Attachment 5A
U.S. Nuclear Medicine Technologists Study
NCI IRB Approval with Stipulations

Department of Health & Human Services **Public Health Service**

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

iRIS Reference Number ***357169***

Type of Action: Initial Review Submission Form
Project Number: P162698

TO: Cari Kitahara
NCI - Radiation Epidemiology Branch

FROM: Chairperson, Special Studies Institutional Review Board, NCI

SUBJECT: Action on Clinical Research Protocol

The Initial Review of your protocol and consent document, "Cancer and Other Disease Risks in U.S. Nuclear Medicine Technologists," was reviewed by the National Cancer Institute Special Studies Institutional Review Board (NCI-SSIRB) by full board review on 04/18/2016.

The IRB has taken the following action:

	Approved as written. Forwarded to the CC OPS for administrative processing.
X	Approved with stipulations pending re-review by SSIRB Chair and reviewers. See review.
	Approved with stipulations pending re-review by a subcommittee of the Board. See review.
	Deferred pending response to stipulations and re-review by the full SSIRB. See review.
	Disapproved. See review.

RESPONSE DUE BY: 05/10/2016

Stipulations/Conditions:

1) State in the recruitment email that the attached consent form is for participants' records only. Clarify in the introduction that participants need to access the consent on-line, read it and sign off if they agree to participate in the study.

2) Include in the consent form the material related to the time required for the study (e.g. 30 minutes), authorization to collect the data (e.g. Public Health Service Act), and other such information. Remove this information from the introduction to the questionnaire.

3) Revise to simplify the on-line material to include just the consent form followed by the questionnaire without the introductory information about whether or not they had read the consent form provided in the e-mail.

4) Add a statement in the recruitment email clarifying that this is a feasibility study.

5) Incorporate in the protocol or consent the substance of the PI responses to the pre-review for:

    a. General Questions/Comments (except the yellow highlighted section regarding future use which will be replaced by language in stipulation 6 below).

    b. Common checklist questions - Regulatory review requirements: item 4 and 6.

    c. Pre-review of consent form: items 1 and 2.

    d. Re-review of consent form: item 14, except for the last sentence of response to item 14. Instead of "data collected up to that time will remain in the study and used for data analysis", revise the protocol and consent to clarify that their data will be withdrawn from the database if requested, but that their data cannot be withdrawn from analyses that have been completed or are underway.

6) Instead of saying "The information you provide will be stored for future use", revise consent form as follows: "The information you provide will be used to evaluate participation and completeness of the data. It will also be used to estimate cumulative organ-specific radiation doses to technologists who perform nuclear medicine procedures".

7) Revise consent form under confidentiality section as follows: The data we collect may be made available to other researchers with interests in radiation exposure and health outcomes, but no personally identifiable information that links your data to you will be provided.

8) Remove reference to the estimated number of subjects for the larger study from the consent form.

PI Name: Cari Kitahara
Protocol Title: Cancer and Other Disease Risks in U.S. Nuclear Medicine Technologists

Précis:

