Incorporating PET into Your Preclinical MRI Facility

Joann Zhang, Ph.D.

Marty Pagel, Ph.D., Professor and Deputy Chair, Department of Cancer Systems Imaging, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX

ABSTRACT

Simultaneous PET/MR imaging with instruments such as Cubresa's NuPET™ in-bore MR-compatible PET scanner can provide preclinical researchers with new insights into the complex mechanisms at work within all living things. Positron Emission Tomography (PET) is a clinically translatable technique used to quantitatively observe biological processes in both humans and animal models.[1] Combining PET and Magnetic Resonance Imaging (MRI)[2] provides both molecular and functional imaging for neurology, oncology, cardiology, and other research topics. Bringing PET as a modality into your laboratory means meeting some regulatory requirements because of the radionucleotide tracers imaged by PET scanners.[3] These requirements, as well as workflow and safety protocols, can and should be addressed before delivery of your NuPET™ scanner, so that your facility can operate in the most efficient way possible.

The quality of your results depends on the laboratory infrastructure surrounding the use of your instruments, including the Cubresa NuPET system. Small-animal imaging researchers may be familiar with the laboratory requirements for either PET or MRI, but they may not be familiar with the requirements for performing both modalities. This White Paper shows that a well-designed laboratory environment can be developed for simultaneous PET/MRI without requiring an unreasonably large investment in time or money.

ABOUT THE AUTHORS

Joann Zhang, Ph.D. has extensive PET imaging experience. She was previously the Chief Scientist for Preclinical Imaging at Gamma Medica (later Trifoil Imaging), and Manager of Application Research, Preclinical Imaging for GE Healthcare. Joann earned her Ph.D. in Biochemistry from the University of Arizona. She subsequently went on to receive her Post Doctorate in Molecular Cell Biology from the University of California, Berkeley.

Marty Pagel, Ph.D. has focused on magnetic resonance research for 30 years, including MRI during the last 15 years in both industry and academia. He is currently a Professor and Deputy Chair of the Department of Cancer Systems Imaging, Division of Diagnostic Imaging at The University of Texas MD Anderson Cancer Center in Houston, Texas. He has successfully added PET to his lab's capabilities and is applying a multidisciplinary approach to molecular imaging to develop novel contrast agents for simultaneous PET/MRI.

Figure 1. The Radiation Safety Officer (RSO) recommends and approves radiation-involved actions, identifies radation safety issues, and initiates any corrective actions that might be needed.

YOUR RADIATION SAFETY OFFICER (RSO)

The easiest path to bringing PET into your laboratory as a medical research imaging modality is by talking to your RSO.[4] Many organizations such as hospitals, universities, and service organizations have one or more staff RSOs to recommend or approve radiation-involved actions, identify radiation safety issues, and initiate corrective actions.

You can leverage your RSO's experience with nuclear medicine for clinical use or for preclinical research. Your RSO can help you plan for:

- Regulatory requirements and licensing
- Laboratory infrastructure
- Animal usage and radioisotope handling procedures
- QA/QC protocols
- Nuclear medicine accessories and supplies

If you don't have an RSO, Cubresa can help you find a nuclear services company or a certified local consultant for your state or region. They can help you create the procedures and protocols necessary to accommodate the short-half-life, low-dose radioactive material that PET utilizes and even file paperwork on your behalf.

Once your facility is licensed, periodic training and monitoring, coupled with good recordkeeping will ensure your laboratory's smooth operation, maintaining the As Low As Reasonably Achievable (ALARA) standard[5] for safely, working with nuclear material and enjoying the benefits of PET's sensitivity and quantitative imaging capabilities.

