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Preface

The purpose of this report is to provide guidance to researchers in preparing protocols that include ionizing radiation exposure to human subjects and to provide guidance to reviewing bodies, such as Institutional Review Boards (IRB), in the process of reviewing such protocols. This includes guidance for assessing proper utilization of radiation, estimation of risk, optimization of radiation dose, and formulation of informed consent statements with consistent, comprehensible and accurate language.

These issues have been dealt with in part by previous National Council on Radiation Protection and Measurements (NCRP) documents, which were generally focused on specific issues, modalities and/or patient populations. Proper utilization, optimization and/or informed consent were specifically targeted in:

- Report No. 70, Nuclear Medicine-Factors Influencing the Choice and Use of Radionuclides in Diagnosis and Therapy (1982);
- Report No. 99, Quality Assurance for Diagnostic Imaging (1988);
- Report No. 102, Medical X-Ray, Electron Beam and Gamma Ray Protection for Energies Up to 50 MeV (Equipment Design, Performance and Use) (1989a);
- Report No. 128, Radionuclide Exposure of the Embryo/Fetus (1998);
- Report No. 149, A Guide to Mammography and Other Breast Imaging Procedures (2004);
- Report No. 155, Management of Radionuclide Therapy Patients (2006);
- Report No. 168, Radiation Dose Management for Fluoroscopically-Guided Interventional Medical Procedures (2010b);
- Report No. 170, Second Primary Cancers and Cardiovascular Disease After Radiation Therapy (2011);
- Report No. 172, Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States (2012b); and
Many of these concepts apply not only to the procedures encountered in normal standard of care for medical practice but also to human trials involving exposure to ionizing radiation.

Specific NCRP reports have also addressed the issues of radiation biological effectiveness, radiation dose and risk estimation. Examples include:

- Report No. 96, *Comparative Carcinogenicity of Ionizing Radiation and Chemicals* (1989b);
- Report No. 104, *The Relative Biological Effectiveness of Radiations of Different Quality* (1990);
- Report No. 116, *Limitation of Exposure to Ionizing Radiation* (1993b);
- Report No. 126, *Uncertainties in Fatal Cancer Risk Estimates Used in Radiation Protection* (1997);
- Report No. 164, *Uncertainties in Internal Radiation Dose Assessment* (2009c);
- Report No. 167, *Potential Impact of Individual Genetic Susceptibility and Previous Radiation Exposure on Radiation Risk for Astronauts* (2010a); and
Although the risks of low-level radiation exposure remain controversial, high levels of radiation exposure are well known to cause tissue effects (such as skin burns and depilation) and stochastic effects (such as cancer or second primary cancers).

In this and other reports, the NCRP has considered various alternatives to ionizing radiation for medical procedures. Examples of these applications and their potential health effects include:

- Report No. 67, Radiofrequency Electromagnetic Fields—Properties, Quantities and Units, Biophysical Interaction, and Measurements (1981);
- Report No. 74, Biological Effects of Ultrasound: Mechanisms and Clinical Implications (1983);
- Report No. 86, Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields (1986);
- Report No. 113, Exposure Criteria for Medical Diagnostic Ultrasound: I. Criteria Based on Thermal Mechanisms (1992);
- Report No. 119, A Practical Guide to the Determination of Human Exposure to Radiofrequency Fields (1993c); and

Other nonionizing radiation techniques, such as thermal imaging (passive mapping of infrared energy from a patient) or transilluminational imaging (transmission of high-intensity visible light through a patient) have not yet been addressed by NCRP.

This Report was prepared by Scientific Committee 4-7 on Evaluating and Communicating Risks for Studies Involving Human Subjects: Guidance for Researchers and Institutional Review Boards. Serving on Scientific Committee 4-7 were:

**Julie K. Timins, Chair**
New Jersey Commission on Radiation Protection
Trenton, New Jersey
The Council wishes to express its appreciation to the Committee members for the time and effort devoted to the preparation of this Report and to the American Association of Physicists in Medicine, Centers for Disease Control and Prevention, and the U.S. Nuclear Regulatory Commission for their support.
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1. Executive Summary

1.1 General

The extent of knowledge about ionizing radiation in general, radiation involved in medical procedures, and the potential adverse effects of radiation varies substantially among members of the public, and within the medical community. Also, although many U.S. academic institutions provide guidelines for the conduct of human research, including research involving radiation, these guidelines lack uniformity. There is a need to provide comprehensive, consistent and accurate guidance on radiation risks of research protocols that involve the use of ionizing radiation to those who develop protocols and conduct research involving human subjects and to institutional review boards (IRBs) that review these protocols. This report seeks to fill these gaps by:

- providing basic information about ionizing radiation and radiation biology, including medical imaging and treatments that involve radiation;
- noting the governmental agencies that oversee research and radiation;
- citing the relevant regulatory requirements;
- providing guidance regarding the estimation of radiation dose and risk in research protocols;
- discussing the ethical considerations involved in human studies research; and
- presenting in detail the requirements for ensuring and obtaining truly informed consent.

Seminal national and international documents have articulated the ethical conduct of human studies research. There are also specific regulatory requirements for human studies research that involves ionizing radiation. Guidelines and rules have been promulgated by national oversight bodies, among which are the Department of Health and Human Services (DHHS), the Office of Human Research Protections (OHRP), the Food and Drug Administration (FDA), and the U.S. Nuclear Regulatory Commission (NRC).
The basic concepts of radiobiology, radiation protection, and radiation dose and dose
metrics apply to human subject research. The biological effects of ionizing radiation must be
understood in order to plan, review and conduct human subject research that entails the use of
ionizing radiation. An understanding of the threefold framework of radiation protection is also
necessary: justification, optimization (also referred to as ‘ALARA,’ the acronym for ‘as low as
reasonably achievable’), and dose limitation. It is also necessary to understand how these
principles are applied to medical exposures.

There are many regulatory requirements for institutional supervision of human studies
research. The institutional review board (IRB), radiation safety committee (RSC), radiation
safety officer (RSO), and for radioactive materials the authorized user (AU) all have roles and
requirements. Interaction with FDA is necessary for clinical studies involving investigational
drugs or biologic products and investigational medical devices.

Various imaging and treatment modalities are used in medical imaging and therapy,
including those that use ionizing radiation (e.g., radiography, computed tomography, nuclear
medicine, fluoroscopy and most image-guided interventional procedures, radiation therapy),
those that use nonionizing (i.e., electromagnetic) radiation (e.g., magnetic resonance imaging),
and those that use other forms of energy (e.g., ultrasound imaging). Radioactive tracers may be
used for basic scientific investigation of physiology and metabolism.

It is essential for the researcher and the IRB to be able to distinguish between ionizing
radiation received by a research subject in the course of standard medical care and ionizing
radiation that is received specifically due to participation in a research protocol. Both the
researcher and the IRB must consider whether the proposed type and frequency of procedures
employing radiation in the research protocol are reasonable and necessary to the research, and
whether other modalities that do not employ ionizing radiation can be substituted.
Researchers must provide estimates of, and IRBs must consider, radiation dose and risk to human subjects. This requires an understanding of applicable radiation dose metrics, the concept of uncertainty in radiation dose and radiation risk estimation, and the factors that influence risk to the individual. Optimization of radiation dose is essential to minimize radiation risks to human research subjects.

Ethical considerations and their importance in the conduct of research involving human subjects can be framed within four ethical principles: respect for autonomy, non-maleficence, beneficence, and justice. These ethical principles interact with the three tenets of radiation protection stated above. Informed consent is required legally and ethically when enrolling individuals in human studies research. It is important to ensure that consent is indeed ‘informed.’ This entails the use of clear, plain language; the obligation to communicate the risks, probability and severity of potential harm from ionizing radiation exposure; writing the informed consent and supporting documents at an appropriate reading level (an eighth-grade reading level is frequently cited); and keeping the length of the informed consent document reasonable and commensurate with radiation and overall protocol risk. Providing comparisons with radiation exposures which are part of normal life, such as air travel and background radiation, can help promote understanding of the radiation risks involved in the research study. Special considerations apply when the study population includes vulnerable populations, such as children or those with impaired decision-making capacity.

Appendix A provides guidance and examples of language for informed consent for human research studies with differing levels of radiation exposure. Appendix B gives additional information and references on generation of dose estimates for computed tomography.

1.2 Recommendations

The following are recommendations developed to provide guidance to those developing research protocols and conducting research on human subjects and to members of IRBs. Recommendations are listed in the order in which they appear in the body of this Report.
These NCRP recommendations are expressed in terms of ‘shall’ (or ‘shall not’), ‘should’ (or ‘should not’), and ‘may,’ where:

- **shall** (or **shall not**) indicates a recommendation from NCRP that is necessary to meet the currently accepted standards of radiation protection;
- **should** (or **should not**) indicates an advisory recommendation from NCRP that is to be applied when practicable or practical (e.g., cost-effective); and
- **may** (or **may not**) indicates a reasonable practice that is permissible.

As appropriate, when radiopharmaceuticals are administered to human subjects for diagnostic imaging research or basic science research, the subjects **should** receive radiation protection counseling specific to the radiopharmaceuticals prior to administration. This may include limitations on close contact with infants or small children or on breast feeding, usually lasting <24 h (Sections 3.1.2.4 and 3.1.2.5).

For subjects undergoing radionuclide therapy or brachytherapy, radiation protection counseling **shall** first be provided to the subject and, when relevant, to family members, by the medical/health physicist or administering physician (Section 3.1.2.4).

The radiation dose metric ‘absorbed dose’ **should** be used as the preferred quantity for estimating the risk of stochastic effects and tissue reactions for human research studies, in the form of the mean absorbed dose to a tissue or organ (Section 3.3.2).

Effective dose (E) **may** be used for estimating the risk of stochastic effects for human research studies, but **should not** be used without considering its appropriateness in light of the characteristics of the study population, including age, gender, genetic predisposition, the body parts being irradiated, and expected life-span (Section 3.3.3).
The radiation a human subject receives specifically through participation in a research protocol, which would not have been received otherwise, shall be considered separately from that received in the normal course of medical treatment, and should be monitored and reported by the research team (Section 5).

The principal investigator (PI) should be educated and knowledgeable regarding the ionizing radiation proposed in the clinical trial. This should include a working knowledge of the basic concepts of exposure, absorbed dose and effective dose (Section 6.1).

The PI should assess the use of ionizing radiation examinations against the potential use of other modalities that do not utilize ionizing radiation (Section 6.1).

When reviewing a clinical trial, IRBs should either have knowledge of the current definition of standard of care (SOC) as it relates to radiological procedures for the population being studied or should solicit the assistance of appropriate medical clinicians and their local Radiation Safety Committees and Radiation Safety Officers for guidance (Section 6.1).

For multi-center research trials an effective, responsive mechanism of communication should be in place to address participating institutions’ concerns about radiological protocols, estimated radiation dose to subjects, and accuracy of dose and risk estimates (Section 6.3).

When clinically appropriate and feasible, an imaging modality that does not employ ionizing radiation should be substituted for one that does, as long as the necessary information can be obtained (Section 6.5). The determination of appropriateness and feasibility may include economic considerations.

When the metrics of dose to a subject indicate that the radiation exposure may cause tissue reactions, there shall be counseling and arrangements for follow-up of the subject. When the radiation dose varies substantially from subject to subject, as in most fluoroscopically guided
interventional procedures, the counseling and follow-up may be limited to only those subjects at significant risk of tissue reactions (Section 6.5).

Use of ionizing radiation in a research study shall meet the criteria of ‘reasonableness’: the specified clinical or basic science trial measure is adequately assessed with delivery of the lowest feasible radiation dose to each subject (Section 6.7).

Radiation doses to human subjects from proposed research studies shall be estimated in order to: (1) enable estimation of the risk to the subjects and development of appropriate risk language for informed consent; and (2) assist in optimizing the study design to keep radiation doses to human subjects ALARA (Section 7).

The IRB shall independently verify the dose estimates provided by the investigator(s) in the research protocol. This responsibility may be delegated to the RSC or other competent entity (Section 7).

Categories of radiation risks to be considered, when appropriate, shall include: (1) stochastic effects, specifically cancer and hereditary effects; (2) tissue reactions; and (3) teratogenic effects (Section 8).

In developing radiation risk estimations, uncertainties in risk estimation shall be derived and expressed, including factors influencing individual risk at the time of exposure (Section 8).

When developing guidelines on cumulative dose for human research subjects, factors to consider should include the radiation risk to the individual based upon factors including but not limited to age, gender, life expectancy, and radiation dose. This should be balanced against the potential societal benefits from the research (Section 8.10).

Research protocols that would impact cumulative effective doses exceeding 250 mSv from diagnostic imaging procedures over a 5 y period should be closely scrutinized to determine: (1)
whether radiation doses can be reduced, and (2) whether the possible benefits from the research justify the risks to the research subjects (Section 8.10).

Administration of ionizing radiation for research purposes, other than radiation therapy research, **shall** be optimized to use a radiation dose that is ALARA for the specific task (Section 9).

The number of research subjects **shall** be limited to the minimum needed to accomplish the goals of the study (Section 9).

The ethical principles of respect for autonomy, non-maleficence, beneficence, and justice **shall** be considered in the design and conduct of human studies research (Section 10.1).

Key considerations in developing the radiation risk statement **should** be brevity and clarity. Radiation risk **shall** be placed into context with the other risks of the protocol. Undue focus **should not** be placed on the risks of radiation in diagnostic imaging research and basic science research, in order to avoid obscuring other risks and possible benefits (Section 11.3).

Radiation dose and radiation risk, as well as the uncertainties involved, **shall** be communicated in a meaningful manner to clinical research subjects (Section 11.4).

When addressing informed consent for human studies research involving radiation, uncertainty **shall** be included with the discussion of risk, along with the benchmark comparisons (Sections 11.4 and 11.5).

The risks and potential harms inherent in the research protocol **shall** be communicated to human research subjects using clear, concise, simple language with consistent terminology, in order to promote understanding (Section 11.2). The presentation of information in the informed consent process **shall** be adapted when necessary to facilitate the subject’s comprehension (Section 11.6).
Informed consent forms *should* be written at no higher than an eighth-grade reading level, as defined in quantitative indices such as the Flesch-Kincaid reading grade scale (Section 11.2).

When individuals vulnerable to coercion or undue influence take part in research, additional safeguards *shall* be included (Section 11.6).

For the purpose of obtaining informed consent, special consideration *shall* be given to children and to adult subjects with impaired decision-making capacity (Section 11.6).

Research on children under the age of majority *shall* require consent by parent or legal guardian, unless by state statutes they are considered ‘emancipated minors’ or ‘mature minors’ (Section 11.6).

Once informed consent has been obtained from the parent or legal guardian, informed assent *may* be obtained from children, if they are capable of providing it. The research team should explain the trial in language the child can understand, appropriate to the child’s development and age (Section 11.6).

If a study arm includes therapeutic radiation, and therapeutic radiation is already a part of the standard of care (SOC), then the informed consent *should* clarify what, if any, excess risk beyond the SOC is incurred by participation in the study arm (Section 11.9).
2. Introduction

Extensive guidance exists in the research and medical literature on the conditions necessary for the ethical performance of research on human subjects. The principles set forth are intended to provide an ethical framework that protects human subjects and ensures that the purpose of the research is valid (i.e., to provide medical benefit and further understanding of the cause, course and treatment of disease and of human biology and physiology).

Some issues in research involving human subjects are specific, and at times unique, to protocols that involve ionizing radiation. Methods of expressing radiation dose vary, and some of the quantities and units used for purposes of radiation protection are arguably less suited for application to medical and research-related radiation exposure. The language employed for risk communication and quantification of radiation is not standardized, and can vary from comparison with numbers of chest x rays to numbers of transcontinental air flights to years of exposure to background radiation. Potential research subjects may better understand one radiation dose analogy than others. There are different types of risks from radiation (i.e., tissue reactions and stochastic effects). Tissue reactions (also referred to as deterministic effects) are unlikely to occur below a threshold dose and increase in severity as the dose increases above the threshold. The likelihood of a stochastic effect increases with increasing dose but the severity of the effect is independent of dose. Some stochastic effects may not be clinically evident until decades after the exposure (Section 3.1.1). It can be difficult to convey these concepts and the lack of predictability or certainty of potential radiation consequences to research subject candidates. This is further complicated by the lack of familiarity of the lay public with scientific concepts and terminology. Even medical professionals often have limited knowledge about radiation science and medical radiation.

Because knowledge about ionizing radiation in general, radiation involved in medical procedures, and the potential adverse effects of radiation is so variable amongst members of the public and within the professional medical community, it is important to provide guidance to researchers and to their IRBs on radiation risks for research studies involving radiation to human
subjects. Researchers and IRB members will benefit from clear guidance on the proper
utilization of radiation in a medical research setting, estimating and communicating radiation
risks and potential benefits, and ensuring that informed consent statements have consistent,
comprehensible, and accurate language.

2.1 Purpose of Report

The purpose of this Report is twofold:

- to provide guidance to researchers in developing and preparing research protocols that
  involve exposure of human subjects to ionizing radiation, and
- to provide guidance to IRB members and other groups on the process of reviewing
  protocols that involve radiation exposure to human subjects.

Components of this guidance include: identification of research protocols that involve
ionizing radiation, assessment of proper utilization of radiation and optimization of radiation
dose, estimation of the radiation doses to the subjects, estimation of the radiation risks,
preparation of a description of the risks, and how best to communicate those risks in the
informed consent process. This guidance specifies the elements necessary for informed consent
when human subjects are exposed to ionizing radiation for research, including formulation of
informed consent statements with utilization of consistent, comprehensible, and accurate
language. Examples of informed consent language are provided in Appendix A. Appendix B
provides details on generating dose estimates for computed tomography. The subjects discussed
in this Report are complementary to information in federal policy for the protection of human
subjects that includes Title 45 Code of Federal Regulations (CFR) Part 46 (DHHS, 2009) and 21
CFR Part 50 (FDA, 2014k), but relate specifically to human research that utilizes ionizing
radiation.
2.2 Background

Tens of thousands of individuals participate annually in clinical trials and other research involving human subjects (Bell et al., 1998; ClinicalTrials.gov, 2015). Many of these studies expose the subjects to ionizing radiation, including diagnostic imaging examinations, such as computed tomography (CT) or nuclear medicine scans, and medical treatments such as fluoroscopically guided interventional (FGI) procedures and radiation therapy. Protocols for treating specific diseases often specify periodic follow-up of subjects with imaging examinations that utilize ionizing radiation. Currently, the guidance available to researchers and reviewing bodies on the application of ionizing radiation to human subjects is quite variable.

The public at large, and even medical professionals, often have limited knowledge of the radiation incurred from common medical imaging examinations, including misconceptions about which imaging examinations utilize ionizing radiation (e.g., CT) and which do not (e.g., magnetic resonance and ultrasound imaging) (Ditkofsky et al., 2016). Very few have an accurate perception of the amount of radiation involved (Baumann et al., 2011; Freudenberg and Beyer, 2011; Irving et al., 2016). Obstetricians and family physicians who care for pregnant women tend to overestimate teratogenic risk from medical radiation exposure in early pregnancy (Ratnapalan et al., 2004; NCRP, 2013). A survey of emergency department patients and physicians at a major academic institution showed that none of the patients, 22% of the emergency department physicians, and only 13% of the radiologists had an accurate understanding of radiation dose from CT (Lee et al., 2004). Similarly, subsequent reports noted that 25% of physicians and 43% of medical students didn’t know that radiological interventional procedures employ ionizing radiation, and 9% of physicians were not aware that CT scans utilize ionizing radiation (Baerlocher and Detsky, 2010; Ricketts et al., 2013). A survey of physicians who order CT scans found that 64% underestimated the radiation doses involved in CT imaging. When asked if the lifetime risk of developing cancer was increased from one CT scan, 75% of physicians responded that this was true for pediatric patients and 58% responded affirmatively for adult patients. However, only 20% of these physicians specifically discussed the risk of radiation exposure with their patients (McBride et al., 2009). The medical and medical
physics communities have responded with a variety of measures to educate the professional and lay public, with on-line web-based programs, social media, and publicity campaigns (AAPM, 2011a; CDC, 2013; FDA, 2014a; Goske et al., 2008; HPS, 2014b; IG, 2014; IW, 2014; NCI, 2013a; NCRP, 2014; RADI, 2014; Timins, 2011).

It is inadvisable to assume that researchers who design human research protocols and IRB members who review these protocols are necessarily well-informed and knowledgeable on all facets of medical radiation, the magnitude and consequences of the radiation doses involved, how best to utilize examinations involving ionizing radiation in a research protocol, and how to communicate radiation-related risks to human subjects for purposes of obtaining informed consent. Additional unique and compounding concerns have to be considered for research related to cancer treatment and follow-up, where standard medical treatments (i.e., chemotherapy and radiation therapy) may increase the risk of stochastic effects such as future development of second primary cancers and radiation-related noncancer effects (NCRP Report No. 170, 2011). These risks should be explained in the context of potential benefit to the subject or, more likely, future benefit to others with the same or similar conditions.

2.2.1 History of Guidance and Regulations for Research Involving Human Subjects

The basic principles for the ethical conduct of human studies research have been articulated by international and national authorities. Among the seminal documents are the Nuremberg Code (NC, 1947), the Declaration of Helsinki (WMA, 2013), and the Belmont Report (DHHS, 1979). The Nuremberg Code was formalized during the Nuremberg Trials, in the aftermath of World War II, as a response to Nazi atrocities committed under the pretense of medical research (NC, 1947). The Code elaborates points defining legitimate medical research, establishes the requirement for beneficence toward research participants, and sets forth the elements essential to informed consent, including the absence of coercion. Additional criteria for informed consent, originally stated in the Declaration of Helsinki in 1964 and revised and expanded in 2013, include (item number 26 in WMA, 2013):
“In medical research involving human beings capable of giving consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

“After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject’s freely-given consent, preferably in writing. If the consent cannot be expressed in writing, the nonwritten consent must be formally documented and witnessed…” (WMA, 2013).

The international community has developed extensive guidelines for the ethical conduct of human research (DOE, 2012), including:

- International Guidelines for Ethical Review of Epidemiological Studies (CIOMS, 1991)
- Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products (WHO, 1995)
- International Conference on Harmonization Guidelines for Good Clinical Practice (ICH, 1996)
- Medical Research Council Good Clinical Practice in Clinical Trials (MRC, 1998)
- Operational Guidelines for Ethics Committees that Review Biomedical Research (WHO, 2000)
- International Ethical Guidelines for Biomedical Research involving Human Subjects (CIOMS, 2002)
• Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TRC, 2010)

The U.S. National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged with identifying the basic ethical principles and providing guidelines for human studies research (NRA, 1974). One product of this Commission was the Belmont Report (DHHS, 1979). The three basic ethical principles evinced in the Belmont Report are: respect for persons, beneficence, and justice.

The President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research was established in 1978 by Public Law 95-622 and issued its First Biennial Report in 1981. This report noted that most federal agencies had rules and policies protecting human subjects and that these largely conformed to the U.S. Department of Health and Human Services (DHHS) regulations, but small differences among these agency regulations created confusion. It recommended that all federal agencies adopt the regulations of DHHS. A prolonged effort in response to this recommendation produced the Federal Policy for the Protection of Human Subjects, also known as the ‘Common Rule,’ published in 1991 (DHHS, 2015a; FR, 1991). At present, fifteen federal agencies have adopted the Common Rule. Additionally, although it is not part of their regulations, the Central Intelligence Agency, the Department of Homeland Security and the Social Security Administration also comply with the Common Rule. Research involving human subjects sponsored, supported or otherwise subject to regulation by these departments and agencies must be conducted in accordance with the Common Rule.

The aforementioned documents have been the basis for on-going development of guidance by DHHS (2009; FDA, 2014k). In addition to elaborating requirements for informed consent, DHHS prescribes protections for potentially vulnerable research populations, including but not limited to pregnant women, children, prisoners, and cognitively impaired individuals, and provides guidelines for obtaining assent of minors. The Office of Human Research Protections (OHRP, 2014) is an oversight body under the auspices of DHHS. As noted on its website,
OHRP: “…provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (DHHS). OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research.”

These guidance documents and regulations apply to specific research circumstances. The Common Rule governs human studies research that is conducted or funded by any federal agencies that have adopted or comply with it. Human subjects research that is not conducted or supported by a Common Rule agency does not need to be conducted in accordance with the Common Rule. Institutions may voluntarily extend the protection of human subjects regulations, subpart A of which is the Common Rule, to all research at that institution regardless of funding source, and ~60% of institutions that have filed a Federal-wide Assurance with OHRP have opted to do so (DHHS, 2015b). The Common Rule has been substantially revised; this revision will take effect on January 19, 2018 (FR, 2017).

FDA regulations (21 CFR Part 50.1) apply to: “…clinical investigations that support applications for research or marketing permits for products regulated by the FDA, including foods, including dietary supplements, that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products…” (FDA, 2014j). While specific to products regulated by the FDA, these FDA regulations are compatible with the Common Rule. Research can be subject to both FDA regulations and the Common Rule (e.g., human subjects research involving an FDA-regulated device that is supported by an NIH grant).

Similarly, the regulations of the U.S. Nuclear Regulatory Commission (NRC) apply to research utilizing radioactive materials regulated by the NRC (10 CFR Part 35.6). State regulations may extend similar protections to research regulated by state agencies. However, some research involving the exposure of human subjects to ionizing radiation may not be subject to these regulatory requirements.
2.2.2 Issues Specific to Research Involving Ionizing Radiation to Human Subjects

The World Health Organization (WHO) and the International Commission on Radiological Protection (ICRP) have built upon the Declaration of Helsinki (WMA, 2013) by providing basic recommendations for the ethical use of ionizing radiation and radionuclides in human research (ICRP, 1991a; WHO, 1977). This has been further expanded upon by ICRP in Publication 62 (ICRP, 1992). In addition to ethical concerns, among the topics discussed are radiation risks, risk assessment, and principles of study design specific to research involving ionizing radiation. The need for and nature of informed consent elaborated in this document provide a good basis upon which to build current guidance.

Recent years have seen the development and increasing utilization of radiological innovations resulting in substantially greater medical radiation exposure to the U.S. population (NCRP, 2009a). This includes diagnostic studies such as CT imaging, PET/CT fusion imaging and CT brain perfusion imaging, FGI procedures, and radiation oncology treatment modalities such as intensity-modulated radiation therapy (IMRT) and particle-beam radiation therapy. Increased radiation exposure has raised the concern of increased potential health risks (Berrington de Gonzalez et al., 2009; Hall and Giaccia, 2012; NCRP, 2009a; Smith-Bindman et al., 2009). The complexities of the newer radiation-based medical technologies can make communication with potential research subjects more challenging. Evidence indicates that some biological effects of radiation, such as cataractogenesis and cardiovascular and circulatory disease, may occur at radiation doses and dose rates lower than previously thought (ICRP, 2012; NCRP, 2010a; 2011; 2016). Radiation exposure, even later in life (i.e., middle age), can be associated with an increased risk of cancer (Shuryak et al., 2010). An understanding of these risks should be conveyed to the prospective study volunteer.

Research protocols routinely include estimates of the risk for the radiation absorbed doses, consideration of the balance of risk to benefit, and informed consent statements. When considering the use of ionizing radiation, it is important to keep in mind that: “...the potential
benefit to society, by increase of knowledge, must be weighed against the potential harm to the exposed individual…” (ICRP, 1992). That is, the level of risk from the radiation doses used in the research study should not be disproportionate to the possible benefit to the research study subjects or to society. Evaluation of the risk to subjects from radiation exposure usually involves: (1) estimation of the radiation absorbed doses to various body tissues and organs of the subjects, and (2) estimation of risks from the calculated doses. Estimation of risks for stochastic effects, except for hereditary effects, is based largely on epidemiological studies of human populations. There are considerable uncertainties in the estimated radiation doses and in the risk per unit dose to specific organs and tissues. It is difficult to predict lifetime risks from the low doses seen in diagnostic medical radiation exposures and the low, protracted radiation exposures often seen in occupational radiation exposures (AAPM, 2011a; Boice, 2010; NCRP, 2012a). Detailed risk estimates can be expensive to generate, and results of risk estimations can vary substantially among investigators and institutions.

Many academic institutions have developed their own guidelines for informed consent in human research, including research involving radiation, resulting in substantial variability between institutions. Institutional informed consent documents employ different quantities and units to express radiation dose. Some use effective dose (E) or equivalent dose in mSv, some use mrem, and some use both mrem and mSv (IU, 2013; NIH, 2001; UCI, 2013; UCSF, 2014; UMMS, 1998). One references radiation exposure comparisons in the unit “mr,” but it is unclear whether this refers to millirem (mrem) or milliroentgen (mR) (Drexel, 2013).

Effective dose relates to stochastic effects, including probability of cancer induction and hereditary effects, but is not applicable to tissue reactions, such as tissue damage. Since E was a metric developed for purposes of radiation protection, if it is used in the context of research then adjustments must be made to the risk estimation. These adjustments account for differences between a healthy worker population of both genders and a human studies population. Alternatively, measures other than E may be used (ICRP, 1991b) (Section 3).
In communicating radiation risks to prospective study subjects, various analogies are being used, such as comparison with numbers of chest x rays, numbers of transcontinental air flights, and years of exposure to background radiation. There is a lack of standardization of language and a lack of uniformity in risk quantification.

The goal of informed consent is to educate prospective subjects about risk and benefits, and to aid them in making informed decisions about participation (Reiman, 2013). Historically, there has been concern regarding the standardization of language in expressing radiation dose and risk estimates for the purposes of informed consent, and in determining what elements are important to convey to the study population (Alazraki, 1982; Cameron, 1991; Castronovo, 1993; Masse and Miller, 1985; Veatch, 1982). The need for clear explanatory language at an elementary school reading level (i.e., eighth grade or lower) has been stated (Paasche-Orlow et al., 2003; NCI, 1998). In addition to simplified language, study populations often benefit from tailored techniques such as interactive instruction, visual examples, and graphic displays to help them understand risk (Doak et al., 1998; Fahey et al., 2011; Marcus, 2014; Picano, 2004).

Levels of radiation exposure and the associated risks vary considerably amongst research studies. For example, research protocols for radiation treatment of cancer usually employ very high radiation exposures, while studies evaluating bone density often use dual energy x-ray absorptiometry, which delivers an extremely low radiation dose. The description of the magnitude of radiation risk in the informed consent document should be sufficient to adequately inform research subjects.

In some research that includes radiation exposure to human subjects (e.g., a study of physiology or diagnostic imaging done to evaluate the success of an experimental therapy), the risk analysis compares the risks from the radiation exposure to risks following no exposure. However, in other cases, the research involves a new method or protocol for medical imaging or a new therapeutic procedure or protocol. In such cases, there is commonly an existing method or protocol that is considered standard of care. In these cases, the risks and potential benefits from
the new method or protocol must be compared with the risks and benefits from the standard method or protocol.

Particularly in radiation oncology research, the goal is to create a new method or protocol for the treatment of disease. However, there is commonly an existing method or methods for the treatment of the same disease. In this case, the goal is to develop a new method or protocol that is more effective than the existing methods, produces less adverse effects, or both. Thus, the risks and the effectiveness of the new method or protocol must be compared with both the risks and the effectiveness of the existing method or methods in curing or palliating the disease. The risks that must be considered are whether acute and/or delayed tissue reactions are more severe than those from standard treatments, whether detriment from second primary cancers is greater than that from standard treatments, and whether the treatment is less effective than standard treatments.

2.2.3 Scope of the Report

Topics included in this Report are:

- basic information on radiobiology and radiation dose metrics;
- regulatory requirements for institutional supervision of research;
- identification of experimental studies utilizing ionizing radiation;
- distinguishing between radiation required for standard patient care and that incurred specifically by research study design;
- assessment of proper utilization of radiation in a research protocol;
- estimation of radiation dose;
- estimation of radiation risks, including adjustments for specific populations (e.g., young children versus terminally ill adults);
- optimization of radiation dose;
- ethical considerations in human studies research;
important elements of informed consent for protocols involving ionizing radiation,
including appropriate risk language; and
examples of language for informed consent.

The use and risks of imaging contrast media, such as iodinated contrast material for some x-ray imaging examinations (e.g., CT and FGI procedures) and gadolinium-based contrast agents for magnetic resonance imaging, are not included in the scope of this Report. Contrast media are regulated by FDA as pharmaceuticals. Additional information on contrast media is available from the American College of Radiology and FDA (ACR, 2013a; FDA, 2007; 2009b).
3. Basics of Radiobiology, Radiation Protection and Radiation Dose

Knowledge of the basic principles of radiation biology and of the metrics used to quantify radiation exposure is important for those designing, conducting or reviewing protocols of research that involves radiation to humans. This Section provides basic concepts of radiobiology, including effects of ionizing radiation on DNA, the distinction between tissue reactions and stochastic effects, and the linear nonthreshold model. There is information on the effects of radiation to people of different ages (i.e., adults versus children), radiation exposure to the fetus, and potential radiation risks to family members of those treated with radioactive drugs (Section 3.1).

Principles of radiation protection have been developed by the international community and have been adopted widely, including in the United States. These are: (1) justification of radiation exposure, (2) maintaining radiation exposure ‘as low as reasonably achievable’ (ALARA) and (3) limitation of dose. These principles are detailed below (Section 3.2).

The deposition of energy from ionizing radiation is quantified in a number of ways, such as radiation dose, absorbed dose, and effective dose. These and other quantities and units of radiation are defined and their applications are described. There is a discussion of the utilization of organ dose and effective dose as dose metrics for risk estimation. Dose metrics particularly applicable to fluoroscopy and computed tomography are defined, as are measures of radioactivity (Section 3.3).

3.1 Basic Radiobiology

Radiation effects to living tissue are believed to be primarily due to damage to deoxyribonucleic acid (DNA) (Hall and Giaccia, 2012). Ionizing radiation can cause damage to DNA indirectly by production of reactive oxygen species, and to a lesser degree by direct energy absorption. This can cause many types of damage, including base damage such as broken rings, oxidized bases, small and large adducts including DNA-DNA and DNA-protein crosslinks,
single-strand breaks, and double-strand breaks (NCRP, 2015). When DNA damage is not adequately repaired, the results may include cell death, lack of cell reproduction, mutation, and/or carcinogenesis (Hall and Giaccia, 2012; NA/NRC, 2006).

The biological effects of radiation exposure are determined by several factors in addition to the doses of radiation to the various organs and tissues. These include the type and energy of the radiation. Types of radiation that produce dense ionization tracks (i.e., high-linear energy transfer), such as alpha particles, are more damaging per unit dose than x and gamma rays which produce sparse ionization tracks. There is some evidence that x and gamma rays with low photon energies, such as those used for mammography, cause more biological damage per unit dose than do those with higher energy photons (NA/NRC, 2006). For radiation therapy and some high dose interventional procedures, the dose rate and fractionation scheme affect the amount of biological damage. Delivering the radiation at a lower dose rate or dividing the dose into fractions separated in time reduces the amount of biological damage. There are genetic factors, discussed below, that affect the amount of damage per unit dose. Some diseases increase the susceptibility to radiation injury. Some chemicals reduce or enhance the amount of damage per unit dose; in particular, some chemotherapy drugs enhance the damage. The effects of these modifying factors are more clearly understood for tissue reactions than for stochastic effects (Hall and Giaccia, 2012).

Several textbooks are available for more in-depth information on the biological effects of ionizing radiation (Hall and Giaccia, 2012; Mettler and Upton, 2008).

3.1.1 Tissue Reactions and Stochastic Effects

Tissue reactions are characterized by cell damage or inflammatory reaction. Clinically significant tissue reactions are biological injuries that result from the death or loss of the reproductive capability of large numbers of cells and perhaps from the body’s reaction (e.g., fibrosis) to this injury. Radiation exposures that cause tissue reactions must be above some threshold dose before a clinically significant injury can be observed. The threshold dose often depends on the dose rate. Once the threshold is reached for a given dose rate, the severity of the injury increases with absorbed dose (ICRP, 2007a). Examples of tissue reactions include skin
and dermal injuries (ranging from erythema to dermal necrosis) and radiation-induced bone marrow depression.

Stochastic effects, in the context of radiation protection, are defined as biological consequences whose probability of occurrence increases with absorbed radiation dose, but whose severity is not dose dependent. Stochastic effects are considered to have no dose threshold. Cancer and heritable genetic effects are considered to be stochastic effects. Increased cancer incidence and mortality have been observed in human populations exposed to large doses of radiation, such as the atomic-bomb survivors in Japan (NA/NRC, 2006). However, such effects have not been detected at lower doses, possibly due to the inherent limitations of epidemiological studies of low-dose effects.

3.1.2 Linear-Nonthreshold Dose-Response Model

A model is necessary to estimate the risk of stochastic effects for people exposed to low doses of radiation (i.e., doses $<100$ mSv). Even if stochastic effects exist at these doses, epidemiological studies lack the power to demonstrate them. For radiation protection purposes, it has generally been assumed that the probability of stochastic effects increases linearly with absorbed dose, without a threshold for the onset of detriment. This paradigm is called the linear-nonthreshold (LNT) dose-response model or theory (NCRP, 2001b; NA/NRC, 2006). An epidemiological study of the United Kingdom Registry of Radiation Workers yielded results consistent with LNT theory (Muirhead et al., 2009). However, experimental observations such as bystander effects and adaptive responses are fostering debate over whether there is a level of ionizing radiation exposure below which there is no increased risk of the late onset of adverse health effects, such as cancer (de Toledo and Azzam, 2006; Tubiana et al., 2009). This is an area of ongoing research and the applicability of these effects, which are seen in animal models and cell cultures, to human exposure is unclear (Groesser et al., 2008; Hei et al., 2008; Sowa et al., 2010). Furthermore, if a lower threshold exists, it is likely to vary in magnitude among individuals, due to environmental factors and genetic susceptibility. Gender is an additional consideration: there is evidence from the Life Span Study (LSS) of atomic-bomb survivors that
radiation dose response among females is consistent with linearity, but a linear-quadratic model may better fit male dose response (Grant, 2016).

The LNT dose-response model or theory was referred to as an ‘hypothesis’ by NCRP in Report No. 136 (NCRP, 2001b). Recognizing that the use of LNT has been focused on radiation protection rather than medical exposure optimization (Section 3.2), NCRP concluded: “…there is no conclusive evidence on which to reject the assumption of a linear-nonthreshold dose-response relationship for many of the risks attributable to low-level ionizing radiation although additional data are needed… the probability of effects at very low doses such as are received from natural background… is so small that it may never be possible to prove or disprove the validity of the linear-nonthreshold assumption.”

3.1.3 Radiation Effects and Risks to the Individual, Fetus, and Family Members

This section details the radiation risks and effects to the individual primarily exposed, and to the fetus and family members who may be secondarily exposed. Also discussed is controlling risk to family members, including nursing infants.

3.1.3.1 Radiation Effects to the Individual. Factors influencing the effects of radiation to the individual include: radiation dose to organs; the individual’s age, weight and genetic predisposition to radiation sensitivity; personal habits such as smoking; state of nutrition; and medications such as specific chemotherapeutic drugs (NCRP, 2011). The expected life span of the individual is also a consideration. All tissues are affected by radiation to some degree. Tissues susceptible to injury (i.e., noncancer effects) include the lens of the eye, cardiovascular system, skin and subcutaneous tissue. Discussed below are tissue reactions affecting representative tissues: the lens of the eye, cardiovascular system, skin and subcutaneous tissue. This is not meant to be a complete discussion, but is provided for illustration.

That radiation can cause cataracts has been known for many years. In the past, the induction of cataracts by radiation was believed to have a dose threshold on the order of 2 Gy if delivered in a single exposure, and as such was regarded as a tissue reaction (ICRP, 1984; 2000).
However, more recent epidemiological evidence points to induction of cataracts at substantially lower radiation doses; therefore, there may not be a definite dose threshold and it is possible that radiation cataractogenesis may be stochastic in nature (Ainsbury et al., 2009; Cucinotta et al., 2001; ICRP, 2012; NCRP, 2016; Worgul et al., 2007).

