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Protection of Subjects, Staff, and the Public in Molecular Imaging Research for Brain Disorders*

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Abstract

The use of molecular imaging in the clinic and in research for brain disorders has become more common over the past decades. As the imaging technology has improved and increased in use, so also has the need grown to protect human subjects, the staff in molecular imaging centers, the institutions administering the procedures, and the public who may be exposed both to subjects of the studies as well as radioactive materials that could be inadvertently released into the environment. This paper describes the techniques used in molecular imaging as well as the methods for protecting individuals and the public.

Keywords

Molecular imaging, brain disorders, radiation safety, radioactive materials, radiopharmaceuticals, clinical research trials, human subject protections.

Contents

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Introduction

This paper reviews the use of molecular imaging in the clinic and in research into neurological diseases. As a brief outline, after a quick introduction to molecular imaging techniques used in neurological research, there will be a discussion of the risks and benefits of molecular imaging to research subjects and others related to the use of radioactive tracers in molecular imaging. The next section will consider the regulatory environment that governs nuclear medicine research in the United States as well as the ethical considerations that all researchers have to address in order to proceed with radioactive imaging. Finally, the best practices and current recommendations will be reviewed.

Molecular Imaging

When we talk about molecular imaging using radiopharmaceuticals, we are talking about using radioactive drugs that will emit usually a gamma photon or characteristic X-ray that can be captured with a radiation imaging device, typically a gamma camera or a PET scanner, located outside of the body. These radioactive pharmaceuticals are infused at what are called tracer doses, which is a small dose of a drug that will interact with the body's physiology. It will be metabolized as a drug normally would, but the dose is too small to cause a pharmaceutical effect in the body. For example, in PET brain imaging, fluorodeoxyglucose is a commonly-used radiopharmaceutical. It is a form of glucose and its metabolism is similar to normal glucose. While the fluorodeoxyglucose is metabolized like normal glucose, the dose that we give is too small to change the blood sugar level of the patient or the research subject. Each radiopharmaceutical is selected to examine a particular physiologic or metabolic process in the body. It is targeted based on how that molecule will interact with specific cells and tissues in the body, so this is different from imaging like MRI or CT, where the structure of the anatomy is visualized. In molecular imaging we are specifically going to see the uptake and the subsequent metabolism of that particular tracer that we've administered to the patient or the research subject.

It is useful to keep in mind that there are several different ways that a clinical trial may be structured when a study is using radiotracers (see Figure 1). By far, the most common use in a research trial is where there is nothing specifically novel about the radiotracer itself. An investigator may be researching a particular drug or medical device, or evaluating the results of a particular procedure or treatment. They want to use a standard molecular imaging test to evaluate the effectiveness

of the drug, device, treatment, or procedure to assess the outcome in the subjects. An example of this would be in cancer drug trials, where patients will have PET/CT scans to evaluate the response of their tumors to the investigational drug. At the base of the pyramid, in these type of trials, there isn't anything inherently investigational about the radioactive tracer or the imaging technique, but the scan is being done specifically for the purpose of the research, rather than as a part of the patient's routine medical care. Therefore, all of the ethical and safety considerations that follow would apply to this scenario.

The next scenario is one where the use of the radiotracer or the imaging technique is more the focus of the research. In this example, there is an established radiotracer that's been approved for a specific use. Here, the aim is to evaluate the tracer for a potentially new or different purpose than what was originally approved. There is a fair amount of information available about how that tracer behaves in the body and about the radiation dose that it gives to a patient, since the radiotracer has already gone through a formal FDA approval process. In this case, the focus of the trial is to examine its effectiveness for this new purpose.

In a third research scenario, researchers may conduct an investigation of a new radiotracer that has not been used previously in humans (or that has only limited use in humans) where there is not yet an established use for a particular purpose. This type of study might be used to collect data required by the FDA for approval of a new drug. As an aside, in any investigation using radioactivity and radioactive drugs for research, any of these types of studies can also involve investigational instrumentation. Studies with either a routine or a new radio tracer could be undertaken, for example, on a new type of scanner which is still investigational or awaiting FDA approval as a medical device. In looking at the design of the study, it is important to decide which aspects of the study are truly investigational versus those that may be routine for clinical care, but where the data may be also used for purposes of the research trial.