The field of nuclear medicine has expanded rapidly since its inception in the mid-20th century, with nuclear medicine technologists now potentially experiencing higher levels of radiation exposure relative to other medical worker populations. Many radiopharmaceuticals and procedures used in previous decades are now obsolete and are being replaced by new and emerging radioisotopes and combined-modality and molecular imaging procedures. While improvements in imaging technologies and the introduction of certain radioisotopes have generally reduced patient exposure to radiation, nuclear medicine technologists have become increasingly specialized in these newer procedures and are performing these and other nuclear medicine procedures with increasing frequency. Furthermore, lead aprons are less effective in protecting workers during nuclear medicine procedures, specifically higher-energy procedures (e.g., positron emission tomography (PET)), compared to other radiation-related procedures, and are seldom used by technologists performing nuclear medicine. As a result, cumulative doses to nuclear medicine technologists are expected to have increased. We hypothesize that certified nuclear medicine technologists may experience higher risks of some radiation-related cancers and other adverse health outcomes compared to most other medical specialty groups. There is currently very little information about radiation-related risks associated with performing these procedures due, in part, to limited information on occupational doses associated with current nuclear medicine practices. To characterize organ-specific doses that could later be used to quantify risks for specific radiation-related disease outcomes, either directly (through subsequent follow-up) or indirectly (through risk projection methods), we plan to collect detailed work history information on nuclear medicine procedures and associated radiation safety practices, as well as badge doses, for a representative sample of 1,500 technologists certified in nuclear medicine in the U.S. This information will complement similar data collected in 2013-2014 from an independent sample of approximately 4,500 general radiologic technologists in the U.S. Radiologic Technologists Study (USRT) who had reported working with these procedures. However, unlike the USRT sample, the proposed sample is expected to be higher-risk, including only those workers with a specialty certification in nuclear medicine who will have been begun working with nuclear medicine procedures much earlier in their career, at ages associated with greater susceptibility to radiation-related carcinogenesis.

Discussion

The Primary Reviewer presented an overview of the protocol and consent as noted below. Comments from the discussion during the meeting appear in red text:

Pre-Review of Initial Review

Protocol Name: Cancer and Other Disease Risks in U.S. Nuclear Medicine Technologists
PI Name: Cari Kitahara
Date of SSIRB meeting: April 18, 2016

General Questions/Comments:

Primary Reviewer:
Will the participants be allowed to consent to the questionnaire but not the dosimetry data retrieval or vice versa?

The statement in the consent "The information you provide will be stored for future use" should be expanded on.

Will subjects be able to obtain their exposure information from the dosimetry accounts?

Some of the documents that were reviewed by the University of Minnesota don't appear to have been submitted to the SSIRB (e.g., the follow-up letter to initial nonresponders).

In the consent, under "Background Information", there is a "to" missing.

Secondary Reviewer: None.
PI response to comments/questions:

We will modify the consent questions to allow participants to consent separately for the two different components of the study: (1) completing the online survey about nuclear medicine work history and employers; and (2) obtaining badge dose readings from commercial dosimetry providers.

The statement about future use will be expanded on the revised consent under 'Procedures'. We will add the following highlighted sections, "The information you provide will be stored for future use in the full-scale study, if determined feasible. You would be contacted again to complete a follow-up questionnaire about your history of cancer and other diseases, and disease risk factors such as cigarette smoking. That information would be used along with the nuclear medicine work history information that you provide now to evaluate disease risks related to working with radioisotopes."

We will not provide dosimetry information to participants because we cannot fully ensure the accuracy of the linkage or the completeness of the dose records. Badge doses readings are routinely provided to badged workers by their employers. Summary findings will be provided through periodic newsletters or study updates in a separate U.S. Nuclear Medicine Technologists Study section on the U.S. Radiologic Technologists Study website.

The follow-up recruitment email is included as Attachment 1 and will be uploaded into the iRIS system.

We will correct the typo under 'Background Information.'

Common Checklist Questions - Regulatory review requirements

1. Risks to subjects are minimized (45 CFR 46.111(a)(1))

Yes

2. Risks are reasonable in relationship to anticipated benefits/benefits, if any (45 CFR 46.111(a)(2))

Yes

3. Subject selection is equitable (45 CFR 46.111(a)(3))

Yes

SSIRB reviewer comments to which PI may or may not respond:

Primary Reviewer: The only exclusion criterion is having worked in the field before 1980.
As noted on page 7 of the protocol, the U.S. Nuclear Medicine Technologist Study target population includes an estimated 25,000 individuals who were first certified in nuclear medicine technology in the U.S. after 1980, are currently alive and residing in the U.S., and are not participants of the USRT study.