Cardiovascular effects of radiation may be seen following the high radiation doses utilized in radiation therapy for cancer, and are due to fibrosis, with capillary and arterial narrowing (Taunk et al., 2015). This can result in ischemic heart disease and myocardial infarction. In survivors of childhood cancer, cardiac-dose-dependent increases in the incidence of congestive heart failure, myocardial infarction, pericardial disease, and valvular disease have all been observed (Mulrooney et al., 2009).

Radiation-induced skin injuries are a well-known complication of external beam radiation therapy and some types of brachytherapy, and have been recognized as a complication of FGI procedures (Hymes et al., 2006; ICRP, 2000; NCRP, 2010b; Shope, 1996; Sovik et al., 1996). Such tissue reactions occur in a localized area and can be predicted by the dose delivered in that area. This dose may have been delivered by one procedure or by a series of procedures. In FGI procedures the most severe reactions occur at the locations in the skin or other organs that have received the highest doses (peak tissue doses). Although commonly referred to as skin injuries, severe cutaneous radiation injuries may extend into the hair follicles, subcutaneous fat, muscle and underlying bone (Balter et al., 2010; Balter and Miller, 2014; NCRP, 2010b).

Tissue reactions commonly occur in radiation oncology and the need to avoid unacceptable tissue reactions may limit the ability to achieve a cure or local tumor control. For external beam radiation oncology and brachytherapy (treatment using sources of radiation, commonly containing radioactive material, placed in or near the target volume), tissue reactions usually occur in tissues near the target volume because of the large radiation doses they receive. In the case of therapy with radiopharmaceuticals (also called radionuclide therapy), where radiation is delivered by binding a radionuclide to a pharmaceutical that transports the compound to a desired target, the tissue reactions may occur in other tissues that accumulate the
radiopharmaceutical. In therapies with intra-arterial delivery of radioactive microspheres, tissue reactions may occasionally occur in distant tissues if blood flow carries a substantial fraction of the microspheres to these tissues. Tissue reactions evolve with time after radiation exposure, in some cases largely or partially resolving and in other cases, worsening. In radiation oncology, tissue reactions are sometimes categorized as acute effects or late effects. The National Cancer Institute-funded Radiation Therapy Oncology Group provides schemes for scoring such toxicities (RTOG, 2015a; 2015b).

Some individuals are genetically more susceptible than others to radiation-induced carcinogenesis, putting them at higher risk (Sigurdson and Stram, 2012). Examples are people with the ataxia telangiectasia mutated serine/threonine kinase gene (ATM) (NIH, 2013) or Nijmegen breakage syndrome gene (NBS) (NIH, 2011a). Genetic factors affect genomic stability as well as the capacity and efficacy of repair of DNA damage. Alterations in the ability to repair radiation-induced DNA damage affect the risk of radiogenic cancer. Homozygous individuals with these mutations are at greatest risk, but studies have shown increased risk to heterozygous individuals as well (Barlow et al., 1999).

Age at exposure affects the risk of radiation-induced carcinogenesis in adults and children, with the risk usually inversely related to age. In general, children are more sensitive to the carcinogenic effects of radiation than adults, both from internal (i.e., administered radionuclides) and external radiation (Hall and Giaccia, 2012). UNSCEAR (2013) noted: “For a given radiation dose, children are generally at more risk of tumour induction than are adults…” possibly by a factor of two to three times that of a population exposed at all ages. When compared to adults, radiation carcinogenesis in children is quite variable, with tumor type a significant factor. For 23 tumor types, children are more radiosensitive for ~25 % of tumors (e.g., leukemia, thyroid, skin, breast, brain), children and adults are equally sensitive for ~15 % of tumor types (e.g., bladder cancer), children are less radiosensitive for ~10 % of tumor types (e.g., lung), there are insufficient data for ~20 % of tumor types (e.g., esophagus), and for ~30 % of tumor types there is no relationship between radiation and risk at any age (e.g., Hodgkin lymphoma, prostate, rectum, uterus) (UNSCEAR, 2013). Another factor contributing to
increased risk of radiogenic cancer in children is their longer life expectancy. As a result, radiogenic cancers with long latent periods (i.e., decades) have time to develop and become apparent.

Children exposed to iodine radioisotopes from the Chernobyl nuclear reactor disaster had an up to 10 times greater incidence of thyroid cancer than children living in affected regions prior to the Chernobyl accident (Demidchik et al., 2007). Similarly, children who received external beam radiation therapy for Tinea capitis (ringworm of the scalp) or to shrink an enlarged thymus gland also had a significantly increased incidence of thyroid cancer (Ron et al., 1995).

NCRP Report No. 174 cites support for a statistical association between childhood leukemia in offspring and the mother’s exposure to diagnostic x rays during pregnancy, with estimated relative risk (ERR) of 1.3 based on a meta-analysis of 32 case-control studies (NCRP, 2013). The Japanese Atomic-Bomb Survivor Study compared adult leukemia and cancer risks following in utero exposure (Kato and Keehn, 1966). A statistically-significant ERR of solid cancers in adulthood was reported (Delongchamp et al., 1997). Comparison was made between persons exposed in utero and those who were aged 0 to <6 y at the time of the bombings. The small number of deaths from leukemia in the in utero cohort and the absence of a dose-response relationship complicate efforts to compare the leukemia mortality risks in the two cohorts (NCRP, 2013). While a statistically-significant radiation-dose related increase in solid cancer risks was demonstrated in both groups at attained 50 y of age, there was a substantially lower increase among those exposed in utero, compared to those exposed in early childhood (Preston et al., 2008).

The radiosensitivity of the exposed anatomical site or organ is important. For many organs radiosensitivity changes over time. The female breast is very radiosensitive in childhood, adolescence and early adulthood, becoming progressively less sensitive with age. However, the risks of some radiation-induced cancers do not drop off sharply with increasing age at exposure. Shuryak et al. (2010) note that: “…there is good evidence…that the excess lifetime risks of lung cancer do not decrease in middle age and indeed may peak at around age 50 years…”
Gender is another factor: women tend to be at higher risk of radiation-induced cancer than men, primarily due to a higher risk of breast cancer and also cancers of the female reproductive organs and the thyroid (Hall and Giaccia, 2012; NA/NRC, 2006). Women with tuberculosis, who underwent multiple chest fluoroscopy procedures during treatment and received substantial radiation to the breasts, had an increased incidence of breast cancer (Boice et al., 1991). So did girls treated with mantle field external-beam radiotherapy for Hodgkin lymphoma (Bhatia et al., 1996). However, men are also at risk from radiation. Between 1920 and 1929, when most physicians were men, in the U.S. radiologists had as much as nine times greater leukemia mortality than physicians not exposed to radiation (Matanoski et al., 1975; Yoshinaga et al., 2004). Uranium miners, virtually all men, had a substantially increased incidence of lung cancer (Roscoe et al., 1995; Roscoe, 1997).

Previous radiation therapy treatment conveys an increased risk for second primary cancer, as well as for cardiovascular disease (NCRP, 2011). More than half of all cancer patients in the United States undergo radiation therapy. The increased rate of cancer survivorship over the past several decades has raised concerns over the risks of radiation-induced second primary cancers and cardiovascular disease.

3.1.3.2 Heritable Genetic Effects. At present there is no direct evidence that preconception radiation causes heritable disease in human offspring (NA/NRC, 2006; NCRP, 2013). Furthermore, follow-up of children whose parent or parents were atomic-bomb survivors from Hiroshima or Nagasaki reveals no increase in death from cancer or from noncancer diseases in these offspring (Grant et al., 2015). However, radiation can induce mutations in microbes and in mammalian somatic cells. Heritable genetic effects from ionizing radiation have been demonstrated in drosophila (Muller, 1959) and mice (Russell and Russell, 1992). Hence, the possibility of heritable effects in humans cannot be ruled out.

3.1.3.3 Radiation Effects to the Fetus. By convention, the age of the conceptus correlates with the starting date of the pregnant woman’s last menstrual period, which is approximately two
weeks prior to conception. Therefore, the ‘gestational age’ (also known as ‘fetal age’) is two weeks more than the embryonic age based upon date of conception. It is important to make this distinction when discussing radiation effects in the developing embryo or fetus.

If the embryo is exposed to a significant amount of radiation (i.e., at least 0.15 to 0.2 Gy) within three to four weeks of gestational age, which are the first two weeks post-conception, there is an ‘all or none’ phenomenon of either radiation-induced embryonic death or survival with no increased risk of fetal malformation (Table 3.1). When radiation occurs at gestational age of five to seven weeks (i.e., three to five weeks post-conception), adverse effects are not seen until the dose exceeds 0.2 to 0.5 Gy. Between 8 and 15 weeks of gestation, during major organogenesis, there is the greatest risk for irreversible whole-body growth retardation.

Development of the central nervous system is active from gestational weeks 10 to 27, during which the fetus is most vulnerable to intellectual impairment and mental retardation. Beyond this time, although adverse effects of radiation may be seen, the fetus is less radiosensitive. It is worth noting that in utero irradiation incurs a lower lifetime risk of radiation-induced malignancy than irradiation during childhood (NCRP, 2013) (Section 3.1.2.1).

### 3.1.3.4 Controlling Risk to the Nursing Infant from Radiopharmaceutical Administrations to the Mother

Some radiopharmaceuticals administered to the nursing mother for diagnostic nuclear medicine imaging or for radionuclide therapy are excreted via the mother’s milk (Stabin and Breitz, 2000). To minimize radiation exposure to the nursing infant, breast-feeding should be managed to incur an effective dose no >1 mSv to the infant (ICRP, 2008; NCRP, 2013). For agents labeled with $^{99m}$Tc, the most commonly used isotope in nuclear medicine imaging, ICRP (2008) recommends interruption of nursing for 0 to 12 h post-administration, depending upon the specific radiopharmaceutical preparation. Milk expressed during this time should be discarded. A three week or longer interruption of nursing is recommended for most diagnostic radiiodine compounds labeled with $^{131}$I and $^{123}$I. When therapeutic doses of radionuclides are administered to the nursing mother, such as $^{131}$I for radiiodine treatment of hyperthyroidism or thyroid cancer, breast feeding should be terminated three to four weeks prior to therapy. This not only protects the nursing infant from ingesting radioactive milk, it also protects the mother from...
### Table 3.1—Summary of health effects from ionizing radiation exposure of the embryo or fetus during pregnancy (adapted from NCRP, 2013).

<table>
<thead>
<tr>
<th>Human Gestational Stage (weeks)</th>
<th>Comments&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heritable Disease</strong></td>
<td></td>
</tr>
<tr>
<td>1st and 2nd weeks prior to conception (begins on the 1st day of the last menstrual period)</td>
<td>Irradiation of ova or sperm prior to conception. The mother has not yet ovulated. In humans, there is no convincing evidence of excess heritable disease in the offspring.</td>
</tr>
<tr>
<td><strong>Embryonic or Fetal Loss, Malformations, Growth Retardation&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
</tr>
<tr>
<td>3rd and 4th weeks of gestation (1st and 2nd weeks post-conception)</td>
<td>Minimum human acute lethal dose for the embryo (derived from animal studies) is estimated to be in the range 0.15 to 0.2 Gy. This is the most vulnerable period for the increased risk of radiation-induced embryonic death. The risk of a viable malformed fetus at term is not increased (&quot;all-or-none&quot; period).</td>
</tr>
<tr>
<td>5th to 7th weeks of gestation (3rd to 5th weeks post-conception)</td>
<td>Minimum human acute lethal dose for the embryo (derived from animal studies) is estimated to be in the range 0.25 to 0.5 Gy. The no-adverse-effect level for the induction of birth defects increases during this period and doses &gt;0.5 Gy are necessary to induce major malformations at the end of this period. The induced growth retardation during this period is not as severe as during the 8th to 15th weeks of gestation, and the embryos have a greater capacity to recover from the in utero growth retardation effect. The no-adverse-effect level is in the range of 0.2 to 0.5 Gy.</td>
</tr>
<tr>
<td>8th to 15th weeks of gestation (6th to 13th weeks post-conception)</td>
<td>Minimum human acute lethal dose for the fetus (derived from animal studies) is estimated to be &gt;1 Gy. The most vulnerable period for irreversible whole-body growth retardation. The no-adverse-effect level is in the range of 0.25 to 0.5 Gy.</td>
</tr>
<tr>
<td>Time Period</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>16th to 25th weeks of gestation (14th to 23rd weeks post-conception)</td>
<td>Minimum human acute lethal dose for the fetus (derived from animal studies) is estimated to be ~2 Gy. Growth retardation can be produced, although the effects are not as severe as occurs from the 8th to 15th weeks of gestation. Since all the organs have been formed, the important risk of irradiation is cell depletion in the brain and gonads.</td>
</tr>
<tr>
<td>26th week to term delivery (24th week post-conception to term)</td>
<td>During the last 15 weeks of pregnancy the doses that have deleterious effects on growth, mortality, the central nervous system, and the gonads would have to be increased. It is difficult to utilize animal studies to determine the no-adverse-effect level for various deleterious effects since there is marked discordance in development of the human brain and the rodent models that are used in this type of research.</td>
</tr>
<tr>
<td>Cognitive Impairment(^b)</td>
<td>Severe mental retardation observed at doses &gt;0.5 Gy (lower 95 % CI(^d) value of ~0.3 Gy). Decreases to intelligence quotient (IQ) and impaired school performance also observed for this period. Severe mental retardation was not observed prior to the 8th week post-conception or after the 25th week post-conception.</td>
</tr>
<tr>
<td>Oncogenic Effects (cancer)</td>
<td>The lifetime risk of oncogenic effects following in utero irradiation appears to be lower than that following irradiation during childhood. There are no data available that inform on which stages of pregnancy may be the most vulnerable to the oncogenic effects of irradiation.</td>
</tr>
</tbody>
</table>

\(^a\)Extended discussions of the health effects are found in Section 3.1.2.2.  
\(^b\)There is no evidence of increased risks of these effects with doses to the embryo or fetus <0.1 Gy.  
\(^c\)All doses refer to the dose to the embryo or fetus and are for low-LET radiation.  
\(^d\)CI = confidence interval
excessive breast irradiation since the physiology of lactation results in substantial uptake of radioactive iodine in the breast (ICRP, 2008; NCRP, 2013). When considering administration of a radionuclide that would require prolonged (i.e., >24 h) suspension or cessation of nursing and when recommending prolonged suspension or cessation of nursing following radionuclide administration, the risks of impairment of lactation and abrupt weaning should be considered.

3.1.3.5 Controlling Radiation Risk to Family Members. It is worthwhile to reassure research participants and their families that exposure of the subjects to external sources of radiation does not pose a radiation hazard to family members, nor does exposure to removable sources of radiation once those sources have been removed. Patients who are administered radionuclides or implanted with sealed sources of radioactive material for brachytherapy can become sources of radiation exposure to their family members and close contacts. For diagnostic agents utilizing 99mTc, which has a relatively short effective half-life, it is reasonable for the patient to refrain from unnecessarily holding an infant or small child for 12 to 18 h following administration (NCRP, 2013). Advice regarding other diagnostic radiopharmaceuticals should be specific for the radiopharmaceutical administered. For patients undergoing radionuclide therapy or brachytherapy, advice should be provided by the medical or health physicist or administering physician.

3.2 Framework for Radiation Protection

The current framework for radiation protection in the United States is based on the U.S. Nuclear Regulatory Commission regulation in 10 CFR Part 20 “Standards for Protection Against Radiation” (NRC, 2008); this framework is consistent with NCRP recommendations published in Report No. 116 (NCRP, 1993b). Of note, NCRP Report No. 116 focused on occupational radiation exposure and did not include discussion of exposure of patients and human research subjects. The 1993 recommendations were based on available information, including the 1990 report by the National Research Council of the National Academies (NA/NRC, 1990) on the effects of low-levels of ionizing radiation on populations, known as the BEIR (Biological Effects of Ionizing Radiation) V report. That report provided information regarding stochastic effects
and tissue reactions derived from the study of populations exposed to ionizing radiation. Risk estimates provided by NCRP (1993a) focused on stochastic risk for the major potential outcomes of cancer or genetic (inheritable) effects following ionizing radiation exposures. As of 2016, the 1993 recommendations are being reviewed and revised, with consideration of information from, among other sources, BEIR VII (NA/NRC, 2006) and ICRP Publication 103 (ICRP, 2007a) recommendations.

In its 1993 recommendations, NCRP (1993b) established a framework for radiation protection composed of three principles:

- **Justification**: the need to justify any activity which involves radiation exposure, on the basis that the expected benefits to society exceed the overall societal costs.
- **ALARA (optimization)**: the need to ensure that the total societal detriment from such justifiable activities or practices is maintained as low as is reasonably achievable (ALARA), economic and social factors being taken into account.
- **Limitation**: the need to apply dose limits to ensure that use of justification and ALARA does not result in individuals or groups of individuals exceeding levels of acceptable risk.

NCRP recognized that the ALARA principle was essentially synonymous with the term optimization of protection used by the ICRP (1989a). A major goal of the effort in NCRP Report No. 116 (NCRP, 1993b) was to relate U.S. recommendations, and any adjustments, to ICRP Publication 60 (ICRP, 1991a) to form guidance for the U.S. Nuclear Regulatory Commission to use in the formulation of rule-making, leading to possible changes in the regulatory dose limits for occupational workers. These three elements are essentially the same as those in current ICRP recommendations on radiation protection (ICRP, 2007a).

When dealing with medical exposures of patients, it should be kept in mind that the concept of ALARA is only part of the concept of optimization of protection. ICRP Publication 105 (ICRP, 2007b) clarified the meaning of ALARA for medical exposures: “The optimisation of
radiological protection means keeping the doses ‘as low as reasonably achievable,’ economic
and societal factors being taken into account, and is best described as management of the
radiation dose to the patient to be commensurate with the medical purpose.” The ICRP concept
implies, more precisely, keeping patient exposure to the minimum necessary to achieve a
required medical objective (diagnostic or therapeutic). In diagnostic imaging and x-ray guided
interventions, it means that the number and quality of images should be sufficient to obtain the
information needed for diagnosis or intervention.

3.3 Quantities and Units Describing Radiation Dose

In the discussion below, it is recognized that much of the historical literature (including
much of what is referenced in clinical trial submissions) uses the traditional radiation protection
units rather than the Système International (SI) units used in nearly all current literature
worldwide (NCRP, 1985). The transition to SI from traditional units has been complicated by the
retention of traditional units in the U.S. regulations for radiation protection (NRC, 2008). Simple
conversion factors are provided in the sections below and shown graphically in Figure 3.1
(BIPM, 2014; Bushberg et al., 2012).

3.3.1 Exposure

The term exposure has been used as a general term for being exposed to ionizing radiation,
but much of the older literature reported exposure as a radiation quantity: the amount of
ionization produced by the absorption of x- or gamma-ray energy in a small mass of air using the
SI unit of coulomb per kilogram (C kg⁻¹). This unit (defined only for photons in air with energy
less than several MeV) was named the roentgen (R) (i.e., 1 R = 2.58 × 10⁻⁴ C kg⁻¹). Older
metrics used in radiology relied on the use of the exposure concept [e.g., entrance skin exposure
Fig. 3.1. Conversion between traditional and SI units for quantities typically cited in radiation protection-related literature (adapted from BIPM, 2014; Bushberg et al., 2012).
3.3.2 Absorbed Dose

Absorbed dose ($D$) is the quotient of $d\epsilon$ by $dm$, where $d\epsilon$ is the mean energy imparted by ionizing radiation to matter of mass $dm$ at a point of interest:

$$D = \frac{d\epsilon}{dm} \quad (3.1)$$

Absorbed dose is a fundamental dose quantity for ionizing radiation, and should be used as the preferred quantity for estimating the risk of stochastic effects and tissue reactions for human research studies.

Mean absorbed dose in an organ or tissue ($D_T$), which is also referred to as organ dose, is calculated by integrating the absorbed dose $D$ over the mass of the organ or tissue and then dividing by the total mass of the organ or tissue. $D_T$ is defined as:

$$D_T = \frac{\epsilon_T}{m_T} \quad (3.2)$$

where $\epsilon_T$ is the total energy imparted in a tissue of organ $T$ and $m_T$ is the mass of that tissue or organ. The SI unit for $D$ and $D_T$ is joule per kilogram (J kg$^{-1}$) with the special name gray (Gy). The traditional unit for radiation absorbed dose was the rad, which was defined as the deposition of 100 ergs of energy in 1 g of matter (i.e., 0.01 J kg$^{-1}$). The conversion factor is 1 Gy = 100 rad.

3.3.3 Effective Dose

Effective dose ($E$) is a quantity used primarily in implementing a radiation protection system for workers and members of the public. It is the sum over specified organs and tissues of the products of equivalent dose ($H_T$) in a specific tissue and the tissue weighting factor for that tissue or organ ($w_T$):

...
where $H_T$ is the mean absorbed dose in a tissue or organ ($D_T$) weighted by a dimensionless value, the radiation weighting factor ($w_R$), for the type of radiation. The set of $w_R$ values accounts for differences in the biological effectiveness between different types of radiations. The $w_R$ values were selected by judgment, as stated by ICRP (2007a), after review of a broad range of experimental relative biological effectiveness (RBE) data and are independent of the tissue or organ irradiated. $w_T$ is the dimensionless factor by which $H_T$ is weighted to represent the relative contribution of that tissue or organ to the total health detriment resulting from uniform irradiation of the body (i.e., radiation detriment) (NCRP, 2013).

$E$ applies only to stochastic effects. The SI unit for both $E$ and $H_T$ is joule per kilogram ($J \text{ kg}^{-1}$) with the special name sievert (Sv). The traditional unit for $E$ was the rem, which was defined as the absorbed dose in rad modified by a radiation weighting factor ($w_R$) or quality factor ($Q$). The conversion factor is $1 \text{ Sv} = 100 \text{ rem}$. Table 3.2 provides $w_R$ values for various types of radiation. Table 3.3 provides $w_T$ values for various tissues or organs (NCRP, 2010a). Further discussion on $E$ is provided in Section 8.3 of this Report.

### 3.3.4 Linear Energy Transfer

Linear energy transfer (LET), $L$, in Equation 3.4, is the quotient of the mean energy $dE$ lost by charged particles due to all electronic interactions in traversing a distance $dl$ through a material:

$$L = \frac{dE}{dl} \quad (3.4)$$

The SI units for $L$ are joule per meter ($J \text{ m}^{-1}$), often expressed as keV $\mu\text{m}^{-1}$, where $1 \text{ keV} \mu\text{m}^{-1} = 1.602 \times 10^{-10} \text{ J m}^{-1}$. X and gamma rays (photons) used in medical research and clinical practice are low-LET radiations. High-energy heavy charged particles (e.g., protons and...
Table 3.2—Radiation weighting factors (w_R) for converting DT to HT for stochastic effects.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Particle Type</th>
<th>w_R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrons, from &lt;1 MeV to &gt;50 MeV</td>
<td>2.5 to 20</td>
</tr>
<tr>
<td>Alpha particles, fission fragments, alpha recoil nuclei, and nonrelativistic heavy ions</td>
<td>20</td>
</tr>
<tr>
<td>Protons, other than recoil protons, energy &gt;2 MeV</td>
<td>2</td>
</tr>
<tr>
<td>Electrons, positrons and muons, all energies</td>
<td>1</td>
</tr>
<tr>
<td>Photons (all energies of x rays and gamma rays)</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adapted from ICRP (2007a).
Table 3.3—Recommended tissue weighting factors ($w_T$).

<table>
<thead>
<tr>
<th>Tissue or Organ</th>
<th>$w_T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow (red), colon, lung, stomach, breast, and remainder tissues</td>
<td>0.12</td>
</tr>
<tr>
<td>Gonads</td>
<td>0.08</td>
</tr>
<tr>
<td>Bladder, esophagus, liver, and thyroid</td>
<td>0.04</td>
</tr>
<tr>
<td>Bone surface, brain, salivary glands, and skin</td>
<td>0.01</td>
</tr>
</tbody>
</table>

$a$Adapted from ICRP (2007a).

$b$Tissues included in the remainder are: adrenals, extrathoracic region, gallbladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (for males), small intestine, spleen, thymus, and uterus/cervix (for females). Determine the average dose to these tissues and apply the 0.12 weighting factor to the average dose.
heavy ions) have high-LET values. Interactions of neutrons, which are uncharged particles, with
matter produce energetic charged particles that have high-LET values (NCRP, 2013).

3.3.5 Other Dose Quantities

Peak skin dose ($D_{\text{skin,max}}$) is the highest absorbed dose accumulated during a fluoroscopic
procedure in any portion of a patient’s skin and is expressed in gray (Gy) (NCRP, 2010b). As of
2017, peak skin dose is not available for reporting in most fluoroscopy units in current use.

$D_{\text{skin,max}}$ can also be calculated for CT scans, though this is rarely necessary (de las Heras et al.,
2013; Leng et al., 2011).

Kerma ($K$) is the mean sum of the initial kinetic energies of all charged particles liberated by
uncharged particles per unit mass of specified material. The SI unit for kerma is J kg$^{-1}$. The
special name for kerma is the gray (Gy). Kerma can be quoted for any specified material at a
point in free space or in an absorbing medium (ICRU, 2011).

Cumulative air kerma ($K_{a,r}$), also referred to as “reference air kerma” or “reference point air
kerma,” reported in mGy or Gy, is the air kerma at a specific point in space (i.e., the air-kerma
reference point) in the center of the fluoroscopic x-ray beam. Most commercially available
fluoroscopy units provide $K_{a,r}$ information: it is required by the FDA on all fluoroscopic
equipment manufactured in the United States since June 10, 2006 (FDA, 2009a; NCRP, 2010b).
Some older publications have used terms such as “reference point dose” and “cumulative dose”
for this quantity. $K_{a,r}$ accumulates during a fluoroscopically-guided procedure. Although $K_{a,r}$ is
commonly used during and after a fluoroscopically-guided procedure to provide information
about the dose to the patient’s skin, it is not the dose to the skin of the patient; the skin may be
closer or farther from the x-ray source than the reference point, the x-ray beam may be incident
upon more than one area on the patient’s skin, the patient support table attenuation is ignored,
and $K_{a,r}$ does not account for air kerma from x-rays scattered from the patient.

Air kerma-area product, which has the symbol $P_{KA}$, is the product of air kerma (in Gy, mGy
or $\mu$Gy) at a point in the x-ray beam and the cross-sectional area of the x-ray beam (in cm$^2$ or m$^2$)
(Balter et al., 2012; Georges et al., 2014; Miller et al., 2012; NCRP, 2009; Padovani and Quai, 2005). As displayed by fluoroscopes, it does not include air kerma from x-rays scattered from the patient. Sometimes it is referred to as ‘dose-area product’ (DAP).

The computed tomography dose index volume \( (\text{CTDI}_{\text{vol}}) \) is approximately the average dose to a cylindrical acrylic plastic phantom, typically in units of mGy. Two phantoms are used, one 16 cm in diameter for the adult head and one 32 cm for the adult body (Bushberg et al., 2012; McNitt-Gray, 2002; NCRP, 2009).

The dose-length product \( (\text{DLP}) \) is the average \( \text{CTDI}_{\text{vol}} \) multiplied by the length (in cm) of the CT scan along the long axis of the patient, with units of mGy-cm. The DLP is a dose metric that is approximately proportional to the amount of x-ray energy imparted to the patient from the CT scan.

Various uses of these terms have been reported in the literature for a wide variety of medical radiographic equipment (Bushberg et al., 2012; McNitt-Gray, 2002; NCRP, 2009).

### 3.3.6 Administered Activity

Administered activity is the quantity of radioactive material, typically in MBq or mCi, given to a patient during a diagnostic or therapeutic procedure or to a research subject as part of an investigation; this is also referred to as the dosage. Administered activity is not the same as absorbed dose (Section 3.3.2). Absorbed dose or dose indicates the radiation dose delivered. The average absorbed doses to the various organs and tissues of the body depend upon the administered activity, the radionuclide, the chemical and physical form of the radionuclide, the route of administration (e.g., inhalation, ingestion, or intravenous injection), and considerations such as the subject’s body size and physiology. If all other factors are the same, the absorbed doses are usually proportional to the administered activity. The SI unit for activity is the becquerel (Bq). The traditional unit for activity was the curie (Ci). Figure 3.1 provides factors for converting between becquerel and curie.
4. Regulatory Requirements for Institutional Supervision of Research

This section provides information on federal guidance and regulation of research involving human subjects, and particularly such research that involves the use of radiation, emphasizing the requirements for radiation control, protection and safety. The roles and constitution of the Institutional Review Board (IRB) are discussed. Oversight of the institution’s radiation protection program by the Radiation Safety Committee (RSC) and Radiation Safety Officer (RSO) is described. There are differences in the regulation of radioactive materials and x-ray equipment. The use of radioactive materials falls under the jurisdiction of the U.S. Nuclear Regulatory Commission (NRC) and the Agreement States. The FDA is responsible for regulation of drugs (including radioactive drugs), biologics, medical devices, and the radiation emission aspects of products, including medical devices, that emit ionizing or nonionizing electronically-produced radiation (‘electronic products;’ e.g., laser pointers, microwave ovens, x-ray security screening systems, CT scanners, fluoroscopes, ultrasound equipment). Discussion of these topics follows.

4.1 U.S. Regulatory Structure for Human Research Radiation Protection

Research involving human subjects that is conducted, supported or otherwise subject to regulation by any federal agency or department that subscribes to the Common Rule (2.2.1) must be conducted in accordance with this regulation, which protects the rights and welfare of human subjects (DHHS, 2009). FDA regulates clinical studies of products (e.g., devices, drugs, or biological products for human use) that are subject to sections 505(1) and 520(g) of the Federal Food, Drug and Cosmetics Act (FD&C) or licensing provisions of the Public Health Service Act. A clinical study of any test article regulated by FDA must comply with 21 CFR Part 50 (protection of human subjects) and 21 CFR Part 56 (institutional review boards) (FDA, 2014k; 2014a; 2014e).
4.1.1 Institutional Review Board

As noted above, research supported by or subject to regulation by a federal agency or department governed by the Common Rule must consider protection of the rights and welfare of human subjects. To ensure this protection, these regulations require formally constituted institutional review boards (IRBs) to review and monitor biomedical research involving human subjects (DHHS, 2009). FDA has also issued regulations for the conduct of human subject research, including the composition, operation and responsibilities of an IRB under 21 CFR Part 50 (FDA, 2014j) and 21 CFR Part 56 (FDA, 2014g). IRBs that review FDA-regulated studies must register with FDA per 21 CFR Part 56.106 (FDA, 2014k). IRB membership requirements for the Common Rule (45 CFR Part 46 and others) and FDA are very similar, but not identical. “Requirements for IRB functions and operations” are also very similar, and differ primarily in reporting requirements, with FDA specifying reporting to the FDA and the Common Rule requiring reporting to the department or agency head and to the Office for Human Research Protection, HHS or the equivalent office within the appropriate federal department or agency (FR, 2017). For a comparison of FDA and HHS Human Subject Protection Regulations, refer to FDA (2009d). An institution that does not have its own IRB may participate in research by arranging for an ‘outside’ IRB to provide initial and continuing review of human studies research (FDA, 2014e).

IRB membership is specified under the Common Rule and 21 CFR Part 56.107(a) with the intention of having: “…members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution” (CFR, 2014). Membership requirements include: representation of both genders, at least one member with a scientific background and one from a non-scientific background, at least one member not otherwise affiliated with the institution, and recusal of members with a conflict of interest related to a matter before the board.

The Institutional Review Board Guidebook notes: “Most medical institutions have a radiation safety committee responsible for evaluating the risks of medical projects involving
radiation and limiting the radiation exposure of employees and patients. Nevertheless, IRBs should have an understanding of radiation and its biological effects so they can evaluate the risks and benefits of research proposals utilizing radioactive materials or X-rays” (DHHS, 1993a).

4.1.2 Radiation Safety Committee and Radiation Safety Officer

Most medical institutions have RSCs, although some smaller or less complex facilities may not. The RSC is the body responsible for all aspects of radiation protection within the institution, including clinical, educational, and research applications of ionizing (and in some institutions nonionizing) radiation. Sources of ionizing radiation may include x rays, as from standard radiography, fluoroscopy or CT scans; nuclear medicine procedures; and/or radiation therapy (Section 5). Most medical facilities are required to establish an RSC in accordance with 10 CFR Part 35.24, or equivalent state regulations, to oversee the uses of radionuclides permitted by the radioactive materials license (NRC, 2012). For facilities that utilize radioactive materials, membership in a medical RSC must include an authorized user (AU) for each type of radionuclide use permitted by the license (e.g., nuclear medicine physician, radiation oncologist), the RSO, a representative of nursing, and a representative of management who is neither an AU nor RSO. The AU is: “…a physician, dentist or podiatrist who meets the training and experience requirements for the type of medical use of radioactive material that they wish to carry out and is recognized by the radioactive materials license as such” (NRC, 2012). The RSC may include other members that the licensee considers appropriate. The RSC establishes policies, rules and procedures for the safe use of radiation and reviews and approves AU applicants.

Licensees are responsible for their radiation protection programs. The licensee’s management must appoint an RSO, who is responsible for implementing the radiation protection program. Minimum qualifications for an RSO include: a baccalaureate college degree or equivalent training and experience in physical, chemical, biological sciences, or engineering; and, training and experience commensurate with the scope of proposed activities (HPS, 2014a). More detailed specifications for a medical facility RSO are delineated in 10 CFR Part 35.50
The licensee must provide the RSO sufficient authority, organizational freedom, time, and resources to perform his or her duties.

The results of protocol reviews by an RSC or RSO are conveyed to the facility’s IRB. Coordination between the RSC or RSO and IRB is essential to assure that clinical trials are conducted responsibly and in compliance with regulatory requirements.

### 4.2 Regulation of Radioactive Materials and Electronic Products

#### 4.2.1 Regulation of Radioactive Materials

The medical, industrial and academic uses of radioactive materials are regulated by the federal government and/or state governments. The federal regulatory agency is the U.S. Nuclear Regulatory Commission (NRC). Portions of NRC’s regulatory authority may be transferred to a state by an agreement signed by the governor of the state and the chairman of the NRC, in accordance with Section 274 of the Atomic Energy Act of 1954 as amended, whereupon the state is termed an “Agreement State” (AEA, 1954). NRC and the Agreement States regulate sealed sources and devices, product manufacturing and distribution, medical and veterinary uses, industrial uses, academic and research uses, general license uses, and exempt consumer product uses of radioactive materials (NRC, 2015). Regulations promulgated by Agreement States must be compatible with those of the NRC. In addition, radioactive materials and devices intended for medical or veterinary use are also regulated by the FDA.

The federal regulations regarding radioactive materials license issuances are found in 10 CFR. NRC or the Agreement State issues specific licenses of limited scope or broad scope to facilities and medical users, based on their levels of experience, technical capabilities and the types of activities that will take place on the license. The type of radioactive materials license will define the authority and uses permissible under the license. The federal regulations applicable specifically to the medical use of radioactive materials are largely found in 10 CFR Part 35. “Medical use” includes the administration of radioactive material, or radiation from radioactive material, to human research subjects. Included in these regulations are “Provisions
for the protection of human research subjects,” which addresses the protection of the rights of human subjects involved in research by medical use licensees. Depending on the type of license held by the institution, prior approval from NRC or the Agreement State may not be necessary if the research is conducted, supported, or subject to regulation by another federal agency that has implemented the Common Rule. Whether or not a license amendment is required, licensees must have prior review and approval of the research activities by the IRB and obtain informed consent from human subjects in accordance with federal policy and regulations. Only radioactive materials authorized by the radioactive materials license may be used in human studies research, and only for the uses authorized in the license.

4.2.2 Regulation of Electronic Products

The FDA regulates products that emit electronically-produced radiation (termed electronic products). Electronic products include those that are not medical devices (e.g., x-ray security systems at airports, laser pointers, household microwave ovens) and those that are medical devices (e.g., CT scanners, ultrasound devices, linear accelerators, medical lasers) (Section 4.4). Medical devices are referred to hereafter as ‘devices.’ FDA may clear or approve medical devices:

- **Cleared medical devices** are ones that FDA has determined to be substantially equivalent to another legally marketed device. A premarket notification, referred to as a 510(k), must be submitted to FDA for clearance. A 510(k) is most often submitted by the medical device manufacturer.

- **Approved medical devices** are those devices for which FDA has approved a premarket approval (PMA) application prior to marketing. This approval process is generally reserved for high-risk medical devices and involves a more rigorous premarket review than the 510(k) pathway (FDA, 2015d).

FDA regulates clinical investigations performed to determine the safety and effectiveness of medical devices. States typically have regulations that apply to the use of x rays in private and
state medical, dental and veterinary facilities, but these state regulations do not apply to federal facilities. When ionizing radiation is delivered by a medical device (e.g., CT scanner, linear accelerator) as part of a clinical trial, and the clinical investigation is not performed to determine safety and effectiveness of the device itself, federal regulations are much less prescriptive. The facility should have a radiation protection program that oversees the use of x-ray equipment. In a facility that has an RSC, that committee typically also reviews human subject protocols incorporating the use of x-ray imaging examinations (e.g., radiographs, CT scans) and machine delivered radiation therapy (e.g., linear accelerators). In a facility without an RSC, the RSO will commonly review the study.

4.3 Investigational Drugs and Radiopharmaceuticals

An investigational drug [21 CFR Part 312.2(a)] may be used in a clinical study if the person (sponsor) responsible for initiating the study submits an Investigational New Drug (IND) application and FDA authorizes the study to proceed. An IND is required for a clinical study of an unapproved drug, or to study an approved product for a new indication or in a new patient population. Clinical studies of approved drugs may be exempted from an IND [21 CFR Part 312.2(b)].

The requirements for sponsors and for clinical investigators conducting a study under an IND are intended to protect the safety and the rights of subjects and are described in 21 CFR Part 312 (investigational new drug application). The person (sponsor) who assumes the responsibility and initiates the clinical study under an IND can be an individual (e.g., a physician) or an organization (e.g., corporation, academic center). A clinical investigator is a person who conducts a clinical study and under whose direction the investigational drug is administered or dispensed. A sponsor-investigator is an individual who initiates and conducts a clinical study. A corporate sponsor will often initiate studies conducted by multiple investigators at many facilities (i.e., a multi-center clinical trial).
FDA encourages sponsors to request advice in the pre-IND stage to promote efficient drug development. During a new drug’s early preclinical development, the primary goal is to characterize the drug product’s chemistry, manufacturing and controls (CMC), establish the pharmacologic target, and determine if the product is reasonably safe for initial use in humans. The pre-IND work focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

The clinical development of a new drug begins when the sponsor (either a drug manufacturer or physician), having screened the new molecule for pharmacological activity and toxicity in animals, is ready to test its safety and diagnostic or therapeutic efficacy in humans. To permit FDA review, IND applications must contain preclinical data (animal pharmacology and toxicology studies), any previous experience with the drug in humans and information pertaining to the chemistry, manufacturing, stability, and controls used for the chemical substance and the final drug product. The IND must also contain detailed protocols for the proposed clinical studies and information on the qualifications of the clinical investigators (generally physicians).

4.3.1 Radioactive Drugs and the Radioactive Drug Research Committee

A radioactive drug [21 CFR Part 310.3(n)] is: “…any substance defined as a drug in Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator\(^1\) which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace amounts of naturally occurring radionuclides…” (FDA, 2014h). In 1975, FDA issued regulations outlining when radioactive drugs for basic research in humans would be generally recognized as safe and effective, and

\(^1\) A nuclide generator contains a radionuclide that decays to another radionuclide (decay product) that is to be extracted and used. The original radionuclide is firmly bound in the generator and remains behind.
would therefore not be subject to the requirements for an IND (i.e., would not require an IND).

To qualify, these radioactive drugs must meet the requirements of the Radioactive Drug
Research Committee (RDRC) regulations (21 CFR Part 361.1). These regulations also provide
operational specifications for the RDRC, including specific committee and protocol requirements
(FDA, 2016b).

