Introduction

Medical devices include ones applied topically, implanted devices which have externalized components and devices which are implanted systemically. Such devices may be used in swine clinically, such as catheters or vascular access ports for vascular sampling procedures. However, swine are also utilized as animal models for the preclinical testing of devices which ultimately are meant to be used for diagnosis, treatment or prevention of disease processes in humans. Such devices include stents, monitoring devices, pacemakers, surgical aids such as new closure devices and any such device which is implanted intravascularly, into a body cavity or into a tissue or organ.

Manuscripts on the therapeutic use of devices in swine and catheter implantation may be found on the Sinclair website.\(^1\) In depth description of surgical procedures in swine have also been published.\(^2\) Recently a manuscript has been published on the regulatory aspects of preclinical trials in minipigs using medical devices has been published.\(^3\) This manuscript will deal mainly with the aspects of using swine as regulatory models in preclinical trials using implanted medical devices.

Regulatory Requirements\(^2, 3\)

The International Standards Organization (ISO) has developed standards for the preclinical testing of medical devices which has largely been accepted internationally. Their testing standards for implanted devices in animals are detailed in ISO-10993: Biological Evaluation of Medical Devices.\(^4\) Depending upon the specific characteristics of the device it may require adherence to up to 20 of its task requirements within that section.\(^3\)

The Food and Drug Administration (FDA) requirements are generally in accord with the ISO-10993 standards.\(^5, 6\) However, they may require additional evaluation procedures particularly if the device is made of a new material or leaches therapeutic agents.\(^3\) Most countries have an agency similar to the FDA which may have variations on these requirements. The FDA prefers that preclinical trials of medical devices in animals follow the requirements of the Good Laboratory Practices Act (GLP) which is mainly an auditing and documentation requirement.\(^6\) They have made exceptions for devices if the ISO-10993 standards have been followed and the devices are made of previously approved materials deemed to be safe in humans and which are not expected to leach toxic products. They also prefer that implanted devices be similar in size to the device expected to be implanted clinically in humans.\(^2, 7\)

Although not required within the various regulatory statutes, accreditation of the animal care and use program by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) is a validated method of ensuring that the animal care components of the various regulations are in compliance.

The length of time which needs to be followed in the protocol for various devices depends upon its ultimate clinical use in humans. Generally these devices can be characterized as having limited (<24 hours), prolonged (1-30 days) or permanent (>30 days).\(^3\) When planning the experiment with the goal of achieving FDA approval, there should be a meeting with the agency to determine what length and types of group exposure they will expect in order to accept the data. For devices implanted systemically for long term, the groups frequently requested are 1 month, 3 months, 6 months and 12 months.

As a general rule miniature breeds of swine need to be used for the chronic exposure groups. It is advisable to perform acute experiments in swine, which may be domestic breeds, in order to obtain pilot data and to determine modifications which need to be made before committing to a GLP study. This is because any data performed as a formal GLP study need to be included in the data submitted to the FDA. Very frequently medical devices which work as anticipated in an in vitro experiment develop unforeseen problems when implanted in animals. The exponential growth of the domestic farm breeds is a complication to these studies because organs such as the heart or the great vessels will also grow and devices can become unattached. As a general rule domestic breeds are not used for experiments beyond 30 days unless growth is part of the study. The miniature breeds also have an advantage if the device is eluding therapeutic agents because of the decreased body weight and reduced dosage of the test substance that will be needed.

The purpose of these various regulations and standards is to ensure that medical devices have proven biocompatibility, safety and efficacy. They are also meant to be an assurance to the regulatory agencies and the public that the standard of care of the animals and the experimental procedures performed have adhered to a high standard which can be duplicated by other labs.\(^8\)
Porcine Models

Swine have a number of anatomic and biologic characteristics which make them a suitable model for preclinical testing of medical devices. The cardiovascular system is of major importance because of their susceptibility to experimentally induced myocardial infarction and atherosclerosis as well as the physiology of wound healing and coagulation within the vasculature. If the device needs to approximate the size that will be implanted in the human, sexually mature Hanford pigs have the heart and blood vessel size which more closely approximates that of humans. The Yucatan breed is frequently used as the porcine model for studies which involve the induction of atherosclerosis with or without diabetes.