4. Informed consent process is adequate and is appropriately documented (45 CFR 46.111(a)(4), 46.111(a)(5), 46.116 and 46.117)

Primary Reviewer: No
Secondary Reviewer: Yes

SSIRB reviewer questions:
Secondary Reviewer: Can UMN verify that it is the correct person with only year of birth and gender?

PI response to questions:
The certification boards will provide the full date of birth, not just year of birth, and the email addresses. Gender will be asked on the questionnaire because we have learned that it is not available from the registries. Subjects will be given a unique study link and password for logging in to complete the consent and questionnaire. UMN will assume that they have reached the correct individual if the full date of birth matches the responder at the email address provided.

SSIRB reviewer comments to which PI may or may not respond:
Primary Reviewer: The University of Minnesota granted a waiver of documentation of consent.
Secondary Reviewer: The Minnesota IRB letter indicated it had approved a waiver of documentation of informed consent. I did not see such a request in the protocol we reviewed. There are ways to document a web-based consent.

It was confusing to have a consent form included with the introductory letter, then to ask on-line if the participant had read the other consent form, and then to have part of the material that is generally included in the consent form included as the introduction to the questionnaire. It would seem less confusing to perhaps expand the introductory letter a bit and then have the entire consent form on-line and to include the introductory information before the questionnaire as part of the consent form.

It is not clear why former employers will be contacted. This is not mentioned in the consent form.

PI response to comments (optional):

We will modify the introduction and consent so that the introduction is slightly longer, and then is followed by the consent. We plan to attach the consent form to the recruitment email so that the participants have a copy for their records. We have no plans to contact employers; this information will be used to link the participants with the dosimetry records. We will clarify this point under the 'Procedures' section (highlighted):

Procedures: If you agree to be in this study, you will be asked to do the following:

- **Complete an on-line survey about your experience working with nuclear medicine procedures. The survey asks questions about the types and frequency of nuclear medicine procedures you performed and related work practices.**
- **Provide a brief employer history, including the names of current and past employers specific to your work in the field of nuclear medicine.**
- **Allow the researchers to obtain historical records of your film badge dose readings from dosimetry providers, such as Landauer. The information you provide about your employers will be used to find your badge dose records.**

There was discussion that a statement should be added to the introduction explaining that this is a feasibility study.

We will have documentation of online consent (yes/no to each component) through the computer-assisted web interview (CAWI), so are not requesting waiver of documentation of informed consent from the SSIRB. We will provide the subject with a unique log-in link and psasword, and will use date of birth as a way to verify the identify of the subject.

5. Data will be monitored to ensure safety of subjects (45 CFR 46.111(a)(6))

N/A

6. When appropriate, there are adequate provisions for privacy & confidentiality (45 CFR 46.111(a)(7))

Yes

SSIRB reviewer questions:
Primary Reviewer: Will the contact information for non-responders be deleted?

PI response to questions:
We do not plan to delete contact information for non-responders. We will use the available information from the certification boards to evaluate potential differences in responders and non-responders. Non-responders would be approached again if the full-scale study proceeds, using more intensive follow-up procedures, such as email verification and other tracing measures. Mortality follow-up would also be conducted on the full eligible population to assess potential differences in mortality between responders and responders.

7. When appropriate, additional safeguards have been included in the study for vulnerable subjects (45 CFR 46.111(b))

Primary Reviewer: N/A no vulnerable subjects
Secondary Reviewer: No

General Requirements

1. Is the proposed research design adequately described and scientifically sound?

Yes

SSIRB reviewer questions:
Secondary Reviewer: Did the SSIRB receive all 6 documents listed as provided to the Minnesota IRB, including the sample follow-up letter?

PI response:

The follow-up email was not included in the initial submission. A copy is provided as Attachment 1 and the document will be uploaded into the iRIS system.

SSIRB comments to which PI may or may not respond:
Primary Reviewer: The study protocol was approved by TEP.

PI response (optional):

Risk category:
The research involves no more than minimal risk to subjects.