WHAT YOU SHOULD KNOW ABOUT A PET LABORATORY

Each institution, state/province, or country has different regulations for tracking and handling radioactive material used for PET. In the United States, PET laboratories in academia and industry are regulated by the US Nuclear Regulatory Commission.[6] In Canada, this oversight is managed by the Canadian Nuclear Safety Commission. European nations have similar national nuclear safety commissions, with some coordination within the European Union through the European Nuclear Safety Regulators Group. Countries in Asia follow similar practices as in Europe, with some coordination through the Asian Nuclear Safety Network. The large number of regulatory governances may seem different, and each may seem murky to navigate. However, most regulatory issues are surprisingly similar among these groups.

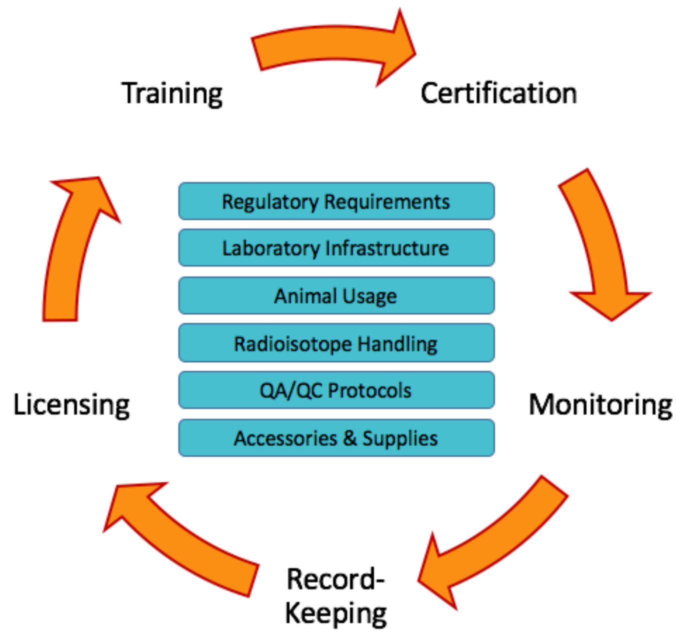


Figure 2. There are both one-time and recurring actions with which your RSO can help. Many of these are similar to actions that you may already be performing as part of using other imaging modalities.

- Most academic institutions and larger companies have a 'broad scope' license that covers a range of radioisotopes and a variety of applications for medical research. Individual laboratories and core facilities with a PET instrument can submit an application to use radionuclides under the institution's broad scope license.
- Researchers working with radionuclide agents will be required to complete a radioactivity training program that can last for 1-4 hours, depending on institutional requirements.
- Access to the PET/MRI laboratory should be limited to researchers who are involved in the experiment, in order to limit radiation exposure to non-essential personnel.
- Ordering and receiving radioisotopes requires authorization and documentation of receipt, use, and disposal.

- Each researcher's exposure to radiation must be monitored. A ring dosimeter should be worn on the dominant, more active hand, and a badge dosimeter should be worn on the front center of the lab coat. The dosimeters can often be stored in the PET/MRI laboratory along with other personal protective equipment.
- A radiation survey must be performed and documented at the start and end of the experimentation session.
- A foundation of radiation safety is the rule of ALARA. The workflow and physical design of the laboratory should, within reason, minimize the exposure of radioactivity to each researcher, preventing researchers from being exposed to unnecessary amounts of radiation.

