R&R: BNL-NN-20230131-0096-00-FORE

Facilitating the Adoption of Non-Radioisotopic Technologies in the Research Community: Reproducibility and Comparability

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May 2023

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I. Introduction

The National Nuclear Security Administration (NNSA) seeks to assist and support all partners in the fields of radiobiology, radiation physics, and related areas to transition from Cesium-based technologies to X-ray technologies. However, there has been ongoing discussion and debate amongst potential 'transitioners' about how feasible this may be for their respective institutions. BNL's recent Alternative Technologies Meta Study (February 2022) uncovered that there is an underlying reason for this debate. A broader 'reproducibility crisis' in the reporting of the research using the X-ray technology itself significantly contributes to the confusion and reluctance a researcher may experience when considering a transition. The lack of standard reporting measures has proven to be a strong deterrent as researchers acknowledge that valuable science always starts with acceptance of recognizable experimental variables that others are able to compare and confer with.

In order to begin moving in a direction that resolves the aforementioned reproducibility issue, NNSA gathered leaders from the fields of medical physics and radiobiology to determine specific parameters that should be included in published literature and projects utilizing X-ray technology. The meeting, titled Compatibility of Irradiation Research Protocols Expert Roundtable (CIRPER), was also an opportunity for federal partners to better understand the nuanced challenges and opportunities researchers face in transitioning. This report describes the major topics that were of discussion during the meeting, as well as BNL's recommendations on how best to proceed.

II. Opportunities and Challenges for Researchers Adopting Alternative Technologies

CIRPER participants reaffirmed a key finding in the BNL Alternative Technologies Adopters Outreach Report (November 2021) suggesting that overall, the transition from Cesium-137 (Cs-137) to x- ray irradiators is not disruptive. Another significant finding was that most researchers considered the transition to have positive impacts on their research. Chief among these were technological innovations built into x- ray devices that allowed users to initiate new lines of research with the enhanced x-ray technical capabilities (variable energy, automated dosimetry, movable shelves, collimators, different filters, enhanced imaging, and CT scanning capabilities) that would not have been possible with Cs-137 irradiators. Additional capabilities identified during the breakout session are captured below:

- X-ray irradiators can form a focal point beam for exposures. This was difficult or impossible with older Cs-137 irradiators.
- X-ray irradiators provide automated dosimetry as well as dose mapping capabilities.
- X-ray irradiators provide turn tables and/or holding devices to secure samples/mice and assure a uniform dose delivery.
- X-ray irradiators allow filters to harden the beam and eliminate low-energy x-rays that can cause skin burns to animals; the variety of filters also allows researchers to modify the beam.
- Sophisticated image-guidance systems mimic complex treatments in experimental and clinical settings.

Participants noted that, with few exceptions, x-ray irradiators can effectively replace Cs-137 irradiators. Exceptions include studies of health effects of long-term exposures (e.g., hormesis studies) which require prorating the dose or dose rate to achieve the desired effect. Other applications for which x-ray irradiators cannot easily provide the necessary dose – such as sterilization or ablation of cells; large animal studies; and radio-resistant bacteria – can be conducted using Linear Accelerators (LINACs).

Therefore, the biggest challenge identified by participants is the absence of standards and other information on experimental procedures, equipment, and physics parameters, which are key to facilitating the transition from gamma to x-ray. It is estimated that 28 billion dollars/year (or approximately 50% of the total expenditures on preclinical trials) is spent on irreproducible research (Freedman *et al*, 2015).

Participants agreed that the lack of standards has a direct and negative impact on the reproducibility and translatability of a sizable portion of radiation biology studies. Only a limited number of published studies reference industry standards for dosimetry evaluations. Often, minimal information is provided regarding the characteristics of the irradiation delivery, including irradiation geometry, dose rate, depth dose distribution, dosimetry methods, delivery point of interest (POI, e.g., surface or depth), and the uncertainty in the dose value. It can also be difficult to repeat the studies of others if there are details missing from the description of the irradiation conditions. Thus, replication of reported values across studies and users is problematic and results in the need to repeat costly studies, while also yielding uncertainty in observed effects and creating difficulties when validating characterized animal models.

Participants also identified large information gaps in reporting field geometry, filtration, or half-life value (HLV), and overall experimental error uncertainty. Thus, replication of reported values across studies and users is problematic, adds ambiguity to observed effects, and produces difficulty in validating a characterized animal model.