For the RDRC pathway to be applicable, the intent of the research project must be to obtain
basic information regarding the metabolism (including kinetics, distribution, and localization) of
a radioactively labeled drug or be related to gaining information on human physiology,
pathophysiology, or biochemistry. It is important that the intent of the study not be for immediate
therapeutic, diagnostic or similar purposes or to determine the safety and effectiveness of the
drug in humans (i.e., to carry out a clinical trial). Certain basic research studies (e.g., studies to
determine whether a drug localizes in a particular organ or fluid space and to describe the
kinetics of that localization) may have eventual therapeutic or diagnostic implications, but the
initial studies are considered to be basic research within the context of RDRC regulations.

Conditions for RDRC approval of the use of radioactive drugs in human studies research
include: (1) the study must be approved by the local RDRC, (2) the amount of active drug
ingredient administered causes no clinically detectable pharmacological effect, and (3) the
subjects must receive the smallest radiation dose with which it is practical to perform the study
without jeopardizing the scientific benefits of the study. Federal oversight requires that the
RDRC submit certain information to FDA, including up-to-date membership and annual
summary reports. FDA also conducts on-site inspections to assure all requirements are being
met. If an RDRC is seriously out of compliance with regulations, its approval may be withdrawn.

Any institution wishing to carry out RDRC studies must establish an RDRC with the
required committee membership, and apply to FDA for approval, or participate on a joint
committee with another medical institution: “Joint committees involving more than one medical
institution which have been established in order to achieve a high level and diversity of
experience will be acceptable” (FDA, 2016b). The RDRC works with the local IRB, and
research conducted under the auspices of the RDRC must also be approved by the local IRB. The RDRC also has direct reporting requirements to FDA under 21 CFR Part 361.1(c)(3). Each institution may establish its own reporting structure, but that does not supersede the FDA-mandated reporting requirements. One caveat to conducting RDRC studies is that under no circumstances can the radiation dose to an adult research subject from a single study, or cumulatively from a number of studies conducted within 1 y, exceed the limits shown in Table 4.1. For research subjects under 18 y of age, the radiation dose cannot exceed 10% of the adult values (FDA, 2016b).

4.3.2 New Drug Application and Abbreviated New Drug Application

When the sponsor of a new drug believes that enough evidence on the drug’s safety and effectiveness has been obtained through clinical trials to meet FDA requirements for marketing approval, the sponsor may submit a new drug application (NDA). The application must contain specific technical information including chemistry, manufacturing and controls, preclinical pharmacology and toxicology, clinical, and biopharmacologic data. If the application is approved, the new drug may be marketed in the United States.

An abbreviated NDA (ANDA) contains data that supports the approval of a generic drug product. Generic drug applications are called ‘abbreviated’ because preclinical (animal) and clinical (human) data to establish the safety and effectiveness of the drug are not required. Instead, an applicant must demonstrate that the generic drug is bioequivalent (i.e., not substantially different in the rate or extent at which the drug becomes available at the site of the drug action) to a reference listed drug (RLD). The RLD is the approved drug that the applicant relies on in seeking approval of the ANDA.
### Table 4.1—Limits for conducting RDRC studies on adult research subjects.\(^a\)

<table>
<thead>
<tr>
<th>Portion of Body</th>
<th>Dosing</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body, active blood-forming organs, lens of the eye, and gonads</td>
<td>Single dose</td>
<td>30 mSv (3 rem)</td>
</tr>
<tr>
<td></td>
<td>Annual and total dose</td>
<td>50 mSv (5 rem)</td>
</tr>
<tr>
<td></td>
<td>commitment</td>
<td></td>
</tr>
<tr>
<td>Other organs:</td>
<td>Single dose</td>
<td>50 mSv (5 rem)</td>
</tr>
<tr>
<td></td>
<td>Annual and total dose</td>
<td>150 mSv (15 rem)</td>
</tr>
<tr>
<td></td>
<td>commitment</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Adapted from 21 CFR Part 361.1(b)(3)(i) (FDA, 2016b)
4.4 Investigational Device Exemptions

With certain exceptions, clinical investigations of medical devices performed to determine safety and effectiveness, including those medical devices that emit electronically-produced radiation (e.g., radiography systems, CT scanners, linear accelerators), are subject to the requirements of 21 CFR Part 812 (investigational device exemptions) (FDA, 2015c), which are intended to protect the safety and the rights of the subjects. An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device. An approved IDE exempts a device from the requirements of certain sections of the Federal Food, Drug, and Cosmetic Act and certain FDA medical device regulations related to: misbranding; registration, listing, and premarket notification; performance standards; premarket approval; banned devices; records and reports; restricted device requirements; certain good manufacturing practice requirements; and color additive requirements [21 CFR Part 812.1(a)] (FDA, 2015c).

FDA distinguishes between devices that are significant risk devices and those that are not. A significant risk device is an investigational device that: “(1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject” [21 CFR Part 812.3(m)] (FDA, 2015c).

A sponsor (i.e., a person who initiates but who does not actually conduct the investigation) must submit an IDE application to FDA if the sponsor intends: to use a significant risk device in an investigation, to conduct an investigation that involves an exception from informed consent under 21 CFR Part 50.24 (exception from informed consent requirements for
emergency research) or if FDA notifies the sponsor that an application is required for an
investigation (FDA, 2014j).

Certain categories of investigations are considered to have approved applications for
IDEs, unless FDA has notified the sponsor that approval of an application is required. One such
category includes devices other than a significant risk device, if the device is not a banned device
and the sponsor has met certain conditions described in 21 CFR Part 812.2(b)(1). One of these
conditions is that the sponsor obtains IRB approval of the investigation after presenting the
reviewing IRB with a brief explanation of why the device is not a significant risk device, and
maintains such approval. Another is that each investigator participating in an investigation of the
device obtains informed consent from each subject under the investigator’s care and documents
it, unless documentation is waived by an IRB (FDA, 2015c).

Another category of device investigation that is considered to have an approved
application for an IDE is diagnostic devices [21 CFR Part 812.2(b)(3)]. However, this category
does not apply to medical devices that emit electronically-produced radiation, because one of the
requirements for approval under this category is that the device does not, by design or intention,
introduce energy into a subject (FDA, 2015c).

FDA considers data and information regarding an IDE to be confidential. FDA will not
disclose the existence of an IDE unless its existence has previously been publicly disclosed or
acknowledged, until FDA approves an application for premarket approval of the device subject
to the IDE, or until a notice of completion of a product development protocol for the device has
become effective [21 CFR Part 812.38(a)]. If the existence of an IDE file has not been publicly
disclosed or acknowledged, no data or information in the file are available for public disclosure,
except for banned devices [21 CFR Part 812.38(b)(3)]. However, FDA can disclose to an
individual on whom an investigational device has been used a copy of a report of adverse device
effects relating to that use [21 CFR Part 812.38(c)] (FDA, 2015c).
4.5 Expanded and Early Access to Investigational Drugs and Medical Devices

4.5.1 Expanded Access (‘Compassionate Use’)

When patient enrollment in a clinical trial is not possible, investigational drugs, biologics and medical devices may be made available to patients with serious or immediately life threatening medical diseases or conditions under expanded access (compassionate use) (FDA, 2015b). This provision is applicable to individual patients, a small group, or large population of patients with the same medical condition. Medical practitioners must determine that there are no satisfactory treatment alternatives, must weigh the potential risks of the investigational treatments, and submit a clinical protocol for the ‘Expanded Access’ use. For the protocol to proceed, FDA must determine that the potential patient benefit justifies the potential risk of the expanded access use of the investigational drug, biologic or device, and that the potential risk is not unreasonable in the context of the condition to be treated (FDA, 2015a).

4.5.2 Humanitarian Device Exemption

A device intended to benefit patients by treating or diagnosing an uncommon or infrequent medical disorder (i.e., a disorder affecting fewer than 4,000 people in the U.S. annually) is termed a Humanitarian Use Device (HUD; FDA, 2014f). A device manufacturer’s research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. FDA provides an incentive for research and development of HUD through the humanitarian device exemption (HDE) application process, which provides exemption from the requirement of effectiveness, as long as the applicant can demonstrate that the device does not pose an unreasonable or significant risk of illness or injury, and the probable health benefits outweigh the risks of use. Additional stipulations are that no comparable devices are available to meet the healthcare need and that without the exemption the applicant could not bring the device to market. Once FDA approves an HDE for marketing of an HUD, use must be approved by the local IRB and device labeling must state that: “The effectiveness of the device for the specific indication has not been demonstrated” (FDA, 2014f).
4.5.3 Treatment Use of an Investigational Device

A device that is not cleared or approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. During the clinical trial or prior to final action on the marketing application, it may be appropriate to use the device in the treatment of patients not in the trial under the provisions of a treatment IDE. The purpose of a treatment IDE is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing begins, and to obtain additional data on the device’s safety and effectiveness. In the case of a serious disease, a device ordinarily may be made available for treatment use under a treatment IDE after all clinical trials have been completed. In the case of an immediately life-threatening disease, a device may be made available for treatment use under a treatment IDE prior to the completion of all clinical trials (21 CFR Part 812.36). For the purposes of 21 CFR Part 812.36, ‘treatment use’ of a device includes the use of a device for diagnostic purposes (FDA, 2015c).
5. Identification of Experimental Studies Utilizing Ionizing Radiation

In the course of standard medical treatment, patients often undergo imaging examinations that utilize ionizing radiation or nonionizing radiation [e.g., magnetic resonance imaging (MRI)], and some may require image-guided interventions or radiation treatments. It is important to be able to distinguish between modalities that employ ionizing radiation and those that do not, because of important differences in their potential biological effects and risks (Section 3.1). Radiography, fluoroscopy, CT, nuclear medicine imaging, and radiation therapy utilize ionizing radiation. Ultrasound employs sound waves and MRI employs magnetic fields and nonionizing electromagnetic radiation (i.e., radiofrequency or radio waves).

There is a wide range of radiation doses among and within imaging modalities, as well as for types of procedures and specific imaging examinations (Bushberg et al., 2012; Hall and Giaccia, 2012; Mettler et al., 2008; Miglioretti et al., 2013; Smith-Bindman et al., 2009; 2015). Jones et al. (2012) provided average effective doses for common emergency department imaging examinations and Mettler et al. (2008) published effective doses for a range of diagnostic radiology procedures, including mammography, bone density, and examinations that involve both fluoroscopy and radiographs (Table 5.1).

Radiation received while in a research study may be the same in type and amount as would be received with standard clinical care, and may not be a component of the research study. Alternatively, research protocols may involve additional radiation procedures beyond those received in the course of standard clinical care, or the radiation procedure itself may be the focal point of the research.

There are some research protocols in which the administration of radiation to subjects is apparent because it is central to the research (e.g., when radioactive tracers are used to study a physiological process, the development of a new nuclear medicine imaging agent, or a comparison of dose fractionation schemes in radiation oncology). There are others in which it is
Table 5.1—Average effective doses from common diagnostic radiology studies (adapted from Jones et al., 2012; Mettler et al., 2008).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Average E (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average background radiation exposure (y(^{-1}))(^a)</td>
<td>3</td>
</tr>
<tr>
<td>Chest x ray (PA(^b) and lateral)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cervical spine x ray</td>
<td>0.2</td>
</tr>
<tr>
<td>Thoracic spine x ray</td>
<td>1.0</td>
</tr>
<tr>
<td>Lumbar spine x ray</td>
<td>1.5</td>
</tr>
<tr>
<td>Pelvis x ray</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdomen x ray</td>
<td>0.7</td>
</tr>
<tr>
<td>Hip x ray</td>
<td>0.7</td>
</tr>
<tr>
<td>Shoulder x ray</td>
<td>0.01</td>
</tr>
<tr>
<td>Knee x ray</td>
<td>0.005</td>
</tr>
<tr>
<td>Mammography (two views each breast)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dual-energy x-ray absorptiometry</td>
<td>0.001</td>
</tr>
<tr>
<td>CT(^c) bone density</td>
<td>0.04</td>
</tr>
<tr>
<td>Upper gastrointestinal series</td>
<td>6(^d)</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>5</td>
</tr>
<tr>
<td>Barium enema</td>
<td>8(^d)</td>
</tr>
<tr>
<td>CT(^c) head</td>
<td>2</td>
</tr>
<tr>
<td>CT spine</td>
<td>6</td>
</tr>
<tr>
<td>CT stroke protocol (CT, CTA(^e) and CTP(^f))</td>
<td>14</td>
</tr>
<tr>
<td>CT chest</td>
<td>8</td>
</tr>
<tr>
<td>CT angiogram of thorax (rule out pulmonary embolism)</td>
<td>15</td>
</tr>
<tr>
<td>Procedure</td>
<td>Dose (mSv)</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Lung V/Q&lt;sup&gt;a&lt;/sup&gt; scan</td>
<td>2.2</td>
</tr>
<tr>
<td>CT abdomen and pelvis</td>
<td>14</td>
</tr>
<tr>
<td>CT angiogram aorta (chest, abdomen, pelvis – rule out dissection or aneurysm)</td>
<td>24</td>
</tr>
<tr>
<td>Trauma CT ‘pan-scan’ (head, neck, chest, abdomen, pelvis)</td>
<td>34</td>
</tr>
</tbody>
</table>

<sup>a</sup>Background exposure (average for U.S. population) provided for perspective (NCRP, 2009a).

<sup>b</sup>PA = posteroanterior

<sup>c</sup>CT = computed tomography

<sup>d</sup>Fluoroscopy and radiographs

<sup>e</sup>CTA = CT angiogram

<sup>f</sup>CTP = CT perfusion

<sup>g</sup>V/Q = ventilation-perfusion
less apparent (e.g., routine nuclear medicine or x-ray imaging performed as part of a study to
assess the effects of different chemotherapy regimens). The radiation a human subject receives
specifically through participation in a research protocol, which would not have been received
otherwise (Section 6), is considered separately from that received in the normal course of
medical treatment, and should be monitored and reported by the research team.

As in standard medical care, radiation dose to human subjects in a research protocol should be optimized, to ensure that the necessary information is obtained with the least dose possible (EPA, 2014; ICRP, 2007b; 2013a; 2013b; Lambert et al., 2014; NCRP, 2010b; 2012b; Smith-Bindman et al., 2009). Section 9 discusses optimization for imaging modalities, image-guided procedures and radiation therapy.

5.1 Diagnostic Imaging Modalities

The standard medical imaging modalities are:

- radiography [conventional projection x-ray imaging (e.g., chest x ray, mammography)];
- dual-energy x-ray absorptiometry (DXA);
- fluoroscopy;
- computed tomography (CT);
- nuclear medicine imaging (including PET and SPECT);
- ultrasound (sonography); and
- magnetic resonance imaging (MRI).

Less common or nontraditional modalities, such as optical-coherence tomography and infrared thermography, are beyond the scope of this document.
5.1.1 Radiography

Radiography involves irradiation of a patient to obtain a static projection image of a body part or area. An x-ray source or tube is placed on one side of the patient and an x-ray detector, such as film or an electronic receptor, is placed on the other side. The differential absorption and scattering of the x rays within body tissues alter the amount and distribution of x rays that exit the patient and reach the detector. The resultant x-ray distribution generates a two-dimensional image of the body part.

Mammography is a type of low-dose radiographic study, utilizing low-energy x rays to examine the human breast. It may be used for the diagnostic evaluation of clinical findings or symptoms, or may be used to screen for occult breast cancer.

The main dental imaging modalities are intraoral imaging, panoramic imaging, cephalometric imaging, and dental cone-beam computed tomography (CBCT; Section 5.1.4).

- Intraoral Imaging: An image receptor is placed inside the mouth against the lingual side of the teeth being imaged and a radiograph is acquired.
- Panoramic Imaging: An x-ray tube is placed on one side of the patient’s head and the image receptor on the opposite side. The x-ray beam is collimated by a slit to form a tall narrow beam. The x-ray tube and image receptor perform a partial rotation about the patient’s head, acquiring a single, relatively thick curved-surface tomographic projection image showing all of the teeth and the surrounding structures.
- Cephalometric Imaging: A radiograph of the facial bones, lower portions of the skull and upper portions of the neck is acquired for the quantitative measurements of various head and neck structures.

5.1.2 Dual-Energy X-Ray Absorptiometry

Dual-energy x-ray absorptiometry (DXA) is a technique used to evaluate bone mineral density (BMD) and body composition. It employs two x-ray beams of different average photon
energies, hence the term ‘dual-energy.’ By quantifying the attenuation of x rays from each beam, values can be derived for bone density at different body sites. Standard sites for BMD measurement include the lumbar spine, the proximal femurs (commonly referred to as the ‘hips’), and the wrists and forearms. When used to follow a patient with low bone density, serial examinations may be performed. The recommended interval between DXA studies in clinical medicine is generally at least 1 to 2 y, because of the usually slow rate of change in bone density. Serial DXA examinations may be employed to evaluate a pharmacological intervention or to follow the course of a disease process. Observation of change in BMD is most accurate when the patient’s serial examinations are at the same office, on the same DXA machine.

In addition to determining bone density, DXA can be used to evaluate body composition. The absorption and relative attenuation of x rays from the two x-ray beams by different body tissues can enable quantification of body tissues: bone mineral, fat-free mass excluding bone, and fat mass (Lee and Gallagher, 2008). Measurements of whole body fat and lean muscle mass can be obtained, and body mass index (BMI) can be calculated.

DXA is readily available, easy to use, and employs extremely low doses of radiation. Typically, patient radiation exposure for DXA bone densitometry corresponds to an effective dose of 1 μSv (HPS, 2010; Mettler et al., 2008). When DXA is used for body composition determination, the maximum effective dose is on the order of 6 μSv (Toombs et al., 2012).

5.1.3 Fluoroscopy

Fluoroscopy is real-time x-ray projection imaging, with the image shown on a display monitor. Originally, fluoroscopy was used for diagnostic studies such as imaging of the gastrointestinal system during administration of contrast material (e.g., an upper gastrointestinal series for visualization of the esophagus, stomach, and proximal small bowel or a barium enema to visualize the colon). In addition to diagnostic applications, fluoroscopy is now frequently utilized to guide interventional procedures (e.g., medical device placement, angiography and stent placements, and embolization and ablation procedures) (Section 5.2). The stored images
may be individual radiographs. Alternatively, series of images may be recorded for cine viewing and analysis.

5.1.4 Computed Tomography

Imaging with computed tomography (CT) is performed by rotating an x-ray source or sources around the body. The x rays pass through the body from multiple angles and impinge upon a detector array. Computerized processing translates the resultant attenuation data into a tomographic or virtual slice image (Bushberg et al., 2012; Hounsfield, 1973). The slices can be reconstructed in different planes and can be rendered into a three-dimensional image that can be manipulated in space. CT enables organs to be displayed while eliminating obscuring superimposed structures, allowing clearer and more accurate depiction of anatomy and pathology than is possible with plain radiography. It is extremely helpful for diagnosis of disease and for follow-up of disease progression or regression during treatment. CT has excellent contrast resolution and good spatial resolution. Enteral and/or parenteral contrast media are frequently utilized during CT imaging to accentuate the differences in tissue attenuation of x rays, thereby enhancing image contrast and facilitating image interpretation. CT can also provide imaging guidance for tissue biopsies and other interventional medical procedures.

Dental CBCT is a special application of CT imaging. The x-ray tube and image receptor are on opposite sides of the patient’s head and perform a half or full rotation around the head. The x-ray beam is collimated to form a wide cone beam. The resultant projection image data are mathematically processed to provide a tomographic image set that can be displayed as axial, coronal, or sagittal images, and that can be reconstructed into various curved, corrected sectional and three-dimensional representations.

5.1.5 Nuclear Medicine

Nuclear medicine involves the administration of radioactive isotopes (i.e., radionuclides), often tagged to a pharmaceutical to direct the isotope to a particular organ system. The radiopharmaceutical may be injected (e.g., intravenous or intracavitary), inhaled, or ingested.
Once adequate physiological distribution has occurred, a radiation detector is used to form a functional image. Alternatively, organ uptake of the isotope can be measured, or the dynamic process of organ uptake and excretion can be followed. Nuclear medicine images generally have good contrast resolution but limited spatial resolution. A particular asset is that these studies can provide physiological or metabolic information. Common applications of nuclear medicine include: counting radioactive iodine uptake over the thyroid gland and performing thyroid imaging, evaluating the osseous structures for metastatic involvement, tumor imaging, and evaluating myocardial perfusion before and after exercise or pharmacological intervention.

Radioactive tracers may be used for basic science research involving metabolism, physiology, pathophysiology, and/or biochemistry. Such studies may involve the kinetics, distribution, and localization of the radioactive drug. When radioactive drugs are used for basic science research, the study may fall under the jurisdiction of a Radioactive Drug Research Committee (FDA, 2016b) (Section 4.3.1).

The most common application of radionuclides in medicine is for imaging procedures. Nuclear medicine imaging can be planar (i.e., standard two-dimensional images) or tomographic (i.e., thin slices which can be reconstructed to form three-dimensional images). Two tomographic forms of nuclear medicine imaging are single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging. SPECT imaging uses one or more position-sensitive photon detectors to detect gamma- or x-ray emissions, utilizing the same radioactive isotopes as planar imaging (Bybel et al., 2008; Tsui, 1996). PET imaging commonly uses a cylindrical array of multiple photon detectors, with the patient inside the cylinder, and specifically employs positron-emitting isotopes. Detection of the resulting 511 keV paired annihilation photons is the basis for image reconstruction (Kapoor et al., 2004). The current most commonly used PET imaging agent is fluorine-18 fluorodeoxyglucose (\(^{18}\text{F-FDG}\)). Table 5.2 provides examples of common nuclear medicine procedure doses. The recommended ranges for administered activity (MBq) vary, although it has been noted that most imaging facilities tend to use the upper end of suggested ranges (Mettler et al., 2008).
### Table 5.2—Effective doses for adults from various nuclear medicine examinations

[modified from ICRP (2015), unless otherwise indicated].

<table>
<thead>
<tr>
<th>Examination</th>
<th>Effective Dose (mSv)</th>
<th>Administered Activity (MBq)</th>
<th>Effective Dose per Administered Activity (mSv/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain ($^{99m}$Tc-HMPAO-exametazime)$^a$</td>
<td>6.9</td>
<td>740</td>
<td>0.0093</td>
</tr>
<tr>
<td>Brain ($^{18}$F-Florbetapir with CT)$^b$</td>
<td>9.0</td>
<td>370</td>
<td>0.019</td>
</tr>
<tr>
<td>Brain ($^{18}$F-FDG)$^c$</td>
<td>14.1</td>
<td>740</td>
<td>0.019</td>
</tr>
<tr>
<td>Thyroid scan (Na-$^{123}$I)</td>
<td>3.8</td>
<td>25</td>
<td>0.15 (16 % Uptake)</td>
</tr>
<tr>
<td>Parathyroid scan ($^{99m}$Tc-sestamibi)$^d$</td>
<td>6.7</td>
<td>740</td>
<td>0.009</td>
</tr>
<tr>
<td>Cardiac stress/rest test ($^{201}$TlCl)</td>
<td>40.7</td>
<td>185</td>
<td>0.22</td>
</tr>
<tr>
<td>Cardiac rest/stress test ($^{99m}$Tc-sestamibi 1 d protocol)</td>
<td>9.4</td>
<td>1,100</td>
<td>0.0079 (stress), 0.0090 (rest)</td>
</tr>
<tr>
<td>Cardiac rest/stress test ($^{99m}$Tc-sestamibi 2 d protocol)</td>
<td>12.5</td>
<td>1,500</td>
<td>0.0079 (stress), 0.0090 (rest)</td>
</tr>
<tr>
<td>Cardiac rest/stress test ($^{99m}$Tc-tetrofosmin)</td>
<td>12</td>
<td>1,500</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiac ventriculography MUGA ($^{99m}$Tc-labeled RBC)$^e$</td>
<td>5.1</td>
<td>740</td>
<td>0.007</td>
</tr>
<tr>
<td>Cardiac ($^{18}$F-FDG)$^c$</td>
<td>14.1</td>
<td>740</td>
<td>0.019</td>
</tr>
<tr>
<td>Lung perfusion ($^{99m}$Tc-MAA)$^f$</td>
<td>2.0</td>
<td>185</td>
<td>0.011</td>
</tr>
<tr>
<td>Lung ventilation ($^{133}$Xe gas)</td>
<td>0.5</td>
<td>740</td>
<td>0.00074</td>
</tr>
<tr>
<td>Liver/spleen ($^{99m}$Tc-sulfur colloid)</td>
<td>2.1 (normal) 2.7 (advanced disease)</td>
<td>222</td>
<td>0.0091 0.012</td>
</tr>
<tr>
<td>Biliary tract ($^{99m}$Tc-disofenin)</td>
<td>3.1 (normal) 1.7 (disease)</td>
<td>185</td>
<td>0.016 0.0094</td>
</tr>
<tr>
<td>Procedure</td>
<td>Tc Activity</td>
<td>Radioactivity</td>
<td>References</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>------------</td>
</tr>
<tr>
<td>Gastrointestinal emptying ( ^{99m}\text{Tc})-labeled solids</td>
<td>0.4</td>
<td>14.8</td>
<td>0.024</td>
</tr>
<tr>
<td>Renal ( ^{99m}\text{Tc})-MAG3(^g)</td>
<td>0.6 (normal)</td>
<td>370</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td>2.3 (abnormal)</td>
<td></td>
<td>0.0061</td>
</tr>
<tr>
<td>Bone ( ^{99m}\text{Tc})-MDP(^h)</td>
<td>5.4</td>
<td>1,110</td>
<td>0.0049</td>
</tr>
<tr>
<td>Gallium-67 citrate</td>
<td>15</td>
<td>150</td>
<td>0.100</td>
</tr>
<tr>
<td>White blood cells ( ^{111}\text{In})(^d)</td>
<td>6.7</td>
<td>18.5</td>
<td>0.360</td>
</tr>
<tr>
<td>Tumor ( ^{18}\text{F})-FDG with CT(^c)</td>
<td>19.1</td>
<td>740</td>
<td>0.019</td>
</tr>
</tbody>
</table>

\(^a\)HMPAO = hexamethylpropyleneamine
\(^b\)CT = low dose CT for anatomic location (Lilly, 2013)
\(^c\)FDG = fluorodeoxyglucose
\(^d\)ICRP (1988)
\(^e\)RBC = red blood cells
\(^f\)MAA = macroaggregated albumin
\(^g\)MAG3 = mercaptoacetyl triglycine
\(^h\)MDP = methylene diphosphonate
5.1.6 Ultrasonography

Ultrasonography uses sound waves, a form of mechanical energy, to produce images. Although ultrasound is not electromagnetic radiation, FDA regulates ultrasound equipment under 21 CFR Part 1050 “Performance Standards for Sonic, Infrasonic, and Ultrasonic Radiation-emitting products” (FDA, 2014i). High-frequency pulsed sound waves reflected off of internal structures are employed to produce images and evaluate blood flow (Bushberg et al., 2012). Ultrasound can produce two-dimensional cross-sectional images, display blood flow or tissue motion over time, or provide three-dimensional anatomical images. Diagnostic medical sonography is extremely safe. Although it can cause slight heating of body tissues and, in limited circumstances, can result in pockets of gas in body fluids or tissues (cavitation), there are no proven adverse effects of diagnostic ultrasound when performed on humans using ultrasound devices cleared by FDA (NCRP, 2002; FDA, 2014d). There are also therapeutic applications of ultrasound, including extracorporeal shock wave lithotripsy for breaking up calculi [e.g., urinary calculi (stones) and gallstones], and high-intensity focused ultrasound for ablation of pathological tissues such as neoplasms and uterine fibroids. Although generally considered less invasive than open surgery, when used therapeutically ultrasound may engender substantial risks. The range of potential adverse effects include: urinary obstruction due to fragmented kidney stones, perforation of the ureters, unintended tissue necrosis, skin burns, and pain (JHM, 2014; Napoli et al., 2013).

5.1.7 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses nonionizing electromagnetic radiation [radiofrequency (RF) waves] and magnetic fields. Magnetic fields and RF waves are manipulated to produce electromagnetic signals from tissues in the body that are processed into cross-sectional images. These images provide both anatomical and physiological information. Functional MRI can enable visualization of brain response to various stimuli and provide insight into human behavior. Dynamic studies can map blood flow and hepatobiliary function. Contrast agents may be employed to better demonstrate anatomical structures or pathology. Exposure to the temporary magnetic fields utilized in medical imaging is not known to cause lasting side
effects, although MRI may induce temporary dizziness or imbalance, particularly ultra-high-field (i.e., 7 tesla) MRI (Theysohn et al., 2014). However, the magnetic field can affect metallic objects such as some internal surgical clips, embedded foreign bodies, or implanted medical devices, which may be heated or moved by the magnetic field. The magnetic field may cause malfunction of implanted devices, including cardiac pacemakers, implantable cardiac defibrillators and neurostimulators. Unless proper precautions are in place, external metallic devices and equipment, such as oxygen tanks, may be forcibly drawn into the magnetic field, potentially causing physical harm to the patient. There is the possibility of thermal burns from heat induced in internal or superficial conductive materials by the stimulating radiofrequency signals. To minimize these potential hazards, there is extensive guidance in the medical literature to promote the safe use of MRI (FDA, 2014b; HPS, 2014c; Kanal et al., 2013; Pomerantz, 2008; Shellock, 2014; TJC, 2008).

5.1.8 Fusion Imaging

In fusion imaging, two or more different diagnostic imaging modalities can be utilized on a patient in close sequence as a single examination, without moving the patient from the imaging table. The most common fusion imaging combinations are PET/CT and SPECT/CT. MRI/CT fusion imaging machines are also commercially available. Fusion techniques for other imaging modalities are in development. The dual-modality images are superimposed (e.g., fusing functional nuclear medicine and anatomical CT or MRI information) thus taking advantage of the best features of both modalities (Bybel, 2008; Kapoor et al., 2004). Imaging benefits are enhanced with fusion imaging: PET/CT superimposes low spatial resolution, high contrast nuclear medicine images that depict metabolic activity on high spatial resolution CT images to assist in locating active neoplastic foci. Other applications include myocardial viability and myocardial perfusion evaluation. Sequential PET/CT imaging can follow the metabolic activity of cancer tissue during therapy and assist in evaluating the efficacy of a treatment regimen. When fusion imaging involves two modalities that employ ionizing radiation, such as PET/CT or SPECT/CT, the radiation dose to the patient is additive and can be high compared to other diagnostic imaging procedures, especially if fusion imaging examinations are performed.
sequentially to monitor therapeutic response (Huang et al., 2009). Strategies to manage radiation
dose in fusion imaging are provided in Section 9 (Section 9.4).

5.2 Image-Guided Interventions

Image-guided interventions can be defined as diagnostic and therapeutic procedures
performed via percutaneous or other access routes, usually with local anesthesia and/or
intravenous sedation, which use ionizing or nonionizing radiation (or both) to localize or
characterize a lesion, diagnostic site, or treatment site; monitor the procedure; and/or guide and
document therapy (NCRP, 2010b). These procedures can be performed with nonionizing
radiation (e.g., ultrasound or magnetic resonance imaging), or with ionizing radiation (e.g.,
fluoroscopy or CT). Often, ultrasound is used together with fluoroscopy. These procedures are
performed by physicians in many medical specialties, and the range of procedures is very wide.
Examples of fluoroscopically-guided interventions (FGI) and the physician specialties that most
commonly perform these procedures are shown in Table 5.3 (note that this is not an exhaustive
list; the types and frequencies of procedures performed and medical specialties involved vary
among institutions; some procedures are conducted by multidisciplinary teams; and existing
procedures are constantly being modified and new procedures are constantly being developed).
Table 5.4 provides patient radiation dose distribution data for selected noncoronary procedures
expressed as $K_{a,r}$ (Gy). Table 5.5 provides median radiation doses expressed as $K_{a,r}$ (mGy) in
coronary angiography and percutaneous coronary intervention for median patient body habitus
from a multicenter study (Crowhurst et al., 2014).

There are several types of experimental studies that involve the evaluation of percutaneously
placed devices or percutaneous procedures to diagnose or treat disease. One type of experimental
study involves the development or evaluation of a new interventional procedure that is intended
to diagnose or treat a specific condition. Examples from the recent literature include: treatment
of acute ischemia of the hand with catheter-directed thrombolysis (Breguet et al., 2014),
localization of lung lesions prior to video-assisted thoracoscopic resection (Iqbal et al., 2014),
guidewire manipulation of malfunctioning peritoneal dialysis catheters (Kwon et al., 2014),
### Table 5.3—Examples of fluoroscopically-guided interventional procedures and the physician specialties that most commonly perform these procedures (adapted from NCRP, 2010b).

<table>
<thead>
<tr>
<th>Organ System or Region</th>
<th>Procedure</th>
<th>Physician Specialties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td>Diagnostic angiography</td>
<td>Radiology, neurosurgery &amp; neurology</td>
</tr>
<tr>
<td></td>
<td>Embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombolysis</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td>Biopsy</td>
<td>Radiology, cardiology, vascular surgery, &amp;</td>
</tr>
<tr>
<td></td>
<td>Thoracentesis</td>
<td>internal medicine</td>
</tr>
<tr>
<td></td>
<td>Chest tube placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary angiography</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thrombolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor ablation</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Diagnostic angiography</td>
<td>Cardiology &amp; cardiac surgery</td>
</tr>
<tr>
<td></td>
<td>Angioplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiofrequency ablation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pacemaker placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valvular repairs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valvular replacements</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Percutaneous gastrostomy</td>
<td>Radiology &amp; gastroenterology</td>
</tr>
<tr>
<td></td>
<td>Percutaneous jejunostomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnostic angiography</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Embolization</td>
<td></td>
</tr>
<tr>
<td>Liver and biliary system</td>
<td>Biopsy</td>
<td>Radiology &amp; gastroenterology</td>
</tr>
<tr>
<td></td>
<td>Percutaneous biliary drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ERCP&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percutaneous cholecystostomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stone extraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIPS&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemoembolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor ablation</td>
<td></td>
</tr>
<tr>
<td>System</td>
<td>Procedures</td>
<td>Specialties</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Kidney and urinary tract</td>
<td>Biopsy</td>
<td>Radiology &amp; urology</td>
</tr>
<tr>
<td></td>
<td>Nephrostomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stone extraction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor ablation</td>
<td></td>
</tr>
<tr>
<td>Reproductive tract</td>
<td>Diagnostic angiography</td>
<td>Radiology</td>
</tr>
<tr>
<td></td>
<td>Embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fallopian tube recanalization</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>Biopsy</td>
<td>Radiology, orthopedics, neurosurgery, anesthesiology, &amp; neurology</td>
</tr>
<tr>
<td></td>
<td>Vertebroplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kyphoplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor ablation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nerve blocks</td>
<td></td>
</tr>
<tr>
<td>Vascular system</td>
<td>Diagnostic angiography</td>
<td>Radiology, cardiology, vascular surgery, nephrology, &amp; neurosurgery</td>
</tr>
<tr>
<td></td>
<td>Diagnostic venography</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angioplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Embolization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent-graft placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venous access</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inferior vena cava filter placement</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Fluid aspiration or collection</td>
<td>Radiology</td>
</tr>
<tr>
<td></td>
<td>Abscess drainage</td>
<td></td>
</tr>
</tbody>
</table>

^ERCP = endoscopic retrograde cholangiopancreatography
^TIPS = transjugular intrahepatic portosystemic shunt

2001
Table 5.4—Patient radiation dose distribution data for selected noncoronary procedures expressed as $K_{arr}$ (Gy) (adapted from NCRP, 2010b).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of Patients</th>
<th>10</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPS creation</td>
<td>134</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
<td>2.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Biliary drainage</td>
<td>123</td>
<td>0.1</td>
<td>0.3</td>
<td>0.5</td>
<td>1.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Nephrostomy for stone destruction</td>
<td>76</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Nephrostomy for stone access</td>
<td>62</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Pulmonary angiogram</td>
<td>104</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Inferior vena cava filter placement</td>
<td>274</td>
<td>0.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Renal or visceral angioplasty without stent</td>
<td>53</td>
<td>0.4</td>
<td>0.5</td>
<td>0.7</td>
<td>1.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Renal or visceral angioplasty with stent</td>
<td>103</td>
<td>0.6</td>
<td>0.9</td>
<td>1.2</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Iliac angioplasty without stent</td>
<td>24</td>
<td>0.4</td>
<td>0.6</td>
<td>0.9</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Iliac angioplasty with stent</td>
<td>93</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
<td>1.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Bronchial artery embolization</td>
<td>27</td>
<td>0.4</td>
<td>0.6</td>
<td>0.9</td>
<td>1.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Hepatic chemoembolization</td>
<td>125</td>
<td>0.4</td>
<td>0.7</td>
<td>1.2</td>
<td>1.8</td>
<td>3.6</td>
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<td>Uterine fibroid embolization</td>
<td>90</td>
<td>0.9</td>
<td>1.4</td>
<td>2.0</td>
<td>3.3</td>
<td>5.7</td>
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<tr>
<td>Other tumor embolization</td>
<td>88</td>
<td>0.5</td>
<td>0.8</td>
<td>1.1</td>
<td>2.1</td>
<td>4.2</td>
</tr>
<tr>
<td>GI$^*$ hemorrhage localization or treatment</td>
<td>94</td>
<td>0.7</td>
<td>1.2</td>
<td>1.9</td>
<td>3.2</td>
<td>5.6</td>
</tr>
<tr>
<td>Embolization-head-AVM$^c$</td>
<td>134</td>
<td>1.6</td>
<td>2.4</td>
<td>3.6</td>
<td>5.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Embolization-head-aneurysm</td>
<td>148</td>
<td>1.9</td>
<td>2.7</td>
<td>3.5</td>
<td>4.4</td>
<td>6.8</td>
</tr>
<tr>
<td>Embolization-head-tumor</td>
<td>51</td>
<td>2.0</td>
<td>2.5</td>
<td>3.4</td>
<td>5.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Procedure</td>
<td>2004</td>
<td>2005</td>
<td>2006</td>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebroplasty</td>
<td>98</td>
<td>0.3</td>
<td>0.6</td>
<td>1.0</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Pelvic artery embolization trauma or tumor</td>
<td>35</td>
<td>0.8</td>
<td>1.1</td>
<td>1.5</td>
<td>2.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Embolization-spine-AVM or tumor</td>
<td>21</td>
<td>3.0</td>
<td>4.0</td>
<td>5.6</td>
<td>7.3</td>
<td>9.3</td>
</tr>
<tr>
<td>Peripherally-inserted central-catheter placement</td>
<td>480</td>
<td>–</td>
<td>–</td>
<td>0.02</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chest-port placement</td>
<td>295</td>
<td>–</td>
<td>–</td>
<td>0.05</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tunneled dialysis-catheter placement</td>
<td>66</td>
<td>–</td>
<td>–</td>
<td>0.04</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*aPercentile for patients with $K_{ar}$ values (gray) equal to or less than the column entry

*bGI = gastrointestinal

*cAVM = arteriovenous malformation
Table 5.5—Median radiation doses in coronary angiography and percutaneous coronary intervention with body habitus data from a multi-center study (adapted from Crowhurst et al., 2014).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Coronary Angiography</th>
<th>Percutaneous Coronary Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2,590</td>
<td>947</td>
</tr>
<tr>
<td>Median patient age</td>
<td>62.71</td>
<td>61.73</td>
</tr>
<tr>
<td>Median patient height (cm)</td>
<td>170</td>
<td>172</td>
</tr>
<tr>
<td>Median patient weight (kg)</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>Median patient BMI</td>
<td>28.7</td>
<td>27.8</td>
</tr>
<tr>
<td>Median fluoro time (min)</td>
<td>3.5</td>
<td>11.2</td>
</tr>
<tr>
<td>Median $P_{KA}$ ($\mu$Gy m²)</td>
<td>3,908</td>
<td>8,736</td>
</tr>
<tr>
<td>Median $K_{sar}$ (mGy)</td>
<td>581</td>
<td>1,501</td>
</tr>
</tbody>
</table>
venous embolization to treat erectile dysfunction (Rebonato et al., 2014), and percutaneous
sacroplasty for sacral insufficiency fractures (Talmadge et al., 2014). In these examples, existing
techniques, drugs or devices are used in new clinical scenarios, sometimes for an off-label
indication, to advance patient care.

