CCAC training module on: farm animals used in biomedical research

Companion Notes

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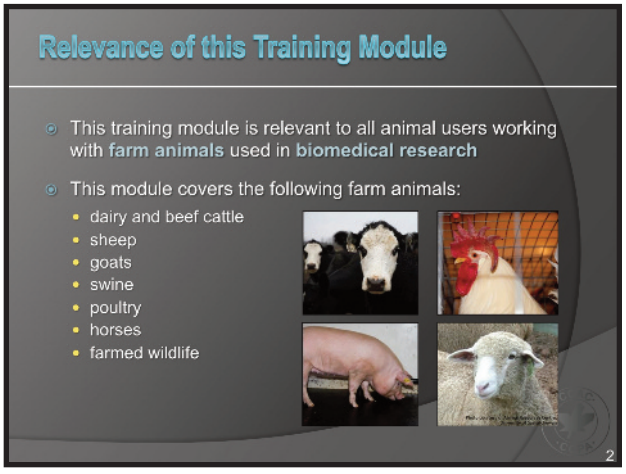
Slide 1 CCAC training module on: farm animals used in biomedical research

When used in biomedical applications, farm animals require special care to balance their needs with the scientific goals of the research. Investigators must be aware of, and be prepared to deal with, the complexities involved in using farm animals as biomedical models.

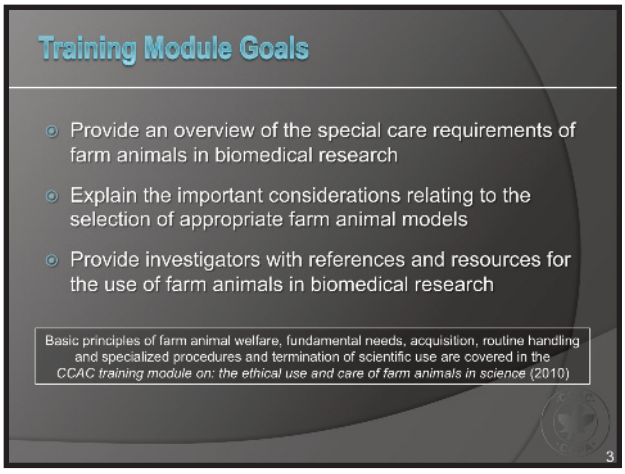
This module is based on section 9. 7 of the *CCAC guidelines on: the care and use of farm animals in research, teaching and testing* (2009) and is meant to be completed in conjunction with the *CCAC training module on: the ethical use and care of farm animals in science* (2010) in which basic principles of farm animal welfare, fundamental needs, acquisition, routine handling and specialized procedures and termination of scientific use are covered. Visit the CCAC website at www.ccac.ca to access and consult this guidelines document and this training module.

Slide 2 Relevance of this Training Module



The general considerations outlined within this training module are applicable to all types of farm animals used in biomedical research, including cattle, swine, poultry, sheep and goats, horses and farmed wildlife.

Slide 3 Training Module Goals



This training module aims to achieve three goals:

1. **To provide an overview of the special care requirements of farm animals in biomedical research.** The challenge of achieving a humane environment while maintaining relevant scientific outcomes is discussed. Issues related to the potential of disease transfer are also covered.

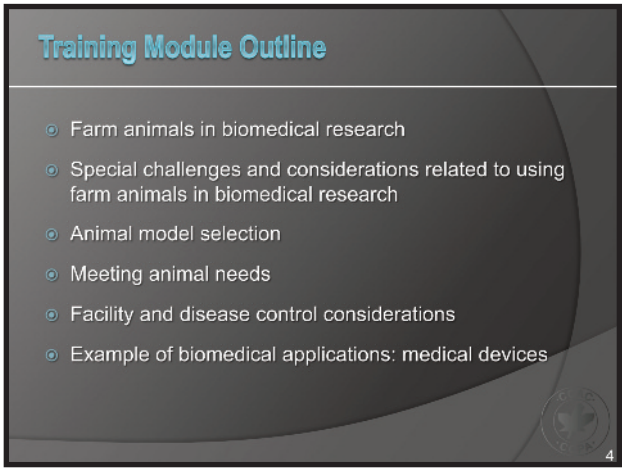
2. **Explain the important considerations relating to the selection of appropriate farm animal models.** Through a discussion regarding special considerations and challenges related to farm animal use in biomedical research, guidance is provided for selecting appropriate farm animal models. The testing of medical devices and its impact on animal welfare is provided as a specific example of a biomedical application utilizing farm animals.

