the study. The establishment of an endpoint monitoring committee is strongly recommended. Such a committee would, for example, be sent information regarding all deaths in the study so they could determine the cause of death. This committee should be independent of the study investigators and industry representatives and should, when possible, be blinded to the patient's treatment assignment.

C. CLINICAL STUDY ANALYSIS

At the earliest stage of defining the study purpose and objectives, the analytical methods to be used to analyze the data should be established. All statistical methods intended for use in analysis of the data should be described in detail in the protocol with references as necessary. This includes the statistical models, justification for data pooling across investigational centers, data exclusions from analysis, and all assumptions. Pooling of data from several investigational sites should be justified by comparing the characteristics of the subjects and the treatment outcomes. Imbalances should be accounted for in the data and for all patients lost-to-followup. Numerous statistical methods exist to analyze the data; for example, survival analysis, chi-square analysis, and regression analyses. All methods should compare the outcome to the control.

Lost-to-followup is defined as when the criteria of effectiveness and safety cannot be evaluated. Dropouts decrease the reliability of the comparisons and may also bias the results. The groups may be less comparable after certain patients drop-out. It is important to distinguish between causes-related cases and unrelated causes to the investigational device. Thus, it is important to check the comparability at the beginning, with all patients entered, and at the end of the study with only patients completing the study. The drop-outs particularly affect analysis of data in: (1) within-patient studies, (2) matched-pair designs, and (3) factorial designs. Studies in which the percent of follow-up is different for the treatment groups must carefully justify their analysis. All patients, however, should be included in the analysis of adverse effects.

II. SPECIFIC IDE REQUIREMENTS

In order to determine whether there is reasonable evidence that a device is safe and effective, FDA must rely on valid scientific evidence (21 CFR 860.7(c)). Furthermore, valid scientific evidence used to determine device effectiveness should be obtained primarily from well-controlled investigations. In order to collect clinical data as evidence to demonstrate that an interventional cardiology device is reasonably safe and effective, the sponsor must submit an Investigational Device Exemptions (IDE) application to FDA and the sponsor must submit the investigational plan (as defined in 21 CFR 812.25) to all institutional review boards (IRBs) of the institutions that will be participating in the study. The IDE application must be approved by both FDA and IRB prior to initiation of the study. The content of an IDE application is outlined in 21 CFR 812.20(b) and in the "Original IDE Review Form" (see Attachment B). The sponsor should ensure the submission of a complete application, with special attention to the requirements specific for interventional cardiology devices. Even though the name of the elements required in the IDE application may differ from those in other clinical trial references, the requirements of the IDE regulation are based on the principles of scientifically sound clinical designs described in FDA regulations (21 CFR 860.7(f)), numerous articles[4,5] and textbooks[8,15] and as previously described on pages 17-24.

INVESTIGATIONAL PLAN

The investigational plan encompasses all features of the designed study. Some investigators refer to this section as the clinical protocol or the clinical investigators manual, and may be submitted in a variety of formats. In order to facilitate an expeditious review, sponsors should use the terminology and order for the elements of the investigational plan, as provided in the IDE regulation (21 CFR 812.25) and as listed below. Sponsors are also encouraged to follow existing guidance for the evaluation of the interventional cardiology device, e.g., the American College of Cardiology and the American Heart Association (ACC/AHA) Guidelines for Percutaneous Transluminal Coronary Angioplasty.[18]

1. Purpose - The purpose must clearly define the following:

    a. Device Name: State the generic and/or proprietary name of the device to be investigated.

    b. Study Objective: Clearly state the purpose and the objective(s) of the study. This can be stated statistically as the null and alternative hypothesis, or the claims the firm seeks to demonstrate and include in the labeling.

    c. Indications: Precisely state all indications and contraindications for use of the device consistent with the study objective(s). It is no longer applicable to use the terms

"relative" and "absolute" contraindications since this distinction is not provided in the device labeling regulation under 21 CFR Part 801. FDA is aware of the previous need for such a distinction based on the limited uses of early PTCA catheters, e.g., discrete, proximal, noncalcific, and subtotal occlusions in a single vessel. With the availability of low profile balloons, fixed-wire balloon catheters and steerable guidewires in the late 1980's, PTCA treatment of coronary lesions is being extended to patients with multi-vessel disease, multiple subtotal stenoses in the same vessel, occlusions of internal mammary artery and saphenous vein bypass grafts, and recent total occlusions in acute myocardial infarction (MI) patients. Unprotected left main arteries are being treated at the physician's discretion but are still considered a contraindication.

d. Duration: State the expected duration of the study (i.e., the number of months or years) consistent with the indications for use and an adequate number of patients to be enrolled and followed in the study.

2. Protocol - The written protocol must adequately describe the methodology to be used and provide an analysis of the scientific soundness of the study, by addressing the following:

a. Inclusion/Exclusion Criteria: Precisely state the inclusion and exclusion criteria to be used for patient selection. These should be stated using standard definitions, be consistent with the study objectives and be strictly adhered to by the investigators. If, however, patients fail to meet these criteria but are nonetheless treated, the circumstances must be described and the patients followed for the duration of the study. These incorrectly entered patients must be included in the initial analysis. In other words, the "intention to treat" approach to analysis of a clinical trial should be initially adhered to. Secondary analyses may also be performed with clearly stated explanations of the assumptions and limitations of these analyses.

(1) Consecutive Patients: Describe the mechanism by which consecutive angioplasty patients meeting the inclusion criteria for the study (i.e., your labeled indication for use) are selected for possible enrollment. For example, all eligible patients who are presented to an investigator should be offered a chance to participate in the study. All situations in which a patient is a candidate for enrollment by virtue of meeting the labeled indication and contraindication criteria, but is not offered a chance by that investigator for enrollment should be documented and the reason recorded. This mechanism is necessary to reduce the potential for patient selection bias. To further reduce the potential for patient selection bias, FDA recommends that studies which compete for the same patient population not be run concurrently at a particular investigative site. The studies should run sequentially. It is suggested that sponsors incorporate this requirement into their investigator agreement documents. If this pathway is not selected then sites that intend to participate in clinical trials which have overlapping patient subsets

should justify how patients will be allocated to the different trials in a nonbiased fashion.