A second type of experimental study involves the evaluation of a new drug or device or of
an existing drug or device that is used in a new way. Examples from the recent literature include:
evaluation of an existing embolization procedure performed with an embolic agent not normally
used for that indication (Fischman et al., 2014; Urbano et al., 2014), evaluation of a new
endovascular stent (George et al., 2014), evaluation of placement of occlusion devices for
closure of multiple septal defects in the same patient (Mehta et al., 2014), placement of a
peripheral vascular stent in the pulmonary artery in a pediatric population (Kudumula et al.,
2014), and evaluation of an existing angioplasty device for a new indication (Lai et al., 2014).

A third type of experimental study involves the research evaluation of one or more existing
devices or techniques used in accordance with device labeling. Examples from the recent
interventional radiology literature include: placement of fiducial markers to guide a specific type
of radiation therapy (Trumm et al., 2014), a comparison of two different embolic agents used for
partial splenic embolization (Masada et al., 2014), evaluation of the safety and effectiveness of
different techniques for retrieval of inferior vena cava filters (Al-Hakim et al., 2014), cone-beam
CT-guided biopsy of lung lesions (Lee et al., 2014), and CT-guided biopsy of subsolid lung
lesions (Maxwell et al., 2014).

Many of these studies, including the majority of those mentioned above, are retrospective
analyses. The procedures were performed originally for clear clinical indications and without
research intent. IRB review is performed later and does not consider radiation risk, since the
procedures have already been performed and were not considered as part of a research study
when they were performed. Less frequently, studies of this kind are performed prospectively. In
this case, IRB review of radiation use is necessary. Recent published examples of this kind of
prospective study include: evaluation of atherectomy for treatment of peripheral vascular disease
(Roberts et al., 2014), evaluation of adenosine infusion in vein grafts used to restore coronary artery blood flow (Kapoor et al., 2014), and comparison of percutaneous methods for treatment of liver cancer (Yu et al., 2014).

A fourth less common type of study involves evaluation of a new imaging device, new software for such a device, or new software for post-processing of images obtained as part of an interventional procedure or diagnostic examination. Many of these studies are conducted on behalf of the imaging device or software manufacturer. These studies are often sponsored or conducted by the device manufacturer and are usually prospective. In some cases, particularly if post-processing software is being evaluated, the study may use imaging data already acquired as part of routine clinical care, so there is no research use of radiation.

5.3 Therapeutic Radiation: Radiation Therapy and Radionuclide Therapy

Radiation therapy uses ionizing radiation to treat cancer and other diseases. Therapy can be delivered through beams of radiation or with brachytherapy sources placed in proximity to the treatment site. Treatment using radiation beams, known as teletherapy, is done most often with photon beams with nominal accelerating potentials ranging from 6 to 18 MV, though electron beams are also frequently employed and, at a few dozen centers in the United States, proton beam therapy is offered. Therapy using brachytherapy sources, also known as short-range sources, may employ temporary treatments with surface applicators or interstitial applicators or may employ permanently implanted sources. Temporary treatments may use either low-dose rate sources or high-dose rate sources, while permanent implants only use low-dose rate sources. All of these therapeutic techniques are well established and mature in their development.

Targeted radionuclide therapy (also called molecular radiotherapy) involves radioactive drugs called radiopharmaceuticals that most often target cancer cells but can also be used to target other types of receptors. Radiopharmaceuticals used for therapy typically consist of a radioactive element (i.e., a radionuclide) combined with a molecule that seeks a target. Some radionuclides have the ability to target specific cells or receptors on their own (e.g., $^{89}$Sr
strontium chloride and $^{131}$I sodium iodide). Radioimmunotherapy using systemically administered monoclonal antibodies linked to radionuclides is approved for treatment of refractory non-Hodgkin lymphoma (i.e., refractory to conventional chemotherapy) and is a promising approach for treating metastatic cancer. This kind of treatment is also referred to as ‘targeted’ radionuclide therapy because it is specific and it can deliver substantial doses of radiation directly to or near the target site while minimizing exposure to normal tissue. Currently, the following beta emitters are used in therapeutic radiopharmaceuticals for humans: $^{32}$P, $^{89}$Sr, $^{90}$Sr, $^{90}$Y, $^{131}$I, $^{153}$Sm, and $^{177}$Lu; and one alpha emitting radionuclide, $^{223}$Ra. While radionuclide therapy is currently used to treat certain cancers and cancer metastases (with the exception of $^{131}$I which is also used to treat hyperthyroidism, a benign condition of the thyroid), researchers are developing and testing new targeted radionuclide therapies to treat a variety of conditions. One example is peptide receptor radionuclide therapy, such as $^{177}$Lu-DOTA-Tyr-Octreotate for neuroendocrine tumors, which has been approved by FDA for expanded access (Kam et al., 2012; NA/NRC, 2007).

The ability to deliver tumoricidal doses is often limited by the dose tolerance of the patient’s nondiseased tissues and organs. External beam doses to the target site may be as low as 2 to 12 Gy for total-body irradiation (TBI), or as high as to 80 to 90 Gy for highly conformal external beam prostate treatments. Except for stereotactic radiosurgery and some palliative treatments, radiation therapy treatments (especially external beam treatments) are fractionated with the total dose divided into smaller doses delivered over weeks or months. In hypofractionated radiation therapy, including intracranial stereotactic radiation therapy and stereotactic body radiation therapy, the total dose is divided into larger than usual doses, with delivery of the total dose over a shorter period of time than conventional therapy. Permanent brachytherapy implants, such as for prostate brachytherapy, extend delivery continuously over several months to safely reach even higher cumulative doses. In contrast, the external beam techniques of stereotactic radiosurgery and stereotactic body radiation therapy rely on high conformality (complex adjustment of the radiation therapy beams to closely encompass the tumor volume in three dimensions) to deliver an ablative dose of radiation in one or several fractions while sparing nearby tissues and organs.
Optimal delivery of radiation therapy requires careful consideration of the radiation biology of diseased and normal tissues and of planning techniques to ensure appropriate conformity to the diseased site. Extra precautions must be taken when radiation therapy is delivered to patients who have received prior radiation, who may be pregnant, or who have implanted electronic devices. Innovation in radiation therapy has occurred rapidly, with emerging technologies advancing both imaging (e.g., on-board cone beam CT, ultrasound, and MRI) and delivery (e.g., electronic brachytherapy and microspheres). Research most often concerns innovation in therapies concomitant with radiation therapy, but also may involve new delivery regimens or imaging techniques.

There are currently over 4,000 active clinical trials in the U.S. related to radiotherapy (ClinicalTrials.gov, 2015). These trials involve the use of such ionizing radiation sources as external beam radiotherapy (e.g., Gamma Knife®, Cyber Knife®, tomotherapy, proton beam therapy), brachytherapy, and radioimmunotherapy. In some cases, the therapy being delivered is the same as would be delivered as standard of care (SOC) and the research variable might be the concurrent chemotherapy or the administration of a radioprotectant drug. In other cases, the radiation being delivered may be the focus of the research. Examples in radiotherapy include variations in the beam modulation or fraction delivery intervals. In the case of radioimmunotherapy, the clinical trial may be attempting to establish the safety and efficacy or the maximum tolerated dose of a new agent. In many cases, these trials are being developed, overseen and carried out by nationally recognized groups. Such groups include the Radiation Therapy Oncology Group (RTOG), SWOG (formerly called the Southwest Oncology Group), and the Children’s Oncology Group (COG), which are composed of scientific teams of experts in their respective fields. In these multicenter trials, the protocol has had extensive review prior to trial site recruitment and the local facility may not need to perform additional review of study elements related to ionizing radiation. In other cases, where the principal investigator (PI) has developed a unique clinical trial and there has not been any oversight or input from an unbiased expert, the local reviewing body should solicit assistance from the institutional RSC or RSO, or from a qualified outside reviewer (Classic et al., 2001).
6. Distinguishing Between Radiation Use for Research and Standard Patient Care

A key component of the informed consent process is distinguishing between ‘research’ and standard patient care. The authors of the Belmont Report (DHHS, 1979) noted that research and standard practice may occur concurrently in a clinical trial, as long as the research component undergoes appropriate review. Indeed, the Belmont Report was stimulated in part by experimental studies using radioactive material and ionizing radiation sources in subjects who were not appropriately informed of the risks of participation. Some of those experimental procedures subsequently became the ‘standard of care’ (SOC) for practitioners of nuclear medicine and radiation oncology (DOE, 1995a; 1995b).

A definition of SOC that embraces all disciplines remains elusive. One legal definition of SOC is: “…the watchfulness, attention, caution and prudence that a reasonable person in the circumstances would exercise” (Hill and Hill, 2002). The National Cancer Institute (NCI) defines SOC as: “…treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals” (NCI, 2014). The challenge for the IRB reviewers of clinical trials is distinguishing which procedures constitute research and which may be considered SOC for the treatment regimen or for monitoring the treatment regimen that is the subject of the trial. When a novel radiopharmaceutical or radiation treatment is the subject of the trial, this distinction is apparent. However, there are circumstances when this distinction is less clear.

This section distinguishes among imaging examinations indicated in SOC, those required specifically by the research study, and those requiring greater frequency because of the research study. There is exploration of the advantages and disadvantages of substituting examinations that require ionizing radiation with those that do not. This is followed by discussions of SOC versus research for image-guided interventional procedures and for therapeutic applications of radiation.
6.1 Imaging Examinations Indicated in Standard Patient Care

In determining if the radiation from imaging examinations is included in the SOC or is related to the research protocol, the IRB must consider whether: (1) the imaging examinations required by the trial are the same as those typically used for the medical condition; (2) the examinations are standard but are performed more frequently in trial subjects; or (3) the imaging examinations proposed in the protocol are not typically used for the medical condition. While some imaging examinations are performed on the basis that they are SOC for people with a particular condition, others are conducted solely in support of a research study (i.e., clinical trial). In the planning stages for a clinical trial, the principal investigator (PI) or sponsor should delineate which of the imaging examinations being conducted are SOC and which are being acquired for research purposes. This applies both to the assessment of proposed diagnostic imaging examinations (such as CT, nuclear medicine, radiography) as well as to fluoroscopy that may be utilized, for example, in support of the placement of an experimental device (such as stents). It is incumbent on the PI to be educated and knowledgeable regarding the ionizing radiation proposed in the clinical trial. This should include a working knowledge of the basic concepts of exposure, absorbed dose and effective dose. It is the responsibility of the PI to assess the use of ionizing radiation examinations against the potential use of other modalities that do not utilize ionizing radiation (e.g., ultrasound, MRI). During the review of a clinical trial, the IRB should either have knowledge of the current definition of SOC for the population being studied or should solicit the assistance of appropriate medical clinicians and their local RSC for guidance (Classic et al., 2001).

Professional organizations have instituted guidelines that address SOC for utilization of imaging examinations for some medical conditions. These have often evolved from study regimens designed for clinical trials. For example, the Children’s Oncology Group Bone Tumor Committee has recommended guidelines for imaging in Ewing sarcoma that are based upon the experience in clinical trials conducted by the Children’s Oncology Group (Meyer, 2008). In practice, the type, number and frequency of imaging examinations used to diagnose or monitor patients may be expected to vary among institutions that have established their own SOC.
Reasons for this may include variations in socioeconomic conditions and the availability of imaging resources at a particular institution or even healthcare provider preferences (Rossi, 2012).

### 6.2 Imaging Examinations Required by Research Protocol

Any procedure included in the research protocol should be regarded as research until proven otherwise. It is the responsibility of the research team to demonstrate that an examination utilizing ionizing radiation is SOC, rather than research.

There are several circumstances where a clinical research protocol may include ionizing radiation examinations that are not SOC. First, the imaging procedure may itself be the subject of the research study, and would not be considered to be SOC under any circumstances. Examples include novel imaging modalities or new radiopharmaceuticals that would be studied under IND or Phase I trials. Such trials may include normal volunteers who may not be expected to incur any benefit, and for whom radiation risk is the primary concern (Huda and Scrimger, 1989). These have become increasingly common in certain research fields, such as Alzheimer’s disease research where cognitively normal subjects are needed for comparison purposes (Ishibashi et al., 2015; Joshi et al., 2014).

Second, the protocol may call for the use of an imaging device that is not FDA cleared or approved, or a radiopharmaceutical that is not FDA approved; it may involve a new intended use for an FDA cleared or approved imaging device or an FDA approved radiopharmaceutical; or the imaging device or radiopharmaceutical may itself be the subject of a separate clinical trial (Section 4.2.2). Third, the protocol may require subjects to undergo SOC examinations employing ionizing radiation that are included in only one arm of the clinical trial. An example would be a clinical trial comparing the efficacy of a new anti-cancer drug compared to those used in standard treatment, where the new drug is known or suspected to have cardiac toxicity. Subjects randomized to the arm of the trial receiving the new drug might undergo multi-gated acquisition (MUGA) cardiac blood pool studies to monitor cardiac function, while subjects
randomized to the control arm might not. Since they may be unaware of the exact nature of their participation at the time of registration, subjects in both arms of the protocol must be informed about the possibility of additional radiation risks due to MUGA studies.

6.3 Imaging Examinations Requiring Greater Frequency by Research Protocol

In research, imaging examinations are often performed more frequently than is typical for SOC, resulting in a higher cumulative radiation dose over the duration of the clinical trial. For example, it may be SOC to perform a CT scan every 12 weeks to assess the tumor burden in cancer patients undergoing chemotherapy but when an experimental chemotherapeutic agent is used in that same patient population, the study design may require CT scans every eight weeks. In this scenario, it may be justified to perform more frequent CT scans to enable timely assessment of the efficacy or detriment of a new drug or treatment and assist in the decision of whether to continue or discontinue the experimental therapy. With many chemotherapeutic agents, the negative consequences of administering an ineffective or toxic drug are far worse than the potential risk from the CT radiation. Nonetheless, the use of imaging examinations that utilize ionizing radiation should be judicious and guided by reason and necessity, and the frequency of imaging may require scrutiny. The trial design should meet the research objectives with the least negative impact on the human subjects.

Multi-institutional clinical trials usually specify the imaging examinations to be employed in the trials and their frequencies. The imaging protocols may differ from the SOC of participating medical facilities. If the number or frequency of required imaging examinations utilizing ionizing radiation exceeds the institutional SOC, then the subjects must be advised that the number of examinations they may have is more than they would expect to have if they were not trial participants, and they must be informed about the radiation risks associated with the additional examinations. Furthermore, participating medical facilities may not agree with the dose and risk estimates provided by the protocol developers. An effective, responsive mechanism of communication should be in place to address participating institutions’ concerns about
radiological protocols, estimated radiation dose to subjects, and accuracy of dose and risk
estimates.

6.4 Substitution of Imaging with Ionizing Radiation by Imaging without Ionizing Radiation

At times, an imaging examination that employs ionizing radiation may be eliminated by
substituting an examination that provides the necessary information but does not use ionizing
radiation. For example, ultrasound-based echocardiography can assess cardiac ventricular
function in lieu of a radionuclide based MUGA study. MRI may be substituted for CT scanning
for some indications, such as monitoring tumor response to therapy in certain cancer patients,
and for assessment of some neurologic and abdomino-pelvic conditions. Inclusion of a
radiologist and a medical physicist as consultants or as part of the research team can provide
expert clinical guidance on both the most appropriate imaging examination to use and
optimization of the radiation if nonionizing radiation modalities are not appropriate.

Some research subjects may not be able to benefit from nonionizing imaging examinations.
For example, a subject’s body habitus may be unsuited to some imaging modalities. Obesity may
result in limited sonographic visualization of organs on abdominal sonography. MRI imaging
may be contraindicated due to the presence of ferromagnetic material in the body or a subject’s
claustrophobic response to the confined space of the MRI tube. Protocol designers may prefer
imaging modalities that utilize ionizing radiation, such as CT, for a variety of reasons. MRI is
very costly, may be less available than CT imaging, and the longer acquisition times for MRI
may make it impractical. If differing modalities are used, there may be difficulty in comparison
of images.

In clinical trials that involve the use of fluoroscopy, there may be limited opportunities to
utilize ultrasound in place of fluoroscopy, but the vast majority will require fluoroscopy.
Optimization of the procedure and ensuring the experience and radiation safety knowledge of the
fluoroscopist are extremely important in minimizing radiation dose to the subject (Kuon et al.,
2014) (Section 9).
6.5 Image-Guided Interventions: SOC versus Research

The implantation of devices such as cardiac pacemakers and cardioverter defibrillators, stents and so forth is commonly performed using fluoroscopic guidance. The use of ionizing radiation in this context is SOC. If the objective of a clinical trial is the evaluation of a new implantable device, then the protocol typically compares outcomes in subjects who are receiving the new device with those receiving SOC. Standard care may include no implantable device or a previously approved device. Subjects in the ‘research device’ arm may receive radiation exposure that exceeds that for the control group for a variety of reasons. The control group may undergo surgery, rather than a fluoroscopically guided procedure. Operators who are less experienced with placing the new device may require longer fluoroscopy times to complete the procedure, resulting in radiation exposure to subjects in the research arm that exceeds that for subjects receiving an implanted device that is considered SOC. The protocol may call for additional views or blood-flow assessments that would not normally be required as part of SOC, resulting in greater radiation exposure. Similarly, evaluations of artificial aortic grafts typically employ contrast-enhanced CT scanning, and the evaluation of novel grafts may include a number of additional CT scans.

If the research protocol involves radiation doses that are greater than those seen with SOC, the additional radiation doses must be estimated and subjects informed of the associated risks, including the possibility of skin injury or radiation-induced cancer. As with patients receiving standard care, subjects in a research study should be provided appropriate follow-up care and counseling (Balter and Miller, 2014; Balter et al., 2010; NCRP, 2010b; Stecker et al., 2009).

The overall benefits and risk of an FGI procedure used in research, when $E > 100$ mSv, should be carefully evaluated (NCRP, 2010b). In particular, the relative impact on radiation risk of the age distribution for a given patient population is fairly well understood and should be taken into account.
6.6 Radiation Therapy: SOC versus Research

A clinical trial in radiation therapy, including radionuclide therapy, may compare two different techniques within the SOC, compare an innovation with a SOC technique, or utilize equivalent radiation delivery but with a comparison of other study components, such as chemotherapy agents. Any experimental modification of radiation therapy treatment delivery (e.g., dose or fractionation) should be supported by clinical evidence with attention paid to patient population, disease characteristics (such as tumor location, size, number of lesions, and biochemical markers) and other facets of radiation delivery (e.g., beam energy, patient motion monitoring, treatment margins).

Unlike radiation from most imaging examinations utilized in clinical trials, therapeutic radiation in oncologic trials is an integral part of the study design, with dose and fractionation differences addressed directly in the hypotheses or specific aims. Phase I trials commonly investigate the feasibility and tolerability of using an alternative dose, fractionation, or delivery modality. Alternatively, a Phase I trial may involve variation in a nonradiation modality (such as chemotherapy or surgery) with or without commensurate adjustment of the therapeutic radiation given. Phase II trials may focus on longer term end points such as progression-free survival, as well as response rate, toxicity, and overall survival. Phase III studies use larger patient sample sizes and frequently assess study arms designed to reveal subtle variations in the clinical end points. For example, a Phase III study may compare two similar prescription doses or two therapies expected to yield similar distributions for the end points.

Many clinical trials compare study arms which differ in whether chemotherapy is or is not used, whether supplemental radiation is or is not used in addition to chemotherapy, or the chemotherapy differs either in terms of dose or kind. Such studies require careful attention to excessive toxicities. Thorough evaluation of the evidence underlying such therapies is necessary. In providing informed consent, the relative risks of the study arms should be referenced to the SOC radiation therapy (Section 11.9).
7. **Estimation of Radiation Dose**

There are two main reasons for estimating the radiation doses to human subjects from a proposed research study that would expose them to ionizing radiation. One is that this information is needed to estimate the risk to the subjects and develop appropriate risk language for informed consent. The other reason is that dose estimates are helpful in optimizing the study design to keep radiation doses to human subjects as low as reasonably achievable (the ALARA principle).

It should be noted that radiation doses are not the only determinants of radiation risk. The dose rate, fractionation of dose, and type and energy of the radiation can also affect the risk. Today, the effect of dose rate and fractionation on tissue reactions is much better understood than the effect on the risk of stochastic effects. Other factors inherent to the subject (such as age, gender, genetic susceptibility, and general health) can also influence risk.

Risks to be considered are: the risk of stochastic effects (specifically cancer and hereditary effects); risk of tissue reactions in subjects; and, in the unusual case of research involving irradiation of pregnant women, risk of teratogenic effects and cancer to the unborn child. To estimate risks of cancer, the necessary information includes average doses to organs and tissues known to be susceptible to radiogenic cancer. For hereditary effects, dose to the gonads is required. For estimating the risk of somatic tissue reactions, in some cases information about the dose distributions to individual organs may be needed. For example, in radiation oncology research the estimated dose to a small length of the spinal cord or the dose to a small region of the rectum may be extremely important.

Obtaining highly accurate dose estimations requires substantial resources and in most instances is unnecessary for the purpose of establishing adequate risk estimates. In fact, requiring extremely accurate dose estimations may hinder or discourage research. A more generalized approach to risk estimation is typically sufficient for most situations, especially when one considers the very large uncertainties of the estimations of stochastic risk per unit dose.
(particularly when stratified by organ, gender and age). While highly accurate organ dose estimations are typically unnecessary, for some research studies that will deliver high radiation doses (e.g., radiation oncology, radioimmunotherapy) that may result in tissue reactions, more accurate dose estimations may be necessary.

Where possible, it is recommended that the dose estimates provided for review by an IRB should be specific for the imaging devices and protocols used at the institution. This may be difficult for multi-center studies, in which facilities use different models or makes of radiological equipment. Nonetheless, in multi-center studies, as in all human studies research, an assessment should be made to ensure that the estimated doses to subjects are optimized (Section 9). For example, a research protocol involving x-ray imaging could place an upper limit for the dose metrics (e.g., CTDI$_{vol}$ and DLP for CT) for a subject of standard size for the study population. The rationale for this guidance is illustrated by a number of instances where unnecessarily large doses were inadvertently used for medical imaging examinations. Examples include tissue reactions from excessive doses from CT brain perfusion studies at several institutions (Bogdanich, 2009; 2010; FDA, 2009c; Zarembo, 2009), the use of adult techniques for CT scans of children (Patterson et al., 2001), a fivefold variation in median effective dose across 15 hospitals and a 200-fold variation in dose among patients for CT evaluation of urolithiasis (Smith-Bindman et al., 2015b), and the failure to utilize dose sparing techniques (e.g., pulse modulation, appropriate collimation, use of multiple imaging orientations) to reduce the risk of skin damage during FGI procedures (ICRP, 2013a; NCRP, 2010b). The source of the dose estimates should be referenced in the research protocol.

It is incumbent upon the IRB to independently verify the dose estimates provided by the investigator(s) in the research protocol. This responsibility may be delegated to the RSC or other competent entity.
7.1 Dose Estimation for X-ray Imaging

There are several methods for estimating radiation doses to research subjects receiving x-ray imaging, including the use of anthropomorphic phantoms (NCRP, 2012b). An anthropomorphic phantom is a model of the human body or part of the human body. Phantoms may be ‘physical’ or ‘computational.’ Physical phantoms are physical objects; those used for dosimetry are typically constructed of materials having attenuation properties similar to body tissues (Figure 7.1). Physical phantoms can be fitted with dosimeters and exposed to provide direct measurement of radiation dose at various depths and within various organs. However, this method requires considerable effort to set up and collect data. Furthermore, commercially available phantoms are expensive and a particular phantom represents only a single human body habitus.

Nonphysical or computational phantoms are mathematical representations and are used for computer simulations of radiation transport and energy deposition in a person, using either analytical or probabilistic methods. Originally developed for radiopharmaceutical dose evaluations in conjunction with the Medical Internal Radiation Dosimetry (MIRD) committee of the Society of Nuclear Medicine (Xu and Eckerman, 2009), they initially applied only to a Reference Man (i.e., a 20 to 30 y old Caucasian of 70 kg weight and 170 cm height). Stylized phantoms were subsequently developed, and include more than 20 organs with improved anatomical features and scaling factors to create age- and gender-dependent phantoms (Cristy and Eckerman, 1987) (Figure 7.2).

Both physical and computational phantoms permit the estimation of dose values with accuracy within a few percentage points if the phantoms accurately represent the geometry and radiation attenuation properties of a defined human body habitus or anatomical section. The main source of error is that the range of body habitus of human research subjects in a study population will likely vary considerably from that of the physical or mathematically simulated phantoms. Tables of radiation doses to specific organs and effective doses have been prepared for many imaging procedures, based upon the methods above (Rosenstein et al., 1979; 1989; 1992). These
Fig. 7.1. The Alderson Rando phantom with examples of slices extracted from various regions of the body (Hara et al., 2010).
Fig. 7.2. The stylized Cristy phantom. Left: exterior view of the adult male. Middle: skeleton and internal organs. Right: Cross-sectional view of third trimester pregnant female (adapted from Xu and Eckerman, 2009).
provide doses per unit entrance exposure or air kerma, taking into account varying x-ray beam characteristics such as half-value layer, but only for a few reference body models. There are also simplified methods for estimating effective dose from dose metrics provided by imaging devices, for example from DLP for CT (AAPM, 2011b; Christner et al., 2010; Huda and Gkanatsios, 1997).

7.2 Dose Estimation for Computed Tomography

CT imaging generates the largest collective radiation dose to the population undergoing medical imaging studies (Figure 7.3). Management of CT has been under intense scrutiny over the past several years, in part because of highly publicized radiation overdose incidents (Bogdanich, 2010) resulting in reporting requirements for CT dose metrics in some states (California, 2010) and because of concerns with over-utilization.

On modern CT scanners, the dose metric values reported (indicative of radiation output by the CT system) are the CTDIvol and DLP (AAPM, 2008) (Section 3.3). DLP is the average CTDIvol multiplied by the length (in cm) of the CT scan along the long axis of the patient, expressed in units of mGy cm, and is approximately proportional to the amount of x-ray energy imparted in the scanned region of the patient from the CT examination. An estimate of $E$ for a given scanned region of the body (e.g., head, chest, abdomen, pelvis) can be determined from individual DLP values multiplied by the region-specific factor, $k$ (in mSv mGy$^{-1}$ cm$^{-1}$) (AAPM, 2008). These values are determined for a model of a reference adult, and to the extent that a given study population differs from this model, the estimates of $E$ will differ from the values of $E$ that would be calculated from the actual average organ doses. The actual absorbed dose is directly dependent on the subject’s size and shape. Dose metrics for estimating patient dose for a ‘typical’ adult underestimate the actual absorbed dose for small and pediatric subjects, and overestimate the actual absorbed dose for obese subjects. Estimates of patient size-specific dose may be determined with an accuracy of ~10 % using CT scanner output metrics and estimates of patient size, body region scanned, and scan length (McCollough et al., 2011). Appendix B provides a detailed discussion of the generation of CT dose estimates.
Fig. 7.3. Percent contribution of various sources of exposure to the total effective dose per individual in the U.S. population (6.2 mSv) for 2006 (NCRP, 2009).
7.3 Dose Estimation for Image-Guided Interventions

In order to evaluate radiation risk of a research protocol involving image-guided interventions, an IRB needs to know, in general terms, radiation dose estimates for a typical human subject for any interventional procedures included in the research protocol. Unfortunately, this information is difficult to provide, even for common interventional procedures. Most diagnostic imaging examinations are standardized, with patient radiation dose dependent upon the examination protocol used and on patient body habitus (Samei and Christianson, 2014). Interventional procedures are not standardized, and patient radiation dose depends primarily on the complexity of the procedure, the skill of the interventionalist, and on patient body habitus (IAEA, 2009; ICRP, 2007; Miller et al., 2009). Complexity is determined by patient, anatomy and lesion characteristics and is usually not quantifiable in a useful way. An exception is percutaneous coronary intervention, for which a method for qualitatively estimating complexity has been established (Bernardi et al., 2000; IAEA, 2009). As a result, there is a very wide range of reported patient radiation doses, even for the same type of procedure performed in the same facility (Dauer et al., 2009; Dragusin et al., 2005; Miller et al., 2003b; 2012; Padovani and Quai, 2005; Peruzzo Cornetto et al., 2012). This is true for CT-guided procedures as well as for FGI procedures (Carlson et al., 2005; Leng et al., 2011).

The most useful dose metric for the estimation of the risk of a stochastic event is organ dose. Data on organ dose are rarely, if ever, available for interventional procedures. The next best dose metric is $E$. It is easier to estimate $E$ for CT-guided interventions, as it can be estimated from the DLP (Section 7.2 and Appendix B). For FGI procedures, patient dose estimates are commonly presented in the literature as $P_{KA}$ or $K_{a,r}$ (Section 3.4). $E$ can be estimated from $P_{KA}$ for radiographic and fluoroscopic procedures using body-part specific conversion factors (Hart and Wall, 1994; Le Heron, 1992). Estimates of $E$ for some FGI, often based on $P_{KA}$ dose estimates, are available in the published literature (Bogaert et al., 2008; Brambilla et al., 2004; Molyvda-Athanasopoulou et al., 2011; Padovani et al., 2008; Panuccio et al., 2011; Peruzzo Cornetto et al., 2012; Stisova, 2004), but this is the exception rather than the rule.
Estimates of $E$ for CT-guided procedures vary depending on the procedure and patient, but can range from $<10$ mSv (biopsy) to $>100$ mSv (tumor ablation) (Leng et al., 2011). For FGI procedures, mean estimates of $E$ can range from $<1$ mSv to $>100$ mSv depending on the type of procedure (Peruzzo Cornetto et al., 2012; Smith et al., 2009). Tables 5.4 and 5.5 provide dose information for noncoronary and coronary procedures, respectively. In general, dose distributions for these procedures do not follow a normal (Gaussian) distribution, and are often log normal with a high dose tail (Kwon et al., 2011), so mean values can be misleading.

For estimation of the likelihood and severity of a tissue reaction to the skin, the most useful dose metric is peak skin dose ($D_{\text{skin,max}}$), an estimate of the highest dose at any point on the skin surface (Section 3.4). For CT-guided procedures, $D_{\text{skin,max}}$ can be estimated from the volumetric CT dose index ($\text{CTDI}_{\text{vol}}$) and phantom measurements (de las Heras et al., 2013; Leng et al., 2011). Leng and colleagues (2011) reported a mean estimated $D_{\text{skin,max}}$ for CT-guided interventional procedures ranging from 128 to 728 mGy depending on the type of procedure, with a maximum of 1.95 Gy.

For FGI procedures, reported $D_{\text{skin,max}}$ estimates vary substantially, and depend on the type of procedure, lesion characteristics, patient body habitus, and procedure complexity. Other than venous access procedures, FGI procedures have the potential to result in doses high enough to be of clinical concern (Miller et al., 2003a; Storm et al., 2006). This is particularly true for percutaneous coronary artery interventions (ICRP, 2013; Koenig et al., 2001; Weinberg et al., 2013), especially those that involve attempts to reopen coronary arteries with chronic total occlusions (Suzuki et al., 2008). Cardiac electrophysiology procedures (e.g., pacemaker insertion, diagnostic evaluations, RF ablations) may also impart substantial radiation doses, and on occasion have caused skin injuries (Bor et al., 2009; Koenig et al., 2001; Trianni et al., 2005). Noncardiac procedures with high-dose potential include transjugular intrahepatic portosystemic shunt (TIPS) creation, angioplasty in the abdomen or pelvis, biliary drainage, embolization procedures, and complex endovascular procedures such as endovascular aortic aneurysm repair (Dauer et al., 2009; Kirkwood et al., 2014; Miller et al., 2003a; Weinberg et al., 2013).
7.4 Dose Estimation for Nuclear Medicine and Other Procedures Using Unsealed Radioactive Materials

Estimating radiation dose for research involving the administration of radionuclides is a two-step process. First, the distribution of administered radioactive material in the body’s organs and tissues must be determined. In the case of most radioactive materials, this distribution varies with time. The number of nuclear transitions is then calculated for specific organs and tissues containing the radioactive material. The time-varying distribution of radioactive material may be determined from experiments in which the material is introduced into animals, which may be followed by limited human pilot studies, because the kinetics in humans may differ from those in animals. Another method is physiological modeling [e.g., compartmental modeling, the Sokoloff model (Sokoloff, 1977; Sokoloff et al., 1977)], which may be done in conjunction with animal experiments and human studies.

The second step is to calculate radiation doses to individual organs and tissues from the radioactive transitions occurring in each organ. In the case of radiations of short ranges, such as alpha and beta particles, the radiation energy released by radioactive decay is almost entirely absorbed in the organs and tissues in which the nuclear transitions occur. However, in the case of penetrating radiation, such as gamma rays and conversion x rays, radiation emitted in a particular organ will deposit some of its energy in other organs or outside the body. The calculations of this second step have been simplified by the Society of Nuclear Medicine and Molecular Imaging’s Medical Internal Radiation Dose (MIRD) method (Loevinger et al., 1988; Zanzonico, 2000). MIRD publications provide tables of absorbed energy fractions in bodily tissues and organs, following administration of various radioactive materials. The published absorbed fractions are based upon probabilistic modeling of radiation transport and interactions in a mathematical phantom of the human body. Simplified tables of radiation doses to specific organs and effective doses have been prepared, based upon the methods above, for many common radiopharmaceuticals used in nuclear medicine and for some other radiochemicals (ICRP, 1988; 1991b; 1998; 2008; 2015).
The uncertainties in dose estimation by MIRD methods have been considered (Howell et al., 1999; Stabin, 2008) and have been estimated to be about a factor of two or more, mainly due to differences in body habitus and in the kinetics of radioactive material transport in specific individuals. Stabin notes that in some applications such as radiopharmaceutical therapies, dose estimations within a factor of perhaps 10 to 20% may be possible if the calculations were to take into account the actual sizes of organs and determination of radioactive material kinetics for the specific individual. However, such individual-specific estimations are not likely to be necessary for preparing a dose estimate for a research protocol.

### 7.5 Dose Estimation for Radiation Oncology

Research protocols involving radiation therapy may involve modified treatment with an established modality (e.g., varying dose or fractionation), treatment with a novel modality (e.g., electronic brachytherapy or radioactive microspheres), treatment with an additional therapeutic agent (e.g., a chemotherapy drug), or a new verification methodology to assess tumor targeting or dose delivery (e.g., on-board x-ray imaging, MRI or ultrasound). The dose estimation will rely on established community standards for dose computation, when available. Those studies using diagnostic imaging tools will adopt dose computation methods appropriate to that tool, as described above. An additional consideration is that chemotherapy agents may act as radiosensitizers, such that the sensitizing effect will perturb tissue response. In this context, dose alone is not enough to describe potential effects on normal and target tissues. The study design should reference preclinical evidence of the synergistic or antagonistic effects of the relevant agents (Flatmark and Ree, 2010).

In addition to the high-radiation doses delivered to relatively small treatment volumes during radiation therapy research, external beam therapy also results in smaller doses delivered to large volumes due to entrance and exit radiation as well as by imaging used in therapy planning and set-up confirmation. Although additional radiation dose due to imaging is not negligible, it typically is <2.5% of the total therapeutic doses delivered (a frequent daily dose is 200 cGy, while a pelvic daily CBCT could add 50 mGy) (Murphy et al., 2007). Unless the
research study is to explore innovations in imaging for therapy planning or set-up confirmation, the contribution of imaging dose should be within the SOC.

7.6 Radiation Dose in Perspective

Human exposure to ionizing radiation from a variety of naturally occurring sources has always been part of our environment. Ubiquitous naturally occurring sources of radiation exposure (often referred to as ‘background radiation’) include: cosmic rays (e.g., high-energy protons, electrons, gamma and x rays) and the radionuclides they produce by interacting with stable nuclides present in our atmosphere and primordial radionuclides with half-lives comparable to the age of the Earth (~4.5 billion years) and their radioactive decay products. The following examples provide a range of dose estimates from various sources to help put commonly encountered radiation doses in perspective.

The average annual per capita effective dose in the U.S. in 2006, from all sources (other than doses to patients from external beam radiation therapy) was estimated to be ~6.2 mSv (NCRP, 2009) (Figure 7.3). Typical effective doses from some common medical x-ray imaging procedures are shown in Figure 7.4. Table 7.1 provides information on doses from several sources of public and occupational radiation exposure. Table 7.2 provides some examples of the amount of radioactivity found in a variety of natural and artificially produced sources. Figure 7.5 illustrates the variation in the annual effective dose from cosmic radiation in North America and Figure 7.6 compares the average annual effective dose from natural background radiation sources in the U.S. to that of a number of European countries and Australia.
**Fig. 7.4.** Doses from some common medical x-ray imaging procedures, where “a” indicates a single CT series, with or without contrast, “b” indicates a rest and stress imaging study with a $^{99m}$Tc-labeled radiopharmaceutical, and “c” from Lilly (2013). The effective dose for FDG PET/CT includes the dose from the PET component and from a limited CT examination for anatomic localization (modified from Mettler et al., 2008).²

²Kroger, L.A. (2016). Personal communication (University of California Davis Medical Center, Sacramento, California).
Table 7.1—Doses from several sources of public and occupational radiation exposure
(adapted from NCRP, 2009; 2010).

<table>
<thead>
<tr>
<th>Radiation Exposure</th>
<th>Typical Effective Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. annual average <em>per capita</em> dose from natural background radiation</td>
<td>3.1</td>
</tr>
<tr>
<td>U.S. annual average <em>per capita</em> dose from medical radiation exposure</td>
<td>3</td>
</tr>
<tr>
<td>Total U.S. annual average <em>per capita</em> dose from all sources</td>
<td>6.2</td>
</tr>
<tr>
<td>Commercial aviation aircrew average annual dose from cosmic radiation</td>
<td>3</td>
</tr>
<tr>
<td>Radiation workers annual average occupational dose</td>
<td>2 – 5</td>
</tr>
<tr>
<td>Coast-to-coast flight, New York City to Los Angeles</td>
<td>~0.025&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Whole body x-ray airport scanner (one scan)</td>
<td>0.00003 – 0.0001</td>
</tr>
</tbody>
</table>

<sup>a</sup>EPA, 2016; FAA, 2017
Table 7.2—Radioactivity of some natural and other materials (adapted from Hall, 1984).

<table>
<thead>
<tr>
<th>Material</th>
<th>Activity (Bq)</th>
<th>Activity (Ci)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kg of granite</td>
<td>1,000 Bq</td>
<td>0.027 μCi</td>
</tr>
<tr>
<td>1 kg of coffee</td>
<td>1,000 Bq</td>
<td>0.03 μCi</td>
</tr>
<tr>
<td>1 kg of coal ash</td>
<td>2,000 Bq</td>
<td>0.054 μCi</td>
</tr>
<tr>
<td>The air in a 100 m² Australian home (radon)</td>
<td>3,000 Bq</td>
<td>0.08 μCi</td>
</tr>
<tr>
<td>1 kg superphosphate fertilizer</td>
<td>5,000 Bq</td>
<td>0.14 μCi</td>
</tr>
<tr>
<td>One adult human (100 Bq kg⁻¹)</td>
<td>7,000 Bq</td>
<td>0.19 μCi</td>
</tr>
<tr>
<td>The air in many 100 m² European homes (radon)</td>
<td>Up to 30,000 Bq</td>
<td>0.81 μCi</td>
</tr>
<tr>
<td>One household smoke detector (with americium)</td>
<td>37,000 Bq</td>
<td>1.0 μCi</td>
</tr>
<tr>
<td>1 kg uranium</td>
<td>25 MBq</td>
<td>576 μCi</td>
</tr>
<tr>
<td>Radioisotope for medical diagnosis</td>
<td>370 MBq</td>
<td>10 mCi</td>
</tr>
<tr>
<td>One luminous exit sign (1970s, ³H)</td>
<td>1,000,000 MBq</td>
<td>27 Ci</td>
</tr>
<tr>
<td></td>
<td>(1 TBq)</td>
<td></td>
</tr>
<tr>
<td>Radioisotope source for medical radiotherapy (Gamma Knife®, ⁶⁰Co)</td>
<td>222,222,222 MBq</td>
<td>6,000 Ci</td>
</tr>
</tbody>
</table>
Fig. 7.5. Color plot of the annual outdoor effective dose from cosmic radiation (in μSv) in North America (Grasty et al., 2004).
Fig. 7.6. Examples of variation in natural background and the sources of the variation (adapted from Green et al., 1992).
8. Estimation of Radiation Risk and Reasonableness of Radiation in Research

This section defines risk and risk terminology, and discusses risk estimation, including uncertainties in risk estimation and factors influencing individual risk. Estimation of the risk of cancer and the role of the metric effective dose are detailed. There is subsequent discussion of hereditary effects, tissue reactions, and fetal effects. The section concludes with determining ‘reasonableness’ in research involving ionizing radiation, weighting societal benefit against planned radiation doses to research volunteers, and with proposed guidelines for cumulative dose in research.