3. **To provide investigators with references and resources for the use of farm animals in biomedical research.** Where appropriate, hyperlinks have been embedded into the module to provide direct access to the detailed texts, guidelines, and training modules.

References cited in this module are intended to provide direction to further information; however, investigators should consult relevant experts and scientific literature for the most recent information on the species and techniques under consideration.

Care has been taken to ensure that any provided web links are up-to-date; however, the dynamic nature of the internet may mean that some links will become out-of-date. Therefore, keyword search suggestions are provided for situations in which links to additional resources may be broken. The keywords can be entered into any standard internet search engine.

Slide 4 Training Module Outline



This training module provides an overview of the special considerations and challenges associated with the use of farm animals in biomedical research, the factors used in selecting an appropriate farm animal model, how to meet animal needs in confinement and discusses the disease control considerations associated with biomedical research. Lastly, examples of farm animals used in biomedical research are provided and one example of biomedical research using farm animals (i.e., development and testing of biomedical devices) is discussed.

Slide 5 Farm Animals in Biomedical Research

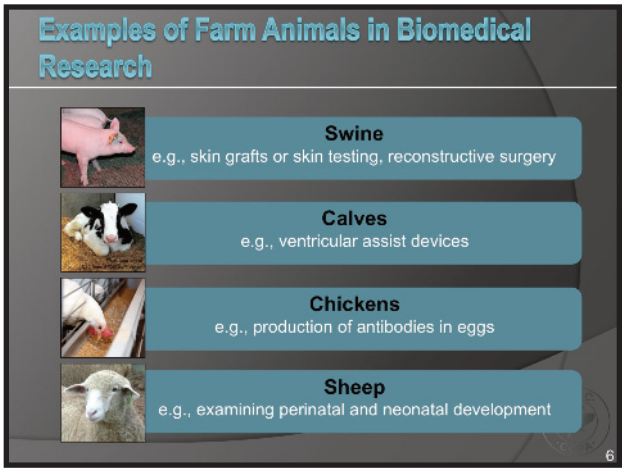
Research aiming to address human health related questions and issues might involve the use of farm animals. Many different applications exist, including but not limited to neurological research, development of pharmaceuticals and medical devices, reconstructive surgery research, and as educational tools in medical schools.

However, the use of all animal models in biomedical research is a sensitive subject and **it is therefore of utmost importance that investigators ensure that they carefully evaluate the necessity of their proposed use of animals. Furthermore, when animal models must be used, investigators must be prepared to balance their research goals with the environmental, physical and behavioural needs of the species being used.** Consideration should be given to the "Three Rs" (i.e., replacement, reduction and refinement); this concept is discussed in more detail on Slide 8 – Considerations for the Three Rs.

Additional References and Resources:

Russell W.M.S. and Burch R.L. (1959) T*he Principles of Humane Experimental Technique*. Potters Bar, Herts UK: Universities Federation for Animal Welfare (UFAW).

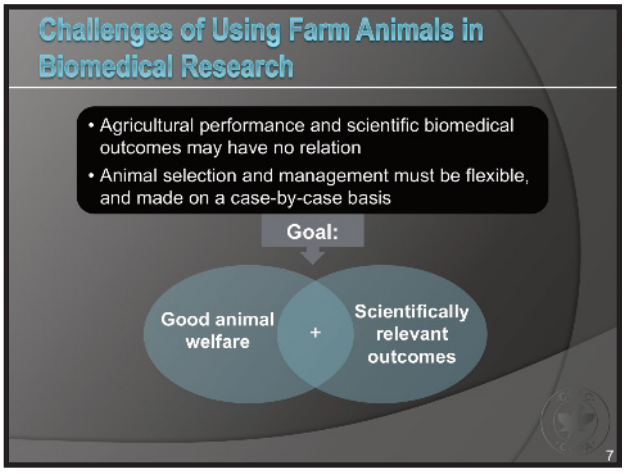
Slide 6 Examples of Farm Animals in Biomedical Research



A number of established farm animal models exist. For instance, swine have similar anatomy and physiology to humans; as a result, swine are used to produce skin grafts for burn victims, to test skin medications, to develop heart valves for heart-disease patients, and for surgical modeling of many of human organs. Similarly, calves have comparable organ and body proportions to humans, which make them ideal models for testing ventricular assist devices (circulatory assist devices or artificial hearts). Furthermore, sheep have also been identified for numerous biomedical applications, including asthma research, vaccine and drug development, perinatal and neonatal research, as well as the refinement of surgical techniques. Conversely, the physical differences between avian species and humans make laying hens ideal producers of antibodies; unlike other mammalian antibodies (e.g., those produced by rabbits), antibodies found in chicken egg yolks do not activate the innate human immune system and can therefore be used in a wide variety of situations, ranging from treating gastrointestinal diseases (e.g., salmonella) to dental applications (e.g., reducing plaque growth).