(2) Baseline Variables: Identify the clinical baseline variables to be assessed in order to properly select patients for the interventional procedure and to ensure comparability of the patients within the cohort and with the control group. These variables must be clinically and medically important and relevant to the study objective(s) and should be precisely identified. Baseline variables should include, for example, patient demographics, status of angina, functional stress tests and angina class according to the Canadian Cardiovascular Society (CCS), coronary artery disease risk factors, history and classification of prior myocardial infarctions, history and classification of prior interventional treatments for coronary artery disease, medications, left ventricular ejection fraction, and identification of the lesion(s) site and description of stenosis (e.g., single or multivessel, lesion length and location, lesion characteristics, percent stenosis and absolute dimensions (in mm)). The lesion characteristics should include lesion length and location, type of vessel involved (i.e., native coronary saphenous venous graft, internal mammary artery graft), lesion morphology (i.e., focal, tubular or diffuse, calcific or non-calcific, eccentric or concentric, thrombus, ulceration), and a description of the lesion history (i.e., de novo or number of prior restenoses). See Attachment C for definitions recommended to be used for identification of lesion characteristics.

(3) Adjunct Device Use: Clearly define the criteria by which a patient is selected for treatment with another marketed device if adjunctive use of other interventional cardiology devices is permitted either before or after a lesion success or lesion failure.

b. Scientific Soundness: Provide an analysis that demonstrates the scientific soundness (i.e., validity) of the investigation by summarizing how the study design will provide the appropriate data to meet the study objective and to ultimately demonstrate whether the device is safe and effective.

c. Definitions: State all definitions to be used during the study in an objective manner. The definitions must be used by all investigators in order to ensure consistent evaluation and interpretation of the data. Attachment C is a listing of some suggested definitions. At a minimum, however, the following variables must be defined in the protocol:

(1) Lesion location and characteristics as identified by angiography
(2) Complications
(3) Restenosis
(4) Success: clinical or procedural, lesion, and technical

(5) Failures: clinical or procedural, lesion, and mechanical

Restenosis constitutes the specific late-term failure of an acutely successful interventional cardiology procedure, due to renarrowing of a successfully dilated segment that results in regionally underperfused myocardium. All current definitions of restenosis, however, rely on the hypothesis that restenosis is a dichotomous event, i.e., it either does or does not occur. Pathophysiologically, restenosis is a continuous, rather than a discrete process. The vast majority of interventional procedures have at least some reduction in luminal dimensions at six-month follow-up. Endpoints that treat restenosis as a continuous rather than discrete variable would be expected to have greater utility in defining differences between treatments. Also, given the multiplicity of dichotomous definitions of restenosis at follow-up [e.g., NHLBI IV[2] (restenosis = late loss > 1/2 the acute gain), Reiber[16] (restenosis = > 0.72 mm), Emory[14] (restenosis = >50% reduction compared to reference lumen diameter)], follow-up results based on dichotomous definitions may result in different conclusions according to various definitions. To standardize comparisons, the Emory definition of restenosis (i.e., restenosis = >50% reduction in lesion when compared to reference luminal diameter) will be considered the definition for restenosis by FDA.

To overcome the limitations of an arbitrarily defined cutoff, the graphical and statistical methods outlined by Kuntz et.al. to treat restenosis as a continuous problem rather than as a discrete event should also be utilized.[13] Briefly, acute and 6-month angiographic results should be summarized graphically in a definition-independent rank fashion that allows comparison of follow-up results among interventions. Usually percent stenosis (x-axis) is plotted against the cumulative distribution of patients (y-axis) to facilitate device comparison.

Analysis should also provide a more detailed breakdown of luminal dimensions into component indices (e.g., acute gain, acute elastic recoil, late loss, etc.). It would be important to know, for example, how acute gain and late loss contribute to final luminal dimensions for each treatment arm of the study. Because acute gain and late loss have normal distributions and residuals, linear and logistic regression modeling should be utilized to provide further insight into the mechanisms of restenosis. Linear modeling can be employed to relate continuous variables, such as pre- and postprocedure luminal dimensions, acute gain, cholesterol level, age, reference diameter, to follow-up luminal dimension, while logistic regression can be used to examine important categorical variables such as gender and vessel treated.

The above approach will require great care in the measurement of angiographic indices related to the initial procedure (pre- and postprocedure) and late 6-month follow-up angiograms. The clinical trial should be constructed so that 100% of angiograms are reviewed at a core laboratory using quantitative methods and

whenever possible, blinding, in order to ensure quality control of the angiographic analysis.

d. Control Group: Describe the control or reference group(s) to be used in the study (e.g., randomized concurrent or historical), including justification of the control group. The control group should be selected to be consistent with the study objective, standard medical therapy, and ethical considerations for assignment of patients to treatment and control groups.

(1) Randomized: A randomized concurrent control is the best method to reduce all potential sources of bias, to support appropriate data analysis, and to improve the scientific integrity and validity of the study. In addition, many important questions regarding the theoretical advantages of new device therapy in creating large lumens with reduced arterial wall injury cannot be adequately answered by sole reliance on animal and clinical observational studies. Despite important recent developments in interventional cardiology, when critically examined, balloon angioplasty still remains the appropriate interventional device for most lesions requiring intervention. Thus, randomization will greatly facilitate determination of a new device's safety and effectiveness, and significantly impact on our knowledge of human atherosclerosis and restenosis.

Randomization should be the first choice in consideration of a control group as this will ultimately facilitate the determination of the device's safety and effectiveness. If a randomized trial is not included in the study design, it is incumbent upon the sponsor to provide evidence for why a randomized study design is not appropriate and select an appropriate contemporary control or reference group to be used in the study. The use of a historical or retrospective control group must be justified by submission and analysis of specific references which illustrate the comparability between the studies on the critical study variables, such as objectives, definitions, baseline characteristics, lesion morphology, follow-up and inclusion/exclusion criteria. A nonrandomized study format could be considered, for example, in submission of an IDE for a PTCA catheter that does not contain any significant adjunctive feature (e.g., ultrasound imaging, drug delivery capability, cutting edge or hot tip device to assist in angioplasty) that might be expected to impact on the safety and effectiveness of standard balloon angioplasty. Of course, this pathway for approval assumes that the manufacturer will not make any labeling claims for the new PTCA catheter that are substantially different from equivalent products on the market.