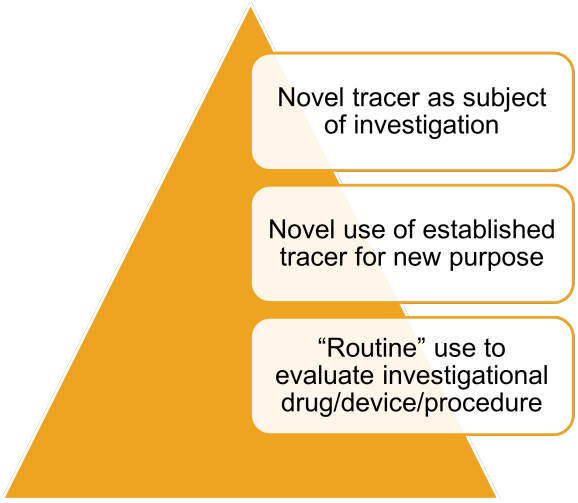

Figure 1: Types of clinical trials with radiotracers.

Generally, when we talk about molecular imaging of the brain, we are referring specifically to either SPECT, SPECT/CT, PET/CT, or PET/MRI. In SPECT scanning, which stands for single photon emission computed tomography, tracers are used that have a single radioactive decay that will emit either a gamma ray photon or a characteristic X-ray photon. In PET imaging (positron emission tomography), the tracers emit a positron particle. This particle undergoes annihilation with an electron, which gives two photons in opposite directions that can be detected simultaneously. This method has a lot of advantages, both for quantitative and qualitative reasons. Instead of seeing solely a picture in a distribution of radioactivity, in PET/CT, very often it's possible to use that data as a means to measure the concentration of the tracer in a particular location in tissue. The detection of two simultaneous collinear photons also has some implications for processing the images to get higher spatial resolution, or better fine detail of structures within a smaller part of the body. PET-CT works well in the brain where the area is smaller than, say, the cross-section of the chest or the abdomen. Primarily, PET/CT is going to be the molecular imaging technique of interest in brain imaging. PET/MRI has also become very useful because it allows the user to combine the imaging of a particular positron-emitting radiotracer with the multiple different types of information obtained by doing a series of different scans in an MRI study and then to overlay those images on top of each other for combined anatomic and functional information.

There are a number of different radiopharmaceuticals that are in common use for brain PET imaging [1]. These rely on a fairly small family of radionuclides which have relatively low atomic numbers. Among these, fluorine 18 is more widely available and has a half-life of just under two hours. A radiopharmaceutical labeled with fluorine 18 can be produced in a commercial radiopharmacy facility and delivered by courier to a clinical site, whereas tracers using carbon 11 and oxygen 15 have half-lives on the order of just a few minutes. These typically have to be produced in an onsite cyclotron and delivered directly from the cyclotron and the radiochemistry facility to the scan room to administer directly to the patient, because the radioactivity decays so quickly. It is very difficult to administer those in any other way. For brain imaging, radiotracers that target amyloid and tau protein are gaining popularity. These tracers have great importance in Alzheimer disease and other neurological research that focuses on examining the accumulation of amyloid plaques or looking at tau proteins.

Risks and Hazards

In a research study, when subjects are going to be given any kind of a radioactive substance for imaging, we want to pay attention to the amount of radiation exposure that those subjects are going to receive as part of that research. Most of that radiation exposure is going to be internal, thus the radiopharmaceutical will deliver radiation exposure to multiple organs once it's introduced into the body. The majority of the dose may or may not be directed to the brain. While many of these radiopharmaceuticals are taken up in the brain, they're also taken up by many other organs and eliminated from the body. They deliver substantial doses to organs like the liver, kidneys, or bladder, which is determined in the early phase studies with these radiotracers. In addition to the internal exposure, subjects may also receive external exposure from X-rays from a CT scan that is part of the procedure. In modern practice with PET/CT, the subject will almost always undergo a CT scan as part the study. The CT scan usually gives a lower radiation dose than the radiopharmaceutical dose, yet it can be a substantial portion of the radiation exposure the subject will receive.