In addition to the examples given, other farm animals are currently used as biomedical models, including goats (e.g., production of anticoagulants), and sheep and horses (e.g., osteoporosis research).

Slide 7 Challenges of Using Farm Animals in Biomedical Research

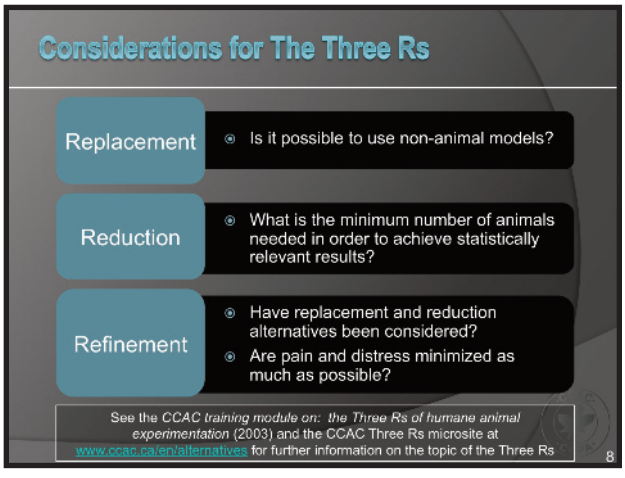


The use of farm animals in biomedical research involves special considerations in addition to those covered in the *CCAC guidelines on: the care and use of farm animals in research, teaching and testing* (2009) and the *CCAC training module on: the ethical use and care of farm animals in science* (2010). Biomedical research involving farm animals should rely on all relevant codes of practice, guidelines and other pertinent, scientific evidence. Considering the advantages and disadvantages of each farm animal species for the specific research questions to be addressed will help investigators ensure they are using the best possible farm animal model.

Biomedical research may place a host of restrictions on farm animals that would not be expected in more traditional production-related research. **A major challenge in using farm animals as models is ensuring good animal welfare while also producing scientifically relevant research outcomes.** Not all farm animals make compatible biomedical models because agricultural applications often focus on production efficiency (e.g., high growth rate). Certain farm animal species may become too big, too quickly, thus negating the presumed anatomic similarities between these animals and humans. Furthermore, large body size may translate to increased research costs (e.g., pharmaceutical trials requiring larger volumes of drugs). As such, investigators must consider the species chosen carefully, and on a case-by-case basis.

Investigators must consider that good animal welfare is based on more than just meeting basic environmental needs. A balance must be achieved between good biological functioning, provision of natural living conditions and positive affective states, and prevention of negative affective states. These factors are discussed in more detail in the *CCAC training module on: the ethical use and care of farm animals in science* (2010). Visit the CCAC website at www.ccac.ca to access and consult this guidelines document and this training module.

Slide 8 Considerations for the Three Rs



The use of farm animals in biomedical research must lead to improved knowledge benefitting human health. **Consideration should always be given towards ensuring good animal welfare standards.** Where the welfare of animals is compromised (e.g., pain is necessary as part of the research), the negative states experienced by the animals must be minimized as much as possible.

Investigators should be familiar with the *CCAC policy statement on: ethics of animal investigation* (1989). This policy mandates an adherence to Russell-Burch's humane experimental technique (replacement, reduction and refinement). It also addresses the need for educated justification for project approval in circumstances where research has negative welfare implications.

Originally introduced by Russell and Burch in 1959 for the use of laboratory animals in biomedical research, the "Three Rs" concept has since been applied into regulations and guidelines worldwide. In 1989, the CCAC included the concepts of replacement, reduction and refinement in their *CCAC policy statement on: ethics of animal investigation* (1989), and have since applied them within all subsequent guidelines. The use of farm animals in science warrants some special consideration when applying the Three Rs.

Replacement

- Investigators should conduct thorough reviews of the literature to assess if alternative models to animal use may be relevant to the intended research goals. **Animals should only be used in research when alternative methodology will not yield the anticipated results.**

Reduction

- Generally speaking, it should be every investigator's goal to **use as few animals as possible while maintaining statistically valid results.** This is particularly applicable in cases where animals are exposed to pain and/or distress.