(2) Registries: Data contained in registries can be useful as a control if the data is relatively current and is comparable to the interventional cardiology device study. The data in the 1985-1986 National Heart, Lung and Blood Institute (NHLBI) PTCA Registry[6] is no longer an appropriate control group since the patient

population is no longer comparable to patients being treated today (i.e., investigators are more aggressive in their treatment methods, different assessment methods and definitions of success are being used, patients being studied have more multivessel disease and lesions of different characteristics and locations, improved technology, and patients are being treated adjunctively with other interventional devices). However, data contained in more contemporary registries, e.g., manufacturer's registries or the NACI Registry[20] could be acceptable if the critical study variables are comparable between studies.

e. Report Forms: Provide examples of all patient report forms (e.g., baseline or preprocedure, operative, and all follow-up evaluations) which are consistent with the study protocol and patient informed consent form. These forms must be completed by each investigator for each patient entered in the study and at each follow-up evaluation. Attachment D contains recommended variables to be included in these report forms.

(1) Baseline: Baseline and/or preprocedure forms should include the dates of evaluation, patient identification, pre-treatment symptoms, CCS functional class, results of tests performed on the patient, and all previous therapies. Space must be provided to record all baseline assessments in an objective and definitive manner. These types of assessments will facilitate comparisons to postprocedure results.

(2) Operative: The operative report forms must include adequate space to record information on device performance and the lesion being treated. Although information about device performance will vary for each of the interventional cardiology devices, the report form should include, for example, the model, size and length of each device and each guidewire used during the procedure (e.g., balloon inflation pressure, balloon diameter, balloon inflation duration, and the number of inflation cycles used in each PTCA procedure); device failures; the total time the patient undergoes fluoroscopy. The form must also provide space to record information about the lesion being treated, including the location and characteristics of the lesion(s), the degree of stenosis (lumen diameter and percent stenosis), success or failure of the procedure according to predetermined criteria, complications, medications required, and any other pertinent data. In addition, all problems encountered with each of the devices used and a description all subsequent therapies must be recorded in order to appropriately assess the device's association to the cause of a complication. Finally, information should be recorded about the intent to treat a specific lesion and which lesion was actually attempted and completed.

(3) Postprocedure: The postprocedure report form must provide adequate space to record measurements of the study variables, as predetermined in the study

protocol, including restenosis assessment based on objective measurements (e.g., caliper measurement, computer assisted or digital subtraction angiography) and on the use of blinded core laboratory analysis; angina status based on CCS classification scores, exercise functional test and electrocardiography.

f. Outcome Variables: Identify all clinically relevant outcome variables or endpoints to be measured and the appropriate time frame for the measurement. The outcome variables should include clinically relevant assessments for vessel patency and restenosis, e.g., percent stenosis or TIMI flow classification. Attachment D provides a comprehensive list of the type of data that should be collected and is consistent with the ACC/AHA Guidance[18] and the NACI Registry.[20]

(1) Core Lab: Describe the method to be used to determine vessel patency. The measurement of a clinical variable by coronary angiography should be subject to an unbiased assessment. Vessel patency should be obtained through rigorous quantitative dimensional analysis of all angiograms. Thus, all patients enrolled in the study must have their initial pre- and postprocedure angiograms analyzed by a core laboratory. Furthermore, all patients who receive angiographic follow-up must also have their angiograms analyzed in this manner.

(2) Follow-up: Instructions to the investigators must clearly state that data must be collected and recorded on the patient report forms immediately after the procedure and at predetermined intervals postoperatively. Patient follow-up after hospital discharge should generally consist of repeat angiography at 6 months on all patients of the initially successful population supporting the indication(s) for use. Results from recent randomized clinical trials indicate that follow-up at 1 year may be necessary to fully evaluate new interventional cardiology devices. Sponsors are advised to continue following patients past the 6-month interval in the event that 1 year follow-up data is required. Exception to the above recommendation would need to be justified. For example, clinical evaluation of a standard PTCA catheter requires 2 month follow-up.

Any patients not evaluated by angiography at 6 months must be evaluated using other acceptable methods, such as stress tests, need for subsequent target vessel revascularization, and clinical history. If non-invasive evaluation is chosen, the sponsor must justify its use and relevance to assessing vessel patency. For example, recent research by Kuntz[12] has resulted in a predictive model for restenosis studies; these types of analyses must be thoroughly evaluated in order to support use in research or marketing applications. There are multiple problems associated with non-invasive follow-up that makes this methodology too unreliable to be used as the sole determinant of restenosis in the angioplasty-treated vessel. Furthermore, an angiographic follow-up rate of less than 80% is not acceptable due to the selection bias introduced by not accounting for the

confounding influences of the patients lost to continued monitoring. In all cases where patients do not receive angiographic follow-up, the reason for failure to obtain it should be well documented. Analyses should demonstrate that there was no investigator selection bias contaminating angiographic follow-up.

g. Complications: Provide definitions and methods of analysis for each potential complication (major or minor), regardless of whether the complication is related to the investigational device, another device or the procedure itself. Major complications include MI, emergency coronary artery bypass graft (CABG) surgery, emergent repeat in hospital intervention or bail out stenting and death. The data should be presented on a per patient and a per complication basis.

h. Patient Accountability: Describe the procedures to be used to ensure accountability of all patients that have been enrolled in the study and at all follow-up intervals, and describe the procedures for any patient who discontinues participation in the study. Statements such as `lost-to-followup' are not sufficient and every effort must be made to account for all such patients. Patients should be followed for a predetermined period of time, including prehospital discharge, 6 weeks, 6 months, and yearly thereafter (until the device receives marketing approval) or until an event such as repeat intervention, CABG or death occurs.

i. Sample Size: Describe the method and calculation formula to be used to determine the number of patients (both treatment and control) needed to evaluate the objective(s) of the study. The method should consider the primary efficacy variables and the specified differences to be detected. Sponsors should still consult with a statistician familiar with device clinical studies for appropriate methods even though some methods have been recognized for use in device studies.[3,4,7,9]

j. Method of Analysis: Describe the statistical methods to be used to analyze the data generated during the study. Methods will depend on the study design and can include such tests as chi-square, student t-test, linear regression and multivariate analysis. The use of 95% confidence intervals rather than point estimates to summarize data (e.g., late restenosis rates) is strongly encouraged. Sponsors should consult with a statistician for selecting the appropriate methods.