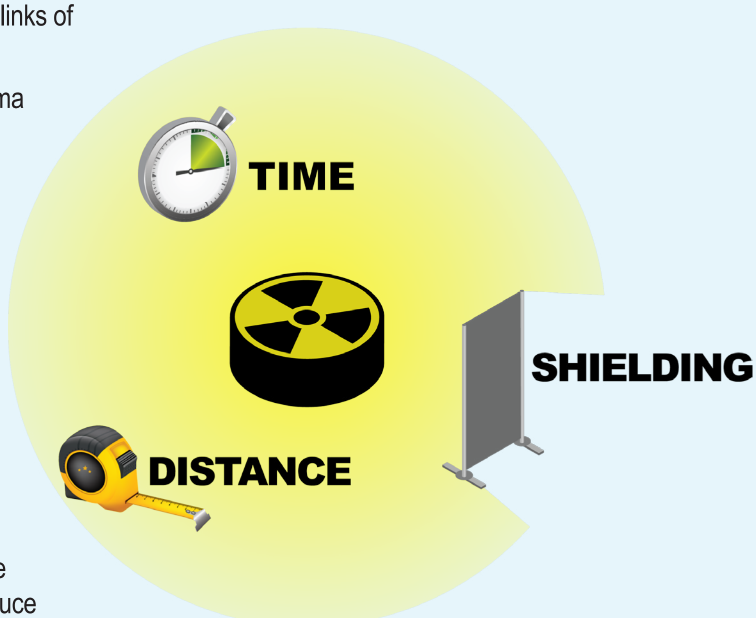
The placement and design of a dosing station should consider the issues of Time, Distance, and Shielding.[7] The dosing station should be placed in close proximity to the entrance to the MRI magnet room to reduce the time for transporting the radioactivity in a syringe or injected animal to the magnet.

Ideally, the dosing station should be placed away from the MRI workstation area, which is also often located near the entrance to the magnet room, so that the PET/MRI researchers are located a substantial distance from the radioactivity in the dosing station area.

The dosing station should consist of sturdy benches that can accommodate the weight of three areas with lead shielding: a "hot" cage for live animals that are slated to be injected with a radioactive dose, a post-injection cage for animals that have recently been injected with radioactive isotopes, and a waste container for radioactive material to be properly discarded.

TIME - DISTANCE - SHIELDING: FUNDAMENTAL TO ACHIEVING ALARA

Time, Distance and Shielding are the fundamentals of all radioisotope handling protocols under ALARA because they are the three weakest links of gamma radiation:



- Time: the most common effect of exposure to gamma exposure is damage from accumulated doses. So plan activities in order to minimize time around radioactivity. This can minimize the danger linearly. For example, laying out your aliquoting tubes and adding the cold components before you enter the "hot" room, performing a "dry run" of the dosing prior to experiment, and consolidating transportation trips (in and out) all help reduce total radiation exposure.
- Distance: gamma radiation exposure levels decrease drastically as distance increases, even in the air. Moving from 1.5 cm to 18 cm, drops the exposure 200 fold! So maximizing your distance as much as possible is another effective way to reduce exposure. Designing the room so that the dosing station–or "hot" area–is at a far corner which can be avoided as much as possible, also contributes to a reduction in radiation exposure.
- Shielding: being in close proximity to the radioisotope and spending time with it is unavoidable, so there is always shielding. Two inches of lead glass can stop 90% of gamma radiation. Laboratories can be equipped with various types of shielding: a portable floor-standing shield with casters, an L-shaped lead glass shield for preparing aliquots, and a lead syringe shield for injection will all help protect the technician and the imaging scientist.

In addition, general rules of Good Laboratory Practice (GLP) should be followed to ensure maximum safety and protection. For example, a "one-direction" protocol from "cold-to-hot" or "low-concentration to high-concentration" should always be insisted upon. Disposable needles, once opened, should not be recapped whether or not radioactive and should always be disposed of behind a shield. Double gloves should be worn when handling hazardous material, and the outer layer should always be switched once out of the "hot" zone, even if no radiation is touched.

The dosing station should have the following components:

- A dose aliquoting area with lead shielding and a viewing window, where the radioactive material is drawn into a syringe for injection.
- A dose calibrator that measures the level of radioactivity just prior to injection into the animal. A new dose calibrator can cost $15,000. However, dose calibrators are very durable, and used dose calibrators can often be found for as little as $2,000.
- A shielded area for temporarily storing an animal after injection of the radioisotope and before preparation for imaging. Some PET agents such as ^{18}F-FDG require time for circulation of the agent in a conscious animal before imaging in order to improve the uptake of the agent in metabolically active tissues.
- A shielded area for storing one or more cages of “hot” animals for a minimum of 10 half-lives of the radioactive material. The ^{18}F radioisotope has a half-life of 110 minutes, requiring 20 hours to reach 5 half-lives. Longer-term storage of “hot” animals may be needed to accommodate other radioisotopes.
- A shielded area for storing radioactive waste. Used syringes and other waste should be promptly placed in a waste container as soon as possible after injection. The waste area should be located in the most remote section of the dosing station.

