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Radioactive Drug Research Committee (RDRC)
Human Use Subcommittee of the
- Radiation Safety Committee (HUS-RSC)

Chair: Jeffrey T. Yap, Ph.D.

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Scope of HUS-RSC/RDRC

HUS- RSC (Human Use Subcommittee of the Radiation Safety Committee)

- Evaluates and approves or disapproves all proposed uses of ionizing radiation sources on or in human subjects for investigational or non-routine clinical procedures.
- Reports to UofU Radiation Safety Committee

RDRC (Radioactive Drug Research Committee)

- Evaluates and approves or disapproves of applications involving investigational or non-routine clinical uses of radioactive drugs without New Drug Applications (NDA) filed with the FDA or without Investigational New Drug (IND) numbers issued by the FDA.
- Reports directly to FDA

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RDRC Members (also HUS-RSC)

1. "Physician(s) recognized as specialist in nuclear medicine": Carl Christensen, MD

2. "Person(s) qualified by training and experience to formulate radioactive drugs": Jeff Krysten, MS, RPH, BCNP; Isaiah Springer, PharmD

3. "Person(s) with special competence in radiation safety and radiation dosimetry": Peter Jenkins, PhD; Jeffrey T. Yap, PhD

4. Other Voting Members: Christopher J. Hanrahan, MD, PhD (Radiology); Shane Lloyd, MD (Radiation Oncology); Scott C. Miller, PhD (Radiobiology), David Moody, PhD (Toxicology), Vikren Sarkar, PhD, DABR (Therapy Medical Physics)

5. Ex Officio Members (Non-Voting): Fred Monette, MS (Radiation Safety Officer); Cynthia Furse, PhD (AVP Research), Randy Jensen, MD, PhD (Chair, Radiation Safety Committee)

- Other Non-Voting : Mary Handy (Radiation Safety)

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RDRC Review/Voting Process

- RDRC Committee Composition
- Mandatory quarterly meetings with > 50% in attendance for quorum
- RDRC Review
- Distributed to all committee members for review
- All members must vote within the allotted time
- In the event that the member does not vote due to absence during the ballotting period, his/her vote will be considered an abstention
- On a protocol in which he/she is a PI, the RDRC member shall abstain from voting
- Majority vote required for approval

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HUS Review/Voting Process

- Exempt: SOC only
  - Distributed for review to chair, former chair, 3 MDs
  - 2 members most vote to approve for diagnostic radiation
  - For therapeutic, must include at least 1 MD
- Late Stage Cancer: Life expectancy <= 2 years
  - No dosimetry estimates required
  - Distributed for review to chair, former chair, 3 MDs
  - 2 members most vote to approve including at least 1 MD
- Low Risk: ED < 500 mrem (5 mSv)
  - Distributed to chair, former chair, 3 MDs, Peter Jenkins, PhD (dosimetry)
  - 3 members most vote to approve including at least 1 MD
- Full Committee: ED => 500 mrem (5 mSv)
  - Distributed to full committee for review
  - 5 members must vote to approved including 1 MD

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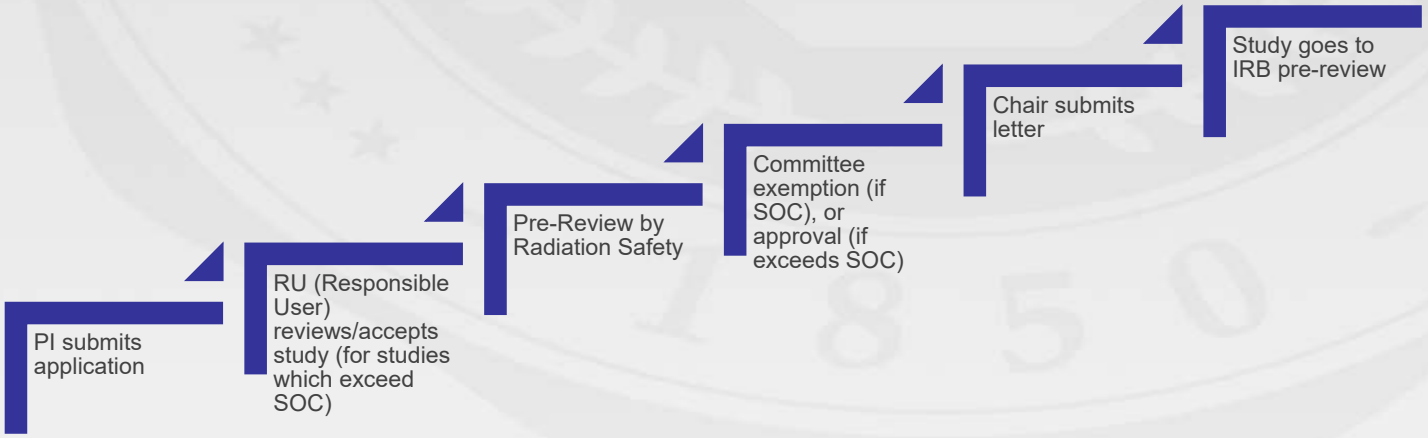
HUS-RSC Review Process