3. Risk Analysis - The risk analysis must adequately demonstrate that the benefit and knowledge to be gained outweighs the risk to the subjects, by addressing the following:

a. Minimize Risks: Describe how the risks to the subjects will be minimized during the investigation. This can include, for example, that the clearly defined inclusion criteria ensures that only properly selected patients will be enrolled, and that patient treatment and followup are consistent with other medically established therapies for the same medical condition.

b. Use Without Adverse Effects: Summarize any data collected that supports use of the device without adverse effects. Foreign data would be acceptable if the identical protocol and devices were used, the collection of follow-up data was complete, the practice of medicine for the diagnosis and treatment of the disease condition in the foreign country is similar to the disease condition in the United States and the study was conducted in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted (whichever offers greater protection to the human subjects).

4. Institutions and Investigators

a. Selection of Investigators: Describe how investigators and institutions are selected. The selections are critical, and should be based on the investigator's training, experience and willingness to conduct the trial as proposed. Certification of the operator's ability to use the device through sponsor training may be required. Since institutions with slow patient accrual will prolong the investigation, careful screening of potential sites is necessary to assure completion of the study within a reasonable period of time. All sites, whether active or not enrolling patients in the study, are counted toward the limit imposed on the study. Furthermore, once a patient has been enrolled in the study at a site, that site is to be counted toward the total study limit. If an investigator discontinues study participation, the sponsor, the investigator and the institutional review board (IRB) at that site must ensure continued followup of patients initially treated by the discontinued investigator in accordance with the investigational plan.

b. Number of Institutions: State the total number of institutions and investigators to be involved in the study based on the total number of subjects to be enrolled in the study assuming equal distribution of patients among all sites (treatment and control) and on the anticipated accrual rate per institution. Although FDA has permitted a maximum of 20 institutions and 250 procedures for a multicenter trial for PTCA catheters, these limitations are no longer applicable since the study sample size must be statistically justified. If necessary, the study size limit established in the investigational phase may be increased with adequate justification (e.g., additional patients are needed to support the study objective(s) of the IDE, the PMA is sufficiently complete for filing, or after an Advisory Panel's approvable recommendation for the device marketing application).

c. Phase I Study: Sponsors should consider initiating a feasibility study prior to establishing the protocol for the multicenter trial. Feasibility studies are useful to permit adequate training and handling of the device, and to maximize device performance before designing an optimal randomized trial. Expansion of a feasibility study to a nonrandomized study conducted by physicians at more than one site, and ultimately to a randomized multicenter trial, will be primarily based on results of the

initial data collected, the design of the multicenter study, and any needs to modify the device or to permit training and device handling by physicians. Standard PTCA balloons do not need a feasibility or phased trial; rather only studies of new, complex catheters or other complex devices that require a learning period should be designed in this fashion.

III. PMA APPLICATION REQUIREMENTS

A premarket approval (PMA) application is the presentation and analysis of the clinical data collected under the IDE application, with the addition of other information required under 21 CFR 814.20, including for example, an extensive description of the manufacturing procedures and marketing of the device outside the United States. The presentation and analysis of the clinical data comprises, in part, a significant portion of the Summary of Safety and Effectiveness (SS&E). The SS&E should be written to include all aspects of the device testing, including in vitro, animal and clinical testing. The SS&E is a summary of the basis for FDA's determination that the interventional device is reasonably safe and effective, and can be granted approval for commercial marketing. Keep in mind that the determination of safety and effectiveness is based principally on four factors, as outlined in 21 CFR 860.7:

- o the persons for whose use the device is represented or intended
- o the conditions of use for the device, including conditions of use prescribed, recommended or suggested in the labeling or advertising of the device, or other intended conditions of use
- o the probable benefit to health from the use of the device weighed against any probable injury or illness from such use
- o the reliability of the device

The PMA regulation clearly identifies the content and format of a PMA application, as well as the requirement for subsequent submissions (e.g., supplements and progress reports). Since the PMA application requirements are lengthy, only pertinent issues relating to interventional cardiology devices are presented here for particular consideration in the preparation of a PMA.

Before initiation of the clinical study, the sponsor must determine the research question which will support the intended labeling claims for the device. The sponsor will not know whether the indication for use is appropriate for the investigational catheter until the data are analyzed. Regardless of the indication for use that is recommended in a PMA, there must be sufficient valid scientific evidence to document safety, effectiveness and clinical utility. The sponsor should consider the following points when making this determination and preparing the PMA application:

- o Do the data support the indications?
- o Have the proper statistics been used based on the design of the study?
- o Have the data been correctly compared to the appropriate control population regarding inclusion criteria, success and failure rates, restenosis and complications?
- o Does the use of the interventional cardiology device offer benefit to the patient which outweighs the risks?

A. SPECIFIC PMA REQUIREMENTS

Sponsors of PMA applications should carefully follow the format for the extensive content of a PMA application as outlined in 21 CFR 814.20 and fully discussed in the "Premarket Approval (PMA) Manual," "Premarket Approval (PMA) Manual Supplement,"* and "The PMA Checklist for Filing Decision" (Attachment F). In addition, however, sponsors should consider the following issues in preparing their PMA application as these problems have repeatedly occurred in other applications.

1. Accountability - The PMA must provide an accounting of all investigational catheters shipped and used during the clinical study, and the number of patients enrolled in the study. The patient is considered enrolled in the study once the treatment assignment for the patient is divulged. Accounting for the number of investigational devices used in the study includes those used in the treatment of the patient, as well as any device package that was opened and the guidewire that was in situ for the purpose of introducing the device.