Benefit category**:**

No prospect of direct benefit to individual subjects but likely to yield generalizable knowledge to further society's understanding of the disorder or condition under study (mainly for healthy volunteers).

Pre-review of Consent Form

1. Statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

Primary Reviewer: No
Secondary Reviewer: Yes

SSIRB comments to which PI may or may not respond:
Primary Reviewer: It isn't clear whether the subjects that participate in this pilot study will be included in the larger study, if it proceeds.

Secondary Reviewer: The expected duration of the subject's participation 30 minutes) is not mentioned in the consent form, but is rather mentioned in the introduction to the questionnaire. This is very confusing.

PI response (optional):
The pilot study participants and non-responders will be re-contacted for the larger study as noted above. The estimated time to review the consent and ask questions is 15 minutes and the estimated time to complete the questionnaire is 30 minutes. We will add the following information about both of these to the revised consent form under 'Procedures': "We estimate that it will take you about 15 minutes to review the consent information and ask any questions that you may have, and about 30 minutes to complete the questionnaire. "

2. A description of any reasonably foreseeable risks or discomforts to the subject.

Primary Reviewer: No
Secondary Reviewer: Yes

SSIRB comments to which PI may or may not respond:
Primary Reviewer: Loss of confidentiality of responses to the questionnaire and dosimetry data should be stated under risks.
Secondary Reviewer: No known risks.

PI response (optional):
We will add a sentence under "Confidentiality" that acknowledges the potential for loss of confidentiality despite taking every precaution to keep the information collected private.

3. A description of any benefits to the subject or to others which may reasonably be expected from the research.
Yes, No direct benefits.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
N/A
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
Yes
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
N/A
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
Yes
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
Yes
Additional elements:
9. A statement that the particular treatment or procedure may involve risks to the participant, which are currently unforeseeable.
N/A
10. A statement that if the participant is or becomes pregnant, the particular treatment or procedure may involve risks to the embryo or fetus, which are currently unforeseeable.
N/A
11. Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participant's consent.
Primary Reviewer: N/A Secondary Reviewer: No, Unlikely to be such circumstances.

12. Any additional costs to the participant that may result from participation in the research.

N/A

13. The consequences of a participant's decision to withdraw from the research.

Yes

14. Procedures for orderly termination of participation by the participant.

No

SSIRB comments to which PI may or may not respond:
Primary Reviewer: The consent form could state specifically that if the subjects wants their responses and other information deleted from the study who they should contact.

Secondary Reviewer: This needs to be addressed.

PI response (optional):
Information about how to withdraw from the study will be added to the revised consent under 'Voluntary Nature of the Study'. We plan to add the following highlighted sections: "Your participation in this study is completely voluntary and failure to answer any particular question or the information collection as a whole will not affect your current or future relations with the University of Minnesota, National Cancer Institute, the American Registry of Radiologic Technologists (ARRT), and the Nuclear Medicine Technologists Certification Board (NMTCB). By contacting the research staff at the University of Minnesota at (800) 447-6466 or email usnmt@umn.edu, you can also withdraw from the study at any time without affecting those relationships; data collected up to that time will remain in the study and be used in data analysis."

There was discussion that participants should be able to withdraw any data not already included in analyses.

15. A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.

N/A

16. The approximate number of subjects involved in the study.

No

SSIRB comments to which PI may or may not respond:
Primary Reviewer: The consent form doesn't include the approximate number of subjects that will be contacted to be recruited into the study.

Secondary Reviewer: This needs to be addressed.

PI response (optional):
We will add to the revised consent under 'Background Information' that about 1,500 NMTs will be asked to participate in the feasibility study and an estimated 25,000 would be eligible for the larger study.

There was discussion that the larger study should not be referenced in terms of the accrual numbers.

17. The amount and schedule of all payments to the participant.
N/A
18. The information that is given to the subject or the representative is in language understandable to the subject or the representative.
Yes