Reviews continually electronically, meets in person quarterly



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HUS Checklist for Reviewing Exempt Studies

1. Are all procedures involving ionizing radiation that are mentioned in the Protocol also listed in the Protocol Radiation Use Review Sheet (PRURS) application?

2. Is the frequency of procedures consistent between the Protocol and PRURS form/HUS Application?

3. Is the frequency of procedures the same for all subjects in the Protocol (e.g., are there differences between cohorts or phases of the trial?)

4. Does the PRURS application have missing or conflicting information?

5. Are all of the research procedures and their frequencies also listed in the ICF?

6. Are any of the procedures indicated as being for research purposes in the either the Protocol or ICF?

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HUS Checklist for Reviewing Exempt Studies

7. Are any of the procedures indicated as being paid for by the study in the protocol or ICF?

8. Do any of the procedures appear to be experimental in nature (e.g., using an experimental device or software without FDA 510K clearance, or using an imaging compound that is not FDA approved for this clinical indication)?

9. Does the frequency appear to be any greater than what is typically indicated as SOC in clinical trials for this patient population or type of study? Note that this is not a determination of SOC by the HUS-RSC but rather, an opportunity to request clarification or confirmation from the PI.

10. Studies with unresolved issues are referred to HUS-RSC medical reviewers (RadOnc: Lloyd, NucMed: Christensen, Radiology: Christensen, Hanrahan) and/or clinical experts and/or Responsible Users as needed (e.g., John Hoffman).

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HUS Review of Late Stage Cancer

- Late-stage cancer studies no longer include diagnostic radiation dosimetry and dose-related life-time cancer risk assessment
- Inclusion Criteria:
    1. Late stage cancer subjects.
    2. Median survival equal to or less than 24 months (to be determined by the PI).
    3. Diagnostic radiation only.
    4. Adult studies only.
    5. Responsibility accepted by a Responsible User (RU)
- Exclusion Criteria
    1. “Umbrella” protocols that might include a range of different kinds of cancers or diagnoses.
    2. Pediatric studies (less than 18 years of age upon entry into the study).
    3. Pregnant or breast-feeding.
    4. Studies proposed under RDRC authority (21CFR361.1)

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Guidance on Informed Consent Language for Late Stage Cancer Protocols

- All procedures, even standard of care, may be included in the consent if it will help the subject put their total treatment into “context”.

- However, “research” procedures that involve radiation must be clearly indicated and distinguished from standard of care procedures.

- Dose-specific risk estimates will not be required unless requested.

- **Suggested consent language**: “*This research study involves exposure to radiation (indicate types of procedures and how many for the first year and frequency if study will continue beyond one year).This radiation exposure is not necessary for your medical care and is for research purposes only. This radiation may involve a low risk of a later cancer, however, we believe that this risk is not clinically relevant. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting this study*.”

