

## **Significant Risk vs Non-significant Risk Medical Device Studies – Information Sheet**

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (SR) and "non-significant risk" (NSR).

An SR device study is defined [21 CFR 812.3(m)] as a study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

An NSR device investigation is one that does not meet the definition for a significant risk study. NSR device studies, however, should not be confused with the concept of "minimal risk," a term utilized in the Institutional Review Board (IRB) regulations [21 CFR part 56] to identify certain studies that may be approved through an "expedited review" procedure.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR part 50].

### **Distinguishing Between SR and NSR Device Studies**

The effect of the SR/NSR decision is very important to research sponsors and investigators. SR device studies are governed by the IDE regulations [21 CFR part 812]. NSR device studies have fewer regulatory controls than SR studies and are governed by the abbreviated requirements [21 CFR 812.2(b)]. The major differences are in the approval process and in the record keeping and reporting requirements.

FDA is usually not apprised of the existence of approved NSR studies because sponsors and IRBs are not required to report NSR device study approvals to FDA. If an investigator or a sponsor proposes the initiation of a claimed NSR investigation to an IRB, and if the IRB agrees that the device study is NSR and approves the study, the investigation may begin at that institution immediately, without submission of an IDE application to FDA. If an IRB believes that a device study is SR, the investigation may not begin until both the IRB and FDA approve the investigation.

### **SR/NSR Studies and the IRB: The NSR/SR Decision**

The assessment of whether or not a device study presents a NSR is initially made by the sponsor. If the sponsor considers that a study is NSR, the sponsor provides the reviewing IRB an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor should provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information that the IRB deems necessary to make its decision. The sponsor should inform the IRB whether other IRBs have reviewed the proposed study and what determination was made. The sponsor must inform the IRB of the Agency's assessment of the device's risk if such an assessment has been made. The IRB may also consult with FDA for its opinion.

The IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without submission of an IDE application to FDA. If the IRB disagrees, the sponsor should notify FDA that an SR determination has been made. The study can be conducted as an SR investigation following FDA approval of an IDE application.

The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses an SR, an IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to subjects could be life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the subject must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device. **Two examples follow:**

- 1) The study of a pacemaker that is a modification of a commercially--available pacemaker poses a SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially-available model. The amount of potential reduced or increased risk associated with the investigational pacemaker should only be considered (in relation to possible decreased or increased benefits) when assessing whether the study can be approved.
- 2) The study of an *extended wear contact lens* is considered SR because wearing the lens continuously overnight while sleeping presents a potential for injuries not normally seen with daily wear lenses, which are considered NSR.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the Agency does not agree with an IRB's decision that a device study presents an NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the Agency will return the IDE application to the sponsor and the study would be presented to IRBs as an NSR investigation.

#### IRB and Sponsor Responsibilities Following SR/NSR Determination

##### **If the IRB decides the study is Significant Risk:**

###### 1. IRB Responsibilities:

Notify sponsor and investigator of SR decision

After IDE obtained by sponsor, proceed to review study applying requisite criteria [21 CFR 56.111]

###### 2. Sponsor Responsibilities:

Submit IDE to FDA or, if electing not to proceed with study, notify FDA (CDRH Program Operations Staff 301-594-1190) of the SR determination;

Study may not begin until FDA approves IDE and IRB approves the study.

Sponsor and investigator(s) must comply with IDE regulations [21 CFR part 812], as well as informed consent and IRB regulations [21 CFR parts 50 and 56].

##### **If the IRB decides the study is Nonsignificant Risk:**

###### 1. IRB proceeds to review study applying requisite criteria [21 CFR 56.111]

2. If the study is approved by the IRB, the sponsor and investigator must comply with "abbreviated IDE requirements" [21 CFR 812.2(b)], and informed consent and IRB regulations [21 CFR parts 50 and 56].