2. Sufficient Data - Regardless of the number of patients to be enrolled in the study, the data should be complete and adequate to support the determination of safety and effectiveness. For a PMA to be filed for any interventional cardiology device, FDA has determined that the PMA must contain data to statistically support the indications for use proposed in the labeling. It is no longer acceptable to provide data from a minimum of 75 or 200 patients who have been successfully treated only with the investigational catheter. All patients intended to be treated with the investigational device must be followed according to the study protocol. A clinical update, submitted as an amendment to the PMA, will be required prior to any scheduled advisory panel meeting, and at any time after receipt of an approvable letter as determined to be necessary by FDA. The study should continue until the PMA is approved by FDA, provided FDA approves an expansion of the study based on adequate justification. After PMA approval, additional postapproval follow-up requirements on the original patient cohort may be required by FDA.

3. Protocol Changes - If changes are made to the protocol at any time during the investigation (e.g., a new patient group or indication is added, or the catheter design has been modified), additional patients may need to be added to the study. The type of change and its effect on the overall data supporting the indications for use will dictate whether additional patients are necessary. When the data are presented in the PMA, each change will have to be addressed and an analysis provided to justify pooling the data before and after the change. Furthermore, to ensure that the scientific integrity of the study as well as the patient's safety are protected, any protocol changes should be submitted and reviewed by the institutional review board at each study site conducting the clinical trial.

* These guidance documents may be obtained from CDRH's Division of Small Manufacturers Assistance by calling (800) 638-2041 or (301) 443-6597.

4. Use of Other Interventional Devices at the Target Lesion - An accurate, detailed history of previous interventional treatment to the target lesion must be obtained for all study subjects. Depending on the study design, patients may or may not be entered into the clinical trial based on their treatment history. Studies which allow entry of patients who have received treatment with other interventional cardiology devices may require subgroup analysis. Since analysis of the data from multiple treatments is complex, the sponsor is reminded of the following factors in presenting the data and any conclusions. First, the results of the investigational device can be assessed only if it was the only device used in the lesion (i.e., attempted use, crossing and/or dilatation). If the investigational device was successful but was followed by another interventional therapy (e.g., PTCA catheter, surgery or medication), these data should be combined with the initial success data from the study cohort in order that a true measure of initial success is represented. Second, in analyzing the complication data, it is rarely possible in an unbiased fashion to ascertain whether the complication was related to the investigational device, a competitive device, an adjunctive therapy or the procedure in general.

5. Standard Definitions for Data Analysis

   Standardized definitions must be used throughout the entire study in order to facilitate and permit adequate statistical analysis of all data. Please refer to Attachment C for recommended definitions.

6. Adjunctive Treatments

   An interventional procedure that was initially determined to be a failure could be subsequently used as supportive data for adjunctive uses. This can occur when the lesion was initially treated with a commercially available catheter or other intervention and successfully completed with the investigational catheter, or the lesion was treated with an investigational catheter without problems or complications, but the dilatation was completed with another intervention or with a commercially available catheter for reasons such as the required balloon size was not available, or the physician determined it was necessary.

   In cases where marketed interventional devices or other investigational devices are used on a portion of the study population, data regarding this subcohort must be thoroughly documented and analyzed separately. For example, specific descriptions of each group must be provided (i.e., the patient inclusion/exclusion criteria) and the rationale for including that group. Also, the physician's reason for subsequent treatment after a successful investigational PTCA must be documented.

7. Presentation of Data - All parameters evaluated (e.g., baseline and endpoint variables) should be presented in tabular format for each patient and should be grouped by investigator. One of the most useful charts is a patient flow chart, which tracks every

patient entered into the study and provides an "at-a-glance" look at the data. Another type of table is one that includes all the patients listed vertically with outcomes pre- and postprocedure listed horizontally. No matter which format is chosen, ensure that the method is consistent for all subjects and that all data is included in the table. The overall study results should be presented in separate tables. See Attachment E for a sample format for presenting study results.

8. Study Endpoints - The study endpoints must be described and the assessment methods must be explained as previously established in the investigational plan. The same endpoints must be used by all investigators and care must be taken to ensure that each patient's result is correctly categorized.

9. Analysis of Patient Deaths - When performing mortality analysis, all causes of death should be included in the first analysis, followed by cardiac death analysis. Every effort should be made to perform an autopsy on all patient deaths to firmly establish the cause of death and determine whether death was device related. The cause of death of any patient who dies during the interventional procedure, or prior to hospital discharge, should be well documented. Information should include the time within the treatment and followup period when the patient expired, whether other commercially available devices were used after unsuccessful dilatation by the investigational device, whether coronary artery bypass surgery was attempted, and whether any other emergency procedures were employed. A complete summary of the opinion of the sponsor and the opinion of a knowledgeable physician should be expressed, with an explanation as to how this opinion was reached, as to whether the death was caused by (1) factors unrelated to the investigational device or the procedure, (2) the specific device used, or (3) the interventional procedure in general. Patients who die during the remainder of the follow-up period should have the circumstances surrounding their death explained as completely as possible; recognizing that this documentation may be less complete than deaths occurring under medical surveillance.

10. Complications - As previously discussed on page 29 and Attachment C, identification of complications must be established prior to beginning the study. Complications occurring during the clinical study should be documented as completely as possible, and the complication rate should be compared to complication rates gathered from the control group or from other contemporary studies or literature.

11. Foreign Data - Foreign data may be acceptable for submission in a PMA application under limited conditions (21 CFR 814.15). At a minimum, the sponsor should ensure that the same protocol and device were used in the foreign study. The sponsor must also demonstrate that the practice of medicine in the treatment of the disease in that country (e.g., method of diagnosis and treatment and prevalence rate) is similar to the disease in the United States population. Finally, the study must be conducted in conformance with the Declaration of Helsinki or the laws and regulations of the country in which the

research was conducted (whichever offers greater protection to the human subjects).

12. Data Analysis

    a. In making comparisons to existing data, consider the source of the data and whether direct comparisons between the study population and study control can be made. Subgroup analysis should be looked at critically since the number of patients in the subgroup may be too small to draw valid conclusions.

    b. Statistical methods, such as the Mantel-Haenszel chi-square test, multivariate analysis and regression analysis, should be used to analyze the study results. Statistically compare the results with an appropriate control and with reported results of other similar studies.

    c. The Division of Biometrics Science, Office of Surveillance and Biometrics, CDRH, has developed a "PMA Review Statistical Checklist" which outlines the minimum requirements for a PMA submission from a statistical viewpoint. Attachment G is a copy of this checklist.

