

FY2019 Plans of Activities

I. Plans of Major Activities

Because much of RERF's research involves longitudinal or large scale long-term studies that take a significant time to plan and conduct, so a number of ongoing plans for such studies have already been presented under research achievements. Here we provide highlights of new research plans or selected plans of note.

1. Research Projects Examining A-bomb Survivors Health

1) Radiation and Cancer:

- *Updated cancer incidence:* A series of papers on cancer incidence risk following radiation exposure for individual sites in the LSS during 1958–2009 will be published in 2019 in collaboration with US National Cancer Institute. Individual organ sites or organ systems expected to be submitted for internal review in 2019 include: upper digestive system, hepato-biliary-pancreatic, uterine, prostate, urinary tract, CNS, and ovary. Papers to summarize the results of individual sites including investigation of different curvature between sexes will be submitted to international journals.
- *Radiation risk at low dose levels:* Current efforts on cancer incidence risk analysis at low-dose levels will be developed, in a collaboration between the Epidemiology and Statistics Departments. Analysis of the non-linear dose-response for all solid cancer incidence risk in males will be continued including analyses of dose-responses for cancer of individual sites. Analyses of potential confounding by geospatial factors and variation in baseline rates, and modeling of baseline rates, will be continued including preparation for studies of mortality risk in the LSS including non-cancer diseases. Dose errors as well as the potential impact of exposure to residual radiation and medical radiation will also be considered. Risk analyses using mechanistic models will be continued in collaboration between RERF and the Helmholtz Zentrum München.
- *Liver cancer program project:* A multidisciplinary program project on radiation and liver cancer will be developed involving researchers from the Departments of Statistics, Molecular Biosciences, and Epidemiology within the cancer research cluster (Projects involve: identification of novel biomarkers for detection, mechanisms, and radiation sensitivity of HCC; mechanisms of radiation-associated HCC with HBV/HCV; mechanisms of radiation-associated non-B/non-C HCC using mouse models; and statistical and epidemiological methodological issues). Overall objectives are to clarify immunologic and metabolic mechanisms of radiation-associated HCC in order to: 1) better understand the underlying biological and clinical aspects; 2) obtain more-precise estimates of risk; and 3) be able to apportion probability of causation in radiation-associated HCC.
- *Breast cancer:* As a part of potential program project, we are considering designing a nested case-control study of breast cancer starting in 2019. We would use the Toshiba Japonica Array developed for analyzing gene polymorphisms in the Japanese population to examine polymorphisms potentially involved in the development of radiation-associated breast cancer. In order to conduct a genome study using a cohort of all AHS subjects, DNA samples extracted from old smear samples must be used. For this reason, it is necessary to determine whether SNP analysis using the Japonica Array is possible by amplifying the whole genome using a very small amount of DNA obtained from blood smear samples stored for many years. In FY 2019, DNA extraction from preserved blood smear samples

will be carried out to examine a suitable preparation method for REPLI-g amplified DNA. Then, we will evaluate DNA availability by analyzing those DNA samples with the Japonica Array.

- *Myelodysplastic Syndrome (MDS)*: We will continue our collaborative program with Nagasaki University and Kyoto University to determine mutations in serially collected blood samples from individuals developing MDS using genomic analysis. Sequencing is expected to be completed in early 2020.

2) Radiation and Non-Cancer Effects:

- *Cardiovascular disease program project*: As part of a new program project that is being reviewed in the Non-cancer Research Cluster, we will develop strategies for assessment of clonal hematopoiesis potentially linking to radiation-associated noncancer diseases, specifically arteriosclerosis, in the AHS. Our hypothesis in this program project is that somatic mutations in epigenetic modifier genes (*TET2*, *DNMT3A*, *ASXL1*, etc) in hematopoietic stem cells drive clonal hematopoiesis, resulting in accumulation of pro-inflammatory monocytes and T cells. Endogenous danger signals—alarmins—may also be involved in inflammatory phenotypes of monocytes and T cells. To strengthen the hypothesis, we will also develop mouse and mathematical simulation models to evaluate clonal expansion of hematopoietic stem cells (HSCs) and pro-inflammatory phenotypes following radiation exposure.
- *Neurocognitive function*: Analysis of radiation effects on the Neurocognitive Questionnaire (NCQ) and the Cognitive Abilities Screening Instrument (CASI) will be expanded to include subjects exposed *in utero*.
- *Cataracts*: We will complete evaluation of cataract severity by June 2019 and start analysis the relationships between several types of cataracts and radiation among subjects who were <15 years of age at the time of bombings (excluding *in utero*-exposed subjects) in collaboration with Department of Statistics. Continue ophthalmologic examinations among *in utero*-exposed subjects until March 2020 and start scoring cataract severity in July 2019.

