

APPENDIX F

SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES

The Investigational Device Exemption (IDE) regulations [21 CFR Part 812] describe two types of device studies, "significant risk" (SR) and "nonsignificant 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. The SR/NSR decision is also important to FDA because the IRB serves, in a sense, as the Agency's surrogate with respect to review and approval of NSR studies. 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. To help in the determination of the risk status of the device, IRBs should review information such as reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria, and monitoring procedures. The Sponsor should provide the IRB with a risk assessment and the rationale used in making its risk determination [21 CFR 812.150(b)(10)].

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:

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. 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 is obtained by the 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]. There is no requirement for the Sponsor to notify FDA of the SR determination.

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].

The Decision to Approve or Disapprove

Once the SR/NSR decision has been reached, the IRB should consider whether the study should be approved or not. The criteria for deciding if SR and NSR studies should be approved are the same as for any other FDA regulated study [21 CFR 56.111]. The IRB should assure that risks to subjects are minimized and are reasonable in relation to anticipated benefits and knowledge to be gained, subject selection is equitable, informed consent materials and procedures are adequate, and provisions for monitoring the study and protecting the privacy of subjects are acceptable. To assure that the risks to the subject are reasonable in relation to the anticipated benefits, the risks and benefits of the investigation should be compared to the risks and benefits of alternative devices or procedures. This differs from the judgment about whether a study poses a SR or NSR which is based solely upon the seriousness of the harm that may result from the use of the device. Minutes of IRB meetings must document the rationale for SR/NSR and subsequent approval or disapproval decisions for the clinical investigation.

FDA considers studies of all significant risk devices to present more than minimal risk; thus, full IRB review for all studies involving significant risk devices is necessary. Generally, IRB review at a convened meeting is also required when reviewing NSR studies. Some NSR studies, however, may qualify as minimal risk [21 CFR 56.102(i)] and the IRB may choose to review those studies under its expedited review procedures [21 CFR 56.110].

Examples of NSR/SR Devices

The following examples are provided to assist Sponsors and IRBs in making SR/NSR determinations. The list includes many commonly used medical 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 Valvoplasty 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 Protheses

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 Protheses

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 Protheses

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

Comments, questions and suggestions for additional examples should be sent to:

Program Operation Staff (HFZ-403)

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Center for Devices and Radiological Health

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