## **EXAMPLES OF NSR/SR DEVICES**

Inclusion of a device in the NSR category should not be viewed as a conclusive determination, because the proposed use of a device in a study is the ultimate determinant of the potential risk to subjects. It is unlikely that a device included in the SR category could be deemed NSR due to the inherent risks associated with most such devices.

## **NONSIGNIFICANT RISK DEVICES**

Low Power Lasers for treatment of pain

Caries Removal Solution

Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)

Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use

Conventional Gastroenterology and Urology Endoscopes and/or Accessories

Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)

Conventional Implantable Vascular Access Devices (Ports)

Conventional Laparoscopes, Culdoscopes, and Hysteroscopes

Dental Filling Materials, Cushions or Pads made from traditional materials and designs

Denture Repair Kits and Realigners

Digital Mammography [Note: an IDE is required when safety and effectiveness data are collected which will be submitted in support of a marketing application.]

Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities)

Externally Worn Monitors for Insulin Reactions

Functional Electrical Neuromuscular Stimulators

General Biliary Catheters General Urological Catheters (e.g., Foley and diagnostic catheters)

Jaundice Monitors for Infants

Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters

Manual Image Guided Surgery

Menstrual Pads (Cotton or Rayon, only)

Menstrual Tampons (Cotton or Rayon, only)

Nonimplantable Electrical Incontinence Devices

Nonimplantable Male Reproductive Aids with no components that enter the vagina

Ob/Gyn Diagnostic Ultrasound within FDA approved parameters

Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain

Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings)

## **SIGNIFICANT RISK DEVICES**

### **General Medical Use**

#### *Catheters:*

- Urology - urologic with anti-infective coatings
- General Hospital - except for conventional long-term percutaneous, implanted, subcutaneous and intravascular
- Neurological - cerebrovascular, occlusion balloon
- Cardiology - transluminal coronary angioplasty, intra-aortic balloon with control system
- Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery,
- urological and dental applications
- Surgical Lasers for use in various medical specialties
- Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

## **Anesthesiology**

Breathing Gas Mixers  
Bronchial Tubes  
Electroanesthesia Apparatus  
Epidural and Spinal Catheters  
Epidural and Spinal Needles  
Esophageal Obturators  
Gas Machines for anesthesia or analgesia  
High Frequency Jet Ventilators greater than 150 BPM  
Rebreathing Devices  
Respiratory Ventilators  
Tracheal Tubes

## **Cardiovascular**

Aortic and Mitral Valvuloplasty Catheters  
Arterial Embolization Devices  
Cardiac Assist Devices: artificial heart (permanent implant and short term use), cardiomyoplasty devices, intra-aortic balloon pumps, ventricular assist devices  
Cardiac Bypass Devices: oxygenators, cardiopulmonary non-roller blood pumps, closed chest devices  
Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable  
Cardiopulmonary Resuscitation (CPR) Devices  
Cardiovascular/Intravascular Filters  
Coronary Artery Retroperfusion Systems  
Coronary Occluders for ductus arteriosus, atrial and septal defects  
Coronary and Peripheral Arthrectomy Devices  
Extracorporeal Membrane Oxygenators (ECMO)  
Implantable Cardioverters/Defibrillators  
Laser Coronary and Peripheral Angioplasty Devices  
Myoplasty Laser Catheters  
Organ Storage/Transport Units  
Pacing Leads  
Percutaneous Conduction Tissue Ablation Electrodes  
Peripheral, Coronary, Pulmonary, Renal, Vena Caval and Peripheral Stents  
Replacement Heart Valves  
RF Catheter Ablation and Mapping Systems  
Ultrasonic Angioplasty Catheters  
Vascular and Arterial Graft Prostheses  
Vascular Hemostasis Devices

## **Dental**

Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications  
Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)  
Dental Lasers for hard tissue applications  
Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants  
Subperiosteal Implants  
Temporomandibular Joint (TMJ) Prostheses