Refinement

- A primary goal of developing an animal care protocol for each research project is to ensure that the best practices are used in order to minimize negative welfare implications. **When possible, exposure of animals to negative states such as pain, discomfort and distress should be minimized.** Investigators must take appropriate measures to mitigate the negative states when they cannot be avoided. Efforts should also be made towards allowing for the expression of natural behaviours.

For more detailed information on the Three Rs:

- CCAC Three Rs microsite: www.ccac.ca/en/alternatives
- *CCAC training module on: the Three Rs of humane animal experimentation* (2003). Visit the CCAC website at www.ccac.ca to access and consult this training module

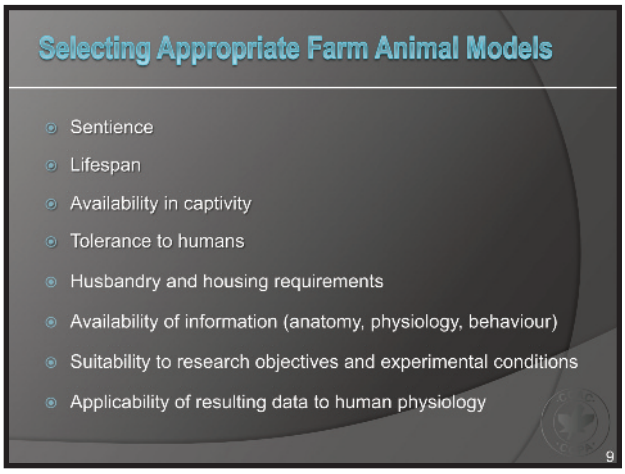
Additional References and Resources:

CCAC policy statement on: ethics of animal investigation (1989). Visit the CCAC website at www.ccac.ca to access and consult this policy statement.

Colditz I.G. (2006) The application of Russell and Burch's Three Rs in commercial livestock experimentation. *Animal Welfare* 15:1–5.

Russell W.M.S. and Burch R.L. (1959) *The Principles of Humane Experimental Technique*. Potters Bar, Herts UK: Universities Federation for Animal Welfare (UFAW).

Slide 9 Selecting Appropriate Farm Animal Models



A number of variables should be considered when deciding on an appropriate animal model; many of these points were outlined by Martin & Bateson (1986), as follows:

- sentience (a level of consciousness that allows for the ability to feel and perceive);
- lifespan;
- availability in captivity;
- tolerance to humans;
- husbandry and housing requirements;
- availability of information (anatomy, physiology, behaviour);
- suitability to study objectives and experimental condition; and
- applicability of resulting data to human physiology.

In regards to farm animals, most of these points are measurable and hence can be addressed when choosing the appropriate species. Farm animals are readily available in captivity and as a result are easily accustomed to tolerate human handling.

As a result of their domestication, the physiological, behavioural and husbandry requirements of farm animals are well documented. However, due to the size of many farm animals, housing requirements can complicate their use in biomedical research (e.g., housing mature cattle in an urban, medical environment).

With the above considerations in mind, often the deciding factor in using farm animals in biomedical research is often how well the species is suited to the research objectives and experimental conditions. Adherence to good animal welfare standards should be included in the decision making process when evaluating animal model suitability to experimental conditions.

Specific models have already been established for some biomedical applications (e.g., swine, calves, sheep). Nonetheless, there are many other unique biomedical applications that do not have well-established farm animal models. For these applications, physiological and life stage considerations are important in determining species suitability. The *Sourcebook of Models for Biomedical Research* (Conn, 2008) provides an in-depth discussion on established animal models.

Additional References and Resources:

Conn P.M. (ed.) (2008) *Sourcebook of Models for Biomedical Research*. Totowa NJ: Humana Press.

Martin P. and Bateson P. (1986) *Measuring Behaviour: An Introductory Guide*. New York NY: Cambridge University Press.

Slide 10 Appropriate Farm Animal Models: Veterinarian & Handler Considerations

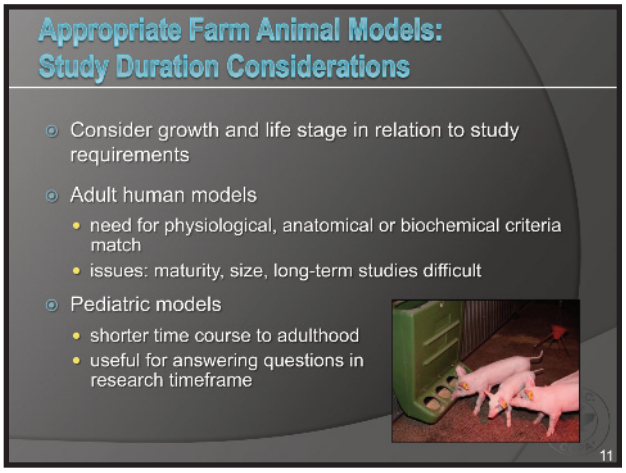
Farm animal models require different care considerations than rodent models. Investigators should ensure that all individuals involved with the farm animals being used in biomedical research (e.g., animal care personnel, students, etc.) receive training in the appropriate care and handling of the specific species. This training should include the special care requirements of the species in a biomedical setting.