In general, a subject could anticipate a radiation dose of anywhere from about two up to about 30 millisievert (mSv) per scan or per procedure if the subject is undergoing one or more PET/CT studies as part

of a research trial. To put that in perspective, in the United States, everyone receives on average about three mSv per year of natural background radiation. The dose per scan is up to the order of about 10 years' worth of natural background exposure. The natural background comes from sources like cosmic rays from space, radon gas coming up from underground, and trace amounts of natural radioactivity that are in soil, water, and minerals in food.

We would usually think of this as harmless because we're all in it all the time. Excess radiation exposure, over and above what we incidentally and naturally receive, is associated at some level with a risk of cancer in the future. Putting some numbers to this exposure, what is well characterized about radiation exposure and cancer risk is that a single dose over 100 mSv delivered at once is associated with excess cancer risk and cancer mortality in the Life Span Study population [2]. Data obtained from studies of the survivors of the atomic bombings in Japan in 1945 showed that in this population, doses above 100 mSv were associated with increased cancer incidence and mortality. Single doses of less than 100 mSv have not been shown directly to increase cancer risk. However, we generally presume that they do as a way to be conservative about what is a safe level of exposure.

The other issue with radiation exposure that is a bit tricky is the issue of cumulative dose and risk. If someone has multiple exposures over a period of time, say 10 mSv today, 10 mSv a month from now, another 10 mSv a month after that, how does that modify risks of cancer? What is true is that an individual who has had many exposures and multiple doses over a period of time will eventually be more likely to have a greater cancer risk as a result of that repeated exposure. What is not true, though, is that each of those exposures increases the risk of the next one. The 10 mSv today has a particular risk associated with it, as does the 10 mSv a month from now, and so on and so forth.

We can think about this using a gambling analogy. If someone goes to a casino table and plays the same game over and over again, unless they are very lucky, eventually, the player will run out of money after playing for many hours and betting $20 each time. Eventually, their money will run out. However, after playing for many hours, placing another $20 bet on the table is no more or less likely to lose on the next roll of the dice or deal the cards then one was likely to lose that first $20 bet when entering the game. This is where cumulative risk is often misunderstood. People may think that someone who has had a lot of medical imaging (and thus had larger amounts of radiation exposure in the past) shouldn't have any further exposure. This misconception is known as the "gambler's fallacy" [3]. The truth is that each of those individual incidents has its own independent benefit-risk calculation requiring a decision in the medical setting. Will this particular diagnostic test help the patient in this situation? If yes, then it should be done, whether they have had 100 CT scans in the past or none. The same is true of research. If a particular patient fits the recruitment requirements for a trial and the radiation exposure being used is justified in the context of the trial, then there is no reason to restrict that subject from participating, even if they've had prior radiation exposure.

In routine medical care, we consider benefit in terms of the medical benefit of doing a diagnostic test. Does the patient need this test to arrive at the appropriate diagnosis or to help guide their treatment or medical management? We know that the risks from the amount of radiation we use are small, and we have evidence-based guidelines that tell us when it's appropriate to do a particular type of imaging for a particular patient in a particular situation. On the research side, the radiation exposure is part of imaging used to obtain data and ultimately to create new knowledge. There may not be any particular benefit to the individual research subject when their images are used for research. Often, research subjects don't find out the results of the research scan, or it doesn't necessarily impact their medical care. However, there is a societal benefit that can justify the radiation exposure of the individuals who participate in research. Our informed consent process needs to be designed to go through those potential risks and benefits for the subject and explain them clearly. This is an area where clinical trials sometimes go a bit astray; physicians and scientists understand that relatively few clinical trials will directly benefit the participant. However, it is sometimes tempting to advertise those trials to patients who are looking for an alternative or who have exhausted all available treatments for their medical situation, even though the design of the trial is not expressly intended to produce specific outcomes in subjects. Clinical investigators must be very careful about informed consent and about suggesting or insinuating to a potential subject that participation in a study might be a cure or an answer for a medical mystery with which they have been living. The purpose of the research is the broader knowledge that's developed as a result of that study.