DEFINITIONS

LESION CHARACTERISTICS BY TYPES

Definitions for lesion characteristics are based on the recommendations contained in the Guideline for Percutaneous Transluminal Coronary Angioplasty as reported in the American College of Cardiology and American Heart Association Task Force Report[18], the NHLBI Registry[6], the NACI Registry[20] and other suggestions from investigational studies. Other definitions for lesion characteristics may be used provided there is adequate justification in support of their use in a research or marketing application.

TYPE A LESIONS

Lesions with an anticipated success rate of ≥85% and a low risk for abrupt closure. Type A lesions include the following characteristics:

- discrete (< 10 mm)
- concentric
- readily accessible
- nonangulated segment <45°
- smooth contour
- little or no calcification
- less than totally occlusive
- not ostial in location
- no major side branch involvement
- absence of thrombus

TYPE B LESIONS

Lesions with an anticipated moderate success rate of 60 to 85% and a moderate risk of abrupt closure. Type B lesions include the following characteristics:

- tubular (10-20 mm length)
- eccentric
- moderate tortuosity of proximal segment
- moderately angulated segment, >45° to <90°
- irregular contour
- bifurcation lesions requiring double guide wires
- moderate to heavy calcification
- total occlusions <3 months old
- ostial in location
- some thrombus present

TYPE C LESIONS

Lesions with an anticipated low success rate of ≤60% and a high risk for acute closure. Type C lesions include the following characteristics:

- diffuse (≥2 cm length)
- inability to protect major side branches
- degenerated vein grafts with friable lesions
- total occlusion >3 months old
- extremely angulated segments >90°
- excessive tortuosity of proximal segment

LESION CHARACTERISTICS BY SPECIFIC FEATURES

Angulation: Vessel angle formed by the centerline through the lumen proximal to the stenosis and extending beyond it and a second centerline in the straight portion of the artery distal to the stenosis measured in a nonforeshortened view; angulations is recorded as nonangulated (vessel angulation at $<45°$); moderate (vessel angulation at 45 -90°); or extreme/severe (vessel angulation at $>90°$).

Bifurcation Lesions: Lesion where a branch vessel of medium or large size originates.

Calcification: Readily apparent densities seen within the artery wall and site of lesion; these can be classified as little/none, moderate or severe.

Collaterals: faint fills partial, fills entire vessel, antegrade or retrograde.

Concentric Lesion

Contour: A smooth or irregular/rough margin

De Novo Lesion: Lesion not previously treated

Eccentric Lesion: Lesion lumen in the outer one-quarter diameter of the apparent normal lumen

Lesion Length: Measured as the distance from the proximal to the distal shoulder in the view that demonstrates the stenosis in its most elongated projection; lesion length is recorded as discrete ($<$ 10 mm), tubular (10-20 mm) and diffuse ($>$ 20 mm)

Lesion Location: Location according to specific coronary artery (i.e., left main (LM), right coronary artery (RCA), left anterior descending (LAD) or left circumflex (LCX)) or bypass graft, and specified as proximal, mid or distal. All lesion location should be accompanied by a coronary artery tree or map.

Multivessel disease: The presence of a $>70\%$ diameter stenosis as measured by caliper method in 2 or 3 major epicardial coronary vessels or bypassed branches.

Ostial Lesions: Lesions involved in the origin of the coronary artery within the first 3 mm.

Reference Diameter of Normal Artery Segment: Angiographic measurement of the artery proximal and/or distal to the lesion intended for angioplasty.

Restenosed Lesion: A stenosis in a previously treated lesion.

Saphenous Vein Bypass Graft Lesion: Lesion in a graft which are identified by age (i.e., number of months), general appearance on angiography, and stenosis locations.

Significant Stenosis: A stenosis that results in a 50% reduction in coronary diameter as determined by a quantitative angiographic method.

Thrombus: Discrete, mobile intraluminal filling defects with defined borders with/without associated contrast staining; these are classified as either absent or present.

Tortuosity: Accessibility to the lesion as influenced by the number of vessel bends that must be transversed by the device to the lesion; lesions distal to 2 bends are classified as moderate and those distal to 3 or more bends are classified as excessive.

Total Occlusions: Lesion with no flow (TIMI 0), usually specified as $<$ or $>$ 3 months.

Ulceration: Lesion will small crater or luminal flap.

DEFINITIONS FOR DATA ANALYSIS

The definitions for success, failure, endpoints and complications are to be defined in a manner consistent with the intended use of the investigational device and the objectives of the study. The following variables should be defined in all clinical studies. Since the sponsor must define the variables consistent with the objectives of the study, only some recommended definitions are provided as obtained from various literature sources, e.g., the NACI Registry[20], the NHLBI registry[6] and the ACC/AHA Guideline[18].

SUCCESS CRITERIA

Clinical or Procedural Success: The achievement of a $\geq$20% change in luminal diameter with a final diameter stenosis <50% and with no major ischemic complications (Non-fatal myocardial infarction (MI), CABG, Bailout Stenting, Emergent repeat intervention in hospital or death) during hospitalization.

Lesion Success

Technical Success

FAILURE CRITERIA

Clinical or Procedural Failure

Lesion Failure

Mechanical Failure

STUDY ENDPOINTS (most frequently used in interventional cardiology device studies)

Restenosis: An assessment of the treated lesion is performed 6 months after initial treatment. Using a binary definition restenosis is defined as a >50% reduction in diameter when compared to the reference luminal diameter. Because restenosis is a continuous rather than a discrete process, the distribution and quantitative characterization of continuous variables that describe the restenosis problem (e.g., percent stenosis, minimal lumen diameter, etc.) should also be examined to define device performance.

Death

Myocardial Infarction

Coronary Artery Bypass Graft (CABG) Surgery

Abrupt Closure

COMPLICATIONS

Abrupt Closure: Obstructed coronary flow in the dilated lesion which was previously documented to be patent with antegrade flow.