3) Immunologic Effects of Radiation:

- *T-cell immunity and liver cancer*: Both adaptive and innate immunity play crucial roles in hepatocellular carcinoma (HCC) development and progression. The T-cell immune response is the most important defense mechanism against viral hepatitis and HCC, but on some occasions exacerbates HCC, whereas macrophages promote liver fibrosis and suppress anti-viral T-cell responses. To test the hypothesis that radiation exposure may accelerate the progression to HCC through dysregulation of T-cell immunity and innate inflammatory response, we will analyze longitudinal data of immune cell parameters in AHS subjects (e.g., naïve T-cell, NK-cell, and monocyte counts), in relation to radiation dose, hepatitis virus infection, inflammation, liver steatosis, fibrosis, and HCC.

2. Research Projects on the Health of A-bomb Survivors Children (F₁)

- *F₁ cohort study*: A cancer incidence paper is expected, but it is difficult to estimate the migration rates of F₁ cohort members out of cancer registry areas. In addition, the RERF Epidemiology Department does not have sufficient information regarding subjects' addresses although the current address of the cohort members provides substantial information for personal identification on crosscheck with cancer patients recorded in cancer registries. It is because we have no direct contact with them and cannot collect such information from municipality offices without agreement by the subjects under legal

restrictions that difficulties arise. On the other hand, subjects in the F₁ Offspring Clinical Study (FOCS) have been contacted by the RERF Clinical Studies Department every year for the health examination program. Therefore, collection of cancer incidence information of F₁ subjects from the national cancer registry system will focus on the subjects in the FOCS by using the contact address as a personal identifier.

- *FOCS*: We will continue to conduct health examinations among the cohort members of both the AHS and F₁ follow-up clinical studies. A high-priority activity in the coming year will be to form a working group to assess appropriate methodology and develop a plan for a risk analysis of the F₁ Clinical Study (FOCS) data when the current cycle (third longitudinal cycle; fourth round overall including the preliminary cross-sectional study) comes to a close. The FOCS design combines baseline disease prevalence with subsequent incidence (the latter among participants who were disease-free at baseline). The study outcomes comprise a number of clinical endpoints, many of which are stages in disease development; the analysis can therefore employ disease transition models. Illness-death processes should also be considered given that truncation due to death can cause bias in longitudinal studies. The working group will conduct its assessment in close collaboration with Clinical Studies researchers. The goal in the coming year is to develop an outline of steps to be taken in the following several years so that a formal analysis plan can be in place to allow us to conduct preliminary analyses at the time the current (third) FOCS cycle (fourth round) ends in the fall of 2022 (albeit some data will continue to accumulate for several years beyond that as backup exams are conducted, so that final analyses based on the fourth round is expected to be completed a few years after that).
- *Integrated genetics program (F₁ umbrella project)*: An integrated program project for radiation effects on the F₁ generation including F₁ mortality and cancer incidence follow-up, FOCS, genomic analysis of trios, and related animal studies will be developed in the Genetic Research Cluster.
- *Sequencing*: As a major part of studies related to the development of the F₁ umbrella project, we plan to conduct WGS analysis of human trio (parents and a child) samples including atomic bomb survivors and their offspring. As a first step, we plan a preliminary experiment using a small number of trio samples. In FY2019, we will develop an experimental plan using the newest technologies and prepare an experimental environment for the conduct of that project, including physical resources for sequencing data analysis, an information security system for the genomic data, and a world-wide scale collaboration network for the project. One of the most important issues is getting an understanding of this WGS project with stake holders (atomic bomb survivors and their children) and citizens. So, we will make a series of communication and education programs for citizens.
- *Transmission of germ-line mutations*: To mechanistically understand how radiation exposure induces mutations in spermatogonia stem cells and how their mutations transmit to the next generation, we have initiated an *in vitro* culture approach to examine mouse spermatogonia cells (hereinafter GS, germline stem cells). Irradiated GS cell culture will be characterized by aCGH and WGS analyses, and then they will be transplanted into Busulfan-treated testes of adult male mice. We will then examine the offspring derived from the GS cells for heritable genetic changes. Along with this experiment, efficiency of spermatogenesis from the transplanted GS cells will be analyzed by testis tissue cross sections. Spermatogonia stem cell division (mitosis) and subsequent meiotic division are divided in several steps, where some of the steps are characterized by specific antigens such as PCNA/Ddx4 (spermatogonia), Stra8 (preleptotene), Spo11 (early prophase), Hspa2 (late spermatocyte). These antigens, cell morphology and localization in seminiferous tubules could determine the progression of meiosis of transplanted GS cells.