In 2020, the National Council on Radiation Protection and Measurements (NRCP) published a report entitled "Evaluating and Communicating Radiation Risks for Studies Involving Human Subjects: Guidance for Researchers and Institutional Review Boards" [4]. The publication is a lengthy, detailed handbook that describes the process and the framework of evaluating radiation risk in research, including how to weigh those risks and benefits for a particular study and how to communicate those risks through the informed consent process. It is focused on radiation use in research, not all the other aspects of conducting a research study. It is an excellent resource with many specific recommendations for how to describe risks of radiation exposure in research to the subjects of a study. This report is strongly recommended to any Institutional Review Board (IRB) or any committee that is advising an IRB on radiation exposure of human subjects in research.

The guiding principle in this work is the standard of "reasonableness." This standard means that a proposed course of action is acceptable if a physician or scientist who is familiar with the study and the subject population can conclude that the action is reasonable in terms of what the radiation dose that is delivered. NCRP provides some additional details to guide the assessment of reasonableness, including classifying radiation doses by the minimum individual or societal benefit required (in a research context) to deem the exposure reasonable [5]. The terms used are somewhat subjective, and some reviewers would likely arrive at different conclusions regarding what constitutes "moderate" versus "substantial" benefit, for example. However, this provides a starting point for objectively assessing the benefit versus risk for radiation exposure in a research study. This scheme was further detailed and clarified in guidance published by the Netherlands Commission on Radiation Dosimetry (NCS) [6]. The terminology used for the level of benefit is more descriptive, particularly for subject radiation exposures exceeding 20 mSv where this report calls for expected benefits directly for participants.

The benefit-risk assessment in action often demands subtle judgments about the nature of the trial and the proposed radiation exposures. For example, an investigator might propose performing a series of PET/CT scans to evaluate an investigational cancer treatment that is being made available to patients who have very advanced disease and for whom all other available treatments have failed. A series of eight to ten such scans, at perhaps 15 mSv each, could deliver a sub-

stantial dose to a subject. However, this dose is delivered over a period of many weeks or months, not all at once. An IRB should take into account the timing of the exposures and should also consider the direct benefit to the subject if the experimental treatment improves survival or quality of life. In this setting, the treatment provides the benefit, not the scans. However, the scans are an essential component of the research trial, without which the treatment would not be possible. In this scenario, it would be appropriate to approve a radiation exposure that is large enough to demand direct benefit to the trial subject.

Research subjects are not the only people who are exposed to radiation during a study. The research staff will also receive some exposure from the subjects. Once subjects have been injected with a radioactive drug, they will emit radiation until that the radioactivity decays or the radioactive drug is eliminated from the body. A nuclear medicine technologist would be exposed while preparing the radiopharmaceutical, administering it to the subject, escorting the subject to the restroom and the scanner, positioning the subject for the scan, and at other points during the time the subject is in the nuclear medicine facility. In addition to staff, there are other members of the public who may be exposed. Employees who are not formally assigned to work with radiation may happen to be in the area where they are exposed to radiation from a research subject. Members of the public including other patients and family members may also be exposed to the research subject. Exposures to this group can come from being in close proximity to a patient or a subject who is radioactive due to a radioactive drug in their body. Waste material that has radioactivity on it must also be carefully collected and segregated from ordinary waste.

Patients and subjects typically finish their scan and leave the department and facility while they are still a bit radioactive and emitting a small amount of radiation. Nuclear medicine facilities are responsible to assess the potential for such exposure and to determine when an individual may safely leave the restricted area after receiving a particular type and amount of radioactive drug. At times the subjects need to stay in the facility for a period of time before it is safe for them to leave depending on what radiopharmaceutical they're given, and how much. This situation is not common with PET because the radionuclides used decay quickly. If there is onsite radiopharmaceutical production, such as in a cyclotron facility, there is also the potential for the release of radioactive gas or radioactive vapor from some of those processes. If the released products are not properly handled and vented to a safe area, this release can also expose members of the public.