For studies where the critical biological endpoints measured have a narrow range (± 5% or less) for example, it is also critical to know the parameters that control the dosimetry. The absence of unified expectations for the reporting of methodological information is further complicated by the absence of awareness ("You don't know what you don't know"), proper training, and overall discipline and enforcement across researchers, editorial boards, and funding institutions. Additional comments and recommendations will be highlighted in subsequent sections.

III. Past and Current Attempts at Establishing Standards

One of CIRPER's goals was to reach an agreement on minimum requirements for the reporting of methodological practices in radiobiological studies to facilitate compatibility assessments between different irradiation modalities (e.g., gamma versus x-rays). As organizers, we were also interested in generating support for other initiatives focusing on the development of methodological Standard Operating Procedures (SOPs) for radiobiology studies. Concerns over compatibility have made researchers reluctant to transition to x-ray irradiators, despite the advantages they provide in terms of security and technological innovation. Inconsistencies in reporting methodological practices and protocols for radiobiological studies using x-ray irradiators represent a significant hurdle to researchers attempting to establish or communicate potential comparability with studies using gamma irradiators.

There have been several attempts at creating standards for dosimetry and experimental set up when using x-ray irradiators in radiotherapy and radiobiology applications:

- In 1998, the International Commission on Radiation Units and Measurements published their report, **ICRU 30 "Quantitative Concepts and Dosimetry in Radiobiology."** This report is more comprehensive than most standards, containing information on measuring accurate absorbed dose using ionization chambers, but it also detailed information on survival curves, linear energy transfer (LET) and Lineal Energy, animal and cell culture exposure systems, scatter, and charge particle equilibrium, along with recommended minimum dosimetry and irradiation geometry information required.

- In 2001, the American Association of Physicists in Medicine (AAPM) released AAPM TG 61 "40-300 kV X-ray Beam Dosimetry in Radiotherapy and Radiobiology". The protocol was based on air-kerma calibration methodology that included dosimeter requirements and phantom configurations for the determination of absorbed dose. The protocol proposed different methods depending on beam quality and point of interest (POI, e.g., surface or depth) as well as quality assurance testing at regular intervals. The protocol did not seem to have a significant impact on radiobiological studies, and since it was created before most of the "cabinet-door" irradiation devices currently used were built, it would need to be revised to be widely adopted today.

- In 2011, several government agencies – the National Cancer Institute (NCI), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Institute of Standards and Technology (NIST) – convened a workshop to address the widespread problem of inadequate measurement and reporting of radiation setups and dosimetry (Desrosiers et al 2013). Recommendations included the need for standard operating procedures (SOPs) in dosimetry for cell culture and for small and large animal experiments, as well as for the reporting of such dosimetry in research journals.

- For megavoltage beams (i.e., energies greater or equal to that of Co-60) that use ionization chambers calibrated to absorbed dose to water, two protocols exist: **AAMP TG 51 "Protocol for Clinical Reference Dosimetry of High-Energy Photon and Electron Beams** (1999, with an addendum released in 2014) and **IAEA TRS-398 "Absorbed Dose Determination in External Beam Radiotherapy..."** (2006). Both focus on how to measure, traceably and accurately, absorbed dose in an external beam, in particular absorbed dose to water, whether for gamma ray, x-ray, LINAC, electrons, or protons, whether using an ionization chamber in air or in water phantom.

- In 2018, the AAPM Task Group 319, "Guidelines for accurate dosimetry in radiation biology experiments," was established; several of its members attended CIRPER. The group is expected to produce two reports, each geared towards a different audience. A brief report intended for radiobiologists will focus on the importance of improving the standardization of dosimetry in radiation biology experiments and providing irradiation information when reporting results. It will stress the importance of consulting and coordinating with medical physicists when making decisions about dosimetry. A second, more comprehensive report will provide guidance specifically to medical physicists on how to manage dosimetry for radiation biology experiments including calibration and relative dosimetry considerations. This report will focus on non-clinical research. While final drafts of these reports have yet to be published, it is expected that one of the recommendations is requiring a standard set of parameters as part of all methodological discussions.

IV. Challenges and Solutions to Standardization of Reporting and Protocols Identified

There were a number of challenges and solutions discussed regarding how to practically achieve the goal set at the outset of the meeting. All of them have been outlined below. It should be noted that the limited availability of dosimetry comparison programs was a challenge that was cited multiple times throughout the meeting. Unfortunately, there was no clear solution. Additionally, the involvement of manufacturers and industry was discussed in depth as an important solution to all of the other challenges discussed. For topics other than the aforementioned ones, a clear challenge and solution was covered (see below).