8.1 Terminology and Definitions of Risk

The terminology of risk is extensive and potentially confusing. Risk is defined as exposure to the chance of injury or loss, or as the probability of harm. The definition of risk may include the potential severity of the harm. The International Organization for Standardization (ISO) defines risk, harm, and hazardous event (ISO, 2014):

- **Risk** is the probability of harm, combined with the potential severity of that harm.
- **Harm** is physical injury or damage to the health of people, or damage to property or the environment.
- **Hazardous event** is an event that can cause harm.

In the context of this Report, exposure to ionizing radiation is the ‘hazardous event,’ and development of radiogenic cancer is the ‘harm’ of principal concern. Other relevant terms include:

- **Absolute risk (AR)** is the probability of experiencing an adverse event or developing a disease over a period of time. More technically, it is the excess risk attributed to exposure and usually expressed as the arithmetic difference between the incidence or mortality rate of disease among those exposed and that obtained in the absence of exposure.
• **Relative risk (RR)** compares the probability of an adverse event or disease (i.e., risk) in different groups, such as a group enrolled in a treatment or screening program versus a control group that does not receive treatment or screening. It is expressed as the ratio of the risk in those exposed to the risk in those not exposed (or differently exposed).

• **Excess absolute risk (EAR)** is the difference in absolute risk between exposed and unexposed or control groups.

• **Excess relative risk (ERR)** quantifies how much the level of risk in an exposed group exceeds the risk of an unexposed or control group. It relates excess risk to the underlying (baseline) risk: \( ERR = RR - 1 \).

• **Lifetime attributable risk (LAR)** is the excess risk of an adverse event or disease that is attributable to an agent, such as radiation, expressed throughout the lifetime of the exposed individual.

When used in the context of human exposure to radiation, a **risk coefficient** is a numerical factor used to estimate: (1) the probability of a cancer (fatal cancer or cancer incidence) per unit radiation dose; or (2) the probability of a cancer per unit activity intake of a radionuclide or per disintegration per unit volume, area or mass of a radionuclide in the environment.

If the average doses to individual organs and tissues are known, the risk of cancer can be estimated using published organ-specific risk coefficients (both for cancer incidence and mortality). These risk coefficients, which are based upon an assessment of a variety of epidemiological studies, have been stratified by age and gender (EPA 1999a; 1999b; 2015; NA/NRC, 2006; NIH, 2015b; UNSCEAR, 2006; 2008; 2013), and are estimations of the lifetime attributable risk (LAR) per unit dose. Estimating risk is performed by multiplying the average dose to each organ or tissue by the risk coefficient for that organ or tissue. LAR assumes the linear-nonthreshold model, i.e., a linear relationship between \( E \) and probability of cancer induction without a threshold dose (Section 3.1.1.1).

A complication of this method is that there is cancer incidence and mortality that cannot be attributed to specific organs and tissues with reasonable statistical certainty. For example, the
BEIR VII Phase 2 LAR tables (NA/NRC, 2006) provide LAR for the cancer site ‘other,’ EPA tables provide LAR for the site ‘residual,’ and those in the NCI Radiation Risk Assessment Tool provide risks for the cancer site ‘remainder.’ Berrington de Gonzalez et al. (2012) state: “There is no straightforward way in which to include these remainder cancer sites if the whole-body exposure is non-uniform because of the difficulty in assigning an appropriate dose. Ignoring the risk from the remainder cancer sites will likely result in some under-estimation of total cancer risk for non-uniform exposures…” and “In cases of non-uniform, whole-body exposures, the user needs to provide organ-specific doses, including a dose to the remainder grouping of cancers. The latter dose could be a weighted average of doses to affected organs, although there is no straightforward way to define those weights” (Berrington de Gonzalez et al., 2012).

8.2 Uncertainties in Risk Estimates

Quantitative information on the risks of stochastic effects in humans is primarily derived from epidemiological studies of populations of people who received large doses of radiation, such as the survivors of the atomic bombings of Hiroshima and Nagasaki. There are large uncertainties in this information due to:

- uncertainties in the radiation doses received by individuals;
- epidemiological and methodological uncertainties;
- uncertainties from low statistical power and precision;
- uncertainties from inadequate modeling of radiation risk data; and
- transport of (or generalizing) risk estimates to other populations.

NCRP Report No. 171 (2012) indicated that uncertainties in lifetime risks of fatal cancer to adult workers or the whole population, expressed as a 90 % subjective confidence interval (CI), ranged from a factor of ~2.5 to 3 below and above the 50th percentile (median) value (NCRP, 2012). The 2002 BEIR VII Phase 2 report made a similar statement: “Because of limitations in the data used to develop risk models, risk estimates are uncertain and estimates that are a factor
of two or three larger or smaller cannot be excluded.” As radiation levels decrease below 0.1 Gy, the relative uncertainty in risk estimates necessarily increases even more.

Regarding the model used to estimate the relationship between exposure to low levels (i.e., <0.1 Gy) of low-LET ionizing radiation and harmful effects, the BEIR VII Phase 2 report stated: “…the linear non-threshold model (LNT) provided the most reasonable description of the relation between low-dose exposure to ionizing radiation and the incidence of solid cancers that are induced by ionizing radiation” (NA/NRC, 2006).

### 8.3 Factors Influencing Individual Risk at Time of Exposure

While there are some differences among experts in the interpretation of the scientific literature, it is fair to say that there is general agreement on five important aspects of radiation-induced stochastic risks:

- Excess cancer risk varies according to which organs are exposed.
- Cancer risk varies with age at exposure and attained age. The cancer risk for most tissues is greater when exposures occur in childhood compared to adult life, with a few notable exceptions where the cancer risk appears to be less (e.g., lung cancer) or similar (e.g., stomach, colon, liver, and bladder cancer) for children as compared to adults (Preston et al., 2007) (Figure 8.1). Preston et al. state: “The lack of an age-at-exposure effect for breast cancer ERR reflects the fact that temporal variation for this site appears to be captured more effectively by decreases in the ERR with attained age” (Preston et al., 2007).
- Cancer risk for total body exposure is greater for females than males (Figure 8.2). These figures provide excess relative risk (ERR) estimates for the ‘other’ category (i.e., cancer cases not included in the organ-specific cancers shown).
Fig. 8.1. Comparison of age-at-exposure for selected sites and for incidence of all solid cancers in the Life Span Study; gender-averaged ERR estimates of developing cancer (y-axis) at 70 y of age after exposure at 10 y of age (red bar) or 40 y of age (green bar) (Preston et al., 2007).

Fig. 8.2. Comparison of gender for selected sites and for incidence of all solid cancers in the Life Span Study; gender-specific estimates correspond to the fitted ERR of developing cancer (y-axis) per gray at 70 y of age for a person exposed at 30 y of age (Preston et al., 2007).
There is a weak or nonexistent link between exposure and risk at any age for ~30% of cancers, such as those of the prostate, rectum and uterus or Hodgkin disease.

There is no convincing epidemiological evidence that radiation causes genetic (heritable) effects in humans.

In as much as there is not a major divergence of opinion expressed in the reports cited above, information on radiation-induced cancer risks in this Report is presented based on the analysis and perspectives contained in BEIR VII (NA/NRC, 2006).

UNSCEAR (2006) cautioned that knowledge about the effect of age at exposure on cancer risk for some tissues is still incomplete: “At present, there are no statistically sufficient projections of lifetime risk for specific tumor sites following exposure at young ages. Currently used estimates do not adequately capture the known variations and additional work is needed.”

Variations of risk as a function of sex and age also occur for tissue reactions in therapeutic applications of radiation (Paulino et al., 2010). Thus, generalizations are best avoided and an evaluation should be based on the radiation quality, magnitude of the dose to exposed tissues, the specific age at exposure, attained age at the time of the assessment, and the particular effects of interest.

### 8.4 Use of Effective Dose in Risk Estimations

The quantity $E$ (effective dose) was created by ICRP for radiation protection purposes, to assess the risk of detriment to workers from stochastic effects caused by occupational exposure to ionizing radiation (Harrison and Streffer, 2007; ICRP, 1991a) (Section 3.3.3). It is also applicable to exposure to members of the public. This quantity utilizes mean tissue weighting values for humans, which are chosen rounded values that are applied to both sexes and all ages. Thus, $E$ does not relate to the characteristics of individuals or specific populations (ICRP, 2007a). When determining the risk of detriment, the dose distribution to the body is usually
nonuniform. The quantity takes into account detriment from stochastic effects but not tissue reactions.

ICRP discusses the limitations of $E$ when applied to medical exposures (ICRP Publication 62, 1991; ICRP Publication 103, 2007). ICRP Publication 103 states: “The use of effective dose for assessing the exposure of patients has severe limitations that must be taken into account by medical professionals. Effective dose can be of value for comparing doses from different diagnostic procedures – and in a few special cases from therapeutic procedures – and for comparing the use of similar technologies and procedures in different hospitals and countries as well as using different technologies for the same medical examination…For planning the exposure of patients and risk-benefit assessments, however, the equivalent dose or preferably the absorbed dose to irradiated tissues is the more relevant quantity. This is especially the case when risk estimates are intended.”

Although $E$ was not intended to be used for assessing risk from medical exposures, there are advantages to the use of $E$ in a research setting where it is commonly used to convey the potential risk from radiation exposure for subjects participating in investigational protocols (Martin, 2008). It provides a single metric for comparison of the stochastic radiation risk from the research exposure, the risk of stochastic effects from other medical imaging procedures using ionizing radiation, and the risk from natural background radiation. It has become common practice to convert estimates of $E$ for particular examinations to radiation risks using nominal probability coefficients for fatal cancer or aggregated detriment (NCS, 2016). As discussed above, there are methods for estimating the $E$ from CT (from DLP), x-ray projection imaging (from $P_{KA}$), and nuclear medicine procedures (from administered activity) (Sections 3.3 and 3.4). Table 8.1 provides terms that can be used to convey risk to the subject.

8.4.1 Cautions in Using $E$ for Risk Comparisons in Research

If $E$ is to be used as a measure of risk, consideration should be given to the appropriateness of this metric for the specific exposures anticipated from the research protocol. If a population of
Table 8.1—Descriptors of risk and commensurate societal benefit relative to effective dose.

<table>
<thead>
<tr>
<th>Range of $E$ (mSv)</th>
<th>NCRP$^a$</th>
<th>EPA$^b$</th>
<th>WHO$^c$</th>
<th>ICRP$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.1</td>
<td>Negligible</td>
<td>Minimal</td>
<td>Negligible</td>
<td>Minor</td>
</tr>
<tr>
<td>0.1 to 1</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Minimal</td>
<td>Intermediate</td>
</tr>
<tr>
<td>1 to 10</td>
<td>Minor</td>
<td>Low</td>
<td>Very low</td>
<td>Moderate</td>
</tr>
<tr>
<td>10 to 100</td>
<td>Low</td>
<td>Low ($&lt;50$ mSv), moderate to substantial ($&gt;50$ mSv)</td>
<td>Low ($&lt;20$ mSv), moderate ($&gt;20$ mSv)</td>
<td>Substantial</td>
</tr>
</tbody>
</table>

$^a$NCRP (2010b)
$^b$EPA (2014)
$^c$Derived from WHO (2016)
$^d$ICRP (2007a)
research subjects differs substantially in age, gender, genetic predisposition, body parts being
irradiated, or expected life-span from the populations for which \( E \) was developed, it should not
be assumed that the risk to the research subjects is the same as the risk to the population of
workers or the public. Adjustments should be made for any substantial differences between the
population of research subjects and the populations for which \( E \) was developed. An adjustment
may be as simple as multiplying the risk that was derived for a working age population by a
factor of two or three if the research subjects are children (NA/NRC, 2006). More elaborate
adjustments are described in other publications (Balonov and Shrimpton, 2012; Wall et al.,
2011). \( E \) can provide a general indication of risk (usually within 30 % for adult populations
under 50 y) and is not likely to be off by more than a factor of three to four in older or younger
populations (Table 8.2) (Ivanov et al., 2013).

When considering the potential adverse effects of ionizing radiation on human research
subjects, it should be noted that \( E \) is only an approximate surrogate for risk in cases of partial-
body exposures. In medicine, where partial body exposures are common (e.g., radiographs, CT
scans), \( E \) can have misleading implications. Thus, in expressing risk for partial-body exposure of
individuals, it is important to use the radiation absorbed dose to the organ exposed along with the
appropriate relative biological effectiveness (RBE) values (NCRP, 2010a; 2010b; 2013). Also, \( E \)
is not the best metric when considering a single organ for which specific risk data are available,
such as the thyroid gland. For example, treatment or diagnostic procedures using radioactive
iodine could give a substantial dose to the thyroid but \( E \) for the procedure might be quite low.

8.4.2 Lifetime Attributable Risk Models

ICRP Publication 62 (ICRP, 1991b) provides guidance on the use of \( E \) in estimating risk to
reference persons (NCRP, 2010a; 2010b). Several radiation risk models have been developed
which allow for calculation of the LAR of radiation-induced cancer and mortality as a function
of \( E \), age and gender of the exposed reference person (ICRP, 2007a; NA/NRC, 2006;
UNSCEAR, 2006). The LAR derived by ICRP for incidence of all cancers was 0.017 % per
millisievert and for mortality from all cancers was 0.004 % per millisievert (averaged over both
Table 8.2—Adjustments to effective dose based on BEIR VII lifetime attributable risk of cancer incidence averaged over selected age intervals (adapted from NA/NRC, 2006).

<table>
<thead>
<tr>
<th>Age at exposure (y)</th>
<th>0 – 5</th>
<th>5 – 10</th>
<th>10 – 15</th>
<th>15 – 30</th>
<th>30 – 60</th>
<th>60 – 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2.2</td>
<td>1.7</td>
<td>1.3</td>
<td>1.0</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Female</td>
<td>2.5</td>
<td>1.8</td>
<td>1.4</td>
<td>1.0</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Male &amp; female</td>
<td>2.4</td>
<td>1.8</td>
<td>1.4</td>
<td>1.0</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Multiply the effective dose by the values in the table to adjust for age and gender of the study population. A separate risk calculation should be done for each interval contained in the study population. Depending on the resulting risk estimates, this approach may or may not necessitate the need for revising the consent form to cover more than one risk interval (Section 10).
genders and all ages in seven populations) (ICRP, 2007a). BEIR VII published an LAR for incidence of all cancers of 0.012 % per millisievert and LAR for mortality from all cancers of 0.006 % per millisievert (averaged over both genders and all ages in the U.S. population) (NA/NRC, 2006). Suggested adjustments to $E$ based on the BEIR VII (NA/NRC, 2006) LAR of cancer incidence averaged over selected age intervals are shown in Table 8.2. Decreased uncertainty resulting from more complex calculations in the determination of these adjustments to $E$ would not improve protection of human subjects and might suggest a degree of precision in the calculations that is unwarranted.

Due to the unique aspects of mammography, where the vast majority of dose is only to the breast tissue and the examination is performed primarily for women who are rarely younger than 20 y old and uncommon for women under 30 y old, the LAR for mammography should be estimated by using the age at exposure, gender- and organ-specific (female breast) risk coefficients from BEIR VII (NA/NRC, 2006). A table of LAR of breast cancer due to radiation exposure from mammography for selected age intervals is shown in Table 8.3.

As stated by ICRP, $E$ is intended to be used as a radiation protection quantity, applying only to stochastic effects, and its use in assessments of risk from actual exposures to individuals is not appropriate (ICRP, 1991b). $E$ should not be used for assessing the likelihood of tissue reactions. For tissue reactions, the assessment should consider the absorbed dose to the relevant organ or tissue, or to a limited volume of that organ or tissue, as well as information about dose fractionation.

### 8.5 Second Primary Cancers Following Radiotherapy

The risk of second primary cancers following radiation therapy is dependent upon patient factors (e.g., age and gender), the volume of the area irradiated, the dose to the treatment site and to tissues throughout the body, and factors such as radiation modality, quality and fractionation (Newhauser et al., 2016). The radiation beams frequently must pass through sensitive normal structures in order to deliver an appropriate dose distribution to the target. In contrast,
Table 8.3—Lifetime attributable risk of breast cancer incidence for selected age intervals expressed as the estimated number of cases of breast cancer per 100,000 women exposed to a single dose of 10 mGy (adapted from NA/NRC, 2006).

<table>
<thead>
<tr>
<th>Age (y) at time of mammography</th>
<th>0 – 10</th>
<th>10 – 15</th>
<th>15 – 20</th>
<th>20 – 30</th>
<th>30 – 40</th>
<th>40 – 50</th>
<th>50 – 60</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of breast cancer cases per 100,000 women exposed to a single dose of 1 mGy</td>
<td>NA</td>
<td>6.33</td>
<td>4.91</td>
<td>3.41</td>
<td>1.97</td>
<td>1.06</td>
<td>0.51</td>
<td>0.22</td>
</tr>
</tbody>
</table>
brachytherapy, nuclear medicine therapy, and radioactive microsphere therapy utilize localized placement of radiation sources or uptake of radiopharmaceuticals, and generally result in lower normal tissue irradiation. Teletherapy and brachytherapy treatments also require a margin of irradiated tissue around the target. This is to ensure appropriate coverage despite variations in patient setup and uncertainty in the extent of the target due to limitations in imaging and perhaps the presence of microscopic extensions of the cancer. Management of dose to normal tissues is a critical component of radiation treatment planning, requiring treatment calculations personalized to the individual. Accurate assessment of second primary cancer risk for the individual patient is not currently possible. The risk of second primary cancers and the detriment from them is likely to be greater in infants, children, and young adults and is likely to be small or even negligible in individuals with extremely limited life expectancies.

NCRP Report No. 170 recommends that the organ-specific absorbed dose coupled with the appropriate relative biological effectiveness for endpoint of interest and radiation type (e.g., electrons, protons, neutrons) should be used for risk assessment (NCRP, 2011). Although models have been developed for computing risk of second primary cancers based on the dose to normal tissue structures (Paganetti, 2014), these models have not yet been routinely implemented for clinical use, nor are they validated for use in clinical decision making. This is in contrast to the typical tissue reactions, which are well understood and are a key component in treatment planning.

8.6 Hereditary Effects

Hereditary effects of radiation have been identified predominantly in insects and animal studies. Establishing that such mutations are radiation induced (as opposed to spontaneous) is difficult and is based predominantly on statistical evaluation of experiments utilizing large numbers of exposed subjects and controls. Epidemiologic investigations of human populations exposed to radiation have failed to demonstrate radiation-induced hereditary effects, although mutations of human cells in culture have been shown.
The largest population studied is the atomic-bomb survivors and their progeny. Based on current risk estimates, failure to detect an increase in radiation-induced mutations in this population is not surprising considering how few are predicted in comparison to the spontaneous incidence. Screening of 28 specific protein loci in the blood of 27,000 children of atomic-bomb survivors resulted in only two mutations that might have been caused by radiation exposure of the parents. Earlier studies of survivors’ children to determine whether radiation exposure caused an increase in sex-linked lethal gene mutations that would have resulted in increased prenatal death of males or alteration of the gender birth ratio were negative. Irradiation of human testes has been shown to produce an increase in the incidence of translocations in spermatogonial stem cells, although no excess chromosomal aberrations have been detected in children of atomic-bomb survivors.

A large cohort study of more than 90,000 U.S. radiologic technologists (RTs) examined the risk of childhood cancer (i.e., <20 y old) among more than 100,000 offspring born between 1921 and 1984 to the technologists (Johnson, 2008). Despite the size of the study population, no convincing evidence of an increase in radiation exposure-related risk of childhood cancer in the offspring of RTs was found. The results from a number of recent studies evaluating the potential for transgenerational effects in the children of cancer survivors treated with radiotherapy have also been consistently negative (Signorello et al., 2010; Tawn et al., 2011; Winther et al., 2009).

The methods developed and used by most scientific organizations (e.g., UNSCEAR and ICRP) for risk estimation are necessarily indirect. They are based on using human data on genetic diseases as a frame of reference, together with mouse data on radiation-induced mutations, to predict the radiation risk of genetic disease in humans. Taking into consideration substantial advances in the understanding of human genetic diseases and the process of germ-line mutagenesis after radiation exposure, the ICRP substantially reduced the proportion of detriment ascribed to the potential heritable effects of radiation exposure. In 2007, the ICRP reduced the detriment adjusted nominal risk for heritable effects in the whole population from 1.3 % per sievert (ICRP, 1991a) to 0.2 % per sievert (ICRP, 2007a). This has also been reflected in a reduction to the tissue weighting factor for the gonads from 0.2 to 0.08.
The gonadal dose from typical diagnostic imaging examinations would not be expected to result in any substantial genetic risk to progeny. Although delaying conception after therapeutic doses of radiation to reduce the probability of transmission of genetic damage to offspring is generally advised, it is not a commonly recommended practice for the relatively low gonadal doses from most diagnostic imaging procedures. As noted previously (Section 3.1.2.2), radiation can however induce genetic effects in drosophila and mice. Therefore, while the probability of radiation induced heritable effects from diagnostic imaging examinations in humans is very small, it cannot be eliminated.

Similar statements and additional information can be found in a number of previous NCRP reports. For example, NCRP Report No. 174 notes: “There is no convincing direct evidence of germline mutation manifest as heritable disease in the offspring of humans and attributable to ionizing radiation…” (NCRP, 2013). Furthermore, in BEIR VII it was stated: “Studies have failed to show statistically significant adverse genetic effects in atomic bomb survivors” (NA/NRC, 2006).

8.7 Tissue Reactions

For most research involving human subjects, the radiation doses to individual organs and tissues are sufficiently low that tissue reactions will not occur. The research protocol can merely demonstrate that the doses to specific organs and tissues are below the threshold values for tissue reactions. However, there are categories of research in which tissue reactions may or will occur. These include research involving potentially high dose image guided interventional procedures and research involving radiation therapy. The latter category includes external beam irradiation, brachytherapy, and radiopharmaceutical therapy. In fact, the frequency and severity of the tissue reactions may be a subject of the research.

The severity of tissue reactions can be affected by the distribution of dose to a specific organ or tissue. For example, a very large dose to a small portion of the bone marrow will likely have
little overall effect on a person, because the remaining bone marrow will be sufficient to supply essential blood cells. On the other hand, damage to a small length of the spinal cord can have a devastating effect (Hall and Giaccia, 2012).

Tissue reactions are sometimes caused by potentially high-dose fluoroscopically-guided interventional (FGI) procedures, such as coronary artery interventions, some cardiac electrophysiology interventions, transjugular intrahepatic portosystemic shunt creation, and endovascular repairs of aortic aneurysms. These tissue reactions most commonly affect the skin and subcutaneous tissues (Balter et al., 2010; Koenig et al., 2001; Shope, 1996), but could possibly affect other tissues. In the case of severe cutaneous injuries, early signs may largely resolve after a few days or weeks, with late effects such as dermal necrosis sometimes occurring months to years after a procedure. Rarely, such cutaneous tissue reactions are sufficiently severe to require surgical repair. The likelihood and severity of cutaneous tissue reactions from an FGI procedure can be estimated from the peak skin dose using the dose thresholds described by Balter et al. (2010). Factors that can reduce dose thresholds for these effects in specific individuals include: some hereditary diseases, particularly those affecting DNA repair; drugs such as some chemotherapeutic agents; and previous large radiation doses to the same skin location. Additionally, large body size and obesity increase the risk of radiation injuries as greater radiation dose is required to penetrate the greater tissue thickness.

There are some tissue reactions for which the existence of a dose threshold has not been established. These include cataracts of the lens of the eye and reduced intelligence and school performance of children who were irradiated in utero (Section 3.1.2.1). However, in these cases, practical threshold values exist below which the likelihood or severity of the effect is not discernable. Regarding cataracts, it is noted in NCRP Commentary No. 26 that: “...the field of lens biology has expanded with new molecular and cellular characteristics revealing underlying mechanisms responsible for the differentiation of the lens epithelial cells into lens fiber cells, and how radiation damage can hinder this process in a dose-dependent manner, perhaps linked to the latency of cataract appearance. Radiation cataracts have been considered the epitome of a deterministic effect or ‘tissue reaction’ that appears only after a dose threshold has been
exceeded. However, the latest understanding of the threshold dose for cataract is that the dose for an effect appears to be lower than we thought previously. Much of the mechanistic evidence can be interpreted in support of a stochastic mechanism…” (NCRP, 2016).

Radiation oncology carefully balances concern for normal tissue reactions with concern for curative dose. These concerns are expressed as the parameters normal tissue complication probability (NTCP) and tumor control probability (TCP), respectively, both of which are a function of radiation dose. Effective radiation therapy demands that there be a range of doses which is both high enough to provide adequate tumor control probabilities and low enough to prevent unacceptable normal tissue complication probabilities. This range of doses is called the therapeutic index or therapeutic window (Section 9.5). Since models for NTCP are not sufficiently predictive, clinical standards instead typically rely on dose volume constraints to ensure that the likelihood of a normal tissue complication leading to a specific clinical endpoint is kept below a certain probability. For example, the likelihood of pericarditis is kept below 15 % if a dose of 30 Gy does not encompass >46 % of the heart, assuming standard fractionated treatment delivery (Emami, 2013). The QUANTEC initiative resulted in a definitive set of papers describing the best estimates for normal tissue constraints and the underlying science (Bentzen et al., 2010). The radiosensitivity of a patient will depend on his or her health and is typically a critical concern in the patient selection criteria of the study design in clinical trials. As mentioned earlier, susceptibility to radiation injury depends on the patient’s age (Sections 3.1.2 and 8.2). In addition, younger patients are susceptible to impairment of growth and maturation (Paulino et al., 2010). A current initiative called PENTEC seeks to replicate the QUANTEC project for a pediatric population (Constine et al., 2014). High-dose low-fraction targeted therapies [known as stereotactic body radiation therapy (SBRT)] are now frequently used, creating the need for appropriate normal tissue constraints for this therapy. SBRT dose fractionation schemes are also addressed in the QUANTEC analyses.
8.8 Fetal Effects

The U.S. Department of Health and Human Services (HHS) provides guidance for research involving pregnant women or fetuses in 45 CFR Part 46, Subpart B, Section 46.204 (DHHS, 2009). The Institutional Review Board Guidebook (DHHS, 1993b) states: “Women of child-bearing potential may be excluded from studies not only because of concern for the welfare of the fetus, but also because of possible legal liability of sponsors and investigators for harm caused by investigational agents or other research activities.” Unless a research protocol specifically addresses pregnancy-related medical conditions, it is unusual for pregnant women to be entered into a human studies research protocol that involves ionizing radiation. Before women and girls of child-bearing age are entered into a research protocol, pregnancy status should be ascertained. If the radiation risks of the protocol are low, this may be determined by medical history, such as menstrual history or means of contraception used. This knowledge helps guide the decision of whether to enroll the individual in the study, and what if any additional radiation protection measures need to be taken. However, if the radiation risks are intermediate to high, or if medical history is inconclusive, then a pregnancy test is prudent and often required by the study protocol.

It is necessary to minimize the risk of harm to the fetus, particularly since the fetus is unable to make decisions about participation in research (Williams, 2005). Because there is a risk of detriment at fetal doses ≥100 mGy, with increasing risk at increasing doses (Section 3.1.2.2), most research protocols involving ionizing radiation require determination of pregnancy status and exclusion of pregnant women, and many stipulate the use of specific contraceptive measures during participation in the trial.

Many types of imaging examinations, especially low-dose radiological imaging examinations of organs and body structures remote from the pelvis (e.g., chest radiography, x-ray mammography, imaging of the head or neck, most extremity radiographs), result in very little radiation to the fetus, especially in the first trimester of pregnancy (Brent, 2009; Chetlen et al., 2016; Dauer et al., 2012; Sechopoulos et al., 2008). For these types of imaging procedures,
routine protective measures, such as collimation of the x-ray beam, suffice to protect the fetus (ACR, 2013b). Although the pelvis and possibly the abdomen may be shielded with lead aprons, the radiation dose to the uterus from nonpelvic radiological imaging is primarily from internal scatter radiation which is not significantly altered by such shielding (ACR, 2013b; HPS, 2016).

As stated by NCRP (2013): “Most diagnostic medical imaging procedures in radiography, computed tomography (CT), conventional fluoroscopy, and nuclear medicine subject the embryo or fetus to absorbed doses of 10 mGy or less.” This report further states: “Doses to the embryo or fetus <0.1 Gy (<100 mGy) have not been found to increase the risk of tissue reactions in humans, including severe mental retardation, at any stage of pregnancy.” In regard to stochastic effects, it is not known which stages of fetal development may be most vulnerable to radiation-induced oncogenesis. However, there are data supporting a lower lifetime risk of cancer induction from prenatal irradiation than irradiation during childhood (Preston et al., 2008). There is no substantiated evidence of an increase in heritable genetic mutations in the offspring of parents exposed to radiation prior to conception (NCRP, 2013).

8.9 Determining Reasonableness of Ionizing Radiation Use in Research Protocols

Key considerations of ‘reasonableness’ are whether or not the imaging examination adequately assesses a given clinical trial measure, and whether it does so while delivering the lowest feasible radiation dose. For example, a protocol studying a new drug that lowers immune response would exclude patients with a history of granulomatous disease, such as tuberculosis or histoplasmosis. The use of a chest CT scan to screen potential study subjects would be unreasonable, since a chest radiograph can accomplish this purpose with a much lower radiation dose. However, if a research protocol calls for measuring tumor extent in three dimensions to assess tumor response to treatment, then a chest radiograph would be unreasonable, regardless of the radiation dose, because it would fail to provide the desired clinical information. The use of imaging examinations employing ionizing radiation in human studies shall be reasonable.
If a clinical trial involves a single imaging examination of a specific radiation modality, and the radiation dose for that modality is known, then the risk of short- and long-term consequences can be estimated and used to judge whether or not the use of the modality is reasonable. However, that judgment is complicated when a trial requires follow-up examinations. The risk of cancer following multiple instances of ionizing radiation exposure is considered to be cumulative, so the number of times a radiation study is used in a trial becomes an important consideration when assessing reasonableness, especially for children. Indeed, it has been suggested that the cumulative radiation exposure incurred in pediatric oncologic clinical trials is excessive and may be harmful to the participants (Robbins, 2008). If the number of radiation studies required in a protocol does not exceed the number clinically indicated as SOC, then a detailed radiation risk assessment is not required. If additional or repetitive studies are required, then the overall risk should be a consideration in determining if the number of additional studies is reasonable. Because there is uncertainty about what constitutes an excessive total radiation dose, protocol designers and IRB reviewers must consider: (1) whether or not the clinical measures are appropriate and are effectively obtained, (2) whether or not the measures are obtained using the lowest radiation dose that is reasonably achievable (ALARA), and (3) whether the estimated radiation risk is appropriate within the context of other protocol risks and any potential benefits (Balter et al., 2011).

Determining reasonableness in radiation therapy research is different from determining reasonableness in other research involving radiation because effects on normal tissues due to therapeutic doses must always be managed. The principle of clinical equipoise guides the protocol development (Freedman, 1987; Jones et al., 2014; Sheehan et al., 2014). This principle describes the situation when neither of two presumed clinically acceptable therapies is known to be superior to the other. This comparison includes efficacy of the treatment, the level of risk for prompt or delayed damage to normal tissues, and perhaps other considerations.

Recommendations on criteria for effective doses to volunteers for human studies research have been published by ICRP (2007a), based on expected societal benefit. The recommendations
for planned radiation exposures range from <0.1 mSv for minor benefit to >10 mSv for substantial benefit (Table 8.1).

### 8.10 Proposed Guidelines for Cumulative Dose in Research

The following are proposed guidelines on cumulative dose that may be applied in assessing radiation risk in human studies research. ICRP (1991b; 2007a) and WHO (2016) have developed risk descriptors based upon $E$ to subjects, with corresponding recommendations of commensurate societal benefit (Table 8.1). The approach taken here is to modify defined risk categories to assess the balance between radiation risks and benefits of a research protocol, providing an $E$ range for each risk category, in the context of risk of developing cancer for an adult male 30 to 39 y of age (Table 8.4). Further modifications and adjustments of dose levels based on age and gender for each risk category are presented in Table 8.5. When consulting Table 8.5, if $E$ for a clinical trial straddles two risk categories, the higher category should be used.

Close scrutiny should be given to research protocols that would impart to individual research subjects cumulative effective doses exceeding 250 mSv from diagnostic imaging procedures over a 5 y period. This should include determining whether the radiation doses can be reduced and whether the possible benefits from the research are sufficient to justify the risks to the subjects.
Table 8.4—Risk category, E, risk of fatal cancer, and associated level of benefit for an adult male 30 to 39 y of age.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>E (mSv)</th>
<th>Risk of Cancer</th>
<th>Level of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;0.25</td>
<td>1:2,000,000</td>
<td>Acquisition of knowledge</td>
</tr>
<tr>
<td>IIa</td>
<td>0.25 – 2.5</td>
<td>1:2,000,000 – 1:200,000</td>
<td>Acquisition of knowledge, resulting in health benefit</td>
</tr>
<tr>
<td>IIb</td>
<td>2.5 – 25</td>
<td>1:200,000 – 1:20,000</td>
<td>Acquisition of knowledge, directly aimed at prevention or cure of disease</td>
</tr>
<tr>
<td>IIIa</td>
<td>25 – 50</td>
<td>1:20,000 – 1:400</td>
<td>Acquisition of knowledge, directly aimed at prevention or cure of serious disease</td>
</tr>
<tr>
<td>IIIb</td>
<td>&gt;50</td>
<td>&gt;1:400</td>
<td>Acquisition of knowledge, directly aimed at saving lives or mitigation of serious disease</td>
</tr>
</tbody>
</table>
Table 8.5—Maximum annual E values (mSv) for males and females in different age groups and corresponding risk categories.\(^a\)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age (y)</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>IIIa</th>
<th>IIIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>0 – 9</td>
<td>0.3</td>
<td>1.3</td>
<td>13</td>
<td>25</td>
<td>&gt;25</td>
</tr>
<tr>
<td></td>
<td>10 – 19</td>
<td>0.3</td>
<td>1.5</td>
<td>16</td>
<td>31</td>
<td>&gt;31</td>
</tr>
<tr>
<td></td>
<td>20 – 29</td>
<td>0.3</td>
<td>2</td>
<td>20</td>
<td>40</td>
<td>&gt;40</td>
</tr>
<tr>
<td></td>
<td>30 – 39</td>
<td>0.3</td>
<td>3</td>
<td>25</td>
<td>49</td>
<td>&gt;49</td>
</tr>
<tr>
<td></td>
<td>40 – 49</td>
<td>0.3</td>
<td>3</td>
<td>30</td>
<td>59</td>
<td>&gt;59</td>
</tr>
<tr>
<td></td>
<td>50 – 59</td>
<td>0.5</td>
<td>4</td>
<td>38</td>
<td>77</td>
<td>&gt;77</td>
</tr>
<tr>
<td></td>
<td>60 – 69</td>
<td>0.5</td>
<td>6</td>
<td>56</td>
<td>112</td>
<td>&gt;112</td>
</tr>
<tr>
<td></td>
<td>70 – 79</td>
<td>1</td>
<td>10</td>
<td>95</td>
<td>190</td>
<td>&gt;190</td>
</tr>
<tr>
<td></td>
<td>80 – 89</td>
<td>2</td>
<td>123</td>
<td>227</td>
<td>250(^b)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>90 – 99</td>
<td>31</td>
<td>250(^b)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>0 – 9</td>
<td>0</td>
<td>0.8</td>
<td>9</td>
<td>17</td>
<td>&gt;17</td>
</tr>
<tr>
<td></td>
<td>10 – 19</td>
<td>0</td>
<td>1.3</td>
<td>11</td>
<td>23</td>
<td>&lt;23</td>
</tr>
<tr>
<td></td>
<td>20 – 29</td>
<td>0.3</td>
<td>1.5</td>
<td>15</td>
<td>29</td>
<td>&gt;29</td>
</tr>
<tr>
<td></td>
<td>30 – 39</td>
<td>0.3</td>
<td>1.8</td>
<td>19</td>
<td>37</td>
<td>&gt;37</td>
</tr>
<tr>
<td></td>
<td>40 – 49</td>
<td>0.3</td>
<td>2</td>
<td>22</td>
<td>44</td>
<td>&lt;44</td>
</tr>
<tr>
<td></td>
<td>50 – 59</td>
<td>0.3</td>
<td>3</td>
<td>28</td>
<td>57</td>
<td>&lt;57</td>
</tr>
<tr>
<td></td>
<td>60 – 69</td>
<td>0.5</td>
<td>4</td>
<td>40</td>
<td>81</td>
<td>&gt;81</td>
</tr>
<tr>
<td></td>
<td>70 – 79</td>
<td>0.8</td>
<td>7</td>
<td>69</td>
<td>137</td>
<td>&gt;137</td>
</tr>
<tr>
<td></td>
<td>80 – 89</td>
<td>2</td>
<td>18</td>
<td>179</td>
<td>250(^b)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>90 – 99</td>
<td>63</td>
<td>250(^b)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)No individual should receive a cumulative dose of >250 mSv over a 5 y period. Level of benefit for each risk category is described in Table 8.4.

\(^b\)Highest annual E is 250 mSv to avoid tissue reactions.
9. **Optimization of Radiation Dose**

Ionizing radiation is used in a large percentage of diagnostic and interventional medical procedures, including projection imaging in radiography, mammography, dentistry, fluoroscopy, interventional imaging, and cardiology; cross-sectional transmission imaging in digital tomosynthesis, CT, and cone-beam computed tomography; nuclear medicine emission planar imaging and counting procedures; and nuclear imaging SPECT and PET studies. There is a range of doses across and within these modalities. As noted previously (Section 5), the radiation utilized in diagnostic and therapeutic procedures should be optimized, both for standard medical care of patients and for human studies research. Optimization means that the radiation dose is tailored to be as low as possible while ensuring that the necessary information is obtained, maintaining adequate quality so the study achieves the specific task. Optimization is important in trials in which imaging studies are primary components of the research being conducted, and also when imaging studies are used as ancillary tests in support of research, such as the use of CT scans to follow tumor response in a trial assessing a new cancer therapy protocol. A corollary in human studies research involving ionizing radiation is that the number of research subjects shall be limited to the minimum needed to acquire the appropriate information with sufficient accuracy (EC, 1998).

In diagnostic examinations, the amount of radiation required to produce an image suitable for diagnosis is dependent upon the x-ray attenuation characteristics of the exposed tissues and the thickness of the body part. More radiation is required to image a large adult than a small adult or child. In research studies, as in clinical medicine, the lowest radiation dose is not necessarily the optimal radiation dose. Image quality must be adequate for the intended research purpose. Modern imaging systems are developed with many features that can be used in the effort to keep dose levels “as low as diagnostically acceptable” (Bushberg, 2015; Hricak et al., 2011; McCollough et al., 2009b).