It is essential that a veterinarian be involved in all steps of biomedical research involving farm animals, including:

- decision-making process required for choosing a suitable farm animal model
- research design (e.g., consideration for specialized procedures required and how these may impact animal welfare)
- acquisition of farm animals
- care of the farm animals used (i.e., prior to, during and following the completion of the research)

Ensuring veterinary involvement throughout the research will help to minimize potential negative animal welfare consequences.

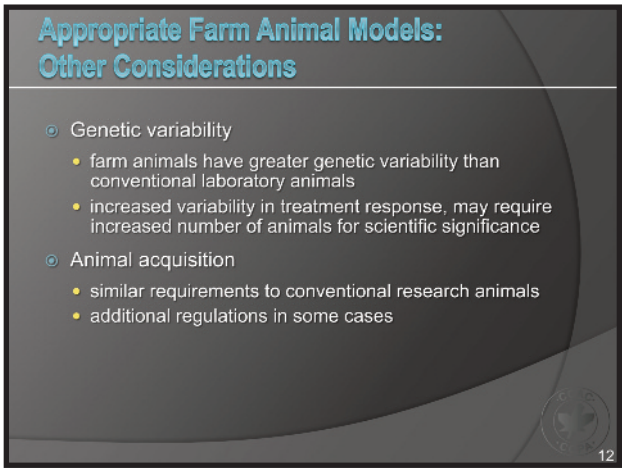
Slide 11 Appropriate Farm Animal Models: Study Duration Considerations



The animal model chosen greatly depends on the intended study duration and anticipated research outcomes. The growth and life cycle of the farm animals being used is very important and if an incorrect model is chosen, the welfare of these animals could be compromised. In the case of models for adult humans, some physiological, anatomical or biochemical matches are necessary in order for an animal model to be valid. However, the growth rate, size and temperament of many farm animals as they mature may make long-term studies problematic. In some cases, smaller adult farm animals (e.g., goats) can be suitable alternatives, providing the required physiological, anatomical or biochemical requirements are met.

Young farm animals are often very suitable models in pediatric studies related to growth. Their relatively short growth period to adulthood allows for research questions to be answered in suitable timeframes.

Slide 12 Appropriate Farm Animal Models: Other Considerations



Another factor that impacts experimental design is genetic variability, which is considerably high in farm animal species compared to rodent species bred for laboratory research. **Greater genetic variability between individual animals will result in greater variability in the response to treatments.** Hence, a larger sample size is often needed to detect treatment differences. As a general rule, the life history of farm animals will need to be weighed more heavily in model selection and study design than when more homogeneous groups of rodents are used as the study species.

In addition to meeting the acquisition, transportation and quarantine needs of conventional research animals, sourcing of farm animals for biomedical research may require further planning. Establishing and maintaining relationships with reputable farm animal suppliers is important towards ensuring that animals are disease free, arrive with accurate medical and health histories and are best suited for the research for which they are sourced. Furthermore, depending on the species of farm animal being used, some transportation restrictions may exist, either due to federal or regional importation/movement restrictions.

Additional References and Resources:

CFIA's Import Procedures for Live Animals: http://www.inspection.gc.ca/english/anima/heasan/pol/pole.shtml#anima (Note: if link is broken, search: CFIA import procedure for animals)

Slide 13 Meeting Animal Needs in Confinement

When developing the experimental design, the investigator should be aware of the species-specific behavioural and social needs of the chosen animal model and should include means to address these needs. Some animals adjust more easily than others to confinement and repeated human handling. Animals must be carefully introduced to these potential stressors in an appropriate fashion and timeframe.

The experimental design should take into account species-specific infrastructure requirements and dietary needs; such requirements may include the provision of feed that is appropriate to typical feeding behaviour of the animals (e.g., foraging), or housing social animals within sight of one another to partially alleviate the impact of isolation. Furthermore, animals housed in strict confinement must be allowed opportunity for regular exercise at a **minimum** of once every seven days. Often biomedical research facilities do not allow for typical exercise means; hence, alternate forms of exercise (e.g., treadmill) or enrichment should be sought out to provide the minimum level of exercise compatible with maintaining good animal welfare.