Limited Availability of Dosimetry Comparison Programs

Participants recognized that a sizable number of researchers and institutions conducting radiobiological studies have limited knowledge of dosimetry and limited access to medical physics resources. Many institutions do not have professional dosimetry staff available. Therefore, researchers must use existing calibrations, the accuracy of which depends on many factors, including the rigor with which quality assurance protocols are followed. At best, absent medical physicists support their team and researchers must rely on the assistance of a Radiation Safety/Security Officers (RSOs) to perform dosimetry measurements. Given the wide range of responsibilities that RSOs fulfill within an institution, and the different sets of skills and training that might qualify them for these responsibilities, this option is not optimal either.

Participants also had the opportunity to gain experience and discuss how NIAID's RNCP is implementing an effort to assess and harmonize dosimetry across their funded portfolio via a contract mechanism with an expert independent third-party dosimetry resource (University of Wisconsin). Typically, phantoms with imbedded dosimeters are sent to participating facilities with a detailed protocol for the irradiation(s). After exposure, the phantoms and dosimeters are returned to a facility that has NIST- traceable standards for analysis and comparison to expected results. This data can demonstrate the level of concordance among facilities as well as between irradiators within each facility and the true expected dosimetry values.

This NIH/NIAID effort has increased awareness of the need to publish more comprehensive details of irradiation conditions and procedures used in experiments conducted by the radiation biologists, with a goal of making the work more accurate, precise, and reproducible across institutes. However, this type of comparison program service is limited.
Besides NIH – that solely supports grant recipients – only MD Anderson Cancer Center in Texas currently provides this service. This leaves institutions to rely on their own internal resources to validate their own dosimetry and comparison programs, which presents a wide range of challenges particularly for smaller institutions.

Industry Engagement- Manufacturers can help

Industry participants from several x-ray manufacturing companies expressed interest in continued engagement with users of x-ray devices to better support the transition process beyond the early phases of installations. Industry representatives agreed to:

- Publicize guidance on their websites and user manuals, once consensus on standards for dosimetry, field geometry and other parameters has been established.

- Consider including the CIRPER "Recommended Dosimetry Parameters" table as part of

the vendor manual and as a decal featured prominently on the machine.

- Determine to either increase the training provided to their users and/or amend current training to emphasize reporting standards for researchers. Training could be provided on site during annual or preventative maintenance visits, or through remote learning. One possible model is to train employees within each institution to serve as in house support staff or "coaches."

- Additional recommendations to the vendor community /included:

- Provide routine calibration and quality assurance as part of a maintenance and warranty contract.

- Compile a list of common Frequently Asked Questions and lessons learned by users. This could include information about best practices in sample set-up, such as information about
  - sample and shelf placement
  - use of racks, filters, collimators
  - estimating scatter (which would help eliminate a typical user error)

- Provide more detailed information on tube voltage and filtration or half-value layer.

- (HVL) would provide additional information to end users.

- Develop a user-friendly manual with "recipes" (like pre-sets on microwaves) for each x-ray irradiator model.

- Offer "remote access" to solve user technical difficulties specific to required reporting parameters.

Additional Topics Discussed: Challenges and identified solutions.

A. Subjective Reviewer Judgements

Challenge

CIRPER participants agreed that coming to a consensus about standards was only part of the problem. Commitment to enforcing standards was equally important, and research journals, along with funding agencies, played a critical role in this enforcement.

Participants noted that in the past research journals have resisted creating requirements for the reporting of methods. Moreover, expectations were uniformly low. Instead, journals rely primarily on reviewers' judgements when deciding whether the methods discussion provided was sufficient. Sometimes reviewers from different disciplines are asked to comment only on specific sections, as a result, it is perhaps not surprising that specialist journals provided significantly more details about dosimetry and experimental set-up.

Solutions

- Journals adopt a set of baseline expectations that include instructions for how to describe the experimental set-up, dosimetry as well as how to report uncertainty. These could appear as a table within the journal's guidelines for submission.

- Provide clearer guidance to reviewers about evaluating the reporting of methodologies.

- Seek a broader range of specialists to review the methodology sections: radiation biologists, medical physicists as well as statisticians.

- Provide links to examples of methodological descriptions that meet the journal's expectations.