It is important for animal cages to be kept at a comfortable temperature, e.g. 37° C, in order to avoid animals becoming hypothermic, and also to help with FDG circulation, creating more consistent results.[8]

Radionuclide agents may need to be injected into an animal while the animal is in the magnet, which is typically performed through a catheter installed in the tail vein. To accommodate this procedure, a clear path from the dosing station to the MRI magnet is important for minimizing the time and distance for handling the radioactive material, which improves the simplicity and repeatability of the injection process. A clear path also applies to the “hot” waste disposal after injection.

In these cases, often when the imaging researcher is performing dynamic PET imaging, the radioactive dose could be delivered from the pharmacy in a shielded syringe, an example of which is shown in Figure 5, ready to administer to an already intubated animal in the imaging room itself.

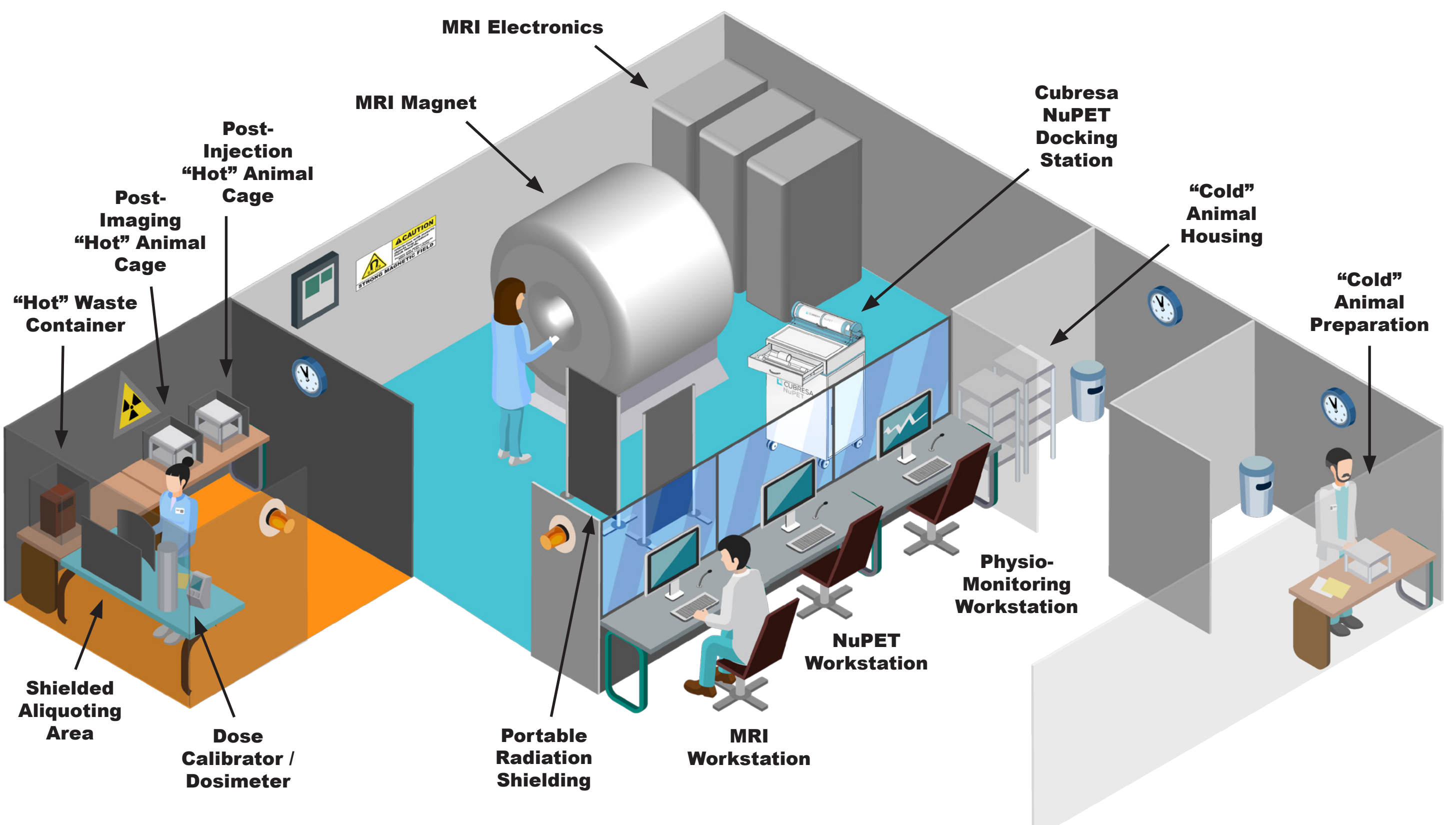


Figure 3. Stylized schematic of a PET/MRI laboratory based largely on the University of Arizona facility. The floor of the PET dosing station area is highlighted in orange and the floor of the MRI room in blue. Doors have been omitted from this illustration for sake of clarity. The layout is designed to maximize efficiency in bringing radioactive material into and out of the laboratory, as well as to minimize the distance and time required to transport radioisotopes or animals dosed with radioisotopes to and from each area. Note that shielding is shown in dark gray: around the dosing station room, enclosing the “hot” animal cages and “hot” waste container, as well as around the aliquoting area. To allow dosing of the animal in the imaging area (for dynamic imaging, for example), portable, repositionable radiation shields are shown near the MRI magnet.