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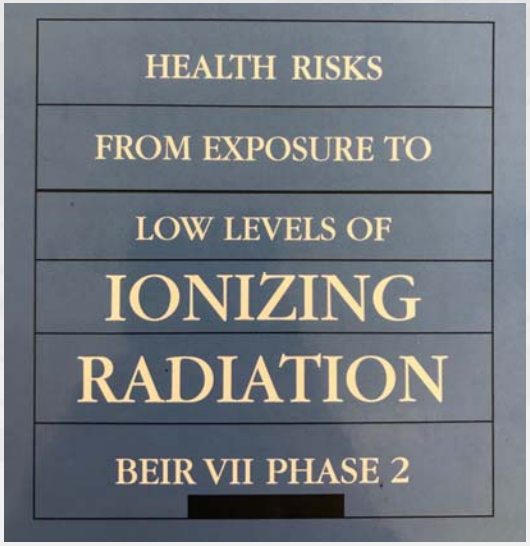
Radiation Risk Assessment

- Very high dose radiation exposure can have immediate tissue damage (Deterministic Risk) and risk of future cancer
- Low dose radiation may have increased long term risk of cancer (Stochastic Risk)
- Most stochastic risk models are based on survivors of catastrophic radiation incidents (atom bomb, Chernobyl)



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BEIR VII: Health Risks from Exposure to Low Levels of Ionizing Radiation

Linear No-Threshold Risk Model

- Assumes no radiation dose is safe
- Risk increases linearly with radiation dose

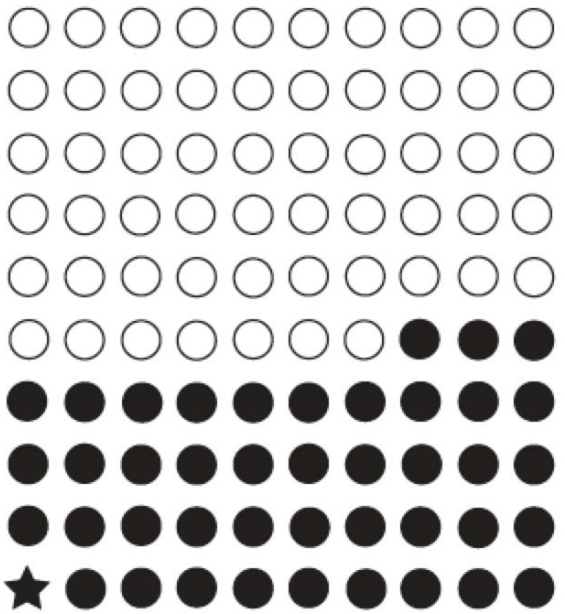

Figure 2. In a lifetime, approximately 42 (solid circles) of 100 people will be diagnosed with cancer[2] from causes unrelated to radiation. The calculations in this report suggest approximately one cancer (star) in 100 people could result from a single exposure 100 mSv of low-LET radiation.

Linear No Threshold Model

- Assume linear relationship between radiation exposure and the risk of cancer
- Assumes that any exposure, regardless of how low, increases risk of cancer
- Greater lifetime risk for exposure at younger age due to greater sensitivity and longer lifespan to potentially develop cancer
- While many experts there may be very low exposures that are safe with negligible risk, this model is still accepted as the conservative approach
- The effective dose used in this model is not intended for individuals and is to be used to estimate risk in populations
- There are some who argue this estimates should only be used for occupational or population exposure and not for medical procedures where there is benefit

TABLE 12D-1 Lifetime Attributable Risk of Cancer Incidence[a]