In addition to technological interventions, application of examination protocols can assist in optimizing the use of radiation. An examination protocol describes the parameters for
performing an examination, including clinical indications for the examination (e.g., chest CT examination for pulmonary embolism or abdominal CT for suspected urinary calculi), and substantially affects the dose to the subject. For each examination, these parameters are commonly stated in a protocol document. The protocol document may contain instructions for the operator (e.g., for a CT examination, anatomic limits for each scan) as well as imaging device settings. For x-ray imaging examinations, these parameters are usually also stored as a protocol in the computer that controls the imaging device. Examination protocols are applicable to simple and complex imaging procedures, clinical screening and diagnostic imaging, and human research studies. A research study involving human subjects may utilize an existing clinical protocol or may require the establishment of a protocol specific to the research study. In either case, optimization of dose to the human subjects entails reviewing and adjusting the protocol and/or establishing criteria for the protocol.

Optimization of doses to human subjects enrolled in multi-center research studies presents a particular challenge to researchers and collaborative groups who design and participate in these studies and to the IRB members who review them. Examples of ways for study designers to optimize radiation in multi-center studies include: (1) requiring that participating institutions use imaging and treatment protocols meeting specified criteria, such as keeping radiation dose for a standard study on a standard-sized subject less than a diagnostic reference level, or (2) having participating institutions include their relevant imaging protocol(s) as part of the application to participate (NCRP, 2012b). The recent National Lung Screening Trial serves as an example of a multicenter trial in which efforts were made to limit the doses to the subjects by reviews of each participating institution’s protocols and also by establishing criteria for the protocols (Cagnon et al., 2006; National Lung Screening Trial Research Team, 2011).

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3 A diagnostic reference level (DRL) is used in medical imaging with ionizing radiation to indicate whether, in routine conditions, the patient dose or administered activity from a specified imaging procedure is unusually high or low for that procedure (ICRP, 2007b; NCRP, 2012b).
This section discusses optimization of radiation dose in projection radiography, CT, fluoroscopically-guided procedures, nuclear medicine and fusion imaging, and radionuclide and radiation therapy. Table 9.1 lists techniques and references for optimization in CT and FGI procedures. On-line resources that cover all diagnostic imaging modalities and describe dose reduction and safety procedures include: the Image Wisely website (IW, 2014) for adult applications and the Image Gently website (IG, 2014) for the pediatric population.

9.1 Dose Optimization in Projection Radiography

As with all imaging using ionizing radiation, projection radiography (i.e., standard or plain x rays), should be performed using the lowest radiation dose that provides the necessary image quality to achieve the purpose. For larger patients, thicker body parts, and body parts or organs with greater x-ray attenuation characteristics, larger radiation doses are generally required, with appropriate adjustment of the x-ray tube kV, mAs, and tube filtration (the latter where adjustable). Also appropriate for larger patients is the use of anti-scatter grids to reduce degradation of the image by scattered radiation. Some methods of reducing unnecessary radiation include: collimating the x-ray beam so only the required body part or area is exposed, and not using anti-scatter grids when imaging pediatric patients, small body parts, and extremities. A technological improvement that can reduce dose is the use of flat-panel digital radiography (DR) detectors in lieu of computed radiography (CR) detectors; this can lower radiation dose to the patient by 50 % or more for a given examination owing to a higher x-ray absorption and conversion efficiency, while also reducing electronic noise (Aldrich et al., 2006). Only the necessary images or views should be obtained. A quality control and continuous quality improvement program should be in place to ensure that repeat imaging due to poor technique is minimized.
Table 9.1—Techniques for optimizing dose and image quality in CT\textsuperscript{a} and FGI\textsuperscript{b} in clinical practice and research.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Technique</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed Tomography (CT)</td>
<td>Optimization of imaging protocols</td>
<td>Trattner et al., 2014</td>
</tr>
<tr>
<td></td>
<td>AEC\textsuperscript{c} and tube current modulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Employing technological advances</td>
<td>Kalender et al., 2008; McCollough et al., 2009b; Raman et al., 2013</td>
</tr>
<tr>
<td></td>
<td>In-plane shielding of sensitive organs</td>
<td>Fricke et al., 2003; McCollough et al., 2009b</td>
</tr>
<tr>
<td></td>
<td>Review and optimization of site-determined default imaging protocols (SOC\textsuperscript{d})</td>
<td>Kofler et al., 2014</td>
</tr>
<tr>
<td>Technological advances</td>
<td>AEC\textsuperscript{c}</td>
<td>McCollough et al., 2009b; McKenney et al., 2014</td>
</tr>
<tr>
<td></td>
<td>Iterative reconstruction algorithms</td>
<td>Seibert, 2014</td>
</tr>
<tr>
<td></td>
<td>Multi-row detector array</td>
<td>Hough et al., 2012; Kalra et al., 2014a; Raman et al., 2013; Yu et al., 2010</td>
</tr>
<tr>
<td></td>
<td>Over-beaming and Over-scanning</td>
<td>Bushberg et al., 2012; Kalra et al., 2014a; Schilham et al., 2010</td>
</tr>
<tr>
<td></td>
<td>Prospective gating techniques</td>
<td>Shuman et al., 2008</td>
</tr>
<tr>
<td></td>
<td>Tube current modulation</td>
<td>Kalender et al., 2008; Mayo-Smith et al., 2014; Raman et al., 2013</td>
</tr>
</tbody>
</table>
## Fluoroscopically-Guided Interventions (FGI)

<table>
<thead>
<tr>
<th>Optimization of imaging procedures</th>
<th>Experience of attending staff</th>
<th>Bryk et al., 2006; Chambers et al., 2011; ICRP, 2013a; Miller et al., 2002; 2010; NCRP, 2010b; 2011; Smith-Bindman et al., 2015a; Wagner, 2007; Wagner et al., 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of modern equipment</td>
<td></td>
<td>Chambers et al., 2011; CRCPD, 2010; Hirshfeld et al., 2004; ICRP, 2009; Miller et al., 2010; NCRP, 2010b; 2013; Smith-Bindman et al., 2015a</td>
</tr>
<tr>
<td>IEC standard for recording dose indices and feedback to interventionalist</td>
<td>IEC, 2010; Mavrikou et al., 2008; NCRP, 2011; Wagner, 2007; Wagner et al., 2000</td>
<td></td>
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<tr>
<td>Technological advances</td>
<td>Image processing</td>
<td>Kohlbrenner et al., 2014</td>
</tr>
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<td></td>
<td>Last frame hold and last sequence loop</td>
<td>FDA, 2009a; ICRP, 2013a; NCRP, 2011</td>
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<td></td>
<td>Variable-rate pulsed</td>
<td>Aufrichtig et al., 1994; Hernanz-Schulman et al., 2011</td>
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<td></td>
<td>Virtual collimation</td>
<td>Bushberg et al., 2012</td>
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<td></td>
<td>X-ray tube filtration</td>
<td>NCRP, 2011; Strauss, 2006</td>
</tr>
</tbody>
</table>

[^CT]: computed tomography  
[^FGI]: fluoroscopically-guided interventions (procedures)  
[^AEC]: automatic exposure control  
[^SOC]: standard of care
9.2 Dose Optimization in Computed Tomography

Computed tomography (CT) is a form of cross-sectional transmission imaging that uses x-rays. As with projection radiographs, the amount of radiation required to obtain a diagnostic-quality study depends in part upon the x-ray attenuation characteristics of the exposed tissues and the thickness of the body part. Other considerations include the purpose of the CT examination, and whether or not contrast media is used. Optimization of radiation dose can be achieved by attention to imaging protocols, which should take advantage of the technological features of the CT systems. A research protocol may also prohibit the use of CT systems that lack specified technological features.

Recent efforts by CT manufacturers have resulted in many technological advances that can assist in lowering radiation dose to patients while maintaining image quality acceptable for the diagnostic task, including automatic tube current modulation (Mayo-Smith et al., 2009; McCollough et al., 2009a), iterative reconstruction algorithms (Hara et al., 2009), prospective CT gating techniques for cardiac examinations (Shuman et al., 2008), automatic kV selection (Hough et al., 2012; Raman et al., 2013), and overbeaming or overscanning correction technologies (Kalra et al., 2004a; 2004b; Schilham et al., 2010). Depending upon the protocol and application, substantial reductions of 20 % to 90 % have been reported by investigators cited above, and use of such technologies should be encouraged for studies involving research.

Imaging protocols are pre-determined ‘cookbooks’ of acquisition parameters and machine settings intended to optimize reconstructed CT images for particular diagnostic tasks. With respect to research protocols, many are designed for specific research requirements (e.g., measurements, quantitative data extraction) and should not be altered. In many research studies, the performing site must provide image data to an evaluation center for verification of acceptable system performance and image quality levels according to the detailed requirements of the research study. The default imaging protocols (without any other information) should represent the site-determined clinical SOC for the requested examination, and should be reviewed and optimized on a regular basis (Kofler et al., 2014).
There are several methods to standardize and optimize CT protocols, such as: eliminating unnecessary contrast phase acquisitions, using automatic tube current modulation, and limiting the length of the body that is scanned (Trattner et al., 2014). Shielding of sensitive organs, such as the breast and thyroid, can reduce radiation doses to these organs (Fricke et al., 2003; McCollough et al., 2009b) but is controversial, and should be used only when deemed acceptable for the research study under consideration.

9.3 Dose Optimization in Fluoroscopically-guided Interventions

In FGI procedures, the radiation dose to the patient is chiefly dependent on the complexity of the case and the experience of the interventional physician (NCRP, 2011). Thus, there is a wide range of radiation dose estimates for such procedures (Section 7.2). Modern FGI equipment incorporates several advances to reduce the dose and dose rate of such procedures, as described below (Miller et al., 2010; NCRP, 2013). Newer systems compliant with the International Electrotechnical Commission (IEC) Standard 60601-2-43 (IEC, 2010) also include features to measure and record radiation dose indices and provide feedback to the interventional physician. In concert, all of these technologies can have a substantial impact resulting in the reduction of the radiation dose for the procedure, with little or no sacrifice of image quality or compromise in the ability of the user to complete the study (Mavrikou et al., 2008; NCRP, 2011; Wagner, 2007; Wagner et al., 2000).

Some factors related to patient dose (such as patient size and weight, density of the body part being imaged) are not under the operator’s control, but many more are. It is incumbent on the operator to control exposure time and dose rate by managing the many technical parameters that can be varied during the procedure. The details are beyond the scope of this document, but are fully described elsewhere (Bryk et al., 2006; Chambers et al., 2011; ICRP, 2013a; Miller et al., 2002; 2010; NCRP, 2010b; Wagner et al., 2000; Wagner, 2007). Mastery of these aspects of interventional procedures requires specific education and training (Chambers et al., 2011; CRCPD, 2010; Hirshfeld et al., 2004; ICRP, 2009; NCRP, 2010b).
9.4 Dose Optimization in Nuclear Medicine and Fusion Imaging

In nuclear medicine, small amounts of radioactive agents (radiopharmaceuticals) are administered to examine molecular or physiological processes within the body. Most diagnostic nuclear medicine examinations are performed using short-lived radionuclides (such as $^{99m}$Tc) which typically do not impart high doses. The radiation doses for all nuclear medicine procedures should be optimized so the subject receives the smallest dose that will provide the required information.

Measures should be employed that will enhance the excretion of the radiopharmaceutical. Because many radiopharmaceuticals are excreted by the kidneys, hydration and frequent voiding are often simple and effective means to reduce radiation dose. Administering a smaller activity of the radiopharmaceutical also reduces the dose. If this approach is taken, it is important to maintain adequate diagnostic quality of the images. It is also important to assess the ability of the subject to lie still, as lower administered activity often requires longer imaging time. Employing precautions to promote a diagnostic-quality study, such as measures to prevent patient motion, will lessen the need for repeating a study and help keep the radiation exposure ALARA.

Administered activity shall be adjusted for the subject’s body habitus. This is particularly important for studies of pediatric subjects. The North American Guidelines for Pediatric Radiopharmaceutical Administered Doses is the guidance document that is endorsed by the Society of Nuclear Medicine and Molecular Imaging, based on an international consensus document published in 2014 (Lassmann and Treves, 2014).

The choice of radiopharmaceuticals is also important. For myocardial perfusion studies, radiopharmaceuticals can be selected that impart a lower effective dose while providing the same diagnostic information (e.g., utilizing $^{99m}$Tc agents and avoiding $^{201}$Tl). For most thyroid assessments, $^{123}$I can be used in place of $^{131}$I. The thyroid dose from $^{131}$I is higher than from $^{123}$I due to the longer physical half-life and the decay scheme of $^{131}$I. Another technique to lower
dose to the subject is to consider the sequence of multi-part examinations. With a radionuclide myocardial perfusion study, if the stress component of the study is performed first and is normal, then the resting component of the study may be cancelled, thereby reducing the dose by up to 50%.

In studies using PET with CT (PET-CT), or SPECT with CT (SPECT-CT), the dose from the CT component of the study must be considered. In some cases, a diagnostic quality CT may be required. However, if the CT is only needed for attenuation correction and anatomic correlation, a lower-dose, limited CT may be performed. Careful consideration should be paid to the acquisition parameters of the CT component when a protocol is developed.

9.5 Dose Optimization in Radiation Oncology and Radionuclide Therapy

In radiation oncology and radionuclide therapy, dose is optimized to exploit the therapeutic window, also referred to as the therapeutic ratio or index, which is the range of doses such that the therapeutic benefit can be achieved without an unacceptable increase in the likelihood of severe normal tissue toxicities (Section 8.6) (IAEA, 2010; Sutlief, 2015; Tannock et al., 2013) (Figure 9.1). The assessment of therapeutic benefit is complex and utilizes clinical studies on many factors, such as: regional control, overall survival benefit, total dose, fraction size, whether the subunits of the tissue act in series or in parallel with each other, whether the tissue is an early-responding tissue or a late responding tissue, dose inhomogeneity within the tissue, the LET and RBE of the radiation applied, other modifying factors (concurrent chemotherapy, certain medical conditions, genetic make-up, etc.), and biochemical control as measured by biochemical markers of malignancy, such as prostate-specific antigen (PSA) and alpha-fetoprotein (AFP). Risk of tissue toxicities is estimated for each irradiated organ using one or sometimes several therapeutic endpoints. For example, high doses of radiation to the larynx can result in edema or vocal cord dysfunction. For external beam therapy and brachytherapy, computerized treatment planning is used to ensure that doses to normal tissues are kept low enough to keep risk of toxicities at reasonable levels. Multi-institutional randomized trials specify constraints for target dose (i.e., dose to the tumor) and dose to specified normal
Fig. 9.1. The principle of therapeutic window. The first curve (light gray) represents the tumor control probability and the second curve (dark gray) the probability of normal tissue complications. A dot appears on each curve to indicate the minimum acceptable tumor control probability and maximum acceptable normal tissue complication probability for this treatment. These thresholds vary based on the treatment. The total radiation therapy (RT) dose shown is typically delivered in 2 Gy fractions (adapted from Sutlief, 2015).
structures. Constraints from such studies are frequently used in clinical treatment planning decisions. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) (Bentzen et al., 2010) is a project comprised of a comprehensive set of such constraints and their supporting clinical evidence (Section 8.7).
10. Ethics in Human Studies Research

Duties toward human subjects are defined by ethics, laws and statutes, and regulations. The following section explicates the basic principles in applied ethics relevant to human studies research: respect for autonomy, non-maleficence, beneficence, and justice. This is followed by a discussion of the application of ethics to the norms of practice used in radiation protection: justification, optimization and dose limitation. The issues of controlling influences and voluntariness are raised. Also addressed are the unique concerns presented by participation of children and other vulnerable populations in research protocols. The section concludes with illustrative scenarios that apply ethical and radiation protection principles to human studies research.

10.1 Basic Ethical Considerations in Human Studies Research

When performing research on human subjects, ethical principles can be applied to the ethical concerns that arise, which help in understanding the incumbent ethical duties. Ethical principles will often result in the formulation of ethical rules to aid in the application of a principle to a given situation, in this case, the use of human subjects in research involving radiation. Rules are sometimes articulated as conditions which must be met for an action to be ethical. They also help in making ethical duties understandable and achievable.

One helpful approach focuses on four principles (Beauchamp and Childress, 2012) which express duties that are often encapsulated in rules. The four ethical principles are:

- respect an individual’s autonomy (autonomy);
- prevent a harm (non-maleficence);
- provide a good (beneficence); and
- act fairly (justice).
In addition to the four ethical principles outlined above, Malone and Zolzer (2016) explicitly include three values: human dignity, prudence and honesty. These values and others are at work when the principles or the rules they generate are applied to a specific radiation concern. As discussed below, human dignity and honesty are embedded in the duty to seek informed consent when applying the principle of respect for autonomy.

A fifth principle of radiation protection, the precautionary principle, was adopted by the European Commission (EC, 2000) and made a statutory requirement in the Law of the European Union (EUR-Lex, 2007). The precautionary principle or approach states that if an action or policy has a potentially harmful effect upon the public or the environment, but that risk cannot be scientifically determined with sufficient certainty, the burden of proof establishing the lack of harm falls upon those taking the action. Thus, in the face of significant uncertainty or lack of knowledge about the extent of harm, one should act to afford the public greater protection from exposure to harm. Sound scientific evidence can ameliorate this duty, but until such evidence is available, precaution should be taken and protections should not be relaxed.

Certain ethical theories provide assurance that the ethical principles discussed in this Report have firm footing. Those theories are deontology, teleology and a virtue-based foundation (Hansson, 2007). A deontologist determines the rightness of an action by some feature of the act itself (e.g., it demonstrates a respect for persons and adheres to this value despite the consequences of the action) (Kant, 1995). A teleologist, on the other hand, determines an act’s ethical status by balancing the consequences produced by the act (e.g., a utilitarian) (Mill, 1975). The more recent interest in a virtue-based foundation emphasizes the character of an individual, one who avoids extreme behaviors in favor of the mean. Using prudence and phronesis (i.e., practical wisdom) in the specific situation is key to determining right from wrong, a concept explored in depth by Aristotle (1998). All three of these approaches to establishing duties in various ways support the four ethical principles evinced by Beauchamp and Childress (2012). Three of the principles were used in the Belmont Report (DHHS, 1979) in addressing ethical issues in research on human subjects. Non-maleficence, a fourth principle, was subsumed under beneficence in that earlier document.
These principles are normally thought to be nonreducible (e.g., respect for autonomy is not merely a form of non-maleficence, since a consequence of respecting autonomy could result in harming self or others). Furthermore, these four principles may sometimes conflict. In those cases, a ranking needs to be established. However, individuals and groups may differ on which principle or duty trumps any other (Farnia et al., 2015; NCRP, 2010a). Ideally, ethical disagreements are resolved between parties when they realize they share the same values. Nevertheless, individuals and groups may continue to differ on fundamental values or on the weight to be placed on the ethical duties these values represent. They may disagree with respect to how and to whom duties apply. Resolving these differences can be difficult, but if a resolution is achievable, it is best accomplished by an appeal to reason.

10.2 Application of Ethics to Fundamental Principles of Radiation Protection

Not all principles applicable to the use of radiation in humans are, strictly speaking, principles of ethics. In addition to the four ethical principles articulated above and the fifth precautionary principle, the international and U.S. radiological communities have established three principles of radiation protection. Kase notes that “…the fundamental principles of justification, optimization, and dose limitation as initially stated in ICRP Publication 26 have been adopted and applied by the NCRP in its recommendations. ICRP and NCRP recommendations on dose limitation for the general public and for occupationally exposed individuals are based on the same analyses of radiation risk, and, while similar, there are differences reflecting the aspects of radiation application and exposure circumstances unique to the United States” (Kase, 2004). These radiation protection principles function as ‘norms of practice.’ They do express commitments to certain values and to the relationship among the values. As norms of practice, they clarify for the radiological community the weight to be placed on some values over others. While not identical to norms of practice, the ethical principles mentioned above can be detected as underlying these norms of practice. The relationship between the ethical principles governing biomedical research and the principles of practice governing radiation protection is illustrated in Table 10.1.
Table 10.1—Relationship between principles of biomedical ethics\textsuperscript{a} and principles of radiation protection\textsuperscript{b}

<table>
<thead>
<tr>
<th>Ethical Principles</th>
<th>Radiation Protection Principles</th>
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<tbody>
<tr>
<td></td>
<td>Justification</td>
</tr>
<tr>
<td>Respect for autonomy</td>
<td></td>
</tr>
<tr>
<td>Non-maleficence</td>
<td>*</td>
</tr>
<tr>
<td>Beneficence</td>
<td>*</td>
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<tr>
<td>Justice</td>
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\textsuperscript{a}Beauchamp and Childress (2012)

\textsuperscript{b}NCRP (1993b)

\textsuperscript{c}The principle of dose limitation may be related to respect for autonomy, such as when a first responder is allowed to voluntarily risk exposure to a higher radiation dose when responding to a radiation emergency.
The principle of justification of radiation exposure requires benefits to outweigh harms. In the context of this Report, benefits that are derived from using human subjects in research involving radiation must outweigh harms or risks incurred by those subjects. While two ethical principles mentioned above support justification (i.e., the principles of non-maleficence and beneficence), beneficence supersedes non-maleficence. The provision of a benefit must not merely be the absence of harm; exposure to radiation must result in a good or multiple goods. If, in applying justification, there is a commitment to ensuring that benefits from the research on human subjects be fairly distributed or, minimally, that harms be equitably shared, then the ethical principle of justice is in play. In radiation research, if harms or the risk of harm disproportionately will fall on certain individuals or groups, gaining informed consent (and the respect for a person’s autonomy it represents) plays a key role in ameliorating such an unjust distribution. There is, however, nothing in the principle of justification as stated that guarantees this.

Optimization is clearly supported by the principle of non-maleficence. The expectation that radiation exposure should be kept to a level as low as reasonably achievable (ALARA) is an outright appeal to prevent harm or the risk of harm. Optimization is contextualized, however, by economic and societal concerns. Hence, what constitutes ‘reasonably achievable’ is related to costs associated with radiation protection as well as societal goods that are achievable in the use of human subjects for research involving radiation.

The principle of dose limitation states that the dose to individuals should not exceed the limits recommended for the appropriate circumstances. Dose limits apply to radiation protection of occupationally-exposed individuals and the public. They do not apply to medical radiation exposure of patients or, in most circumstance, to human research subjects. This principle of radiation protection receives its support from the ethical principles of non-maleficence and justice. It does not require the balancing of good (such as a societal benefit) that might be achieved versus potential harm. Neither does it require that greater harm or increased risk might be justified at higher radiation exposure than is allowed by the recommended limits. This
principle does allow for different dose limits depending on the circumstances (e.g., emergency exposures), presuming that respect for autonomy plays a key role in accepting greater risks in these situations.

The principle of dose limitation is closer to a deontological ethical foundation or even a virtue-based foundation which emphasizes precaution, whereas justification and optimization both appeal to a teleological ethical foundation.

10.3 Ethics in Clinical Medicine versus Research

There is a distinction between ethics involving radiation utilized for standard patient care (Section 6) versus that used in human studies research. The areas of clinical medicine and research have different goals and, therefore, different ethical justifications. The goal of scientific research is generalizable knowledge for societal benefit. The ethical justifications are adjusted, based on differing goals (Miller, 2006; Miller and Brody, 2003). Less oversight is needed in standard patient care than is required in research studies because the justification of the former is in the patient’s best interests and the justification of the latter is to the benefit of others. Although this is generally true, in some instances (e.g., Phase III clinical trials) there may be a substantial likelihood of benefit to the research subject. Yet, as noted in Section 6, there is often overlap between elements of standard care and research. Both might be justified, for example, by non-maleficence and therefore might not require separate and distinct ethical principles to justify conduct. However, in the differing roles of clinician and investigator, there are possible conflicts of obligation and of interest that must be kept in mind (Beauchamp and Childress, 2010).

10.4 Respect for Autonomy and the Rule to Seek Informed Consent

The ethical rule to require informed consent from human subjects before proceeding with research using radiation is derived from the principle of respect for autonomy. Informed consent includes three key components, which if not present, raises doubts as to the validity of informed consent: (1) that human subjects are informed in such a way that they understand the risks and benefits of participating in radiation research; (2) that the decision to participate in such research
is not because of controlling influences; and (3) that their consent is voluntary. Assuring the first
compONENT is of prime importance to researchers who must use human subjects in their
protocols. However, it can be overemphasized to the point of overlooking the importance of the
other two components of informed consent. Below all three components involved in obtaining
informed consent are discussed.

10.5 The ‘Informed’ Part of Informed Consent

Communicating the risks involved in research using ionizing radiation on human subjects is
paramount. ‘Risk’ implies that it is possible that the subjects may be inconvenienced, subjected
to discomfort or even subjected to actual physical, emotional or psychological harm. Persons
may be subject to a low probability of severe harm, a high probability of minor inconvenience, a
high probability of severe harm, and/or a low probability of minor harm. In a qualitative sense,
severity of harm and probability of harm occurring can be viewed as a matrix resulting in
extremes and gradations thereof (Figure 10.1) ranging from ‘negligible risk’ through ‘small risk’
to ‘high or significant’ risk. Such terms have inherent ambiguity, so the information regarding
risks, including the distinction between probability and severity, must be presented as clearly as
possible (DHHS, 1979).

In communicating the possibility and severity of harm to subjects, it is important that every
attempt be made to gain the understanding of the human subject. As stated in the Belmont report
(DHHS, 1979): “The manner and context in which information is conveyed is as important as the
information itself … Because the subject’s ability to understand is a function of intelligence,
rationality, maturity and language, it is necessary to adapt the presentation of the information to
the subject’s capacities.” Ionizing radiation, as employed in clinical trials, may incur radiation-
related risks that range from a negligible chance of harm (e.g., bone densitometry, radiography of
the hands or feet) to a virtual certainty of harm (e.g., therapeutic radiation, where the occurrence
of tissue injury is virtually certain).
**Fig. 10.1.** Matrix of risk as a function of probability versus severity of harm (adapted from WIKI, 2015).
10.6 The ‘Consent’ Part of Informed Consent and Intentionality

Consent to participate in research includes the ethical requirement of intentionality and voluntariness on the part of the subjects. Intentional participation is contrasted with accidental participation (i.e., it denotes more than merely complying or agreeing). It involves the authorization by the individual to engage in the research project as a subject. This requirement can create dilemmas for the research community around studies involving children and studies that require randomized, blind research groups.

In ionizing radiation research, the intentional act of nondisclosure hampers the research subject’s ability to act intentionally. This occurs in randomized, controlled trials and the use of blind or double-blind research groups. The primary objective of research is to increase and improve knowledge. In order to produce reliable knowledge and to ensure scientific integrity, the research protocol should include mechanisms to reduce bias. Blinding and randomization in research trials are among the means of reducing study bias.

How, then, is a participant’s autonomy protected if they cannot be adequately informed of the risks to which they are consenting? This is possible if human subjects are informed that they will not know whether they belong to the treatment or control group, and are given the opportunity to avoid the risk by not participating in such a research project. Then, if they do consent under such information constraints, they do so intentionally and the scientific and ethical integrity of the clinical research is preserved. As previously noted (Section 6.2), when human subjects are randomized into trial arms that receive differing amounts of ionizing radiation, at the time of registration they must be informed about the maximum amount of radiation they might receive and the associated risks. It is reasonable to inform subjects that they might receive less radiation than the estimated maximum.

10.7 Consent – Voluntariness and Controlling Influences

Informed consent must include voluntariness. Influences abound but some are sufficiently controlling that a subject’s ‘consent’ is in effect coerced (i.e., not voluntary). Ethicists
distinguish between persuasion, manipulation, and coercion. These types of influences form a continuum of controls which might mitigate against freely given consent. At one end, persuasion that is based in sound reasoning and factual information engages the potential participant in reasoned dialogue, while at the other end, coercion represents forced, unreasoned control over the participant. To give consent to participate in radiation research voluntarily does not mean the human subject must be free from ‘all’ influence in directing his/her own action. Of the three types of influence, coercion is generally considered unethical because, by definition, the subject cannot direct his/her action under coercive conditions. There are forms of manipulation, such as subtle control, that exert pressure on the potential participant thereby hampering his/her self-direction.

Human subjects may have read reports in the popular press about the health effects of medical radiation exposure. Depending upon the bias inherent in reporting about scientific research by the media, subjects may have formed opinions about the benefits and potential harms of medical radiation before ever reading a consent form. Even when presented with factual information in simple language, the prospective participant’s decision to participate may be influenced by values held by the scientific community, not merely scientific facts. Epistemic values (i.e., values related to truth and knowledge) are used in the creation of knowledge (Rudner, 1953). The subject may also be influenced by: “…the manner in which a health care professional or researcher presents information-by tone of voice, by forceful gesture and by framing information positively…” (Beauchamp and Childress, 2010).

A less subtle form of influence, coercion, may be exemplified by management recruiting volunteers from a population of workers. Management may have a stake in ensuring that the research is performed and may know which workers agree to participate and which workers decline. Workers may feel pressure to participate in the research in order to avoid repercussions.

In human studies research, influence is more likely to be manipulative rather than coercive. Nevertheless, all forms of influence are ethically problematic.
10.8 Vulnerable Populations

Under 45 CFR Part 46.111(b) some demographic groups are considered to be vulnerable populations, who are particularly at risk for coercion or undue influence in a research setting. These groups include children, wards of the state, prisoners, pregnant women, persons who are mentally disabled or otherwise cognitively impaired, and economically or educationally disadvantaged persons. When recruiting research subjects from a vulnerable population, their participation must be justified and additional safeguards must be put in place to minimize the risks to the specific demographic group. Pregnant women are rarely intentionally recruited into research studies involving ionizing radiation.

10.9 Cumulative Dose and Human Studies Research

Cumulative dose is the total estimated radiation dose an individual receives from repeated exposures to the same part of the body or to the whole body. It is a concept used primarily for population-based data gathering, rather than in decisions related to the care of individual patients (Durand, 2011). When a person is considered for inclusion in a research protocol, that individual’s cumulative dose is often not known and usually not considered, unless the individual has received and the research protocol involves high doses of radiation (i.e., radiation therapy or image-guided interventional procedures). A human research subject may have received doses of radiation from occupational sources as well as medical sources. The radiation community has a difference of opinion about their ethical duties regarding the use of information about the effects of cumulative doses of radiation, whether that information comes from the subjects themselves or from their occupational records (EC, 1998; NCRP, 2010a; Shrader-Frechette, 1991).

On the one hand, whether or not one can exercise ‘full informed consent’ without informing the subject of the effects of cumulative doses is challenged (Shrader-Frechette, 1991). Shrader-Frechette argues for the establishment of a national radiation dose registry so that occupational workers (and by extension, potential human subjects of research protocols involving ionizing radiation) can be more fully informed when they give their consent to accept greater risks. On the other hand, proponents of not including cumulative dose in informed consent point out that
being fully informed of all one’s radiation exposure sources is not possible, given a number of factors such as incomplete medical and occupational record keeping systems, dose information that is not comparable, and ignorance of environmental exposures (NCRP, 2010a).

The biological effects from exposure to ionizing radiation fall into two categories: stochastic effects and tissue reactions (Section 3). Under the current approach to radiation protection, the linear-nonthreshold model (Section 3.1.2), the risk of a stochastic effect (e.g., cancer induction) is linearly related to radiation dose without a dose threshold, but the severity of the effect is not dose related. Thus, the radiation risk from a research protocol is related only to the radiation delivered as part of the research. Previous radiation exposure, and therefore estimated cumulative dose, is not relevant for stochastic effects (Durand et al., 2012). However, in regards to the risk of a tissue reaction, previous radiation exposure may be relevant. For example, if a research study involves fluoroscopically-guided placement of a coronary stent, the risk of skin injury is related to the radiation dose to the skin from the research procedures and also previous radiation exposure to the same area of skin from previous interventional cardiology procedures. In this case, the total dose (i.e., estimated cumulative dose) to the area of the skin is necessary to predict the likelihood and severity of a tissue reaction, and therefore knowledge of both previous skin dose and current skin dose is relevant for informed consent.

10.10 Scenarios Applying Ethical and Radiation Protection Principles to Human Studies Research

The following hypothetical scenarios are presented to illustrate the application of ethical and radiation protection principles to human studies research. Some are based on actual human research protocols submitted to an IRB. It should be kept in mind that the radiation protection principle of dose limitation applies specifically to occupationally exposed individuals and the public; it does not apply to medical exposures of patients and rarely applies to human research subjects. Also, whereas the ethical principle of beneficence generally does not apply to the individual research subject volunteer, who often does not benefit from the research and may indeed incur negative health effects, when the goal of human studies research is the advancement
of scientific knowledge and the overall improvement of healthcare, there is a future benefit to society.

Scenario 1:

An investigator wants to establish the safety/efficacy of a novel cancer therapy in children. The drug is known to be cardiotoxic. The protocol calls for a MUGA study (i.e., radionuclide ventriculogram) at screening to monitor ventricular cardiac function, and before and after each cycle of the drug. Eight treatment cycles are planned. The parents are fully informed of the radiation risks and the minor subjects are given the opportunity to assent.

Comment: The number of MUGAs is excessive. The total effective dose may exceed 85 mSv, exposing the subjects to risk of a second malignancy later in life. Furthermore, echocardiography is equally effective in assessing ventricular function. Hence, this practice would not meet the ethical duties of beneficence and of non-maleficence nor the radiation protection principles of optimization (keeping radiation dose as low as reasonably achievable, ALARA) and justification. The duty to respect the child’s autonomy is exercised through the parents as long as they are made aware of the radiation risks and excessive number of MUGA studies.

Scenario 2:

A researcher studying stress fractures in runners recruits female post-graduate fellows from his laboratory. The protocol requires a radionuclide bone scan. The consent form tells the subjects that they will receive no payment or benefit, that they must undergo testing to exclude pregnancy, and that the radiation exposure is “the same as that for a simple chest x ray.”

Comment: Radionuclide bone scans are sensitive and relatively cost effective methods for early diagnosis of stress fractures, meeting the radiation principle of justification. If the administered activity of the radiopharmaceutical for the bone scan is kept ALARA, the study
adheres to the radiation protection principle of optimization. The protocol partially invokes non-maleficence by protecting a vulnerable population by exclusion (pregnant women). However, this scenario exhibits two forms of manipulation. First, the subjects may feel obligated to participate in their supervisor’s research, which is a form of coercion. Second, the radiation exposure from a bone scan is far higher than that of a chest x ray, which leads to a false impression that the radiation exposure is negligible, which is manipulation in the form of false information. Hence, the ethical principles of justice and respect for autonomy are breached. The scenario further raises questions of justice by placing the radiation risk on only one population (female graduate students).

**Scenario 3:**

An investigator wants to study the efficacy of a drug in treating metastatic breast cancer in women. The protocol includes SOC CT scans every eight weeks, and a research-related PET/CT scan at initial screening for participation in the trial. Pregnant women are excluded from the study. The informed consent form is written at an eighth-grade reading level, compares the PET/CT exposure to 5 y of natural background radiation to promote comprehension by the research subjects, and informs subjects that the CT scans would be performed even if the subjects were not in the study. A study team member is available to answer subjects’ questions.

**Comment:** This protocol generally adheres to the radiation protection principles of justification and optimization, and to the supporting ethical principles of respect for autonomy and non-maleficence. Justice may or may not apply, depending on the detailed selection criteria and composition of the subjects (e.g., ethnicity, race, socioeconomic background).
11. Informed Consent

Obtaining truly informed consent is essential to the ethical conduct of human studies research. The Federal Policy for the Protection of Human Subjects and equivalent regulations of the FDA require informed consent to be “documented by the use of a written consent form approved by the IRB and signed by the subject or the subject’s legally authorized representative,” except under specified circumstances (FR, 2017). A completed and signed consent form is a legal document. However, obtaining a signed consent form by itself does not constitute adequate informed consent, no matter how well the consent form is written, regardless of its established level of comprehension and use of plain language, and even if the IRB has determined that the information contained in the form is adequate. “Informed consent is a process and not the simple act of signing a formal document” (ACR, 2016). The process of obtaining informed consent necessitates communication and dialog between the individual obtaining consent and the subject or patient (ACR, 2016; AMA, 2016; Sacks and Warren, 2015).

The individual designated to obtain informed consent should be a medical professional who is credible and knowledgeable, able to answer the patient’s or subject’s questions, and “should ideally be skilled in interpersonal communication, be able to convey empathy, use active and effective listening strategies, and be respectful of patient’s concerns” (Dauer et al., 2011). Risks and potential harms inherent in the research protocol must be communicated to human research subjects using clear, concise, and simple language to promote understanding. Because few members of the public are familiar with radiation science, analogies are often used to enhance comprehension; graphic presentations and multimedia formats may also be useful.

In this section detailed elements in the informed consent process and the development of the informed consent document are examined, and guidance on how to meet the obligation of communication with the research subject is provided. Some of the unique problems of conveying radiation risks are presented. There is discussion of the adjustment of risk language for different radiation dose levels. Appendix A provides examples to assist in the development of informed
consent documents for human studies research involving ionizing radiation, with language targeted to different radiation dose estimates.

11.1 Clear Language

The use of clear language contributes to the effectiveness of communication. One aspect of ‘clear language’ is the use of ‘plain language’ (i.e., the use of words and phrases that people use in everyday speech). In accordance with federal law (U.S. Congress, 2010), federal agencies have added ‘plain language’ guidance to their web sites that instruct employees on how to write documents: “…that the public can understand and use” (CDC, 2009). Studies have shown that using simple language and lower reading grade levels in consent forms can substantially improve readability, improve the comfort level subjects have with the proposed research, reduce anxiety, and improve satisfaction with the consent process (Coyne et al., 2003; Davis et al., 1998).

Although comprehension of the contents of the consent form was not substantially improved by plain language in the case of a cancer chemotherapy trial (Coyne, 2003), the use of plain language was associated with lower consent anxiety and higher patient satisfaction; it did not affect study accrual rates. For the presentation of the quantitative, technical information needed when explaining medical imaging and radiation effects, plain language is not detrimental and optimally may improve comprehension.

There is also the possibility of masking important facts through the use of plain language and this must be avoided. Strategies to assist readers in understanding the radiation risk information in consent forms include the following: (1) use active voice and simple verb forms, (2) use pronouns to speak directly to readers, (3) use consistent terminology for a specific thought or object, (4) avoid technical language and jargon, and (5) write short sentences using short words (PLAIN, 2011). Table 11.1 gives examples of how ‘plain language’ may be employed in simplifying the consent forms for clinical research studies that use radiation imaging examinations or therapeutic procedures.
Table 11.1—Examples of plain language to simplify consent forms for clinical research studies using ionizing radiation.

<table>
<thead>
<tr>
<th>Original Language</th>
<th>Plain Language</th>
<th>Strategies Employed</th>
<th>Grade Level Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>A chest radiograph will be performed to rule out tuberculosis.</td>
<td>You will have a chest x ray to make sure you don’t have tuberculosis.</td>
<td>Use active voice and avoid technical terms.</td>
<td>9.5 → 4.9</td>
</tr>
<tr>
<td>All subjects who participate in this protocol will undergo a two-phase chest-abdomen-pelvis CT scan, if one has not been performed in the past 60 d.</td>
<td>You will have a CT scan of your body using a contrast agent, if you have not had one in the past two months.</td>
<td>Speak to participants using ‘you’ and the active voice; avoid technical terms where feasible; use shorter words and sentences.</td>
<td>13.5 → 7.5</td>
</tr>
<tr>
<td>A fluoroscopy-guided placement of the novel cardiac pacemaker will be performed for all subjects who participate in this protocol. There is a risk of transient erythema consequential to this procedure.</td>
<td>If you take part in this research, you will have a new kind of heart pacemaker placed in your chest. The doctor will use x rays to place the pacemaker. You may have temporary reddening of your skin by the x-ray beam (like sunburn).</td>
<td>Speak to participants using ‘you’ and the active voice; avoid technical terms where feasible; use shorter words and sentences.</td>
<td>13.4 → 5.6</td>
</tr>
<tr>
<td>The radiation dose you will receive</td>
<td>If you take part in this research, you Use short words and sentences;</td>
<td></td>
<td>17.9 → 9.4</td>
</tr>
</tbody>
</table>
from the chest CT scan as a result of your participation in this study is 1 mSv, which is equal to 33 % of the annual natural background radiation exposure.