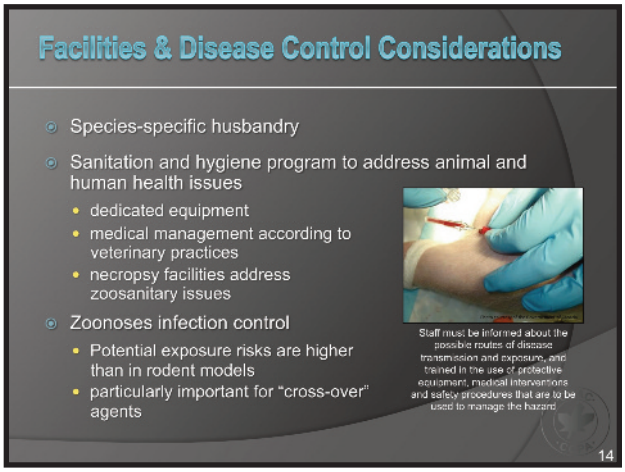
In some cases, intended research outcomes require that the experimental design include behaviourally restrictive factors (e.g., long-term isolation of social herd animals). The investigator should be aware of the potential impacts of such requirements on the animal and the research results. **If the animals' ability to perform characteristic behaviours is severely restricted, poor welfare will result, which will in turn have an effect on the results; poor welfare conditions impacting research outcomes will need to be considered during the interpretation of data.**

For more specific information regarding improving and enriching the environment of confined farm animals:

- CCAC Three Rs microsite: www.ccac.ca/en/alternatives
- *CCAC training module on: environmental enrichment* (2003)
- *CCAC training module on: the ethical use and care of farm animals in science* (2010)

Visit the CCAC website at www.ccac.ca to access and consult these training modules.

Slide 14 Facilities & Disease Control Considerations



Biomedical facilities must be safe and comfortable for the animals, and be fitted with equipment specifically suited to the intended species and purpose. Easily sanitized handling and transportation equipment, which is suited to the species, should be available.

Appropriate husbandry, sanitation and hygiene programs are required to address animal health concerns and infection control. **Animal to human disease (zoonoses) control programs must be implemented.** Due to the complexity of handling, breeding and caring for large numbers of farm animals in completely biosecure conditions, it is often more difficult to ensure the same level of sterility in farm animals as is achieved with rodents. For instance, *Coxiella burnetii* (a bacteria causing a highly infectious zoonotic disease called "Q fever") can remain dormant in the environment even after disinfection measures have been implemented; hence, the bacteria can readily spread to new groups of animals. Therefore, even carefully sourced farm animal models may still be potential exposure sources for a variety of zoonotic pathogens.

Special consideration should be given when dealing with species known to carry crossover agents (infectious agents capable of crossing the species barrier; e.g., bird and swine influenzas). The potential impact of disease transfer is increased when animal models have been altered (e.g., animals genetically modified to carry human genes). When available and recommended by the physician making the assessment, all personnel should be vaccinated against diseases with increased exposure. Additionally, **animal care personnel should be trained on disease transfer mitigation procedures and wear protective gear as appropriate.**

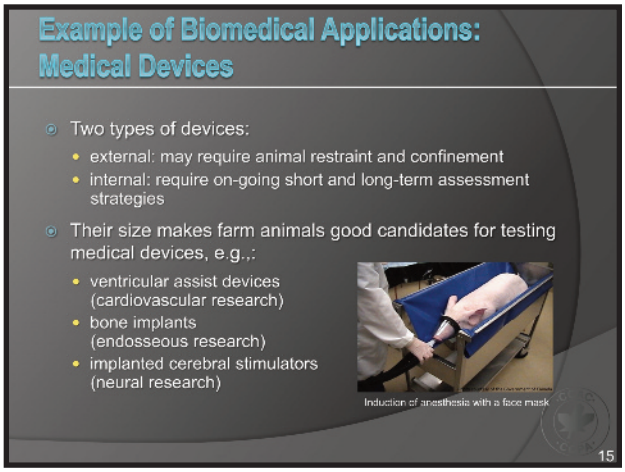
Detailed information is available from the Public Health Agency of Canada:

- Material Safety Data Sheets (MSDS) for infectious substances, including many commonly found zoonotic agents: http://www.phac-aspc.gc.ca/msds-ftss/ (Note: if link broken, search: public health MSDS infectious).