- Encourage the editorial boards of recognized journals such as the publications of Radiation Research Society (RSS) and American Association of Physicists in Medicine (AAPM), to collaborate more closely in discussing and disseminating irradiation protocols to support their adoption

B. Complexity of Descriptions

Challenge

Methodological descriptions can be extremely complex, involving highly specialized terminology and statistical knowledge. Describing experimental protocols clearly and succinctly can be a daunting task. To comply with limitations on page and word count, it is customary practice to focus on listing the variables while leaving out the "recipe" – the process crucial for obtaining the results on which the findings are based. And yet, this "pre-producibility" is crucial for the reproduction of results and establishing comparability.

Solutions

Submit protocols to centralized database, where they would be categorized, labeled, and listed. When reporting on their experiments, researchers would cite and provide links to the protocols submitted. Determine details regarding this database such as where it would be housed and how it would be maintained.

Create a glossary for the terminology that should be used to describe measurements and delivery of dosimetry, field geometry, and other aspects of experimental methods and set up. Adoption by funding agencies could encourage editorial journals to follow suit.

C. Calibration Reporting

Challenge

Participants also noted that published studies rarely noted whether the measured dose reported was based on irradiator calibration or the target dose delivered to the cells or small animals.

Solution

There was widespread agreement that reporting the calibration dose is insufficient; the target dose is what should ultimately be communicated by investigators in publications. In addition, there was a sense that quality assurance practices, including a schedule for device calibration, should also be noted.

D. Absence of Diagrams and Illustrations

Challenge

Along with limitations on page and word count, there is a limit on the number of illustrations that can be submitted with any given article. Authors tend to prioritize graphs that summarize their results.

Solution

There is a compelling argument to be made that descriptions of the experimental set up, including field geometry, could also be enriched by the inclusion of diagrams and illustrations.

E. Uncertainty Budget

Challenge

For researchers to conclude that an x-ray irradiator can replace a Cs-137 irradiator, they need to decide on the level of uncertainty, often referred to as "uncertainty budget" in the dose received by limiting the sample to be irradiated. Most radiobiologists focus more on ensuring reproducibility (precision) of dose across a study group than on accuracy of dose (traceability) because their main desire is for their biological endpoint data to have minimal size error bars. However, accuracy of dose should be equally important if they want to validate or compare their data to other studies.

Some applications may tolerate +/- 20% in the delivered dose or non-uniformity in dose across specimen, while others only +/- 5%. However, there are large biological differences that are influenced by genetic sensitivity. In addition, there are environmental factors that change the background response to radiation. If a researcher is trying to achieve a molecular response, the data suggests that there are huge biological differences between tissues, between species, between strains and cell types, and that biological dose response variability can be large (e.g., seven main uncertainty components can easily add up to errors of 25% or more).

Solution

This supports that researchers may benefit from the dosimetry comparison programs and the development of standards.

F. Funding Concerns

Challenge

Presenters indicated that funding agencies do not require a specific radiation source or modality. This is also the case for ORS's Reduce mission, which encourages the adoption & development of non-radioisotopic alternative technologies on a voluntary basis. Those decisions are left up to researchers to make based on the requirements of their research programs and resources available to them. If an institution or researcher decides to switch to x- ray technology, most participants indicated that they received a combination of external federal assistance and internal institutional funding (operational monies or competitive grants) to make the technology change. However, researchers often must repeat experiments with the x-ray technology to obtain baseline data that demonstrates comparable results. These dosimetry comparisons may not be covered by institutional funds and are typically taken from limited research grants. Given that these costs were not anticipated in the original requests for funding, they can pose a strain on research budgets.

Solutions

More can be done to bridge the information gap between granting institutions and grantees through better guidance and funding for conducting comparability studies. Government agencies and grant-making organizations should consider funding more comparative evaluations to assist researchers in making the technology change and to remove the financial burdens required by the change in technology modality. Creating a database of comparability studies that can be accessed by researchers considering a transition away from gamma technologies would have a significant and positive impact on facilitating the adoption of alternative technologies.

G. Institutional Limitations – Establishing multidisciplinary teams atmaller institutions

Challenge

Multiple stakeholder involvement is needed to establish comparability protocols and dosimetry parameters. Radiation equipment and methods are increasing in variety and complexity. Machine-to-machine variations also complicates efforts to align irradiation protocols across devices. Given the highly specialized requirements for accurate radiation dosimetry, biologists and physicists must work together in the design, execution, and interpretation of radiobiology experiments. However, this is often a challenge for smaller institutions who have limited specialized staff and fewer radiation physicists who are trained in the unique characteristics of the equipment.