All users of nuclear medicine must plan for radiation protection according to the ALARA principle, or As Low As Reasonably Achievable, which means keeping exposures to staff and the public as low as reasonably achievable. The definitions of "low" and "reasonable" are contextual, meaning "low" for a nuclear medicine technologist is not the same as "low" for a department secretary, for example. Similarly, "reasonable" is subject to cost limitations. Nuclear medicine services do not take measures that are very costly to achieve small reductions in exposure. However, measures that have modest cost and a large decrease in exposure should always be taken. ALARA is accomplished using the practical methods of minimizing time of exposure, maximizing distance between the radiation source and the individual at risk, and then using shielding to further reduce exposure rates. The measures have to be appropriate to the purpose of the activity, meaning doing what is reasonable in the context of being able to accomplish the research aims. There is also a public interest component to many considerations regarding the ALARA principle. Public policy drives the laws and regulations that dictate how ALARA is implemented. These also govern how nuclear medicine is practiced.

There are a number of other risks not directly related to radiation or radiopharmaceuticals which are important considerations for participation in molecular imaging trials as well as many other types of clinical trials. The risk of breach of subject privacy or confidentiality can happen any time there is loss or theft of documents or hard drives or breach of electronic security (computer viruses, malware, hacking, etc.). Subjects could experience anything from discomfort to injury or infection from the study procedures since many radiopharmaceuticals are injected into the body. There is also the potential for the radiotracer to cause extravasation, where the radioactive drug escapes the vein into which it was injected and localizes in the tissue at the site of the injection. This can cause minor discomfort or more serious injury in addition to failure of the imaging procedure. Some studies administer other medications to subjets in addition to the radioactive drugs. For example, if the subject is having a PET/CT scan, contrast may be used, which may cause a reaction in some people.

Finally, of particular importance during the ongoing pandemic, for many trials, the study design includes a patient population that may have underlying conditions, such as being immunocompromised. Careful consideration must be given to the possibility that their participation in the trial will expose them to additional risk on top of those risk factors that they have based on their disease process. Asking a patient who is immunocompromised to undergo study procedures in a facility which is also taking care of patients who have a highly infectious disease can be a serious risk factor, depending on the design of the study and the study population.

Regulatory Frameworks

The conduct of clinical research on human subjects that potentially involves using experimental drugs, experimental medical devices, and radiation exposure is subject to a variety of overlapping regulations and oversight requirements. While the details of these differ, they can be thought of as the detailed implementations of a more uniform set of ethical principles. In the United States, radioactive materials are under the jurisdiction of the US Nuclear Regulatory Commission (NRC). The NRC has delegated that authority to a number of states to implement directly; these are called Agreement States. The NRC (or Agreement State) regulations set forth the detailed requirements for radiation protection and the exposure of humans to radiation produced by radioactive materials. Machines and devices that produce radiation, such as x-ray machines, are regulated differently. Entities that design, manufacture, market, and sell such equipment are regulated by the US Food and Drug Administration (FDA). Meanwhile, the end user of the equipment (such as a hospital) is regulated by the rules of the individual state radiation protection program where they are located. While individual states are free, for the most part, to develop their own regulatory requirements, in practice Agreement State regulations for radioactive material are largely consistent with the federal NRC regulations, and state regulations for radiation generating equipment are largely consistent with the FDA regulations that govern the design and manufacture of the devices.

Regardless of the regulatory authority and jurisdiction, an institution will always be required to have a license to possess radioactive material. Any time humans are deliberately exposed to radiation, the

exposed individual must be either: a patient with a valid medical purpose for exposure under the authorization of a licensed physician; or a subject enrolled in a research trial that is supervised by an IRB. This is the point where the IRB ties into the radiation protection requirements directly. Licenses and regulations require that doses to workers and the public be limited to not more than a maximum limit, and users of radioactive material are required to develop reasonable estimates of those doses and demonstrate that they meet the limits. There are numerous regulatory requirements for monitoring and limiting radiation exposure, detecting and cleaning contamination, transporting radioactive materials, and disposal of radioactive waste. There must be inventory procedures to make sure that all radioactive materials are accounted for and security procedures in place to safeguard radioactive materials against loss or theft. These standards apply to any facility that uses radioactive material for any purpose, research or clinical.

