Becoming a Researcher: Grants and Budgets, Reviewing and Writing Papers, and the Institutional Review Board (IRB)

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Grants and Budgets

How to Write a Successful Grant

One of the basic tenets of academic medicine is original contribution of new knowledge, which will advance our field of Radiation Oncology, generated through research activities. This applies to the entire spectrum ranging from basic laboratory, translational, clinical trials, quality of life, health economics, imaging/technology, artificial intelligence, to education research activities. The conduct of research requires resources, such as supplies, personnel, and services, which need funding. Fortunately, our system has multiple sources for such funding, ranging from clinical departmental support, philanthropy, industry, to peer-reviewed agencies. Each source has slightly different criteria, but the basic principles to capture these funds successfully are fundamentally the same.

The essence of any successful request for funding is the compelling premise as to what new knowledge will be created by your proposal, and how will it impact our cancer patients? Then, as the hypothesis is being formulated and strengthened, the research proposal needs to be organized in a scientifically logical manner to address the overarching hypothesis. Commonly, there will be three major aims, each with sub-aims, which will either prove or refute the hypothesis, contribute insight into the process under investigation, and advance the state of knowledge in the chosen area of enquiry. The major aims need to be interrelated, but they cannot be

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constructed to be interdependent, such that failure of one aim would lead to the collapse of the entire premise. As an example, if one were to examine the role of cyclins in altering radiosensitivity of human cancers, and one of the aims is too narrowly focused on a specific member of that pathway, and is proven to be irrelevant, then one might conclude cyclins play no role in affecting radiation response. Hence, it is important to design the aims thoughtfully to address the scientific hypothesis appropriately, but not so restrictive or dogmatic to lead to a dead end.

In order to convince the reviewers that the chosen area for investigation warrants further investigation, the provision of preliminary data is key and critical. Hence, during the preparation of a grant application, the investigator needs to plan carefully as to what pieces of evidence would be necessary to compel the reviewer (and the applicant him/herself) that the stated hypothesis is worthy of further enquiry. One way to think of this situation is from an investment perspective. Research dollars are precious; the reviewers need to decide that among the 10 grants they are currently reviewing, which one or two applications would they recommend investing, for the highest return on investment ("ROI")? The strength of the preliminary data is crucial in convincing reviewers to advocate for specific grants; these data need to be compelling and intriguing, hence the planning of experiments to generate the preliminary data is definitely worthy of significant time and energy expended by the applicant during this phase of grant writing.

Oftentimes, we are asked as to how much experimental details are necessary to include in a grant application. In general, young investigators would need to provide more details than a more experienced applicant [1]. The reviewer needs to be convinced that the applicant has the scientific know-how to successfully execute the proposed studies, particularly for complex and novel experiments (e.g., in 2020, it might be single-cell RNA sequencing). It is helpful to refer to previously published methodologies by the applicant to save space, or have a letter from a collaborator with expertise in the proposed methodology. On the topic of letters, as a new investigator, it is important to demonstrate independence from his/her previous mentor or supervisor. In fact, oftentimes, it would be prudent and valuable to have the previous supervisor provide such a letter specifying independence. This can be clarified by the previous supervisor indicating that a specific cell line or mouse model has now been gifted to the current applicant, or there is an agreement that the proposed area of enquiry will only be pursued by the younger investigator and no longer of interest to the senior supervisor.

One very important aspect of the design and construction of aims is to provide a section at the end of each aim, as "Anticipated Outcomes and Alternatives." This section refers to interpretation of the anticipated data, with an alternative plan briefly described, if the anticipated outcome were not observed. The value of providing this section is to first focus the reviewers' attention on the scientific objective of the proposed aim, and interpretation of the anticipated data. The second value of providing an "alternative" is to illustrate the scientific open-mindedness of the applicant; scientific roads are rarely linear, it is the pursuit of the unexpected, that often leads to the most exciting discoveries!