3. Research to Elucidate Individual Radiation Doses and the Effects of A-bombs

- *Radiation dosimetry and dose error:* We will continue to support and collaborate with the organ dosimetry working group, based on their recommendations. In relation to dose uncertainty, we will assess the impact of dose uncertainty on the dose-response at low doses, based on plug-in estimators that can accommodate both classical and Berkson (or, grouping) error; and reconstruction of a marginal distribution of unobservable true doses among the LSS, based on pre-bombing population estimates, sampling fractions, and estimated shielding distributions, in parallel with development of methods that avoid assumptions regarding the parametric distribution of unobservable true doses.

We will also investigate an alternative approach to dose-error handling by treating radiation dose as a latent variable in MIMIC (causal) models and compare this to the standard use of regression calibration substitution dose estimates. A key component of this work will be to assess the impact of dose-error handling on inference regarding indirect effects of radiation on latent-factor indicators.

Missing data represent, perhaps, the most extreme case of measurement error. In DS02R1, survivors with unknown or complex shielding histories not accommodated by the dosimetry system have unknown doses. A goal for the coming year is to begin constructing imputation models for missing doses by using all available information from the dosimetry system, and compare results to findings based on exclusion of survivors with missing dose.

4. Project to Release of Research Results and to Collaborate with Other Scientific Organizations

- *Continuing collaborations:* Long term collaborations are listed below and these are expected to continue in 2019:
 - a. Partnership with the University of Washington
 - b. Partnership with Kurume University
 - c. Collaborations with the US National Cancer Institute
 - d. Collaborations with the University of Florida
 - e. Collaborations with Outside Investigators:
 - 39 Japanese Institutions
 - 18 North American Institutions
 - 14 European Institutions
 - 3 Asian, Oceanian Institutions
 - Nuclear Emergency Workers Study (NEWS): 11 Japanese Institutions

5. Training Programs for Domestic and Overseas Specialists

RERF will hold a training seminar for non-epidemiologist radiation researchers to learn the basics of epidemiological research and increase understanding of radiation health risks. In addition, RERF will train persons capable of working in the fields of radiation protection, radiation emergency medical care, and radiobiological research.

Activity plans for FY2019

- i) RERF will hold an epidemiological training seminar for radiation biologists in Japan again in FY2019 for enhanced understanding of results from epidemiology research on A-bomb survivors.
- ii) RERF will accept overseas research trainees to support the activities of such organizations as the Hiroshima International Council for Health Care of the Radiation-

exposed (HICARE), the Nagasaki Association for Hibakusha's Medical Care (NASHIM), and the Japan International Cooperation Agency (JICA).

- iii) RERF will accept students from domestic and overseas schools/universities for facility tours, and will provide training sessions on the foundation's research activities.
- iv) RERF will continue to review directions as to its training activities and publicly invite overseas trainees in the International Exchange Research Program for FY2019 also.