## **Ear, Nose, and Throat**

Auditory Brainstem Implants  
Cochlear Implants  
Laryngeal Implants  
Total Ossicular Prosthesis Replacements

## **Gastroenterology and Urology**

Anastomosis Devices  
Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)  
Biliary Stents  
Components of Water Treatment Systems for Hemodialysis  
Dialysis Delivery Systems  
Electrical Stimulation Devices for sperm collection  
Embolization Devices for general urological use  
Extracorporeal Circulation Systems  
Extracorporeal Hyperthermia Systems  
Extracorporeal Photopheresis Systems  
Femoral, Jugular and Subclavian Catheters  
Hemodialyzers  
Hemofilters  
Implantable Electrical Urinary Incontinence Systems  
Implantable Penile Prostheses  
Injectable Bulking Agents for incontinence  
Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)  
Mechanical/Hydraulic Urinary Incontinence Devices  
Penetrating External Penile Rigidity Devices with components that enter the vagina  
Peritoneal Dialysis Devices  
Peritoneal Shunt  
Plasmapheresis Systems  
Prostatic Hyperthermia Devices  
Urethral Occlusion Devices  
Urethral Sphincter Prostheses  
Urological Stents (e.g., ureteral, prostatG)

## **General and Plastic Surgery**

Absorbable Adhesion Barrier Devices  
Absorbable Hemostatic Agents  
Artificial Skin and Interactive Wound and Burn Dressings  
Injectable Collagen  
Implantable Craniofacial Prostheses  
Repeat Access Devices for surgical procedures  
Sutures

## **General Hospital**

Implantable Vascular Access Devices (Ports) - if new routes of administration or new design  
Infusion Pumps (implantable and closed-loop - depending on the infused drug)

## **Neurological**

Electroconvulsive Therapy (ECT) Devices  
Hydrocephalus Shunts  
Implanted Intracerebral/Subcortical Stimulators  
Implanted Intracranial Pressure Monitors  
Implanted Spinal Cord and Nerve Stimulators and Electrodes

## **Obstetrics and Gynecology**

Antepartum Home Monitors for Non-Stress Tests  
Antepartum Home Uterine Activity Monitors  
Catheters for Chorionic Villus Sampling (CVS)  
Catheters Introduced into the Fallopian Tubes  
Cervical Dilation Devices

### *Contraceptive Devices:*

- Cervical Caps
- Condoms (for men) made from new materials (e.g., polyurethane)
- Contraceptive *In Vitro* Diagnostics (IVDs)
- Diaphragms
- Female Condoms
- Intrauterine Devices (IUDs)
- New Electrosurgical Instruments for Tubal Coagulation
- New Devices for Occlusion of the Vas Deferens
- Sponges
- Tubal Occlusion Devices (Bands or Clips)

Devices to Prevent Post-op Pelvic Adhesions

Embryoscopes and Devices intended for fetal surgery

Falloposcopes and Falloposcopic Delivery Systems

Intrapartum Fetal Monitors using new physiological markers

New Devices to Facilitate Assisted Vaginal Delivery

Thermal Systems for Endometrial Ablation

### **Ophthalmics**

Class III Ophthalmic Lasers

Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use

Corneal Implants

Corneal Storage Media

Epikeratophakia Lenticules

Extended Wear Contact Lens

Eye Valve Implants (glaucoma implant)

Intraocular Lenses (IOLs) [21 CFR part 813]

Keratoprotheses Retinal Reattachment Systems: fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, tacks

Viscosurgical Fluids

### **Orthopedics and Restorative**

Bone Growth Stimulators

Calcium Tri-Phosphate Hydroxyapatite

Ceramics Collagen and Bone Morphogenic Protein Meniscus Replacements

Implantable Prostheses (ligament, tendon, hip, knee, finger)

Computer Guided Robotic Surgery

### **Radiology**

Boron Neutron Capture Therapy

Hyperthermia Systems and Applicators