Finally, success comes to those who are best prepared, as summarized in publications on this topic [2, 3]. In addition to the planning and generation of preliminary data, it is critical to start writing drafts of these grants months ahead of the deadline. Not only does this allow editing the proposal as a function of newly generated data, but also allows feedback from mentors or colleagues prior to the final submission, particularly for young investigators. In some research-intensive institutions, there are internal grant review processes prior to submission, which are extremely valuable, and have been demonstrated to increase success rate of research grants, as one would expect. If such opportunities are available, they should definitely be capitalized, for obvious reasons. Persistence and passion are critical; if one is convinced of the value of a particular line of enquiry, even if not initially successful, persistence will pay off. Many of our scientific icons in oncology, such as Judah Folkman and John Dick, have both described personal difficulty in capturing external funding in their earlier years, since reviewers were averse to investing in untested hypotheses of tumor angiogenesis or cancer stem cells. It took them years to convince grant panels that these entities actually exist and are relevant – the rest is history!

Budgets

The easiest way to assemble a budget for any research proposal is to read a budget from a previous grant application of a similar nature, for the same funding agency. This is where networking and mentoring are key and critical since these mechanisms allow access to such previous applicants. The major elements of most research budgets include personnel, supplies, services, and "others." Each agency might have slightly different rules in terms of who can be funded, for what component of time, etc. It is critically important to read and follow the rules stated, and if they are unclear, contact the agency directly to ensure there is a clear understanding of the expectations in terms of documentations or other requirements.

For personnel requests, it is important to justify each individual's role in contributing to the research project. The justification does not need to be detailed to the minute or hour, but must make sense to the reviewer. For example, if there are very few mouse experiments proposed, yet there is a request for a full-time animal technician throughout the entire duration of the grant, reviewers will start to question that specific request; thereby risking reduction of that specific budgetary request. It is also helpful if specific individuals are identified (e.g., an actual name), which will strengthen the justification that such a person with appropriate skillsets has already been hired for that specific role (e.g., technician, graduate student, or postdoctoral fellow).

Similarly, requested supplies and reagents also need to be justified. For a first-time applicant, reading a previous budget would be critical to learn the appropriate

amount of such requests, and strategy for justification. If a piece of equipment is requested, a quote from a vendor would need to be included; one needs to be thoughtful since some agencies mandate that once funded, that piece of equipment MUST be purchased from the original vendor, so it behooves the applicant to ensure that the best vendor has indeed been selected for that hardware.

If there are animal (e.g., mouse) experiments being proposed, the number of mice MUST be justified so statistical expertise would be required for such justifications. Clinical or translational studies would of course require biostatistical expertise to justify cohort size of groups of patients or number of samples. With any type of complex omics-data, bioinformatics expertise to assist in the design of such studies as well as their analyses are of paramount importance. Finally, with clinical studies, please remember to include underrepresented minority (URM) groups, and if such populations cannot be included, that must be clearly justified.

Finally, many funding agencies seek partnerships (e.g., with industry) in order to amplify the impact, or expedite commercialization efforts. Again, it is critically important to pay attention to the eligibility criteria (e.g., sometimes, donors or philanthropy can serve as partners), which might be an alternative to an industry partner, although each situation would be different and unique. These partnerships occasionally can be complicated by the need for data transfer agreements, protection of personal health information (PHI), or sharing of intellectual property (IP). By all means, one should not avoid these opportunities, but additional vigilance would be required; ideally, the host institution has offices with such expertise to facilitate such partnerships, which oftentimes can be extremely fruitful.