The risks of radiation therapy include epilation in the treatment field, dermal blistering or necrosis, and bone marrow depression, which may result in anemia, coagulopathy and opportunistic infections.

The radiation therapy you will have will have a chest CT scan, which uses radiation. The radiation dose you will get is equal to about one-third of the natural radiation everyone gets in 1 y.

The radiation therapy may cause hair loss and skin burns in the area being treated. It may also cause drops in your blood cell counts. As a result, you may experience fatigue, easy bruising, problems with stopping bleeding from cuts, and infections.
11.2 Addressing Literacy and Numeracy

There are varying reading level recommendations for informed consent documents. Paasche-Orlow et al. (2003) give the most conservative recommendation, with a target reading level of fourth grade to sixth grade (Paasche-Orlow et al., 2003). Young et al. (1990) advocate a sixth grade reading level, while Davis et al. (1998) report good results with clinical trial consent forms written at the seventh grade reading level. For informed consent for cancer clinical trials, Baer et al. (2011) cite recommendations of sixth to eighth grade reading levels. The National Heart, Lung and Blood Institute website states: “Most IRBs will request that Informed Consent Forms be written at a sixth to eighth grade reading level” (NHLBI, 2011), which is supported by NCI (1998) and by the World Health Organization (WHO, 2017).

All clinical research subjects must be informed about the risks of participation in a form that they can read and understand (DHHS, 1979; 2009). The information must be read to subjects who cannot read, and the spoken information must be in a form that is easily understood. For subjects who can read, the level at which the material is written will influence their ability to understand the material (DHHS, 1979) and affect their level of confidence in the consent process (Coyne, 2003). Even highly educated subjects prefer information that is written at lower grade levels, because it is easier to read and understand (Weiss, 1997).

Transmitting complicated medical and technical information to subjects in an easy-to-read form is not achieved easily. Although NCI recommends that consent forms be written at an eighth grade reading level (Baer et al., 2011), IRBs commonly approve text in informed consent forms that falls short of this standard, and even falls short of their own readability standards (Paasche-Orlow et al., 2003).

Once the radiation risk statement has been written, a number of quantitative indices of readability are available that can assist in reducing the reading grade level of a document. Some basic readability scales were introduced by Flesch and were based upon the average number of words per sentence and the average number of syllables per word (Flesch, 1948). The indices
were suitable for manual calculation of reading grade level for papers of a few paragraphs, but were not practical to use at the document level. Subsequent automation of the process by Kincaid and coworkers led to the development of the widely-used Flesch-Kincaid reading grade scale (Kincaid et al., 1975). Methods other than simplifying language may be employed to improve the readability of consent forms. For example, the use of serif fonts is preferred in text because the serifs provide a kind of ‘railroad track’ that facilitates horizontal eye movement and improves readability. Similarly, the use of white space to break up long blocks of text, and explanatory charts and graphics improve readability (Degani, 1992). The following paragraphs provide an example of how the simplification of language and the substitution of a table for a complex block of text can improve the readability and comprehension of, and lower the reading grade level for, language that might be included in a consent form.

An original paragraph in a consent form (Flesch-Kincaid Level 15.4) stated: “In addition, one tube of blood (about one teaspoonful) will be collected at the following time points to determine the amount of the drug (name of drug) in your blood: before you receive your first dose, between 15-45 minutes after you receive your first dose, between 4-6 hours after your first dose, and 7 and 14 days after beginning treatment (two samples will be obtained at least one hour apart on days 7 and 14). Additionally, if you begin study treatment taking 3 pills per day, and your doctor indicates you may begin to take 4 pills per day, one tube of blood will be collected before you begin to take 4 pills per day. Similarly, if your doctor indicates you may begin to take 5 pills per day, one tube of blood will be collected before you begin to take 5 pills per day. Finally, one tube of blood will be taken 28 days after you have been taking 5 pills per day. Your doctor may ask you to avoid certain antacid medications, if possible, on the days these blood samples are collected. The samples will be sent to a central laboratory to be analyzed.”

After removing passive voice and simplifying the language in the above (Flesch-Kincaid Level 10.0), it then read as: “We will take one tube of blood (about one teaspoonful) at several time points to determine the amount of the drug (name of drug) in your blood. These times are as follows: before you take your first dose, about 30 minutes after you take your first dose, about 2 hours after your first dose, about 5 hours after your first dose, and 7 and 14 days after
beginning treatment. We will take two samples at least one hour apart on those two days. If you
begin study treatment taking 3 pills per day, and your doctor says you may start taking 4 pills per
day, we will take one tube of blood before you start taking 4 pills per day. If your doctor says
you may start taking 5 pills per day, we will take one tube of blood before you start taking 5 pills
per day. Finally, we will take one tube of blood 28 days after you have been taking 5 pills per
day. Your doctor may ask you not to take certain antacid medications, if possible, on the days we
take these blood samples. We will send the samples to a central laboratory for analysis.”

Furthermore, after substituting a table for the long description of sample regimen and further
simplifying language (Flesch-Kincaid Level 6.8), it read: “We will take one or two tubes of
blood at several times points to measure the amount of the study drug in your blood. Each tube
holds about one teaspoonful of blood. The chart below (Figure 11.1) shows the times we will
take blood samples and the number of tubes we will take. Your doctor may ask you not to take
certain antacid medications on the days we take these blood samples. We will send the samples
to a central laboratory for analysis.”

Related to reading comprehension and literacy is numeracy: the ability to understand
numbers and the fundamentals of arithmetic. It is estimated that 22 % of adults have below basic
numeracy skills; this deficiency increases to 34 % for older adults (Marcus, 2006). Quantitative
literacy may be substantially lower in the American population, depending upon the complexity
of the mathematical task administered (Kirsch et al., 2002). Lack of numeracy skills affects the
individual’s ability to understand risk-benefit information and can adversely affect healthcare
choices (Peters et al., 2007). Better comprehension is achieved when only the most relevant
information is presented, in a simple format (e.g., if number values are compared, indicating that
a higher number is “better”). Additional aids include using visual displays and keeping the
denominator constant when comparing probabilities.
<table>
<thead>
<tr>
<th>Times Blood Will be Taken</th>
<th>Number of Pills Per Day As Directed By Doctor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start at Three Pills</td>
</tr>
<tr>
<td>Before you take first pill</td>
<td>1 tube</td>
</tr>
<tr>
<td>About 30 minutes after first pill</td>
<td>1 tube</td>
</tr>
<tr>
<td>About 2 hours after first pill</td>
<td>1 tube</td>
</tr>
<tr>
<td>About 5 hour after first pills</td>
<td>1 tube</td>
</tr>
<tr>
<td>Seven days after start of treatment</td>
<td>2 tubes</td>
</tr>
<tr>
<td>Two weeks after start of treatment</td>
<td>2 tubes</td>
</tr>
<tr>
<td>Four weeks after start of treatment</td>
<td>1 tube, if you stay at three pills per day</td>
</tr>
<tr>
<td>Eight weeks after start of treatment</td>
<td>1 tube, if you stay at three pills per day</td>
</tr>
<tr>
<td>End of treatment</td>
<td>1 tube</td>
</tr>
</tbody>
</table>

**Fig. 11.1.** Chart demonstrating a method of improving communications in the informed consent process.
Another aspect of the informed consent document to consider is its length. An analysis of data on the length of clinical consent forms from 1978 to 2002 shows that the length of the forms has increased at a rate of ~5% per year (Albala, 2010). A projection of this trend to 2013 predicts a length of about 10 pages for clinical consent forms. One study determined that the length of research consent forms was over twice that of clinical consent forms (Hopper et al., 1995). The combination of ‘length creep’ and the additional material included in research consent forms predicts a current length of about 20 pages. This is consistent with the experience of one academic institution, where the average length was about 17 pages for consent forms for protocols that involved ionizing radiation studies. To address this trend, NCI updated its guidelines and sent a letter to IRB chairs and members advising them to limit the length of these forms (Baer, 2011; NCI, 2013a). The recommended maximum length for the required sections in the new template is about 12 pages, with about four pages devoted to all the risks in the protocol, including the risks from ionizing radiation studies.

For drug trials, the known risks from the study drug may far outweigh the hypothetical stochastic risks of ionizing radiation. Furthermore, some radiation examinations require the administration of contrast agents or the use of conscious sedation. Both incur well-characterized risks, including anaphylaxis, end-organ failure and death. Undue focus on the radiation risks may distract readers from other risks and possible benefits, and may not be in the subject’s best interest (Balter et al., 2010). To avoid inappropriate over-emphasis on radiation risks, the length of the radiation risk statement should be commensurate with the risks and should be as short as feasible. However, the amount of information provided should not be reduced to the extent that it jeopardizes comprehension. Also radiation risks should be placed in context with the other risks of the protocol. Judgment should be carefully exercised in this matter to ensure that the length of

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4 Reiman, R.E. (2014). Personal communication (Duke University Medical Center, Durham, North Carolina).
an information document or, indeed, an interactive participation with research subjects, enhances their understanding of the risks involved, rather than limiting their comprehension.

Estimates of cancer risk due to low-dose diagnostic procedures increase as the effective dose \( (E) \) increases. There are several ways to express the degree of risk at different dose levels (EPA, 2014; NCRP, 2010b; WHO, 2016). Table 8.1 provides suggested terms for describing risk and societal benefit (ICRP, 2007a).

### 11.4 Communicating Risk, Uncertainty and Latency in Research Involving Radiation

The biological and human health effects of ionizing radiation have been studied for over a century, and an understanding of the relationship between radiation dose and effect has evolved over time. Mathematical models relating the probability of occurrence of radiation-induced cancer to radiation dose have been developed for populations of different genders, attained ages and ages at exposure (NA/NRC, 2006). These models can produce quantitative estimates of the risks from ‘low-dose’ diagnostic studies that are not available for other agents, and provide clarity in the informed consent process that is unique to ionizing radiation.

Radiation risk to a human subject as a consequence of participation in a research study depends in part upon the subject’s age and gender, the nature of the radiation utilized in the examinations required by the trial, and the total radiation dose delivered (Sections 7 and 8). To a large extent, these factors can be defined for a particular trial. However, uncertainties complicate the informed consent process. These uncertainties include: (1) translating dose into risk, (2) accounting for the long latency period that may occur between the radiation exposure and the occurrence of clinically evident disease, (3) the cumulative effect of multiple examinations, and (4) the longevity of the individual. There is no consensus on how best to communicate uncertainty about harms and benefits of medical interventions to patients (Politi et al., 2007).

There are many challenges in expressing radiation risk to research subjects. Estimation of risk from ionizing radiation is technically complex, and presenting quantitative or qualitative
information about possible radiation effects in a comprehensible manner is challenging. Subjects may have read reports in the popular press about the health effects of medical radiation exposure. Many have little understanding of the scientific concepts involved in radiation exposure. Depending on the bias inherent in either the exaggerated reporting or the underreporting about scientific research by the media, subjects may have formed opinions about the benefits and potential harm of medical radiation before reading a consent form. Even when presented with factual information in simple language, prospective subjects’ decisions to participate will be influenced by their individual perception of the risk, and their overall level of tolerance of risks.

It is generally recommended that risk be communicated as absolute risk (AR), as opposed to relative risk (RR) (Section 8.1) (Fagerlin et al., 2011; Politi et al., 2007). For example, if a baseline disease incidence is 6 %, and the intervention (e.g., treatment) reduces disease incidence to 3 %, the AR of the disease is reduced from 6 to 3 %; however, the RR of the disease is reduced by 50 %. Emphasizing the RR could misrepresent the benefit of the intervention (e.g., treatment) to the subject. There is debate over whether statistical information is better understood when presented as percentages or frequencies; people with low numeracy skills often are more comfortable with frequencies (e.g., ‘1 out of 10’ as opposed to ‘10 % incidence’) (Fagerlin et al., 2011). Graphic material, especially pictographs, can be of substantial assistance when presenting risk information (Fagerlin et al., 2011; Fahey et al., 2011), and summary tables can help in explaining protocols with numerous risks and benefits (Fagerlin et al., 2011).

11.5 Benchmarks and Circularity in Communicating Information on Radiation Dose

Expressing radiation dose and radiation risk in a way that is meaningful to research subjects is challenging. The overwhelming majority of prospective research participants are not familiar with the concepts of organ dose and \( E \). If radiation doses are presented as some number of ‘millisieverts’ in the consent form, most subjects will not find that information helpful, and some may even misinterpret it if they do research about radiation risk on their own. Although inclusion of quantitative dose information is reasonable, it is more important to express risk in ways that
put the information in perspective and enable subjects to make a value judgment about whether or not the radiation risk is acceptable to them (Reiman, 2013).

$E$ is the index of risk that is most widely accepted and utilized for occupational radiation protection purposes. The weighting factors used to calculate $E$ (Section 3.3.3) are derived from population data, so it is not strictly valid to use $E$ to estimate risk to an individual (Sections 7 and 8). Instead, $E$ values are applied to individuals in the context of investigational levels and dose limits for radiation protection purposes. However, $E$ can be useful in the context of informed consent because: (1) it is the quantity reported for dose for many radiation studies reported in the literature, and (2) it may be easily compared to ‘dose benchmarks.’ Dose benchmarks are everyday experiences associated with radiation exposure for which typical effective doses are known. For example, the effective dose passengers receive during a one-way coast-to-coast, nonstop airplane flight from New York City to Los Angeles (~0.025 mSv) might be used as a benchmark (EPA, 2016; FAA, 2017). Thus, the consent form for a study that included one PA chest radiograph (~0.02 mSv) (FDA, 2016a; HPS, 2000) might state that the radiation dose incurred by participation in the study would be equivalent to that received during a one-way flight from New York City to Los Angeles.

Use of the ‘airline flight’ benchmark becomes cumbersome for $E$ greater than a few hundred microsievert. Cameron proposed the BERT (i.e., background equivalent radiation time) as a radiation dose unit that members of the public would understand better than ‘millirem’ or ‘millisievert’ (Cameron, 1991). Normalizing the radiation dose from a radiological study to the average annual $E$ received from natural background sources in the United States at sea level (3 mSv), and multiplying by 1 y, results in a unit of time that may be converted into days, weeks, months, or years, whichever is most convenient. Conversion to background equivalent time is the method of benchmark comparison used in the sections devoted to radiogenic risks in the NCI informed consent template (NCI, 2013a). Using background radiation (or background equivalent time) is informative. However, like the airplane example above, this analogy alone is insufficient to justify the acceptability of dose without further explanation. Otherwise, merely equating the natural (i.e., background radiation) with the good (radiation exposure in the research protocol)
involves accepting the premise that “if it is natural, it must be good” without further support of that premise.

Similarly, caution should be exercised when using one radiation study as a dose benchmark for another radiation study. Consider the example of comparing CT procedures with standard radiographs. Although the statement that: “A CT scan of the abdomen gives the same radiation dose as 250 chest x rays” may be quantitatively correct, it is circular in nature because it depends upon the reader’s perception of the dose and risk of a chest x ray. If subjects don’t have a basis for making a value judgment about the risk of chest x rays, they may come to incorrect judgements about the risk of CT scans (Reiman, 2013). Another analogy, comparing doses received by research subjects with occupational dose limits, should also be used with caution. Prospective research subjects may presume that radiation workers commonly receive doses approaching the occupational limits and conclude that such doses convey no significant risk, whereas the vast majority of radiation workers receive doses that are small fractions of the limits.

11.6 Studies Involving Children and Other Vulnerable Populations

There are instances described in oral histories compiled as part of the U.S. DOE Openness Project in which radioactive material was administered to subjects with limited capacity to give consent or assent. Examples include: $^{131}$I administered to the children of Oak Ridge National Laboratory employees and $^{45}$Ca administered to mentally retarded boys for metabolic studies (DOE, 1995a). Informed consent was not given by these populations. In fact, the duty to prevent harm should have been exercised by responsible parties and questions should have been raised about whether these children and disadvantaged populations such as mentally compromised adults were capable of giving their informed consents from the outset.

Participation of children in a clinical trial affects the way information regarding radiation risks is transmitted to subjects and their guardians. It also raises the question of whether children can engage in the intentionality required of consent. The risk of radiation-induced cancer is higher for individuals irradiated in childhood than for those irradiated while adults (NA/NRC,
2006) (Sections 3, 7, and 8). Differences in the effective radiation doses for diagnostic studies used in clinical trials, differences in the dose-to-risk conversion factors for children and differences in reading grade levels all influence the way in which radiation risk is expressed in consent forms.

Ethical guidelines and government regulations require the assent of children who are capable of providing it (DHHS, 2009; FDA, 2014k; Wendler, 2006). Informed assent is the term used to describe the process by which minors may agree to participate in research studies. It has been established that, in general, children between the ages of 14 and 18 y are capable of making independent judgments regarding participation in a clinical trial (Wendler, 2006). Age alone, however, cannot predict decision making capacity. Indeed, children between 7 or 8 y and 13 y of age may be able to assent on an individual basis. The National Commission for the Protection of Human Subjects of Biomedical Research (NCPH, 1977) concluded that: “While there is debate about precise ages, the Commission has selected age seven as the age that may be considered as the time when children become capable of some reflective judgment.”

In the pediatric assent process, “The research team explains the trial to the child in language the child can understand, including what it means to take part and what the child can expect” (NIH, 2016). The assent form “should be brief and study specific, with subheadings or numerical paragraphs, and contain language that is both appropriate to the child’s development and age. The assent form should have a simple format that is easy to read and when possible, limited to one page” (UCLA, 2016). There is a potential role for web-based, multimedia presentations in obtaining both parental permission and assent of the child in pediatric clinical trials that may substantially improve understanding and overall comprehension of research procedures (O’Lonergan and Harwood, 2011).

Healthcare proxies for children (i.e., parents and legal guardians) who decide to enroll children in research studies are ethically bound to act in the best interests of the children. This is likewise the case for healthcare proxies of people with intellectual disabilities, although strategies are being developed to communicate the risks and benefits of research protocols to this
patient population to engage them more directly in the informed consent process (Marcus, 2014).

The Common Rule requires additional safeguards when individuals vulnerable to coercion or undue influence take part in research. This is an increasing concern for individuals with impaired decision-making capacity or impaired consent capacity as the U.S. population ages (OHRP, 2009). A wide range of health issues may alter decision making capacity in adults, such as dementia, strokes, traumatic brain injury, and serious mental illness. Federal rules refer to state and local laws to determine who may provide consent for research on behalf of such individuals. The ‘Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research’ has recommended new guidance and additional regulations to provide research protections for individuals with impaired consent capacity (OHRP, 2009).

11.7 Informed Consent for Studies Involving Diagnostic Examinations

The primary risk from ionizing radiation due to diagnostic imaging examinations is the possibility of cancer induction. For many diagnostic x-ray, CT and nuclear medicine examinations, a reasonable estimate of the effective dose has been established, and there are several methods for expressing radiation risk. There are several factors that influence both the statement of risk and the subject’s ability to make a judgment about whether or not the risk is acceptable.

First, the risk is believed to be very low: extrapolations of the LAR estimates for radiation-induced cancer from doses in the diagnostic CT and nuclear medicine range are on the order of 1 to 2% over the baseline cancer incidence (Berrington de Gonzalez et al., 2009; NA/NRC, 2006). Cancer induction is a ‘low probability’ but ‘high impact’ risk of diagnostic radiation, and is the primary reason for including radiation risk statements in consent forms of protocols that use only diagnostic studies.

Second, the occurrence of a radiation-induced cancer may not become clinically apparent until decades after the radiation study was performed. Depending upon the age of the subject at
the time of enrollment in the study, this fact may influence their perception of the radiation risk in the context of other study risks.

Finally, there is disagreement in the scientific community about whether there is any increased risk at all for diagnostic radiographic, CT and nuclear medicine studies (Siegel, 2014; Siegel et al., 2015; 2017; Ulsh, 2014). On one hand, BEIR VII recommends linear extrapolation of risk estimates without considering a threshold dose (NA/NRC, 2006) (Section 3.1.1.1). For this model, every radiation dose carries some risk of stochastic effects, even if vanishingly small. On the other hand, some scientists believe that the LNT model is implausible from a radiobiological standpoint, and that some radiation exposures carry no increase in risk. AAPM has stated that: “…risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged” (AAPM, 2011a).

While uncertainty abounds in research, communicating about ionizing radiation risk takes on a special character because of the three features described above. Risk is defined as the possibility of loss or injury, whereas harm is defined as injury. Many people do not understand ‘risk’ as the possibility or probability of harm. They tend to equate risk and harm. Informing subjects that there is a genuine uncertainty in any risk estimate may help promote their understanding about the level of radiation risk compared to any other risks in the research protocol.

11.8 Informed Consent for Studies Involving Image-guided Intervention

Most interventional radiology and interventional cardiology studies, as well as many other image-guided interventional procedures, use fluoroscopy. Depending upon the skill of the operator, and the nature and complexity of the procedure, patient radiation dose varies, possibly by as much as an order of magnitude or more (Section 5.2.2). This leads to variability in the
anticipated $E$, which makes informing subjects about the stochastic radiation risk of a particular interventional procedure difficult. At best, a typical range of values for $E$ is used as the basis for the risk statement for stochastic effects. As with diagnostic studies, a statement regarding uncertainty in the stochastic risk is appropriate.

In addition to the stochastic risks, interventional procedures carry the risk of tissue reactions to the skin. The $D_{\text{skin, max}}$ is the variable that correlates best with the risk of severe injury to the skin (FDA, 1995), but $D_{\text{skin, max}}$ is not easily measured. At present, $K_{\text{a,r}}$ is recommended as the best dose metric that is readily available (Balter et al., 2010; Miller et al., 2010; NCRP, 2010) (Section 3.4). The risk of transient effects such as erythema and epilation, as well as the risks of desquamation and dermal necrosis, should be conveyed to prospective research subjects for potentially high-dose procedures (e.g., percutaneous coronary interventions, embolizations).

11.9 Informed Consent for Studies Involving Therapeutic Radiation

In providing informed consent, the relative risks of the study arms should be compared to those of SOC radiation therapy. If the study combines both radiation therapy and another modality, such as chemotherapy or surgery, then the possible side effects should be itemized separately for each modality. Informed consent should also discuss the likely enhancement of effects (i.e., tissue reactions) when radiation is combined with one or more chemotherapeutic agents. Typically, diagnostic imaging is not included in the informed consent unless integral to the study design. Imaging used for either treatment planning (typically CT-simulation, MRI or PET) or for treatment setup verification (such as MV Ports, kV image pairs or cone-beam CT) is also omitted from informed consent documents, as these sources add minimal risk to the high radiation doses accrued in the course of therapy.

For therapeutic radiation, tissue reactions are virtually certain, and the risk of stochastic effects is higher than that for diagnostic or interventional studies. This is true for both external beam therapy, brachytherapy and systemic radionuclide therapy. Depending upon the area of the body irradiated, tissue reactions may include skin injury, bone marrow depression, injury to the
gastrointestinal tract, cataracts, and adverse neurocognitive effects. Despite advances in the 
ability to limit the area treated to the primary tumor and/or metastatic disease, external beam 
therapy invariably irradiates nearby normal tissues to doses that are much higher than those due 
to diagnostic examinations. Due to radiation and other potentially confounding factors, the risk 
of second primary cancers later in life is real and measurable, and depends upon the type of 
treatment employed, the age of the subject at irradiation and other factors (NCRP, 2011; Stovall, 
2008; Travis, 2002; 2003). This is another special dimension of risk that must be explained to 
subjects participating in clinical radiation therapy and radiation therapy research.

Most research protocols involving radiation therapy include radiation therapy in every study 
arm. Studies which randomize patients for treatment with or without radiation therapy are 
exceptionally uncommon. Thus, in practice, the study arms will all involve the statement of 
underlying risks associated with radiation therapy (ACR, 2014). The Radiation Therapy 
Oncology Group provides extensive sample informed consent statements (RTOG, 2008). These 
statements do not distinguish between those radiation therapy risks which are inherent to the 
therapy versus those risks unique to the research protocol. In addition to general risks to the 
patient, it is common to include separate statements about risks related to pregnancy (CFR, 
2014), reduced or lost fertility, and to implanted devices. The American College of Radiology 
guidance for informed consent in radiation oncology says that the physician must notify patients 
of complications that, although rare, are serious and frequent enough that the patient would want 
to know about them before deciding on a treatment (ACR, 2014).
12. Summary and Conclusions

Knowledge about ionizing radiation in general, radiation involved in medical procedures, and the potential adverse effects of radiation, is variable among members of the public and within the medical community. It is therefore important to provide guidance to researchers and institutional review boards (IRBs) on radiation risks for human research studies involving radiation.

12.1 Regulatory Requirements

The basic principles for the ethical conduct of human studies research have been articulated by international and national authorities. Seminal documents include the Nuremburg Code, the Declaration of Helsinki, and the Belmont Report. The Federal Policy for the Protection of Human Subjects, also known as the “Common Rule,” was published in 1991 and codified in separate regulations by 15 federal departments and agencies. Although not part of their regulations, the Central Intelligence Agency, the U.S. Department of Homeland Security, and the Social Security Administration also comply with the Common Rule. Research involving human subjects sponsored, supported or otherwise subject to regulation by these departments and agencies must be conducted in accordance with the Common Rule. The Office of Human Research Protections (OHRP), a component of the U.S. Department of Health and Human Services (DHHS), is the oversight body for human studies research sponsored, supported or otherwise subject to regulation by DHHS.

To ensure this protection, these regulations require formally constituted institutional review boards (IRBs) to review and monitor biomedical research involving human subjects. The Radiation Safety Committee (RSC) is the body responsible for all aspects of radiation protection within an institution, including clinical, educational, and research applications of ionizing (and in some institutions, nonionizing) radiation. Most medical facilities are required to establish RSCs in accordance with 10 CFR Part 35.24 to oversee the uses of radionuclides permitted by the
radioactive materials license. The licensee’s management must appoint a Radiation Safety Officer (RSO), who is responsible for implementing the radiation protection program.

For research on the development of a drug or a medical device that will be marketed, or to establish the safety and effectiveness of a new indication or new use for an existing drug or device that is currently legally marketed, an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application may be required by the U.S. Food and Drug Administration (FDA).

12.2 Radiobiology and Radiation Protection

Ionizing radiation can cause damage to DNA by direct energy absorption and indirectly by production of reactive oxygen species. Ionizing radiation is a component of radiation therapy and of many medical imaging examinations [e.g., radiography, fluoroscopy, computed tomography (CT), and nuclear medicine imaging]. Ultrasound employs sound waves and magnetic resonance imaging (MRI) employs magnetic fields and nonionizing electromagnetic radiation.

The biological effects of radiation exposure are determined by many factors including: type and energy of radiation; radiation doses to the various organs and tissues; time course over which the radiation is administered; and the individual’s age, gender, genetic predisposition to radiation sensitivity, state of nutrition, personal habits such as smoking, and medications including specific chemotherapeutic drugs. Biological effects are classified as tissue reactions and stochastic effects.

The risks of ionizing radiation to humans include the risk of stochastic effects (specifically cancer and hereditary effects); the risk of tissue reactions in subjects; and, in the unusual case of research involving irradiation of pregnant women, risk of teratogenic effects and cancer to the unborn child. The system of radiation protection in use throughout the world is designed to prevent when possible, and when prevention is not possible, to minimize the occurrence of tissue
reactions and reduce the likelihood of stochastic effects to a degree that is acceptable in relation to the benefits to the individual and society.

The three main elements of radiation protection are:

1. **Justification**: any radiation exposure should be justified in terms of expected benefits to society, compared to overall societal costs.

2. **ALARA**: radiation exposure should be at levels ‘as low as reasonably achievable’ while taking into account economic and social factors. This principle is also known as optimization of protection. For medical radiation exposures, this means that the exposure is kept commensurate with the clinical purpose of the examination.

3. **Limitation**: individual dose limits are applied to ensure that use of justification and ALARA does not result in individuals or groups exceeding levels of acceptable risk. Although dose limits do not apply to medical exposures for standard of care examinations, dose limits may apply to radiation use in medical research.

### 12.3 Estimating Radiation Dose

Two main reasons for estimating radiation doses to human subjects from a proposed research study are: (1) this information is needed to estimate the risk to the subjects and develop appropriate risk language for informed consent; and (2) dose estimates are helpful in optimizing the study design to keep radiation doses to human subjects ALARA. Additionally, dose and risk estimates help in determining whether risks are commensurate with potential benefits and whether studies are justified.

Obtaining highly accurate dose estimations requires substantial resources. In most instances it is unnecessary for the purpose of establishing risk estimates, and may be so burdensome as to hinder or discourage research. In view of the large uncertainties in estimation of stochastic risk per unit dose, a more generalized approach to risk estimation suffices for most situations. However, for research studies involving high radiation doses (e.g., radiation therapy,
radioimmunotherapy) that may result in tissue reactions, more accurate dose estimations may be necessary.

Radiation dose may be measured as mean absorbed dose in an organ or tissue ($D_T$), which is calculated by integrating the absorbed dose ($D$) over the mass of the organ or tissue and then dividing by the total mass of the organ or tissue. This is used in epidemiological and other research studies to relate specific health outcomes, such as cancer, to exposure from ionizing radiation. Absorbed dose is the appropriate metric to utilize when considering radiation to an organ or tissue, or to a limited volume of that organ or tissue, and when considering tissue reactions.

Effective dose ($E$) is used primarily in implementing a radiation protection system, and is the sum over specified organs and tissues of the products of equivalent dose ($H_T$) in a specific tissue and the tissue weighting factor for that tissue or organ ($w_T$). It can be used in radiation protection for comparing patient exposures that might result from different procedures, and for conveying a measure of future risk associated with diagnostic or therapeutic procedures. $E$ may be used as a rough indicator of stochastic risk to an average person of a particular age and sex, but $E$ is not patient specific and so should not be used as a measure of individual risk for expressing probability of tissue reactions or for medical treatment planning.

### 12.4 Estimating Radiation Risk

If the average doses to individual organs and tissues are known, the risks of cancer incidence and mortality can be estimated using published risk coefficients for these organs and tissues, stratified by age and gender. However, some cancer incidence and mortality cannot be attributed to specific organs and tissues with reasonable statistical certainty, as in the case of nonuniform whole-body exposures.

There are large uncertainties in radiation risk estimates. As radiation doses decrease below 0.1 Gy, the relative uncertainty in risk estimates necessarily increases even more.
In a research setting, $E$ may be used to convey the potential risk from radiation exposure to participating human subjects. It provides a single metric for comparison of the stochastic radiation risk from the research exposure, the risk of stochastic effects from other medical imaging procedures using ionizing radiation, and the risk from natural background radiation. However, adjustments should be made for any substantial differences between the population of research subjects and the populations for which $E$ was developed, for characteristics including: ages, genders, genetic predispositions, the body parts being irradiated, and expected life spans.

The risk due to ionizing radiation from diagnostic examinations is often small compared to other risks due to participation in the research protocol. For interventional image-guided procedures and therapeutic radiology, there is the possibility of tissue reactions, in addition to the risk of cancer later in life. The expression of the risk of cancer induction is complicated by latency and the scientific uncertainty about the magnitude of the risk.

When assessing the risk of tissue reactions, specific dose information is needed. For example, for assessing the risks of skin injuries from FGI procedures, peak skin dose is the preferred metric. To minimize the chance of rectal injury from permanent seed implant brachytherapy for prostate cancer, the volume of the rectum receiving or exceeding the dose prescribed to the target volume is commonly employed.

Proposed guidelines are presented on cumulative dose limits to human research subjects that may be applied in assessing radiation risks in human studies research. The defined risk categories are modified from ICRP (1991b; 2007a) and WHO (2016) to assess the balance between risks of developing radiogenic cancer versus potential societal benefits of research protocols. Guidelines include adjustments of dose levels based on age and gender for each risk category.
12.5 Research Use of Radiation

The radiation a human subject receives specifically through participation in a research protocol, which would not have been received otherwise, is considered to be part of the research and should be documented by the research team.

As part of the informed consent process in human studies research, one must distinguish between imaging examinations or therapies utilizing ionizing radiation that are considered research versus those considered ‘standard of care’ (SOC) (i.e., accepted and widely used by healthcare professionals). Examinations employing ionizing radiation utilized in a research study shall meet the criteria of ‘reasonableness’ by adequately assessing the given clinical trial measure while delivering the lowest feasible radiation dose.

There is a wide range of radiation doses between and within imaging modalities, as well as for types of procedures and specific imaging examinations. The lowest radiation dose is not necessarily the optimal radiation dose. Both research and routine clinical procedures and imaging examinations should be optimized to use a radiation dose as low as acceptable for the specific task.

The principle investigator (PI) or sponsor involved in human studies research involving ionizing radiation should have a working knowledge of the basic concepts of radiation exposure, absorbed dose and effective dose. The PI should delineate which of the imaging examinations being conducted are SOC and which are being acquired for research purposes, and should assess the use of ionizing radiation modalities against the potential use of other options that do not utilize ionizing radiation (e.g., ultrasound, MRI).

Research protocols should include estimates of the risk for the radiation absorbed doses, consideration of the balance of risk to benefit, and informed consent statements. The level of risk from the radiation doses used in the research study should not be disproportionate to the possible benefit to the human subjects or to society.
Researchers and collaborative groups who design multi-center trials shall incorporate methods for optimization of radiation dose in their research protocols. An effective, responsive mechanism should be in place to address participating institutions’ concerns about radiological protocols, estimated radiation dose to subjects, and accuracy of dose and risk estimates.

12.6 Ethical Framework and Informed Consent for the Research Use of Radiation

Four ethical principles are applicable to human research studies:

- respect an individual’s autonomy (autonomy);
- prevent a harm (non-maleficence);
- provide a good (beneficence); and
- act fairly (justice).

A fifth principle to consider, the precautionary principle, states that if an action or policy has a potential harmful effect, but the risk cannot be determined with sufficient certainty, the burden of proof in establishing the lack of harm falls upon those taking the action. Additional ethical values that may be applied to radiation protection in diagnostic medical imaging and to the use of ionizing radiation in human studies research are: (1) human dignity; (2) prudence (keeping in mind possible long-term risks of actions); and, (3) honesty (share knowledge with those concerned truthfully).

Obtaining truly informed consent is a process involving dialog between the research team and the subject, and is essential to the legal and ethical conduct of human studies research. The ethical rule to require informed consent from human subjects before proceeding with research using radiation is derived from the principle of respect for autonomy. Informed consent includes three key components: (1) that human subjects are informed in such a way that they understand the risks and benefits of participating in radiation research; (2) that their decisions to participate in such research are not because of controlling influences; and (3) that their consent is voluntary.
The informed consent document and the informed consent process must address the risk associated with the radiation used for research purposes. Uncertainties complicate the informed consent process, including: (1) uncertainties in translating radiation dose into risk, (2) accounting for the long latency period that may occur between the radiation exposure and the occurrence of clinically evident disease, (3) the cumulative effect of multiple examinations, and (4) the longevity of the research subject.

Many factors affect the ability of research subjects to understand the information in informed consent forms, including risk statements. These factors include: literacy, maturity, level of education, intelligence, rationality, numeracy, and native language and fluency in the language of the consent form.

The use of clear language, adjusting language to the reading level of most subjects, and the use of easily understood expressions of radiation dose and risk can contribute to the overall goal of informed consent (i.e., helping subjects come to a decision about whether or not to participate in a clinical trial that involves exposure to ionizing radiation). It is recommended that consent forms be written at no higher than an eighth grade reading level. Judgment is needed to ensure that the length of an informed consent document or an interactive participation enhances the research subjects’ understanding of the risks involved and does not compromise their comprehension.

When children and vulnerable or disadvantaged populations, such as adults with impaired decision-making capacity and prisoners, are considered for participation as research subjects, issues of non-maleficence and respect for autonomy are of particular concern. Whether or not these populations possess and can exercise the autonomy necessary to give informed consent and whether or not proxy consent prevents harm and provides good to these populations are key considerations.
Ethical guidelines require the assent of children who are capable of providing it. In general, children between the ages of 14 and 18 y are capable of making independent judgments regarding participation in a clinical trial, and children between 7 or 8 y and 13 y of age may be regarded as being able to assent on an individual basis. It is recommended that the pediatric assent form be written in language that the child can understand, appropriate to the child’s development and age.
Appendix A

Examples of Language for Informed Consent for Human Studies Research
Involving Ionizing Radiation Based on Radiation Exposure

The language utilized in informed consent documents and in associated informational materials for the research protocol should reflect the type and quantity of ionizing radiation exposure to the participating subject. The following examples are offered to assist in developing language for protocols of different radiation exposure levels. It is the expectation that these examples will be adapted and modified to fit the needs of specific research protocols and local institutional requirements.

Research studies involving ionizing radiation usually exclude pregnant women and, if radionuclides are involved, either exclude or provide specific precautions for subjects who are breast feeding. Protocols addressing pediatric patient populations differ in several ways from those for adult patient populations. For example, ‘you’ in the informed consent may be explicitly defined to refer to the child subject and parent/legal guardian. The parent/legal guardian signs the consent and, if the child is old enough to understand but not old enough to sign the consent, he or she may be asked to sign an ‘assent’ (Section 11.6).

Assessment of the total radiation risk to the study subject from the research requires the summation of risk from each research test or procedure involving radiation to which the subject is exposed (Wiatrowski et al., 1996). Radiation that the subject receives from standard of care (SOC) examinations and procedures is not included in the risk statement or informed consent for research participation (Section 6). The dose metric effective dose (E) can be used to stratify diagnostic imaging examinations and image-guided interventions on the basis of risk from stochastic effects for a reference population. To put E in perspective, an analogy is generally used. For low-dose radiation a common analogy is equivalence to average ‘background radiation’ (~3 mSv y⁻¹). Other comparisons might include radiation incurred in a one-way coast-to-coast flight from New York City to Los Angeles (~0.025 mSv) or number of days spent at
high altitude [e.g., Denver, Colorado (12.4 mSv y\(^{-1}\))] (ISIS, 2015; NCRP, 1987). It is noteworthy that in the dose range below 50 mSv there is no conclusive evidence for an increased risk of cancer. However, because many people correlate exposure to radiation with cancer causation, a statement of the theoretical increased risk of cancer may be provided. Ways to express cancer risk might include: quantitative increased risk of developing cancer, increased risk of fatal cancer, and comparison to risks of activities in daily living and risks of behaviors such as tobacco use. A tool such as the “NCI DevCan – Probability of Developing or Dying of Cancer” may be used to generate estimates of comparable risk (NIH, 2015a). When using a fraction, keep the denominator the same (e.g., increased risk from 800 in 2,000 to 801 in 2,000) to promote understanding and assist the subject in the decision process.

For moderate dose ranges, as are common with research protocols involving image-guided interventional procedures or multiple sequential high-dose imaging examinations (e.g., sequential PET/CT imaging), or for high radiation dose ranges, such as received in radiation therapy research protocols, the preceding dose comparisons are not appropriate. Additionally, the metric effective dose is not utilized for radiation therapy, where the appropriate metric is absorbed dose (Gy). Although informed consent in radiation therapy should address the risk of second primary cancers due to therapeutic radiation, greater emphasis is placed on tissue reactions and their likelihood. Radiation therapy informed consent documents frequently do not specify dose, which is a matter of prescription specified in the study protocol document. Instead the informed consent document focuses on risks, stratified by frequency (e.g., “likely,” “less likely,” or “rare but serious”). This stratification may be quantified by language such as: “In 100 people receiving pelvic radiation, from 4 to 20 may have…” for the risk and “Occasionally, these effects may be serious” for side effects severity.

Examples of informed consent language follow. As noted above, these examples should be considered as assistance, to be adapted and modified to fit the needs of the research protocol and local institutional requirements. The radiation doses and dose levels that follow refer only to radiation received due to participation in the research study, and do not include radiation received in the course of standard medical care (Section 6).
A.1 Studies Involving Radiation from Diagnostic Examinations

A.1.1 Very Low Dose – Effective Dose <3 mSv

Example 1:

If you take part in this research, you will have tests that use very small amounts of radiation. These tests are: (indicate types of examinations: x-ray examinations, DXA scans, etc.). This radiation is in addition to what you may get as part of your regular medical care. Everyone gets low levels of natural radiation, called ‘background radiation.’ This comes from outer space and from rocks and minerals in the soil. Natural background radiation is greater at higher altitudes. The average yearly background radiation in the United States is 3 mSv. The amount of additional radiation you will get by participating in this study will be <3 mSv.