The integumentary system is frequently used for transdermal toxicology and wound healing studies because of the similarities to humans in terms of wound healing pathway, dermal metabolism and dermal turnover. In terms of medical devices it is useful for studying the effects of topical patch treatments and device implantations which have exteriorization through the skin as part of the study.

The digestive system has been utilized for a number of medical device studies. These include interventional laparoscopic studies, natural orifice transluminal endoscopic surgery (NOTES), tumor ablation catheters and anti-obesity device surgery. The physiology of digestion and the metabolism of nutrients by the intestinal tract, liver and pancreas are primary reasons for the selection of porcine models for these types of studies.

The brain of the pig has been difficult to access using catheterization techniques due to the presence of the rete mirabile which prevents catheters from passing at the circle of Willis. However, implantation of anti-thrombotic devices in the vascular system to prevent ischemic stroke has been performed.

The urogenital system of the pig is closely analogous to that of the human in anatomy and function. The kidney and bladder have been used in studies requiring stents and monitoring devices for blood pressure measurements. The ureter of a 25 kg pig is similar in size to that of humans.

As a general surgical model, devices have been implanted in many systems and tissues including the oral cavity, the subcutaneous tissues, muscle layers and bone and joint tissues.

Surgical and Perioperative Care Issues

Exceptions would include protocols involving device implantation in heart failure models on implants into the intestinal tract which change peristalsis or intestinal transport time.

In surgical implantation of devices the key issue is sterility of the implant procedure. The principles of surgery those specific to the porcine species have been published in detail. In brief, a key issue to remember is that none of the skin preps sterilize the skin of the animal or the surgeon. A number of skin preps have been accepted to reduce the bacterial load on the skin and the methods used in our laboratories with a complication rate of <1% will be described.

The skin is prepped in a room separate from the OR. In that room the skin is shaved and alternating scrubs of betadyne and alcohol are applied. In the prep room other procedures are performed such as attachment of ECG electrode patches, intubation and vascular access. The pig is transported to the OR and set for monitoring during surgery. The surgeon preps in a separate room using traditional scrub methods approved by the American College of Surgeons. The surgeon or surgical assistant then performs a sterile prep on the pig within the OR. At the end of the alternative scrubbing technique an iodine impregnated sticky drape is applied to the skin. The pig is then totally covered with a cloth or paper drape. Using this method the surgeon never touches
the skin because the incision with the scalpel is made directly through the sticky plastic drape. If a cavity is entered during the procedure a donut shaped flexible wound protector is applied within the incision to provide additional protection (Figure 1).

The procedures described above prevent any contamination from the skin or the properly prepared surgeon. This is important because antibiotics will not prevent an implanted biomaterial from being colonized or infected by bacteria. Studies in both humans and animals have demonstrated that the dose of antibiotic that is important is the dose that is in the blood stream at the time of surgery. Therefore, it is advised that an iv antibiotic, such as a cephalosporin, be administered during the preoperative prep procedure. Administration of antibiotics for a prescribed period postoperatively is not necessary in most cases unless there has been a contamination during surgery. The exceptions would be if there is surgery being performed in areas which cannot be rendered sterile by prep such as the oral cavity or the colon.

Other surgical principles which should be followed include immobilization of the device, avoiding the use of inflammatory suture materials and secure closure of the skin with subcuticular suture patterns. Silk, surgical gut and antimicrobial coated suture materials are highly inflammatory in swine and should be avoided. Ethibond is the preferred non absorbable suture material for implantation. Vicryl and PDS are the preferred suture materials for muscular, subcutaneous, and subcuticular closure.

Discussion

Medical device testing along with other types of preclinical regulatory testing, such as for pharmaceuticals, has increasingly utilized swine as the model. The major anatomic and physiologic comparisons to humans have been detailed. Regulatory agencies have increasingly recognized the pig as a valid alternative to the traditional canine and primate models. For chronic studies the miniature breeds are essential due to the exponential growth of the domestic farm breeds. In order to be successful with chronic implantation the surgical procedure must be performed skillfully with strict adherence to aseptic technique.

Selected References

1. Sinclair Research Center: [http://www.sinclairresearch.com/Literature/Literature.aspx](http://www.sinclairresearch.com/Literature/Literature.aspx)
5. FDA Medical Device Testing [http://www.fda.gov/MedicalDevices/default.htm](http://www.fda.gov/MedicalDevices/default.htm)