Angiographic Complications: perforation, occlusion, intimal flap, dissection, loss of side branch, non-occlusive thrombus, transient spasm, distal embolization, etc.

Clinical Complications: Non-fatal MI, elevated CK, prolonged angina, hypotension, hematoma, bradycardia, ventricular tachycardia, ventricular fibrillation, groin repair, etc.

Coronary Artery Bypass Graft (CABG) Surgery: Emergent or elective

Coronary Spasm: Transient or permanent narrowing >50% in a region where a <25% stenosis had previously been noted.

Death: Specified as in-hospital or after discharge, and as associated with angioplasty procedure, other coronary heart disease or other specific causes.

Dissection: Graded levels of luminal abnormality in the contrast column in the dilated segment based on mild, moderate and severe, or by the NHLBI criteria (e.g., Types A - luminal haziness to Type F - dissection with total occlusion).

Distal Embolization: Migration of a filling defect or thrombus to distally occlude the target vessel or one of its branches.

Intimal Flap: A discrete filling defect in apparent continuity with the arterial wall.

Loss of Side Branch: TIMI 0 or 1 flow in a side branch previously normal of more then 1.5 mm in size.

Major Complications: Non-fatal MI, emergency CABG surgery, or death occurring during hospitalization; acute MI should be recorded as fatal, non-fatal without CABG or non-fatal with CABG; CABG should be recorded as fatal or non-fatal; and an overall major complication rate should be given.

Myocardial Infarction (MI): Diagnosed based on 2 of the following 3 conditions - clinical symptoms, ECG and enzyme changes (more than double upper normal limits of creatinine kinase(CK) and/or presence of
CK-MB).

Perforation: Extravasation of contrast outside the arterial lumen; identified as localized (confined to pericardial space immediately surrounding the artery and not associated with clinical tamponade) or nonlocalized (not confined to pericardial space immediately surrounding the artery, potentially associated with clinical tamponade).

Repeat Angioplasty: by device under study or other interventional device or CABG.
Side Branch Occlusion/Successfully treated with PTCA: Loss of side branch with restoration of coronary flow with repeat PTCA.

Thrombus: Discrete angiographic filing defect with/without staining.

Bailout Stenting

Emergent repeat intervention in hosptial

FORMAT FOR REPORT FORMS

This document lists the recommended types of report forms and the recommended information to be contained in the respective report forms. The protocol should also contain a description of this same information that is to be collected from all patients enrolled in the study, including definitions and methods for their assessment. Other report forms may be used provided there is adequate justification in support of their use in the research or marketing application.

BASELINE/PREOPERATIVE FORM

Dates of Admission and/or Examination

Patient Demographics: age, sex, date of birth, race, identification number, etc.

Medical Condition relating to Coronary Artery Disease Risk Factors: hypertension, diabetes requiring treatment, cholesterol, cigarette smoking status and amount, family history of coronary artery disease, menopausal status.

Non-Cardiac Disease Conditions: renal, cancer, etc.

Angina Status: Canadian Cardiovascular Society (CCS) functional score, stable or unstable and duration of symptoms; exercise functional testing; thallium scan.

Prior Myocardial Infarction (MI): date of most recent MI, location, Q-wave or non Q-wave, ST segment change and CK enzyme elevation ($\geq$ 2 times normal lab levels) and/or presence of CK-MB isozyme.

Previous Angioplasty Treatment: number of previous treatments, type of treatments and date of most recent treatment.

Prior Coronary Artery Bypass Graft (CABG) Surgery: date of most recent treatment and location.

Symptomatic Congestive Heart Failure: New York Heart Association (NYHA) functional class (1, 2, 3 or 4)

Current Medications: e.g., nitrates, beta blockers, CA channel blockers, antiplatelet agents, diuretics, ace inhibitors, insulin, antiarrhythmic agents, etc.

Activity Status

Baseline Laboratory Data: complete blood count (CBC), electrolytes, creatine kinase and CK-MB isozymes, creatinine, BUN, cholesterol, HDL, LDL, TG, SGOT, SGPT and alkaline phosphatase

OPERATIVE/PROCEDURAL FORM

This form includes information to be collected during catheterization and during the angioplasty procedure. Identification of the target lesion(s) to be treated should be accompanied by coronary artery maps appropriately numbered to correspond to the location of the target lesion(s).

Date of Procedure
Circumstance for Procedure: elective, urgent, emergency or salvage; angina, silent ischemia, acute MI or other.
Medications: preoperative, operative and postoperative
Total Procedure Time, including total fluoroscopy time
Angina Status: CHC classification, stable or unstable
MI Status: date of most recent MI
Angiographic Data of Lesion Location: see Attachment C for definitions of lesion characteristics - for example; single or multivessel disease; right coronary artery (RCA), left anterior descending (LAD), left circumflex (LCX), left main (LM), or graft; ostial, proximal, mid or distal; collaterals present (receive or supply).
Lesion Morphology: discrete, tubular, diffuse/irregular, ulcerated, aneurysm, intimal flap, calcified, eccentric, concentric, angulated, bifurcation, tortuous, ostial, ectasia, thrombus, degenerated vein graft.
Vein Graft Age: < or > 3 months
TIMI Flow: 0, 1, 2, 3
Left Ventricular Ejection Fraction: from angiogram, echocardiography or RVG
Reference Vessel Size: proximal and distal to lesion
Minimal Lumen Diameter (MLD) and Percent Stenosis: preprocedure and postprocedure
Percent Diameter Stenosis: Preprocedure and postprocedure using two dimensional analysis
Lesion Length: mm
Device Used for Angioplasty: Intended treatment method, specific method used and model of device; e.g., PTCA balloon require the exact type, size, number and duration of inflations, highest dilation pressure); see below for recommended report forms for specific device uses.
Success Evaluation: procedural, clinical, lesion or technical.
Failure Evaluation: procedural, technical, lesion or clinical.
Complications: See Attachment C for complications; e.g., dissection, perforations, spasm, abrupt closure
Medical therapy regimen: anticoagulants (drug duration, heparin duration, sheath duration, platelet count, PTT and ACT measurement.
Creatinine Phosphokinase: CK evaluation; and if elevated CK, MB isozyme and 12-lead ECG assessment

FOLLOW-UP/POSTPROCEDURE FORM

Date of Follow-up

Follow-up Interval: 6 weeks, 6 months, 1 year, etc.