6. Public Information Programs

Activity plans for FY2019

i) RERF Open House event

RERF will hold its 25th and 23rd Open House events at the Hiroshima and Nagasaki RERF Laboratories, respectively. The event will feature various programs, including exhibitions as well as lectures, and is once again scheduled to be held during FY2019 in Hiroshima and Nagasaki in August.

ii) RERF Public Lecture

RERF will hold public lectures to provide the general public with an opportunity to enhance their understanding of the foundation's research and to learn more about radiation's health effects.

iii) Enhance social media activities

RERF will expand its reach through use of social media networks, by putting more emphasis on Facebook content and initiating a Twitter account. The Twitter project would take place only in an English version to begin and move to Japanese after we can test the kind of response RERF tweets receive in English from the international community.

iv) Improve-media-relations project

This new project was initiated with two meetings (one with broadcast media, one with print media) at the beginning of 2019 (Jan.), with the aim of increasing the probability for neutral coverage of ABCC/RERF and its research results by the media. Such media-communication meetings will be held again during FY2019, aiming at fostering closer relations with the media.

v) Enhancement of new RERF website

Following the launch of the new RERF website in FY2018, the information on the homepage will continue to be updated and enhanced. A focus will be placed in particular on effectively conveying readily understandable information to the public, such as by using more video and other methods.

vi) Creation of new online news-delivery system

Following the discontinuation of the printed *Update* newsletter at the end of 2016, a new email magazine system (a subscriber-list online news-delivery system, by which RERF will regularly send out informative email to people who subscribe to the service to read the latest about RERF) will be created and used to not only distribute the latest research results and information about RERF events and activities but also to attract subscribers to RERF as "members," by offering a sense of "buy-in" with respect to RERF as an organization.

vii) Improvement of social media techniques

RERF will attempt to attract younger people to our cause through the use of social media, such as Facebook and Twitter, by joining with the independent U.S.-based Think Global School (TGS) high school once again in FY2019, as was done in FY2018. To help us attract more young followers, TGS will collaborate with RERF to improve our Facebook page content and to formulate project plans geared toward use of Twitter and other social media platforms.

viii) School Visit Program

This program was first established in FY2016 in an attempt to convey to young school students the reality of radiation health effects. Each year, the number of requests for such classes increasing yearly and a now firm stable of teachers being established have provided the opportunity to teach an increased number of classes. In FY2019, in addition to the conventional school visit program, we will also work to expand the project by teaching students about radiation and about how to teach the basics of radiation to their peers, in a student-led education drive.

ix) Other public relations activities

- RERF will actively promote the foundation's important scientific papers to the domestic and overseas media via press releases and press conferences.
- With the aim of improving public understanding of RERF research, the Office initiated in FY2018 a new series of paper synopses that explain research with simpler prose and smaller word counts than used previously in our "summary explanation" series for specialists. Through continuation of this series in FY2019, the Office will aim to improve understanding by the public of RERF work.
- In continuation from RERF's first-ever press conference at the Foreign Correspondents' Club of Japan in February 2017, as well as the joint press meeting with ICRP at the University of Tokyo in December of the same year, RERF will hold another such event in Tokyo during FY2019.
- A persistent goal again this fiscal year is the training of more RERF personnel to handle the tours in English for overseas visitors.
- With the aim of improved transparency related to RERF research and establishment of good communication with the public, in particular A-bomb survivors and their children, by increasing our effort at communicating RERF's research, the Public-Awareness Campaign Working Group was formed in January 2019. The Working Group will attempt to provide information on important topics such as the human genome and our gene studies, and so on.
- RERF will continue to target small public groups of A-bomb survivors and their children, who will be invited to come to RERF and speak with directors and staff about ABCC/RERF history and research results, with the aim of achieving greater understanding about RERF with more personal, small-scale opportunities.

II. Activities necessary for the above projects

1. Research Resource Center

The Research Resource Center (RRC) is a core RERF infrastructure to store, document, and index all RERF resources and to integrate research data with biosample data to promote research.

A White Paper has been completed that lays out a 3-year timeline for getting the RRC through its primary phases of development. Seen broadly, there are two main areas of development.