Solution

In an optimum set-up, the cooperation between the biologist and physicist can ensure an efficiently designed experiment that uses appropriate equipment with reference to establish protocols as well as appropriate interpretation of the observed results, both in the initial design of the experiment, but also in training and reviewing of experiments. Statisticians also need to be involved to determine the required sample size of the experiments, the accuracy and precision required by a given experimental design and the methods needed to achieve these.

H. Navigation and Application of Calibration Standards

Challenge

To assist in standardization of calibration methodologies, several referenced protocols have been published by national and international organizations. It was noted that many of these standards often pose challenges to navigate and do not directly correlate to routine radiobiology experiments involving cell and small/large animals.

Solution

A key recommendation was that the research community should determine where gaps exist in written standards and protocols and publish standards to fill those needs. As noted in earlier sections, researchers should make a distinction between irradiator calibration, calculated using a NIST-traceable detector, and target dose delivered to the cells or small animal. Ideally, a smaller detector - a TLD, OSLD, film, plastic scintillator, pinpoint ion chamber, etc., should be used to measure the dose to the animal or animal phantom under experimental conditions. It is this dose that should be communicated by investigators in publications.

V. Recommendations

The NNSA/ORS should consider the following recommendations as key takeaways from the CIRPER:

- Adopt the CIRPER Table of "Recommended Parameters for Dosimetry" as the standard for ORS funded research.
- Encourage the abovementioned Table's adoption by funding agencies, through targeted outreach.
- Conduct targeted outreach to research journals in the preclinical irradiation fields to encourage compliance with existing practices and protocols, such as those proposed by CIRPER and those forthcoming from AAPM TG 319.
- Finalize CIRPER Methodological Framework, consisting of a glossary of common terms that should be included in methodological discussions, along with examples of best practices in the documenting and reporting of protocols and methods.
- Facilitate the drafting of an "Op Ed" or consensus letter based on this report's recommendations. This document could be sent to editorial boards of key research journals, professional associations, key funding organizations and x-ray manufacturers.
- Explore whether a formal dosimetry comparison and support program needs to be implemented. Such a program would not only expand the capability to harmonize dosimetry and calibration among institutions**,** but potentially provide reach back capabilities in particular for smaller institutions that have limited technical and personnel resources to set up new irradiation models.
- Work with manufacturers/industry to help irradiator users meet the reporting requirements through additions to vendor manuals, training, etc.

- Engage with other relevant funding agencies, standards bodies, and journals and explore how their program priorities can support the long-term transition to non-radio isotopic technologies, through education and outreach, publishing, procurement or grant-making, standards development, and research and development processes.

The NIH should consider the following recommendations as key takeaways from the CIRPER:

- Explore how to extend the benefits of NIAID's RNCP dosimetry harmonization program to research teams and laboratories from institutions with limited resources.

- Consider hosting a public forum – webinar, conference session, or the like -- to publicize the findings of the NIAID's RNCP dosimetry harmonization program and its adoption of the CIRPER Methodological Framework.

The Radiation Research Journal, Public Library of Science (PLOS) and other leading editorial boards should consider the following recommendations as key takeaways from the CIRPER:

- Include the CIRPER Methodological Framework or similar expectations as part of the guidelines for publication as well as in the guidelines for reviewers.

The National Institute of Standards (NIST), the NCI and other federal agencies funding radiation research should consider the following recommendations as key takeaways from the CIRPER:

- NIST should consider reconvening its 2011 workshop, revisit its recommendations and use the forum to support formalizing the CIRPER methodological recommendations.

- NCI should consider incorporating the CIRPER methodological recommendations into its funding requirements to improve the consistency and reproducibility of research it supports.

Methodological Framework[1]

*Asterisk indicates requirement

Device Parameters
*Manufacturer and Model
*Energy (kVp)
*Time (mAs) ***or*** Dose Rate
*Absorbed Dose to Water at midline ***or*** Device calibration details (air kerma)
*Filters (Materials and Thickness)

Experimental Setup
*Field Size
*Distance from source and orientation
*Sample description
*Sample Shielding
Sample Holder
Other Sources of Scatter

Calibration Details
*Frequency
Energy at which dosimeter was calibrated
Calibration Detector (Make and Model)

[1] The framework below only reflects the consensus at the in-person CIRPER meeting. Since then, there has been conversation (via email) regarding edits and changes to the framework amongst the participants and organizers.