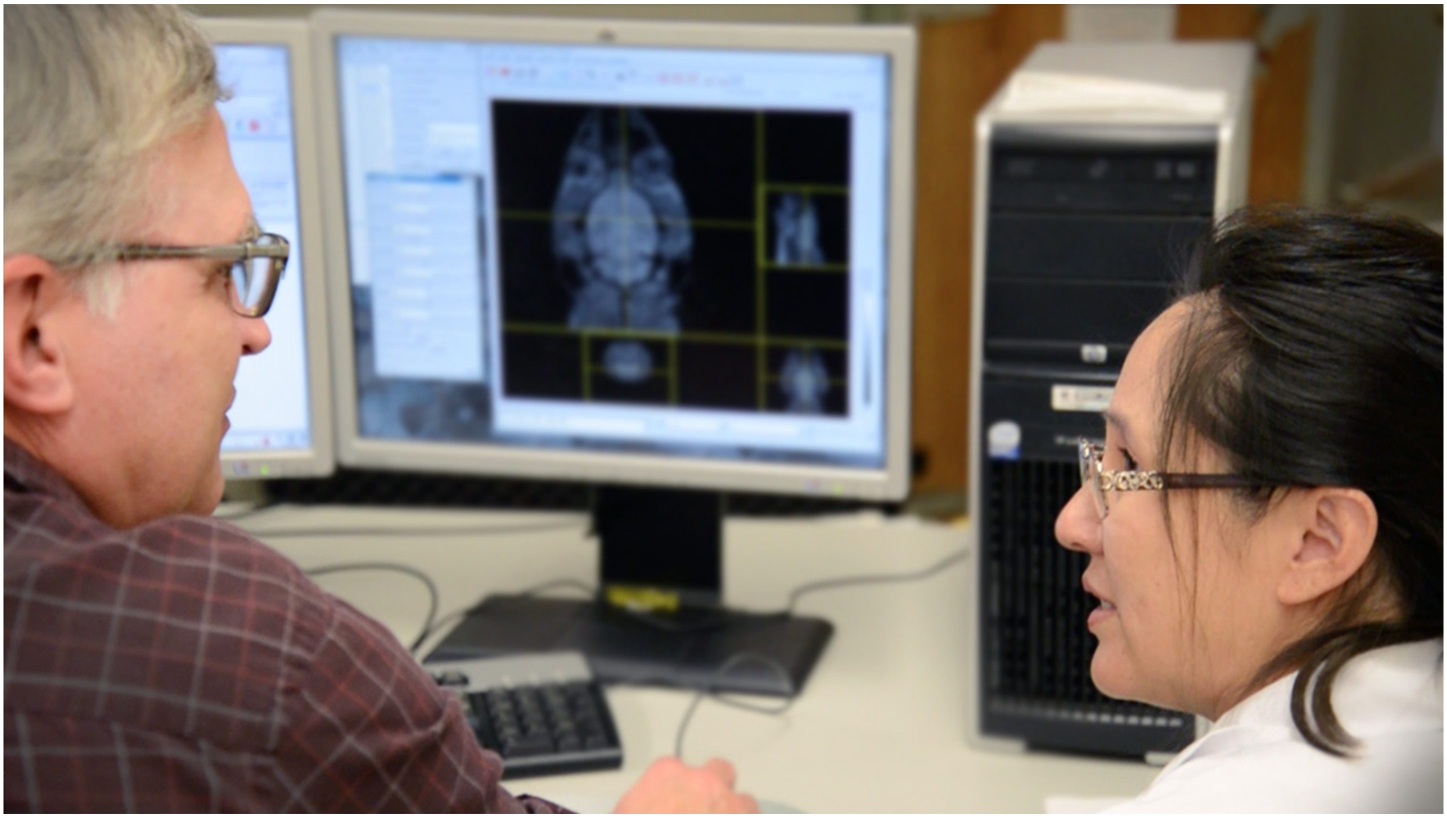


Figure 4. As with MRI laboratories, facilities using PET must adhere to regulations regarding safety and best practices for optimum efficiency in the facility. Instruments like Cubresa's NuPET imaging system can typically be operated from the same workstation area that already exists for the MRI technicians.

WHAT PET EXPERTS SHOULD KNOW ABOUT AN MRI LABORATORY

Regulations regarding MRI focus largely on safety practices in a strong magnetic field. Each institution typically develops a magnet-safety protocol to suit specific needs. In addition, some safety training is required to ensure that the cabling of MRI coils and components is performed with care to avoid radiofrequency (RF) burns, and to avoid damage to the coils and RF components.

The strong magnetic field of a MRI magnet poses an invisible danger to researchers, maintenance technicians, and others who may enter the magnetic field. Engineering design controls are critical for placing a physical barrier between the magnetic field and unsuspecting individuals. For example, the MRI magnet is often placed in an enclosed room, with a minimal path from the door to the magnet bore. Permanent signs are placed on the magnet room door and the main door to the laboratory facility to warn individuals and emergency first responders that the magnet is "always on". Some MRI manufacturers provide a "cap" that seals the ends of the magnet bore. Alternatively, a non-metallic, plastic board can often be fashioned into a "bore blocker" that hangs in front of the bore entrance when the MRI scanner is not being used in order to prevent potentially hazardous items from being pulled into the bore. Because the strength of the magnetic field rapidly increases closer to the magnet center, an individual may not realize the potential danger until he or she has moved too close to the magnet. To offset this problem, caution tape is often adhered to the floor at the point where the magnetic field strength is 5 gauss at waist height in order to provide a visual cue.

Figure 5. Shielded syringes can be utilized in the MR imaging room so that animals can be dosed as part of a dynamic imaging session.

Reduced foot traffic into and out of the magnetic field minimizes potential for an inadequately trained researcher to enter the magnetic field, and minimizes the potential for an experienced researcher to forget his or her location in the laboratory.

Plastic shelving and drawers can be placed within reach of the magnet bore, so that investigators who are preparing small animals for insertion into the magnet have (non-metallic) supplies that are readily accessible, which also minimizes traffic into the magnetic field.