Key personnel roles are defined for the radiation protection program. The Authorized User (AU) is a physician who is allowed to prescribe and administer radioactive drugs to humans (or to use radioactive sources on humans, in the case of radiation therapy). There are different categories of use, meaning that the AU is evaluated for their training and experience and granted authorization for specific medical or research purposes. Generally, a physician who is allowed to use radioactive material for imaging in a clinical setting would also be allowed to do the same type of imaging procedures in a research trial. Any trial that uses radioactive drugs needs to have an AU designated for the appropriate type of procedure. The Radiation Safety Officer (RSO) has authority for safety on the radioactive materials license [7]. This is the person who is specifically qualified to run the radiation protection program [8], [9]. The RSO must be given personal authority to shut down any operations that they deem unsafe or non-compliant with the regulations. This authority is granted in writing directly from the president, CEO, or senior-most official in charge of the institution holding the radioactive materials license.

All pharmaceuticals are regulated by the FDA. They give clearance for specific drugs for specific uses. The process to gain approval of a radiopharmaceutical is through the investigational new drug (IND) application process. If a researcher wants to develop a new drug and gather data to support an eventual application for full FDA approval, they typically start with the IND process. This regulatory approach is required both for a new use of existing drug and for an entirely new drug, including radiopharmaceuticals. Any work with investigational devices is also subject to FDA regulations [10], [11]. Any drug for human use needs to be prepared according to current good manufacturing practices or cGMP. This reflects the FDA regulations [12], [13], and the policies of the institution's pharmacy department and regulations of the state pharmacy board or health department may apply as well.

Trials of radiopharmaceuticals typically start with preclinical studies using animals to determine which organs and tissues are targets for the tracer in the body [14]. Phase one human trials are then used to extend the preclinical information to the human body [15]. Important data points include kinetics (how quickly does the drug take to get to the target organs) and dosimetry (to which organs does it deliver a radiation dose). These phase one trials may be done either under an IND approval from the FDA or under the jurisdiction of an RDRC within the institution. The pathway taken depends on the resources that are available to the research trial. Once that information has been established in the phase one trials, phase two trials are then used to show that the radiopharmaceutical works for a particular diagnostic purpose. This type of trial is also where the amount of radioactivity administered to the subject is fine-tuned. This is the information that is ultimately listed in the package insert once the drug becomes a commercial product. The insert states the dosing guidelines, the indications for use, and what the tracer can be used to detect and diagnose. It also describes the radiation dose information. The contents of the package insert are approved by the FDA based on their review all of the data submitted for approval of the pharmaceutical [16].

Human subject research in the United States is regulated under Title 45 of the Code of Federal Regulations (CFR) by the US Department of Health and Human Services through the Office for Human Research Protections (OHRP). This is the federal regulatory agency that authorizes IRBs within institutions to oversee human subject research. The IRB provides the local oversight and enforcement of these regulations, which describe the process of gaining approval from an IRB and the IRB's jurisdiction over the ongoing research. Most IRBs have a formal policy requiring researchers to complete specific training or certification in human subject protections, ethical principles, and federal regulations before commencing any human subject research or requesting any approvals from the board. The bulk of the IRB's interaction with trials takes place in the form of oversight and ensuring that appropriate safety is in place for the subjects.

In the performance of clinical research in molecular imaging, IRBs look to institutional radiation safety committees to provide subject matter expertise and guidance on whether the proposed study procedures and the radiation safety precautions in a given trial will comply with the applicable regulations and provide a reasonable level of safety for participating subjects. In molecular imaging trials that can involve investigational radioactive drugs, investigational imaging or measurement devices, and investigational treatments or interventions, the IRB faces a very complex task in assessing the safety and regulatory compliance of all facets of the trial as well as ensuring that adequate and appropriate information is provided to potential subjects in the informed consent process.

Ethical Considerations

Ethics guide all clinical care and research trials. In all matters related to any study, it is important to ensure that all human subject protections are handled according to three ethical principles that are laid out in the Belmont Report [17] published in 1979. These three principles are respect for persons, beneficence, and justice. It is the responsibility of the principal investigator (PI) of each study to make sure that they uphold these principles and remain compliant with all applicable regulations. Subject selection, or definition of the study population, is a key step for the application of the ethical principle of justice. It is important to fairly distribute the risk, as well as to ensure that the study fairly provides the benefit across all of the people that could potentially be included or excluded from the study. Both the PI and the IRB should take care to examine the study population for any deficiencies of justice in the inclusion or exclusion criteria for the trial.