BEIR VII

Cancer Site	Age at Exposure (years) 0	5	10	15	20	30	40	50	60	70	80
Males											
Stomach	76	65	55	46	40	28	27	25	20	14	7
Colon	336	285	241	204	173	125	122	113	94	65	30
Liver	61	50	43	36	30	22	21	19	14	8	3
Lung	314	261	216	180	149	105	104	101	89	65	34
Prostate	93	80	67	57	48	35	35	33	26	14	5
Bladder	209	177	150	127	108	79	79	76	66	47	23
Other	1123	672	503	394	312	198	172	140	98	57	23
Thyroid	115	76	50	33	21	9	3	1	0.3	0.1	0.0
All solid	2326	1667	1325	1076	881	602	564	507	407	270	126
Leukemia	237	149	120	105	96	84	84	84	82	73	48
All cancers	2563	1816	1445	1182	977	686	648	591	489	343	174
	2.5%				0.98%				0.49%		
Females											
Stomach	101	85	72	61	52	36	35	32	27	19	11
Colon	220	187	158	134	114	82	79	73	62	45	23
Liver	28	23	20	16	14	10	10	9	7	5	2
Lung	733	608	504	417	346	242	240	230	201	147	77
Breast	1171	914	712	553	429	253	141	70	31	12	4
Uterus	50	42	36	30	26	18	16	13	9	5	2
Ovary	104	87	73	60	50	34	31	25	18	11	5
Bladder	212	180	152	129	109	79	78	74	64	47	24
Other	1339	719	523	409	323	207	181	148	109	68	30
Thyroid	634	419	275	178	113	41	14	4	1	0.3	0.0
All solid	4592	3265	2525	1988	1575	1002	824	678	529	358	177
Leukemia	185	112	86	76	71	63	62	62	57	51	37
All cancers	4777	3377	2611	2064	1646	1065	886	740	586	409	214
	4.8%				1.6%				0.59%		

NOTE: Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy.

- Note: 0.1 Gy = 100 mSv = 10 rem
= twice the annual occupational exposure limit

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Originally submitted (adult) dosimetry

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Alternate Dosimetry Report for RPR 48A and B Applications

Study Title: A randomized trial of targeted temperature management with whole body hypothermia for moderate and severe neonatal encephalopathy in premature infants 33-35 weeks gestational age – A Bayesian Study

Investigator: Roger Faix, MD

Application Date: Mar 23, 2016

IRB Number: IRB_00090354

Protocol	No.	Mins	mCi	ED (mSv)
GenRad Chest AP[2]	1	–	–	1.6E-2
Total Effective Dose (ICRP 103[1]):				**1.6E-2**

The maximum exposed body part for the indicated protocols is the Thymus (7.6E-2 mGy).
Number of body parts to be dosed in excess of 150 mGy is 0.

Disclaimer

The dose estimates given above are based on standard procedures for a "reference person" at the University of Utah. *This information should only be used for estimating dose in preparation RPR48 applications.*

Risk Assessment

The estimated increased risk of cancer incidence associated with 1.6E-2 mSv is less than 0.01%. The incidence of cancer (all types) within the US population, regardless of a patient receiving this dose, is approximately 38% for women and 45% for men. Within the US population, approximately 25% will die from cancer.

References

1. ICRP, 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann. ICRP 37 (2-4).
2. U of U Medical Physics Monte Carlo Estimation, 109 kVp @ 2 mAs, 180 cm SID, (U of U Radiology GenRad Room #2 Siemens Ysio DR default protocol), "PCXMC Simulation Parameters" document, 03/04/2015

Revised (pediatric) dosimetry

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Department of Radiology

Alternate Dosimetry Report for RPR 48A and B Applications

Study Title: A randomized trial of targeted temperature management with whole body hypothermia for moderate and severe neonatal encephalopathy in premature infants 33-35 weeks gestational age – A Bayesian Study

Investigator: Roger Faix

Application Date: Jul 18, 2016

IRB Number: 00090354

Protocol	No.	Mins	mCi	ED (mSv)
GenRad Premature Newborn (2.4 kg) Chest AP[2]	1	–	–	4.3E-3
Total Effective Dose (ICRP 103[1]):				**4.3E-3**

The maximum exposed body part for the indicated protocols is the Breast (1.1E-2 mGy).
Number of body parts to be dosed in excess of 150 mGy is 0.

References

1. ICRP, 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann. ICRP 37 (2-4).
2. U of U Medical Physics Monte Carlo Estimation, 2.4 kg newborn, 50 kVp @ 0.5 mAs, 100 cm SID, (U of U Radiology Carestream Revolution DRX portable exam), "PCXMC Simulation Parameters" document, 07/15/16.

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Screening: ACRIN NLST

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team

N Engl J Med 2011; 365:395-409 | August 4, 2011

Comments open through August 10, 2011

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Screening: ACRIN NLST

- 53,454 persons at high risk for lung cancer
- 645 vs 572 cases per 100,000 person-years in low-dose CT vs X-ray
- 20.0% relative reduction in mortality from lung cancer with low-dose CT