1. A data integration project
2. An archiving/preservation project

The data integration project will require expertise and software that is not available within RERF. Therefore, outside experts will need to be brought in to help the initial installation and development. Over the past 18 months a number of experts around the world have been consulted to identify systems at other institutions that may be suitable for our needs. Recently, the “Gen3” system, a “Data Commons” used by the NIH and other institutions was investigated. Gen3 is a cloud-based software platform for managing, analyzing, harmonizing and sharing large datasets. Gen3 is an open source platform for developing data commons. RERF management has decided to proceed with a pilot project using Gen3 to test if it is compatible with the scientific needs at RERF.

The archiving/preservation project is for protecting RERF assets. Research assets collected since 1947 represent the entire life history of one of the world’s most unique cohorts and are impossible to replicate. World experts have been invited to RERF including Dr. Christy Henshaw, Digital Production Manager at the Wellcome Trust. Priorities for which resources will be scanned first have been set and production procedures are being worked out, including software installation requirements.

A location for the RRC has been selected and will include an archiving room with temperature and humidity controls (already installed), a scanning room, a secure network room for collaborative whole-genome-sequence studies, a developer’s area, and a classroom area.

2. Planned employment of general employees

Currently, the age-distribution for RERF employees is uneven as many employees are of advanced ages. Almost 70% of employees, excluding those reemployed, are 50 years old or older. For the smooth intergenerational succession of duties, we will consider postponing mandatory retirement ages, or both, while taking account of governmental and social factors. We will discuss the merger of sections and offices within RERF and sharing duties among employees from different departments/sections, cutting and reducing workloads. We will continue to actively convert employees with limited terms of appointment, including temporary employees, to permanent staff members and hire fixed-term general employees after carefully considering the necessity of their duties, RERF’s financial situation, and our personnel cap.

3. Continuation of long-term leadership training

To raise employee motivation for becoming management-level personnel, we have planned a total of six leadership training sessions for those in assistant section chief positions or lower over a four-fiscal-year period starting from FY2017. The fourth and fifth sessions will be held in July and November FY2019, respectively, in Hiroshima and Nagasaki. The training theme for this fiscal year is leader communication training, such as sharing a common goal, giving proper instructions, and motivating their subordinates, and leadership training. Through this training, participants are expected to learn about capacity and resourcefulness required for the leaders.

4. Introduction of an attendance and work management system

On June 29, 2018, a package of work-style reforms bills passed and became laws. So, RERF needs to promote work style reforms and streamline clerical work. We will introduce an attendance management system in FY2019 to objectively discern the working hours of all staff and create workflows for all paid leave forms and overtime forms. By doing so, we aim to streamline attendance management duties and make salary calculations more efficient by linking attendance management data to the payroll system.

Attendance management means that companies properly grasp their employees' working status. In concrete terms, all staff members will keep IC cards and pass their cards through a card reader that will be placed at the entrance to record and check the time at which they come into work and go home, work effort, overtime work, and application and acquisition of paid holidays. Most Japanese central government ministries and agencies already use this attendance system.

5. Facility upgrades

(1) Facility upgrades to the Hiroshima Laboratory

We are in the second year of a three-year plan we are implementing to replace all air conditioners currently in use by FY2020, as the units are deteriorating and some contain banned fluorocarbons.

(2) Facility upgrades in Nagasaki

RERF will renovate the exterior walls for the second time to prevent water from leaking due to deteriorating exterior wall paint, and pieces of exterior walls from falling due to cracks. The first renovation was conducted in FY2003. RERF and the Nagasaki Prefectural Board of Education will share the costs.

6. Continuation of internal audit process

As in FY2018, RERF will sign another entrustment contract for internal audit with an outside auditing company in FY2019.

7. Revision of regulations

The internal audit conducted by Deloitte Touche Tohmatsu LLC found that RERF had neither prepared rules regarding expenses for meetings nor ethical regulations on preventing corruption such as bribery. RERF had not prepared written rules on taxi use, either. As a public interest incorporated foundation operating with national subsidies, RERF has decided to prepare strict rules on expenses for meetings and disbursement of taxi fares and ethical regulations on preventing corruption.