The ethical principle of beneficence remains the key consideration when examining the risks and the burdens that subjects will incur through their participation in the trial. The aim of the trial must be clearly articulated, whether it is to assess a drug, a technique, or a treatment - or merely to gather data which may not relate to a particular intervention. The study design should be carefully scrutinized

to determine whether or not there is an expectation of direct benefit to the subject arising from their participation in the trial. If there is direct benefit, the magnitude of that benefit should be considered. As a separate question, what is the societal benefit that is expected from the study? All research is designed to produce new knowledge, but some new knowledge will have greater or lesser impact depending on the size and composition of the population that it could benefit, the severity of the disease or condition that it seeks to understand or treat, and so forth. The PI should attempt to articulate, and the IRB should endeavor to discern, the most likely benefits that the trial could be anticipated to provide.

The informed consent process is one mechanism that researchers use to satisfy the ethical principle of respect for persons. This process must carefully describe and disclose the anticipated risks and benefits. Informed consent helps a prospective subject to understand the trial and to freely give their consent to participate. It is important to emphasize that the informed consent documents need to describe all information clearly, accurately, and in a manner that is consistent with all of the other study documentation.

Current Recommendations

The guidelines, principles, and regulations described above provide a useful framework both for the PI designing a study and for the IRB reviewer evaluating it for protection of research subjects. In studies using radiotracers for molecular imaging, the identity, sourcing, and regulatory status of the radiopharmaceuticals are key considerations in the assessment of risk. The lowest risk are those radiotracers which are already FDA-approved drugs manufactured commercially. For drugs produced under an IND, it is essential to identify the holder of the IND and closely examine the manufacturing and quality assurance processes. If an investigational agent is being used under the supervision of an RDRC, close coordination and effective communication between the RDRC and the IRB should be established at the beginning of both bodies' approval processes.

The IRB should always consult with a Qualified Medical Physicist (either from among its members or in consultation as an outside resource, possibly as part of the institutional radiation safety committee) to evaluate the radiation exposure and risk to subjects. The IRB should ensure that the PI discloses all radiation exposure to subjects and clearly delineates which exposures are specifically required for the research trial and which are part of subjects' routine medical care. The medical physicist should verify that the radiation dose to the subjects is consistent with the imaging of the procedures described in the study protocol document and that the language disclosing and describing radiation exposure risk in any informed consent documents is accurate and appropriate. This is a particular challenge given the highly technical nature of radiation exposure and risk and the accepted practice of writing informed consent documents in plain language that are understandable to subjects with low literacy levels. The medical physicist or radiation safety committee should also provide guidance to the IRB on the appropriateness of the balance between the anticipated study benefit and the subject radiation exposure and associated risks.

Finally, the study must comply with all local institutional policies. This includes verifying that all the investigators have completed any training or certification that the IRB requires. A more subtle consideration is that the IRB must verify that the investigator has access to the necessary facilities, equipment, personnel, and other resources that would be needed to fulfill the safety and regulatory requirements that apply to their study. Indeed, this is one of the benefits of the local nature of an IRB: the members of the IRB and their consultative subject matter experts are likely to be generally familiar with the institution's facilities and personnel so that they can more readily identify any gaps between an investigator's safety and compliance plans and the realistic ability to carry them out.

Molecular imaging research is a broad team effort. The team includes the institution itself, the principal investigator, the authorized user, the radiation safety officer, the study staff, the technologist in the nuclear medicine facility, and, of course, the subject-patient, as well as their family, who have a key role in participating in the trial and giving their informed consent to participate. For molecular brain imaging research, given the multiple regulations and agencies that have jurisdiction over specific aspects, it can be difficult to figure out exactly what the requirements are. By using the framework of ethical principles, and incorporating accepted radiation protection principles and practices, both PIs and IRBs can simplify the picture and focus on the key questions of maximizing study benefits and minimizing subject risks.

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