The amount of radiation involved in this research is very small, but may slightly increase your risk of getting cancer. Scientists are not certain about the actual cancer risk at these very small doses, and there may be no risk at all. Any increase in risk may be about 1 chance in 2,000 or less. For comparison, your risk of developing cancer at some time in your life, even if you do not receive this additional radiation, is ~40% (800 in 2,000). By participating in this study your risk may increase to 801 in 2,000.

Example 2:

If you take part in this research, you will have tests that use very small amounts of radiation. These tests are: (indicate types of examinations: x-ray examinations, DXA scans, etc.). This radiation is in addition to what you may get as part of your regular medical care. If you were to fly on an airplane one-way coast-to-coast from New York City to Los Angeles, you would receive a radiation dose of ~0.025 mSv. The amount of additional radiation you will get will be less than that from (specify number of coast-to-coast flights) airplane trips from New York City to Los Angeles.
The amount of radiation involved in this research is very small, but may slightly increase your risk of getting cancer. The degree of risk is similar to the risks you accept every day, like riding in a car. Scientists are not certain about the actual cancer risk at these very small doses, and there may be no risk at all. Any increase in risk may be about 1 chance in 2,000 or less. For comparison, your risk of developing cancer at some time in your life, even if you do not receive this additional radiation, is \(~40\%\) (800 in 2,000). By participating in this study your risk may increase to 801 in 2,000.

A.1.2 Low-to-Moderate Dose – Effective Dose Between 3 and 50 mSv

If you take part in this research, you will have tests that use small to moderate doses of radiation. These tests are: (indicate types of examinations: x-ray examinations, CT scans, nuclear medicine studies, PET scans, etc.). This radiation is in addition to what you may get as part of your regular medical care. Everyone gets low levels of natural radiation, called ‘background radiation.’ This comes from outer space and from rocks and minerals in the soil. Natural background radiation is greater at higher altitudes. The average yearly background radiation in the United States is 3 mSv. The amount of additional radiation you will get will be \(~[\text{specify here}]\) mSv. This is equal to \(~[\text{specify here number of years of natural background equivalent}]\) y worth of natural radiation. This is less than the maximum amount a person working with radiation is allowed to get in 1 y.

The amount of radiation involved in this research is small, but may slightly increase your risk of getting cancer. Scientists are not certain about the actual cancer risk at these low doses, and there may be no risk at all. The extra cancer risk may be about 1 chance in \([\text{specify here approximate cancer risk}]\). For comparison, your risk of developing cancer at some time in your life, even if you do not receive this additional radiation, is \(~40\%\) (800 in 2,000). By participating in this study your risk may increase to \([\text{specify here – As noted above, when using a fraction, keep the denominator the same (e.g., increased risk from 800 in 2,000 to 801 in 2,000).}]\)
A.1.3 Moderate Dose – Effective Dose Between 50 and 100 mSv

If you take part in this research, you will have tests that use moderate doses of radiation. These tests are: (indicate types of examinations: x-ray examinations, CT scans, nuclear medicine studies, PET scans, FGI procedures, etc.). This radiation is in addition to what you may get as part of your regular medical care. Everyone gets low levels of natural radiation that comes from outer space and the Earth called ‘background radiation.’ The average yearly background radiation in the United States is 3 mSv. The amount of additional radiation you will get will be \(\text{[specify here]}\) mSv. This is typical of the radiation you would get from a {insert a comparable standard procedure [e.g., a cardiac catheterization; (insert number) CT scans of the abdomen; (insert number) PET/CT scans; an angioplasty procedure to open an artery (blood vessel)]}.

This clinical trial involves moderate radiation exposure that is higher than typical tests that use radiation. Exposure to radiation may be harmful. Although scientists are not certain about the actual cancer risk at these doses, the amount of radiation involved in this research may slightly increase your risk of getting cancer. This extra cancer risk may be about 1 chance in [specify here approximate cancer risk]. For comparison, your risk of developing cancer at some time in your life, even if you do not receive this additional radiation, is \(\text{\sim 40 \% (4 in 10; or 80 in 200)}\). By participating in this study your risk may increase to [specify here – As noted above, when using a fraction, keep the denominator the same (e.g., increased risk from 800 in 2,000 to 801 in 2,000)]. When cancer or leukemia (cancer of the bone marrow) is caused by radiation, it usually doesn’t occur until years to decades after the radiation has been received.

A.2 Studies Involving Radiation from Image-Guided Interventions

Image-guided interventional procedures utilizing ionizing radiation (e.g., fluoroscopy or CT) have a wide range of reported patient radiation doses. Most interventional procedures have effective doses well below 50 mSv (Mettler et al., 2008). However, prolonged or complicated image-guided procedures may incur the risk of tissue reactions. When tissue reactions are a

\[5\text{When using a common, standard or alternate procedure as an analogy, it is important to provide accurate risk information for that procedure to promote understanding and advance the informed consent process.}\]
consideration, specific risk language should be added to the informed consent document. Any provisions for follow-up of radiation effects should be discussed with the subjects.

**Example:**

Although unlikely, some extended fluoroscopy studies that are part of this research may result in an injury to your skin. If your skin is injured, your injury may be greater than if you had received only standard care. Skin injuries are very rare and usually happen only during prolonged or complicated procedures or when there are problems during the procedure. Skin injuries are usually limited to reddening of the skin (like sunburn), but may also involve loss of hair or blistering. Rarely, there may be permanent skin damage. Skin injury may happen months or rarely years after the fluoroscopy study.

**A.3 Studies Involving High Dose Therapeutic Radiation: External Beam, Brachytherapy and Radionuclide Therapy**

Therapeutic procedures involving high doses of ionizing radiation incur the increased risk of initial and second primary cancers, including leukemia. Additional side effects may arise as early or late reactions. Studies that involve high-dose radiation therapy virtually always cause tissue reactions. For external beam radiation therapy and brachytherapy, tissue reactions usually occur in tissues very close to the target volume (Section 3.1.2.1), although they may also be seen in nearby or adjacent radiosensitive tissues. Knowing the organs and tissues that are likely to be affected facilitates development of the statement of potential effects and side effects of these forms of radiation therapy.

However, with radionuclide therapy (e.g., $^{131}$I radioiodine therapy, radioimmunotherapy, radioactive microspheres), tissue reactions may occur in the target tissue or in other tissues that accumulate the radiopharmaceutical. Blood flow delivery of a therapeutic radiopharmaceutical (e.g., $^{90}$Y Zevalin®) and some forms of brachytherapy (e.g., radioactive microspheres) may deposit substantial radiation in organs or tissues distant from the intended target, as may dissociation of the radionuclide from the transporter. In these circumstances, the risk statement
may need to include side effects to distant tissues and organ systems. Due to the unique nature of trials with therapeutic radiopharmaceuticals, only generalized consent language is provided that is applicable to this type of therapy.

Due to the many types of study arms (with or without chemotherapy, differing doses of radiation, differing radiation modalities, differing diagnostic decision points), an appropriate radiation risk statement should be developed to address the unique context of the study. Informed consent statements may discuss chemotherapy and radiation therapy risks collectively, individually, or both collectively and individually. Consideration should be given to expressing the latent period associated with the risks, as stochastic radiation risks often have a latency of years to decades. In radiation therapy research, this time frame may far exceed the subject’s life expectancy. The example wording shown here is substantially similar to that found in RTOG and COG informed consent documents (Sections 5.3 and 11.9), although the specific informed consent statement should be expanded to address all facets of risk and side effects pertinent to the research protocol.

Example 1: Radionuclide Therapy

Risks and side effects of these high doses of radiation might include: lower blood counts, with risks of infection, bleeding and anemia; immune suppression (acute or prolonged); nausea, vomiting, and/or diarrhea; sterility; risk of genetic damage to offspring; hypothyroidism; development of initial or second malignancy, including leukemia. Even though there is an increased risk of cancer and leukemia, it is usually years to decades before this might happen. There is also the potential risk of long-term or delayed-onset damage to organs such as the heart, lungs, and brain.

Example 2: External Beam Radiation Therapy

All treatments of cancer, including monitoring without active treatment, carry risk. The usual treatment for your cancer includes radiation therapy, whose risks and side effects are listed
below. The experimental component of your treatment may not benefit you and may be found to
be worse than the usual treatment. The risks and side effects shown below are those found to be
most common. The study doctor will monitor all participants for any side effects and you will
receive treatment for side effects. The risks of the radiation treatment used in the study are
similar to those common in radiation therapy. It is possible that other risks and side effects may
occur which are not yet known to the study designers. If unanticipated side effects arise, the
study doctor will discuss these with you.

Risks and side effects related to radiation therapy include:

Likely (in 100 people receiving standard radiation, more than 10 may experience):
- [List of risks and side effects]

Less likely (in 100 people receiving standard radiation, three to nine may experience):
- [List of risks and side effects]

Rare, but serious (in 100 people receiving standard radiation, one or two may experience):
- [List of risks and side effects]
Appendix B

Generation of Dose Estimates for Computed Tomography

The CT dose metric computed tomography dose index (CTDI) was developed in the late 1970s (Shope et al., 1981) as a method to use a single scan to estimate the multiple scan average dose of a 10 cm long contiguous CT scan to a standardized cylindrical plastic [poly-methyl methacrylate (PMMA)] phantom of 15 cm length and 32 cm diameter (as a surrogate for adult body examinations) or 16 cm diameter (as a surrogate for head examinations). On modern CT scanners, the dose metric values reported are the volume CTDI (CTDI$_{vol}$) and dose length product (DLP) (AAPM, 2008). CTDI$_{vol}$ is derived from individual air kerma measurements for single CT scan acquisitions using a 100 mm long pencil ionization chamber placed in holes at the center of the phantom and at the periphery of the phantom. The measured air kerma in mGy is corrected for x-ray beam collimation width and chamber calibration factor, resulting in CTDI$_{100}$ values at the center and peripheral positions. The numerical measurements are combined mathematically (i.e., 1/3 center + 2/3 peripheral) to compute the weighted CTDI (CTDI$_{w}$) for a stationary scan. From this measurement, CTDI$_{vol}$ (mGy) = CTDI$_{w}$ / pitch, where the pitch is a unitless number equal to the ratio of table travel distance to the collimated x-ray beam width at the isocenter for a 360 degree rotation of the x-ray tube.

CTDI$_{vol}$ is not patient dose, but an estimate of the dose to a standardized phantom for given CT technique factors (kV and mAs) (McCollough et al., 2011). When the CTDI$_{vol}$ metric is used, the size of the phantom (i.e., 16 or 32 cm) should be specified, or significant discrepancies in estimated dose can result because patient size and attenuation characteristics of the body do not match the standardized PMMA CTDI phantom (Seibert et al., 2014). To the extent that the CTDI phantom diameter differs from the patient effective diameter, there will be considerable under- or over-estimation of the indicated CTDI$_{vol}$ (mGy) compared to the actual dose to the patient (mGy). This can be ameliorated with the use of size-specific dose estimate (SSDE) methods, which describe conversion factors to compensate for the difference (AAPM, 2011b; Li et al., 2016).
DLP is the average CTDI\textsubscript{vol} multiplied by the length (in cm) of the CT scan along the long axis of the patient, expressed in units of mGy-cm, and is a dose metric which is approximately proportional to the amount of x-ray energy imparted in the scanned region of the patient from the CT examination. DLP has a high correlation with the estimated E, based upon Monte Carlo studies that generate E as a function of DLP for different types of CT scans including head, chest, abdomen and pelvis. Conversion constants, known as k-factors, are slightly different for CT scans in different parts of the body (Table B.1). An estimate of E for a given scanned region of the body can be determined from individual DLP values multiplied by the region-specific factor, k (in mSv mGy\textsuperscript{-1} cm\textsuperscript{-1}) (AAPM, 2008). Note that these values are determined from average size adult distributions, and to the extent that a given population differs from the average, the estimates in E will be subject to greater error. There are also k-factor tables derived as a function of age for the pediatric population (AAPM, 2008).

For more granular estimates of radiation dose for a particular CT examination and acquisition technique factors, estimates of organ dose from CT examinations can be obtained with the ImPACT CT dosimetry tool with ICRP Publication 103 (ICRP, 2007a) or ICRP Publication 60 (ICRP, 1991a) weighting factors (ImPACT, 2011).
Table B.1—Dose length product (DLP) and normalized effective dose (E) factors for the adult

(AAPM, 2008)

<table>
<thead>
<tr>
<th>Region of Body</th>
<th>k factor (mSv mGy$^{-1}$ cm$^{-1}$)</th>
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<tbody>
<tr>
<td>Head</td>
<td>0.0021</td>
</tr>
<tr>
<td>Neck</td>
<td>0.0059</td>
</tr>
<tr>
<td>Chest</td>
<td>0.014</td>
</tr>
<tr>
<td>Abdomen</td>
<td>0.015</td>
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<tr>
<td>Pelvis</td>
<td>0.015</td>
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</table>
Abbreviations and Acronyms

ALARA as low as reasonably achievable
AR absolute risk
AU authorized user
CBCT cone-beam computed tomography
CI confidence interval
CT computed tomography
$D_{\text{skin,max}}$ peak skin dose (previously PSD)
$D_{T}$ radiation absorbed dose (J kg$^{-1}$ or Gy)
DAP dose area product
DLP dose length product
E effective dose
EAR excess absolute risk
ERR excess relative risk
FGI fluoroscopically-guided interventional procedure
$H_{T}$ equivalent dose (J kg$^{-1}$ or Sv)
IDE investigational device exemption
IND investigational new drug (application)
IRB Institutional Review Board
$K_{a,r}$ air kerma at the reference point
LAR lifetime attributable risk
MRI magnetic-resonance imaging
$P_{KA}$ air kerma-area product
PENTEC pediatric normal tissue effects in the clinic
PET positron-emission computed tomography
PI principal investigator
QUANTEC quantitative analyses of normal tissue effects in the clinic
RBE relative biological effectiveness
RDRC Radioactive Drug Research Committee
<table>
<thead>
<tr>
<th></th>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>4804</td>
<td>RF</td>
<td>radiofrequency electromagnetic nonionizing radiation</td>
</tr>
<tr>
<td>4805</td>
<td>RR</td>
<td>relative risk</td>
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<td>4806</td>
<td>RSC</td>
<td>radiation safety committee</td>
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<td>4807</td>
<td>RSO</td>
<td>radiation safety officer</td>
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<td>4808</td>
<td>SOC</td>
<td>standard of care</td>
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Glossary

**absolute risk** (AR): The probability of experiencing an adverse event or developing a disease over a period of time. The excess risk, attributed to exposure and usually expressed as the arithmetic difference between the incidence or mortality rate of disease among those exposed and that obtained in the absence of exposure.

**absorbed dose** $D$: The quotient of $\frac{\text{d}E}{\text{d}m}$, where $\text{d}E$ is the mean energy imparted by ionizing radiation to matter of mass $\text{d}m$ at a point of interest. In the Système International (SI), the unit for absorbed dose is J kg$^{-1}$ with the special name gray (Gy).

**accelerator**: A device that accelerates charged particles (e.g., protons, electrons) to high speed in order to produce ionization or nuclear reactions in a target; often used for the production of certain radionuclides or directly for radiation therapy. The cyclotron and the linear accelerator are types of accelerators.

**activity**: Rate of transformation (or “disintegration” or “decay”) of a designated amount of radioactive material. The SI unit of activity is the reciprocal second (s$^{-1}$), and its special name is the becquerel (Bq). In conventional units often used by federal and state agencies, activity is given in curies (Ci); 1 Ci = $3.7 \times 10^{10}$ Bq.

**acute radiation exposure**: Radiation exposure received during a short time period (e.g., hours).

**administered activity**: The amount, in terms of activity, of radioactive material given to a patient during a diagnostic or therapeutic procedure. (Although the term “dose” is often used in practice referring to the administered activity, the latter quantity is not the same as absorbed dose).

**administration (of radioactive material)**: Introduction of radioactive material directly into the body by injection, oral administration or by some other route.

**Agreement State**: Any state which the U.S. Nuclear Regulatory Commission (NRC) has entered into an effective licensing agreement under Section 274(b) of the Atomic Energy Act of 1954, as amended, to enable the state to regulate source, special nuclear, and byproduct materials.

**air kerma-area product** $(P_{KA})$: The integral of the air-kerma free-in-air (i.e., in the absence of backscatter) over the area of the x-ray beam in a plane perpendicular to the beam axis.
air kerma at the reference point ($K_{a,r}$): The air kerma at a point in space located at a fixed distance from the focal spot expressed in gray. For isocentric fluoroscopes (C-arms), the reference point lies on the central axis of the x-ray beam, 15 cm on the x-ray tube side of isocenter. The location of the reference point relative to the x-ray gantry does not change when the source-to-image-receptor distance is changed. Referred to as reference air kerma by IEC.

angiography: The radiographic visualization of blood vessels following introduction of contrast material.

as low as reasonably achievable (ALARA): A principle of radiation protection philosophy that requires that exposures to ionizing radiation be kept as low as reasonably achievable, economic and societal factors being taken into account. The ALARA principle is satisfied when the expenditure of further resources would be unwarranted by the reduction in exposure that would be achieved.

ataxia telangiectasia mutated (ATM): Ataxia telangiectasia (AT) is a slowly progressive multisystem disorder appearing in early childhood at the onset of walking, including but not limited to dilation of small or terminal vessels of a body part, and recurrent infections. Individuals with the AT mutated (ATM) gene have cancer predisposition and significantly increased radiosensitivity.

autonomy (ethics): The principle of respect for autonomy recognizes the rights of individuals to self-determination.

background radiation: As used in this Report, background radiation includes external exposure from extraterrestrial sources (such as solar particles and cosmic rays), external exposure from terrestrial radiation (such as uranium and thorium), internal exposure from naturally occurring radionuclides incorporated in the body (such as $^{40}$K), and internal exposure from inhalation of radon and thoron from elevated levels in buildings.

beam: A flow of electromagnetic or particulate radiation that is either (1) collimated and generally unidirectional or (2) divergent from a small source but restricted to a small-solid angle (e.g., charged-particle beam, neutron beam, photon beam).

becquerel (Bq): The SI special name for the unit of radioactivity. 1 Bq equals one disintegration per second ($s^{-1}$). 37 MBq (megabecquerels) = 1 mCi (millicurie) (see curie and activity).
beneficence (ethics): The term beneficence refers to actions that promote the well-being of others.

biopsy: Removal of an entire abnormality (excisional biopsy) or a sampling or portion of an abnormality (core biopsy and incisional biopsy) for microscopic examination in order to diagnose a problem.

body habitus: This refers to the physique (i.e., the body build and constitution) of an individual.

brachytherapy: A method of radiation therapy in which an encapsulated source is utilized to deliver photons or beta particles to a treatment site at a distance up to a few cm from a surface, intracavitary or interstitial applicator.

cancer: A general term for more than 100 diseases characterized by abnormal and uncontrolled growth of cells.

carcinogenesis: Induction of cancer by radiation or any other agent (a somatic effect).

C-arm: A fluoroscopic system where the image receptor and x-ray tube are mounted at the opposite ends of a C-shaped arm. This design allows the x-ray tube and image receptor to be rotated about the patient through at least 90 degrees relative to the patient with no motion of the x-ray tube relative to the image receptor.

charged particle: An atomic or subatomic quantity of matter (e.g., electron, proton, alpha particle, ionized atom) having a net positive or negative electrical charge of one or more elementary units of charge.

Children’s Oncology Group (COG): A national clinical cooperative group funded by the National Cancer Institute and devoted exclusively to childhood and adolescent cancer research.

collective effective dose (person-Sv): Most frequently the product of the mean effective dose for a population and the number of persons in the population, but, more precisely, and preferably, the sum of all individual effective doses in the population of concern (contrast with cumulative absorbed dose).

computed tomography (CT): An imaging procedure that uses multiple x-ray transmission measurements and a computer program to generate tomographic images of the patient.

computed tomography dose index (CTDI): A dose index quantity obtained by integrating over the dose profile resulting from a single CT axial rotation. When obtained using a 100 mm
long ionization chamber positioned in a cylindrical polymethyl methacrylate (PMMA) phantom of either 16 cm diameter (chiefly head CT studies) or 32 cm (chiefly body CT studies), it is designated $\text{CTDI}_{100}$. When normalized per milliampere-second (mAs), it is designated $\text{nCTDI}_{100}$. The weighted CTDI ($\text{CTDI}_w$) is obtained from measurements of $\text{CTDI}_{100}$ in the center and periphery of the CTDI phantom, calculated as: $\text{CTDI}_w = 1/3 \text{ center } \text{CTDI}_{100} + 2/3 \text{ periphery } \text{CTDI}_{100}$. The volume CTDI ($\text{CTDI}_{vol}$) is determined from $\text{CTDI}_w$ as $\text{CTDI}_{vol} = \text{CTDI}_w / \text{pitch}$, where pitch is a parameter in helical CT acquisition that describes the amount of table travel (mm/s) divided by the x-ray beam collimation width at the isocenter of rotation. The pitch adjusts the $\text{CTDI}_w$ estimate by the amount of overlap (or lack of overlap) of the x-ray beam incident on the patient during an acquisition.

**confidence interval (CI):** A measure of the extent to which an estimate of risk, dose or other parameter is expected to lie within a specified interval (e.g., a 95% confidence interval of a risk estimate means that, based on available information, the probability is 0.95 that the true but unknown risk lies within the specified interval).

**cumulative absorbed dose** (Gy): A real-time integration of absorbed dose to the whole body from photons provided by many modern x-ray machines (e.g., during radiography, fluoroscopy, CT) (contrast with collective effective dose).

**curie** (Ci): The conventional special name for the unit of radioactivity equal to $3.70 \times 10^{10}$ becquerels (or disintegrations per second) (see becquerel).


**deontology (ethics):** The normative ethical position that judges the morality of an action based on a feature of the action itself. For example, if the act conforms to natural law (natural-law theory) or if it is inherently logical [i.e., one would be willing to universalize the contemplated action by saying all should be able to do so, without being caught in a contradiction (Immanuel Kant Categorical Imperative)]. It is sometimes described as duty-based ethics, from the Greek “deon.”

**detriment**: Measure of stochastic effects from exposure to ionizing radiation that takes into account the probability of fatal cancers, probability of severe hereditary effects in future...
generations, probability of nonfatal cancers weighted by the lethality fraction, and relative
years of life lost per fatal health effect.

**diagnostic reference level (DRL):** A radiation dose level serving as an investigational level.

When doses exceed the DRL established, the reasons for the higher doses should be investigated. A process known as optimization is used to assure that the image quality is adequate for the clinical task and that the patient doses are appropriate for the clinical task. DRL are typically established as the 75th percentile of a distribution of doses or dose metrics from a representative sample of institutions. DRL do not apply to individual patients.

**distributive justice (ethics):** The allocation of benefits and burdens in accordance with defensible criterion such as merit, need, or treating like cases alike.

**dosage:** The amount of radiopharmaceutical given to a patient, measured in becquerels (Bq).

**dose:** General term denoting the quantity of energy from ionizing radiation absorbed in a tissue or organ from either an external source or from radionuclides in the body. When unspecified, dose refers to the quantity of absorbed dose, measured in gray (1 Gy = 1 J kg⁻¹)
or rad (1 rad = 100 ergs g⁻¹). Depending upon the context in which it is used, the generic term dose may also refer to equivalent dose, effective dose or other dose-related quantities.

**dose length product (DLP):** A dose index quantity obtained using the following formula:

\[
DLP = \frac{L}{p} \left( \frac{1}{3} CTDI_{100,c} + \frac{2}{3} CTDI_{100,p} \right)
\]

where L is the length of the patient scanned, p is the pitch, and \( CTDI_{100,c} \) and \( CTDI_{100,p} \) are CTDI₁₀₀ values determined at the center and periphery of a standardized phantom (see computed tomography dose index).

**dose limit:** A limit on radiation dose that is applied for exposure to individuals in order to prevent the occurrence of radiation-induced tissue reactions or to limit the probability of radiation-induced stochastic effects to an acceptable level.

**dose rate:** Dose per unit time; often expressed as an average over some time period (e.g., a year).

**dosimeter:** A radiation detection device worn or carried by an individual to monitor the individual’s radiation exposure. May also refer to devices or objects that accumulate dose
and can be evaluated to estimate the dose delivered to a person or region (e.g., biological dosimeter).

dosimetry: The science or technique of determining radiation dose.

effective dose ($E$): The sum over specified organs and tissues of the products of the equivalent dose in a tissue ($H_T$) and the tissue weighting factor for that tissue or organ ($w_T$). The tissue weighting factors have been developed from a reference population of equal numbers of both males and females and a wide range of ages. Effective dose applies only to stochastic effects. The quantities $E$, $w_T$, and $H_T$ are used primarily in implementing the radiation protection system. The unit for $E$ is J kg$^{-1}$ with the special name sievert (Sv).

enteral: Within, by way of, or pertaining to the small intestine for medical procedures. Involving or passing through the gastrointestinal tract, either naturally via the mouth and esophagus, or through an artificial opening.

equity (ethics): Treating like situations alike. Fairness or justice in the way people are treated that does not rely merely on equality of treatment.

equivalent dose ($H_T$): The equivalent dose is the mean absorbed dose in a tissue or organ ($D_T$) weighted by the radiation weighting factor ($w_R$) ($H_T = D_T \times w_R$), a dimensionless value for the type of radiation, such as x or gamma rays. For external exposure $w_R$ applies to the radiation type incident on the body.

ethics: A subfield within axiology (value theory) that provides a systematic understanding of right and wrong. Ethics is often expressed in terms of virtuous behavior or rule-governed behavior.

excess absolute risk (EAR): The difference in absolute risk between exposed and unexposed (control) groups. The absolute difference between the instantaneous incidence or mortality rates between two groups of people (e.g., those exposed to radiation at a given level and those unexposed) (also termed ‘attributable risk’ or ‘risk difference’).

excess relative risk (ERR): An expression of excess risk relative to the underlying (baseline) risk; if the excess equals the baseline the relative risk is two ($ERR = RR − 1$).

exposure: Most often used in a general sense meaning to be irradiated. When used as the specifically defined radiation quantity, exposure is a measure of the ionization produced in
air by x or gamma-radiation. The unit of exposure is coulomb per kilogram (C kg\(^{-1}\)). The special unit for exposure is roentgen (R), where 1 R = 2.58 \times 10^{-4} \text{ C kg}^{-1}.

**fluoroscopically-guided interventional (FGI) procedures:** An interventional diagnostic or therapeutic procedure performed via percutaneous or other access routes, usually with local anesthesia or intravenous sedation, which uses external ionizing radiation in the form of fluoroscopy to: localize or characterize a lesion, diagnostic site, or treatment site; monitor the procedure; and control and document therapy.

**fluoroscopy (fluoro):** The process of producing a real-time image using x rays. The machine used for visualization, in which the dynamic image appears in real time on a display screen (usually video), is a fluoroscope.

**fractionated radiation therapy:** The delivery of radiation in a series of sessions in order to improve the therapeutic ratio.

**fractionation:** The delivery of a given total dose of radiation as several smaller doses, separated by intervals of time.

**gamma radiation:** Electromagnetic radiation emitted in de-excitation of atomic nuclei, and frequently occurring in decay of radionuclides. Also called gamma ray and sometimes shortened to gamma (e.g., gamma-emitting radionuclides) (see photon and x ray).

**genetic effects:** Changes in reproductive cells that may result in detriment to offspring.

**gray (Gy):** The SI special name for the unit of the quantities absorbed dose and air kerma.

\[ 1 \text{ Gy} = 1 \text{ J kg}^{-1}. \]

**harm:** Physical injury or damage to the health of people, or damage to property or the environment.

**heavy ions:** Synonymous with heavy charged particles, heavy nuclei, high-Z particles, or HZE particles (see high atomic number, high-energy (HZE) particles).

**heritable effects:** Changes in reproductive cells that may be passed on to offspring of persons, animals or other organisms. Often called genetic effects (see genetic effects).

**high atomic number, high-energy (HZE) particles:** Heavy ions having an atomic number greater than that of helium (such as boron, carbon, nitrogen, neon, argon, or iron ions that are positively charged) and having high kinetic energy.

**incidence:** The rate of occurrence of a disease, usually expressed in number of cases per million.
intake (radionuclides): The amount of radioactive material taken into the body by inhalation, absorption through the skin, ingestion, or through wounds. It is distinguished from “uptake,” which is the amount of material that eventually enters the systemic circulation, or “deposition,” which is the amount of the substance that is deposited in organs and tissues.

internal dose: Dose to organs or tissues of an organism due to intakes of radionuclides (e.g., by ingestion, inhalation, through wounds, or dermal absorption).

ionizing radiation: Any radiation capable of displacing electrons from atoms or molecules, thereby producing ions. Examples include alpha radiation, beta radiation, gamma or x rays, and cosmic rays. Minimum energy of ionizing radiation is a few electron volts (eV);

1 eV = 1.6 × 10^{−19} J.

irradiation: Exposure to ionizing or nonionizing radiation (see also exposure).

justification (radiation protection): The part of the decision-making process in which the options that are expected to do more good than harm are identified.

justice (ethics): The moral obligation to act on the basis of fair adjudication between competing claims. As such, it is linked to fairness, entitlement, equality, and equity.

kerma (K): ‘Kinetic energy released per unit mass’ is the sum of the initial kinetic energies of all the charged particles liberated by uncharged particles in a mass of material. The unit for kerma is J kg\(^{-1}\), with the special name gray (Gy). Kerma can be quoted for any specified material at a point in free space or in an absorbing medium (e.g., air kerma).

LET: Linear-energy transfer, the average amount of energy lost per unit of particle track length and expressed in keV \(\mu\text{m}^{-1}\).

low-LET: Radiation having a low linear-energy transfer (e.g., electrons, x rays, and gamma rays).

high-LET: Radiation having a high linear-energy transfer (e.g., protons, alpha particles, heavy ions, and the interaction products of fast neutrons).

lifetime attributable risk (LAR): The excess absolute risk (of cancer) due to an agent like radiation expressed throughout the lifetime of the exposed individuals. Attributable risk is determined in epidemiology by measuring the difference in rate of a condition between an exposed population and an unexposed population. Determination of LAR is often done using cohort studies, differentiating between exposed and unexposed populations.
magnetic-resonance imaging (MRI): An imaging modality using a strong magnetic field and radiofrequency (RF) signals to produce multiplanar images of the body. A superimposed magnetic field gradient enables spatial localization of the image plane. Image contrast is based on the hydrogen concentration, molecular response to RF signals, and flow of structures within the part of the body being imaged.

mammography: An x-ray examination of the breast.

neutrons: Particles with a mass similar to that of a proton, but with no electrical charge. Because they are electrically neutral, they cannot be accelerated in an electrical field.

noncancer effects: Health effects other than cancer (e.g., cataracts, cardiovascular disease) that occur in the exposed individual.

nonionizing radiation: Electromagnetic radiation that includes the ultraviolet (UV), visible, infrared (IR), microwave, radiofrequency (RF), and extremely-low-frequency (ELF) portions of the electromagnetic spectrum. Unlike ionizing radiation, nonionizing radiation is unable to ionize atoms in its interactions with matter.

non-maleficence (ethics): The principle that we should act in ways that prevent harm to others.

nuclear medicine imaging: An imaging technique in which the patient is administered a radionuclide that emits photons, which impinge upon a radiation detector and are processed to form an image.

optimization: Although for occupational radiation protection the term ALARA is used as equivalent to or in replacement of the term optimization used in ICRP Publications 120 and 121 (ICRP, 2013a; 2013b), ALARA is only a part of the concept of optimization. The entire concept when applied to medicine means that the radiation dose to the patient is suitable for the medical purpose, and radiation that is clinically unnecessary or unproductive is avoided. For imaging procedures, patient radiation protection is optimized when imaging is performed with the least amount of radiation required to provide adequate image quality, diagnostic information and, for fluoroscopy, imaging guidance. In radiation oncology, optimization is the process of selecting an appropriate balance between achieving successful tumor response and minimizing detrimental normal tissue response.

parenteral: Not through the alimentary canal but rather by injection through some other route, such as subcutaneous, intramuscular, intraorbital, intravenous, etc. for medical procedures.
paternalism (ethics): The intentional overriding of a person’s known preferences or actions by another person who justifies this behavior by a claim that the person interfered with will be better off or protected from harm.

photon: Quantum of electromagnetic radiation, having no charge or mass, that exhibits both particle and wave behavior, such as a gamma- or x ray.

phronesis (ethics): The Greek word for a type of wisdom or intelligence. It is more specifically a type of wisdom relevant to practical things, requiring an ability to discern how or why to act virtuously and encourage practical virtue (i.e., excellence of character) in others.

positron-emission tomography (PET): An imaging technique using radionuclides that emit positrons (positively charged electrons), whose annihilation photons are imaged in coincidence to form tomographic views of the body.

potentially-high radiation dose procedure: A procedure for which >5 % of the cases of that procedure result in a peak skin dose ($D_{\text{skin,max}}$) exceeding 2 Gy, or, for fluoroscopically-guided procedures for which the $D_{\text{skin,max}}$ is not known, a $K_{\text{a,r}}$ exceeding 3 Gy, or if $D_{\text{skin,max}}$ and $K_{\text{a,r}}$ are not known, a $P_{\text{KA}}$ exceeding 300 Gy cm$^2$ (see air kerma-area product and air kerma at the reference point).

principal investigator (PI): The NIH definition of a principal investigator (also includes the title ‘program director’) is defined as the individual(s) judged by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program supported by the grant. The applicant organization may designate multiple individuals as PIs who share the authority and responsibility for leading and directing the project, intellectually and logistically. Each PI is responsible and accountable to the applicant organization, or, as appropriate, to a collaborating organization, for the proper conduct of the project or program including the submission of all required reports. The presence of more than one identified PI on an application or award diminishes neither the responsibility nor the accountability of any individual PI (NIH, 2011b).

prudence (ethics): The ability to govern and discipline oneself by the use of reason. It is classically considered to be a virtue.

Radiation Therapy Oncology Group (RTOG): A national group funded by the National Cancer Institute and dedicated to the management of radiation oncology protocols.
radiography: The production of images on film or other media by the action of x rays transmitted through an individual or an object.

radiology: That branch of the healing arts and sciences that includes the use of medical imaging in the diagnosis of disease, image-guidance in diagnosis and treatment of disease, and the application of ionizing radiation in the treatment of disease.

radionuclide: An unstable (i.e., radioactive) nuclide (termed ‘isotope’ in older literature). A species of atom that is characterized by the constitution of its nucleus (i.e., the number of protons and neutrons) and the excess energy available in the unstable nucleus.

radiopharmaceutical: A radioactive substance administered to a patient for diagnostic or therapeutic nuclear-medicine procedures. A radiopharmaceutical contains two parts, the radionuclide and the pharmaceutical [e.g., $^{99m}$Tc-DTPA (diethylenetriaminepentaacetate)]. In some cases, the two are one (e.g., $^{133}$Xe gas).

relative biological effectiveness (RBE): For a specific radiation (A), the ratio of absorbed dose of a reference radiation required to produce a specific level of response in a biological system to absorbed dose of radiation (A) required to produce an equal response. The reference radiation normally is x or gamma rays. Relative biological effectiveness generally depends on dose, dose per fraction if the dose is fractionated, dose rate, and biological endpoint.

relative risk (RR): The ratio of the risk of a given disease in those exposed to the risk of that disease in those not exposed. The ratio of disease rates in different groups (e.g., an exposed compared with an unexposed group) or for different exposure conditions (e.g., people exposed to a specific dose compared with people with no or different exposure). It is often useful to view the relative risk as a function of variables, such as dose, sex or age.

retributive justice (ethics): Refers to providing persons what they rightly deserve.

risk: Exposure to the chance of injury or loss; probability of harm, combined with potential severity of that harm. In the context of radiation-related health effects, risk refers to the probability that an event of interest (e.g., incidence of cancer) will occur during a given time period (e.g., the rest of life following an exposure). Risks can be estimated using evidence from epidemiological investigations of previously exposed populations. The results from such retrospective risk assessments often are used, with appropriate modifying and
adjustment factors, to make inferences about the risk in other exposure situations involving different populations for which direct epidemiological data on the dose response are not available.

**risk coefficient:** (1) Probability of a cancer (fatal cancer or cancer incidence) per unit radiation dose; or (2) probability of a cancer per unit activity intake of a radionuclide or per disintegration per unit volume, area or mass of a radionuclide in the environment.

**sentinel event:** This is an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. Serious injury specifically includes the loss of a limb or function.

**severity:** In the context of this Report, the quality or power of afflicting, distressing, or paining an individual or organ system from exposure to an environmental insult, such as ionizing radiation, that in the extreme would cause pain or anguish and possible clinical sequelae in the individual.

**sievert (Sv):** Special name for the SI unit of dose equivalent, equivalent dose, and effective dose. 1 Sv = 1 J kg\(^{-1}\).

**single-photon emission computed tomography (SPECT):** An imaging technique in which one or more (typically two opposed) photon detector heads rotate around a region of the body and acquire images at various angles around the body. The collection of such images is then used to generate tomographic images (“slices”) analogous to CT images. The computational methods (i.e., reconstruction techniques) used for generating the tomographic images include filtered back-projection and estimator-based (e.g., maximum likelihood) iteration.

**somatic effects:** Biological effects (of radiation or otherwise) that occur in the exposed individual, as opposed to genetic (or heritable) effects which occur in the descendants of exposed individuals due to genetic mutations in the germline (see heritable effects).

**stochastic:** Describes random events leading to effects whose probability of occurrence in an exposed population (rather than severity in an affected individual) is a direct function of dose; these effects are commonly regarded as having no threshold; hereditary effects are regarded as being stochastic; some somatic effects, especially carcinogenesis are regarded as being stochastic.
SWOG: A cancer research cooperative group that designs and conducts multidisciplinary clinical trials which include radiation therapy (http://www.swog.org/).

Système Internationale (SI): The International System of Quantities and Units as defined by the General Conference of Weights and Measures in 1960 and periodically revised since. These units are generally based on the meter/kilogram/second units, with special units for radiation including the Becquerel, gray and sievert.

telangiectasia: Dilation of capillary vessels and very small arteries.

teleology (ethics): A theory of ethics according to which the rightness of an act is determined by its end or consequences.

therapeutic ratio (index, window): The relationship between the minimum radiation dose to achieve an acceptable probability of local tumor control and the maximum acceptable dose such that normal tissues have sufficiently low acute and late morbidity; a therapeutic ratio may be described as favorable or unfavorable.

tissue reaction (deterministic effect): Injury in populations of cells, characterized by a threshold dose and an increase in the severity of the reaction as the dose is increased further. In some cases, tissue reactions are modifiable by post-irradiation procedures including biological response modifiers. Examples for irradiation of the embryo or fetus are radiation-induced malformations and mental retardation in the live-born child.

tracer: A radiopharmaceutical used to trace a physiological or biochemical process without affecting it. Strictly speaking, a tracer does not have to be radioactive (e.g., it could be a stable isotope), but in common usage it is.

ultrasonography (ultrasound, sonography): The use of sonic energy (sound) to produce a pictorial representation of an internal structure. The image is produced by pulse-echo techniques, with detection and display of tissue interfaces rather than densities.

ultrasound: Sound at a frequency above the upper limit of human hearing, usually taken to be 20 kHz (20,000 cycles per second).

uncertainty: Lack of sureness or confidence in predictions of models or results of measurements. Uncertainties may be categorized as those due to stochastic variations, or as those due to lack of knowledge founded on an incomplete characterization, understanding or measurement of a system.
uptake: Quantity of a radionuclide taken up by an organ or organ system, following administration (e.g., injection into the blood, absorption from compartments in the respiratory or gastrointestinal tract, or absorption through the skin or through wounds in the skin).
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