Patient Identification

Other Revascularization Procedures

Clinical Data:

(1) recurrent angina: date of onset, CCS functional class, duration, unstable/stable
(2) MI: date of onset, anatomical location, Q-wave or non-Q wave, ST segment changes, CK peak, CK-MB isozymes.
(3) Exercise test: date, protocol, angina during ETT, ST changes >1 mm, percent maximal heart rate, final stage achieved, total cumulative seconds, RPP, thallium results (reversible defect).

Angiographic Data: date of angiography, recorded view, lesion morphology, collaterals, reference size vessel, minimum lumen diameter (MLD), percent stenosis, lesion length, fluoroscopy time and amount of contrast dye.
Status of Other Medical Conditions: Congestive heart failure, etc.
Concurrent Medications

MAJOR EVENT FORM

Date of Event: in-hospital or out of hospital
Patient Indentification
Interventional Device(s) Previously Used
Identification of Event: Death, CABG, MI

Information for Patient Death:
Date of Death
Location at onset of event
Was it observed and by whom
Autopsy Findings, if performed
Cause of Death: cardiac (direct cause or contributory), noncardiac, accident, unknown, etc.

Summary of circumstances leading the Death
Information for CABG Surgery:
Date of Surgery
Conditions for Surgery: elective, urgent, emergency
Number, Types and Location of Grafts

BALLOON PTCA FORM

Date of Procedure
Patient Identification
Intended Mode of PTCA Treatment: only device, adjunct (prior to or after), after device failure, for abrupt closure or suboptimal results, etc.
Lesion Characteristics: see Attachment C
Minimum Lumen Diameter/Percent Stenosis: pre- and postprocedure
Name and Model of PTCA Balloon Catheter(s)
Number of Inflations
Maximum Balloon Size
Maximum Inflation Pressure
Longest Single Inflation (secs)
Complications: abrupt closure, dissections, etc.
Reasons for Failures: failure to cross guide wire or device, failure to dilate, etc.

STENT FORM

Date of Procedure
Patient Identification
Intended Mode of Stent Use: only device, adjunct (prior to or after), after other device failure, for abrupt closure or suboptimal results, etc.
Lesions Characteristics: see Attachment C
Minimum Lumen Diameter and Percent Stenosis: pre- and postprocedure
Name, Model and Serial Number of Stent
Number of Stents Implanted
Delivery Balloon Diameter (mm)
Deployed Stent Diameter and Length
Post Placement Enlargement and Final Balloon Size
Complications
Reasons for Failures

LASER FORM

Date of Procedure
Patient Identification
Intended Mode of Laser Use: only device, adjunct (prior to or after), after other device failure, for abrupt closure or suboptimal results, etc.
Lesions Characteristics: see Attachment C
Minimum Lumen Diameter and Percent Stenosis: pre- and postprocedure
Name and Model of Laser
Laser Catheter Names and Diameter

Laser Procedural Information:
- Pre-laser catheter fluence (mJ/mm2)
- Total Lasing Time (sec)
- Number of Passes and Pulses per Pass
- Maximum Fluence
- Maximum Hertz
- Post Laser Catheter Fluence
- Total Energy Delivered

Complications
Reasons for Failure

ATHERECTOMY FORM

Date of Procedure
Patient Identification
Intended Mode of Atherectomy Use: only device, adjunct (prior to or after), after other device failure, for abrupt closure or suboptimal results, etc.
Lesions Characteristics: see Attachment C
Minimum Lumen Diameter and Percent Stenosis: pre- and postprocedure
Name and Model of Atherectomy Device
Size of Catheter (Fr or burr)
Description of Catheters Used: guide size, device size, maximum pressure, etc
Number of Insertions and Passes
Number and Weight of Tissue Samples (if applicable)
Pathology of Tissue Sample
Complications
Reasons for Failure

Attachment E

FORMAT FOR PRESENTING STUDY RESULTS

The following categories of study results should be present in tabular form and compared against three main categories: Sole Treatment % (numerator/denominator), Adjunctive Treatment % (numerator/denominator), and Total Treatment % (numerator/denominator).

OVERALL NUMBERS

Patients
Procedures
Lesions

LESION CHARACTERISTICS

Saphenous Vein Graft (SVG)	Discrete (< 10 mm length)
Native RCA	Tubular (10-20 mm length)
Native LAD	Diffuse (> 10 mm length)
Native LCX	Eccentric
Native LM	Concentric
Ostial	Calcified
Proximal	Non-calcified
Mid	Total Occlusions
Distal	Thrombus
De Novo Lesion	Angulated
Restenosed Lesion	Bifurcate

OVERALL ACUTE SUCCESS

Saphenous Vein Graft (SVG)	Discrete (< 10 mm length)
Native RCA	Tubular (10-20 mm length)
Native LAD	Diffuse (> 10 mm length)
Native LCX	Eccentric
Native LM	Concentric
Ostial	Calcified
Proximal	Non-calcified
Mid	Total Occlusions
Distal	Thrombus
De Novo Lesion	Angulated
Restenosed Lesion	Bifurcate

MAJOR COMPLICATIONS

Death
Non-fatal MI without CABG
Non-fatal MI with CABG
Non-fatal CABG
Overall Complication Rate

ANGIOGRAPHIC COMPLICATIONS

Perforation
Occlusion
Intimal Flap
Dissection
Others
Loss of Side Branch
Non-Occlusive Thrombus
Transient Spasm
Distal Embolization

CLINICAL COMPLICATIONS

Non-fatal AMI
Elevated CK
Prolonged Angina
Hypotension
Hematoma
Bradycardia
Ventricular Tachycardia
Ventricular Fibrillation
Groin Repair
Other

LONG-TERM FOLLOW-UP

Angiographic Follow-up at 6 months
Clinical Follow-up
Restenosis: Native De Novo Lesions
Native Restenosed Lesions
SVG De Novo Lesions
SVG Restenosed Lesions
Overall Angiographic Restenosis
Overall Restenosis with Clinical

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