A variable unique to biomedical applications is that investigators conducting research on animals may also come in contact with human patients, particularly those which are ill; the potential for disease transfer, especially to immunocompromised human patients, must be understood and carefully outlined in standard operating procedures (SOPs). Furthermore, general occupational health and safety risks associated with the experiment must be clearly outlined in the experimental protocol. Of specific note are necropsy facilities, which should be equipped to safely handle carcasses and limit exposure of personnel to biological materials.

Slide 15 Example of Biomedical Applications: Medical Devices

Farm animals are used in a variety of biomedical applications; physiological similarities to humans, as well as their size, make some farm animal species good models for testing biomedical devices. As such, the impacts of developing and testing such devices are covered in more detail as an example of how biomedical applications may affect farm animal welfare.



Two types of medical devices exist:

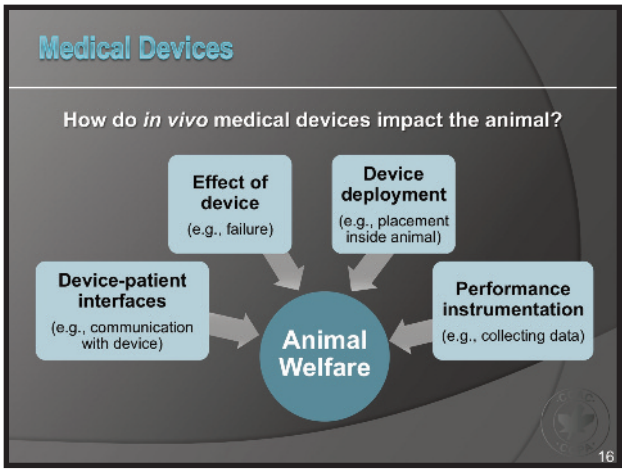
External devices, such as intravenous pumps, may require animals to be restrained and closely confined. The welfare impacts of such restrictive handling and housing requirements should be considered.

Internal devices, such as coronary intravascular stents (inserted to keep arteries open), may have short- and long-term welfare impacts. The experimental design should include SOPs for short and long-term assessment of the invasiveness of internal devices on the animals.

Medical device testing on farm animals requires careful attention to potential welfare impacts. Depending on the type of device, animals may require special care and monitoring. In many cases device failure is possible, and therefore detailed endpoints must be outlined prior to any medical device testing and/or utilization occurs.

Slide 16 Medical Devices

Research involving *in vivo* medical devices must take into account the effect of the device, device deployment systems, device-patient interfaces and performance instrumentation in relation to animal welfare and successful use of the device.



Device Deployment

The placement of many medical devices requires an invasive procedure; all invasive procedures impact animal welfare to some extent.

- *Example: Vascular Stent*. In order to place this device within an animal, the animal must be anaesthetized, a distal artery exposed, and via a

balloon catheter, the stent is inserted into the artery. This is a major surgery requiring significant pre- and post-operative care.

Device-Patient (Animal) Interfaces and Performance Evaluation Equipment

In order to control and gather data from a device, a means of communication must be established. Two methods of communication exist, and both may have an impact on animal welfare.

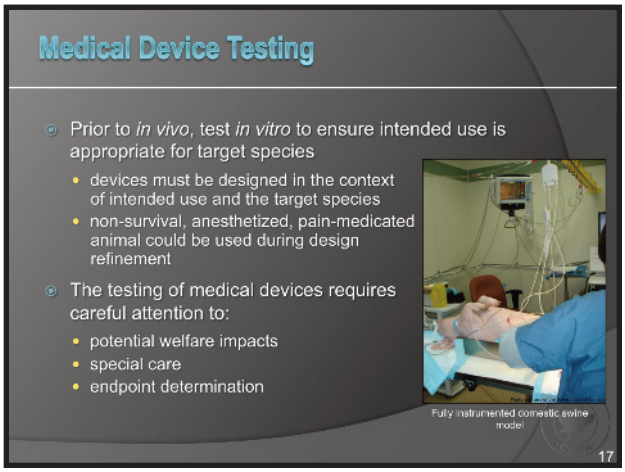
- *Wired Connections*: Physical connections are used for data collection from devices. Wiring, and other components, must therefore be secured to the animals. Typically, this is coupled with the animal's movement being restricted as well. Affixing device communication systems to the animal and restricting its movement may result in negative physical, psychological and behavioural consequences.