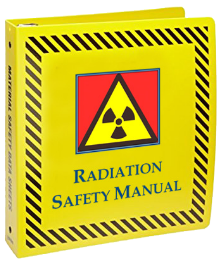
OBTAINING A LICENSE

It is highly likely that your institution or an umbrella organization already holds a license to handle radioactive material for medical use. Many labs can submit an application to use isotopes already covered under a broad-scope license, so ask your RSO. They can describe the necessary documents need and in most cases help you prepare them.

An RSO can also visit your facility and recommend any changes needed, such as shielding for areas that will accommodate radioactive material, temperature and humidity control, and optimized layouts for rooms where short-lived isotopes will be brought in, utilized, and stored for proper disposal. If you are building a new facility, an RSO can provide invaluable assistance for now and for any usage envisioned for the future.

TRAINING YOUR STAFF

Training and certification of your staff will be readily available if your institution or an umbrella organization already holds a license to handle radioactive material for medical use. Your RSO can recommend training courses and study material to obtain and maintain certification.



MAINTAINING A MONITORING PROGRAM

Your existing laboratory procedures require continuous monitoring of performance and adherence to minimum standards. Maintaining a monitoring program to stay certified is no different. Technicians and researchers safely work with radioisotopes at hospitals, universities, and research organizations because they have been properly trained and follow validated and well-documented protocols.

KEEPING A CLEAN RECORD

Proper records of obtaining, storing, utilizing, and disposing of your radiotracers must be kept as part of your licensing and certification requirements. Hospitals maintain records like these for the radioisotopes that they use and for the medical waste generated as part of normal operating procedures.

CONCLUSION

Bringing the PET imaging modality into your laboratory should not be feared. Thousands of facilities already utilize radioisotopes every day for research or for clinical therapy. You may already have resources available to you. And if you need to reach out to a third-party, there are certified consultants available whose job it is to advise, train, and help you maintain good practice in obtaining, storing, utilizing, and disposing of the short-half-life, low-dose PET radioisotopes that your lab will be using. If you have any questions about adding PET to your arsenal of imaging modalities or about PET imaging systems such as Cubresa's NuPET™ MR-compatible PET scanner, please do not hesitate to reach out to us.

NOTES & REFERENCES

[1] Society of Nuclear Medicine and Molecular Imaging (SNMMI) and definition of Positron Emission Tomography (PET). http://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=5646

[2] International Society for Magnetic Resonance in Medicine (ISMRM) definition of Magnetic Resonance Imaging (MRI). http://www.ismrm.org/resources/information-for-patients/#What%20is%20MRI

[3] Regulatory requirements differ by country and by state in the United States. This white paper was written with facility requirements in the United States in mind and some generalizations have been used. Cubresa recommends consulting with your facility's or organization's RSO. If you do not have an RSO, we recommend utilizing a consultant who is properly certified by your state or country.

[4] United States Nuclear Regulatory Commission (NRC), section 35.24 definitions. http://www.nrc.gov/reading-rm/doc-collections/cfr/part035/part035-0024.html

[5] United States Nuclear Regulatory Commission (NRC), section 20.1003 definitions. http://www.nrc.gov/reading-rm/doc-collections/cfr/part020/part020-1003.html

[6] United States NRC website homepage. http://www.nrc.gov

[7] United States NRC principles of minimizing radiation exposure. https://www.nrc.gov/about-nrc/radiation/protects-you/protection-principles.html

[8] U Front. Phys., Quantitative preclinical PET imaging: opportunities and challenges, C. Kuntner and D. Stout, https://doi.org/10.3389/fphy.2014.00012

CUBRESA
Molecular Imaging Solutions

Cubresa, Inc.
300-136 Market Ave. Winnipeg,
MB R3B 0P4 Canada
T: +1 (204) 272-2409
E: info@cubresa.com
Web: Cubresa.com