- *Wireless Connections*: Devices communicate with external receivers via infrared, radio frequency, over a wireless local area network, and in some cases cellular frequencies. With the exception of the latter, the limitation of wireless communication with devices is that animals need to be housed within a set proximity to the receiver, which may involve restricting the animal's movement. If the device itself does not have its own transponder, one would need to be inserted or affixed to the animal as well.

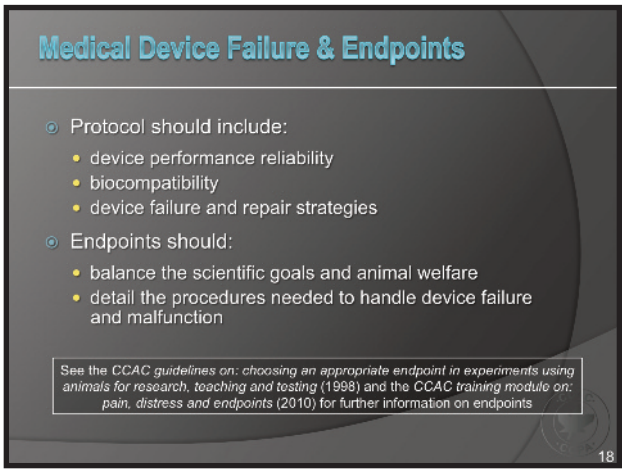
The type of device, the way it is deployed, controlled and monitored, and how device failure is handled, will have impacts on the animal, which will affect both the ability to maintain the physiological state necessary to test the device, and the welfare of the animal.

Slide 17 Medical Device Testing

Before devices are tested in an animal model, they should be tested *in vitro*. The type of testing will depend on the particular device and the complexity of its components. For example, testing will need to take into account the mechanical operation, circuitry, power source, intended output, biomaterials, and proposed clinical and experimental device-patient interfaces. Devices must be designed in the context of intended use and the target species. During the final design refinement stages, it may be appropriate to use a non-survival, anesthetized, pain-medicated animal model; doing so may help identify preventable device complications from occurring in live-animal models.



Slide 18 Medical Device Failure & Endpoints



The performance reliability of a medical device and its biocompatibility with the animal model are important. If device failure or bio-incompatibility occurs, there may be serious implications for both animals and animal care personnel. For instance, a failing cardiac device may cause an animal to collapse onto its handler. Therefore, it is extremely important for personnel to be aware of the potential dangers device failures may have on their personal safety. For the animals, endpoints must be in place to deal with device failures. Repair or removal and replacement of the device or a failed component may be appropriate in some cases; however, if replacement or repair requires a major second surgery the animal should be euthanized. The potential impacts of device failure on animal welfare must be considered in the animal use protocol, and endpoints must be established.

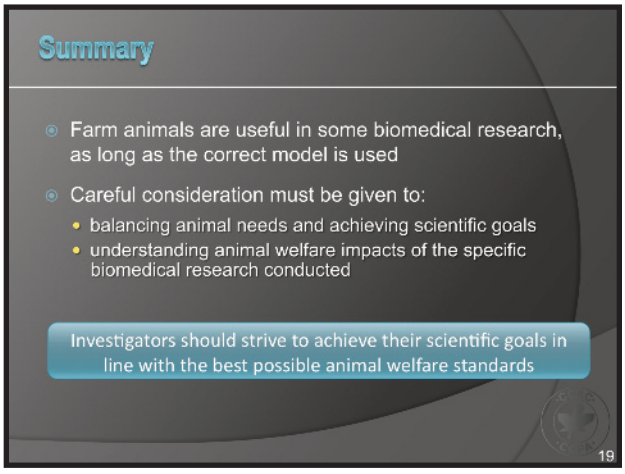
Endpoints should focus on addressing the balance between the scientific goals and ensuring the best possible animal welfare standards; detailed procedures should be outlined for device failure and malfunction. These endpoints must be reviewed by the ACC as part of the protocol.

For more detailed information on endpoints:

- *CCAC guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing* (1998)
- *CCAC training module on: pain, distress and endpoints* (2010)

Visit the CCAC website at www.ccac.ca to access and consult this guidelines document and training module.

Slide 19 Summary



The purpose of this training module is to provide an overview of the use of farm animals in biomedical research. Focus is given towards the importance of choosing the appropriate model for the intended research. Alternatives to animal models should be considered whenever possible.

When farm animal models are used in biomedical research a key objective should be to balance good animal welfare with research goals. It is important for investigators to be aware of how their specific protocol impacts animal welfare, and how they can address animal welfare issues. **Investigators should strive to achieve their scientific goals in line with the best possible animal welfare standards.**