Once a grant is obtained successfully, this is the moment for celebration, and breaking out that bottle of champagne! Unfortunately, this moment of elation usually only lasts a few days, followed by the realization that now the hard work has just started, new data must be churned out, in preparation for the next grant. This is the true challenge of this academic path – running an independent laboratory is essentially like running a small business. One becomes an entrepreneur (like it or not); one needs to be opportunistic in pivoting to areas where there are sources of funding (e.g., breast or prostate cancer). One needs to be able to develop a budget skillfully to leverage the precious research dollars already captured. As an example, if there are opportunities for graduate students to obtain scholarships, such awards must be capitalized for the students – creating obvious win–wins! Developing effective collaborations is absolutely necessary in this competitive world of science. Just as no business can be successful *in silo*, neither can research. From a research budget perspective, if there is a neighboring collaborator with whom a research personnel (e.g., graduate student, animal technician) can be shared, then these are the partnerships, which will be of mutual benefit. Pursuing an academic career and running a successful laboratory program are decisions, which I have made early in my own career, that I have found to have been immensely gratifying. I would not have traded this for any other choices, and watching my graduate students and other trainees who have now carved out their own careers successfully brings me boundless joy and satisfaction.

Reviewing a Manuscript

Peer review is foundational to high-quality scientific advancement of the field of radiation oncology. Published literature becomes a permanent scientific record that will be referenced by future studies. Publications also help set the agenda for further areas of exploration. Peer review relies on a principle of reciprocal altruism [4]. There is often no recognition or monetary compensation and it costs the reviewer time and effort; nonetheless, it is a necessary responsibility for all researchers to help guide what scientific content gets published [5]. The quality of peer review depends on both the regularity of engagement of altruists and the contributions of each altruist in providing careful, constructive, objective criticism [4].

We acknowledge, however, that most of us have never been trained on how to perform peer review [6]. Engaging in peer review activities, reading the comments of other reviewers, and seeking guidance from researchers actively engaged on editorial boards of journals may be helpful to develop these skills [7]. Additionally, this section focuses on some key items to attend to as a reviewer to help facilitate and encourage your involvement in this important activity. There are many types of manuscripts that are submitted to journals for publications. We will focus on the peer review of original research articles (i.e., those articles publishing empirical findings).

Preparing to Review a Paper

Prior to accepting a review, all potential reviewers should ensure that they are free from conflict of interests with the authors of the paper and equipped with sufficient expertise to perform a quality review [6]. Without these two basic elements, the reviewer should decline and await future opportunities where they may be better suited to engage as a peer reviewer.

Without obvious conflicts of interest, reviewers may still be affected by some common biases. For example, for a given paper, if the authors of a manuscript are well known or from well-recognized institutions, there is often an increased rate of acceptance of those papers by reviewers [8]. One way to decrease this bias is blinding. Typically, authors are blinded to the reviewers (single-blind), but in double-blind review, reviewers are also blinded to the authors. This has been implemented by some journals to reduce three types of biases that result from knowing the manuscript's authors and affiliations: the Matilda effect (bias toward valuing contributions from males over females) [9], the Matthew effect (crediting collaborative papers mainly to the well-established researchers on a paper) [10], and the famous institution effect [8, 11]. In absence of a double-blind review process, we hope that awareness of these effects may better help you avoid these tendencies and achieve objectivity in your reviews. With the right mind set, you can now begin the review!

The Beginning and End

Every paper is constructed with a beginning and an end. It should start with an introduction that includes two to three paragraphs providing context and support for the hypothesis and goals of the study, and end with a discussion section that reviews and summarizes the study findings in the context of the greater literature [7]. Together, these sections should communicate the originality and importance of the results. Originality could come in the form of a conceptual, analytical, technological, or translational advancement in the field. Discussing the timeliness of the article results in addressing an urgent need, and/or direct implications on clinical practice are critical to include. As a reviewer, evaluating the logical flow of ideas and writing will help the investigator communicate their findings clearly and maximize their impact. Suggestions could include expanding or limiting the text in these sections to address the above items or improve the succinctness of their manuscript.

Methods

Next, reviewing the methods of a study is foundational. The design and methodology need to be able to test the proposed hypothesis for the results to be reliable and meaningful. The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network has established reporting guidelines for different types of health research studies that could be used as a checklist to understand if a study has been designed and conducted in a manner that is acceptable to the health research community [12]. For example, Consolidated Standards Of Reporting Trials (CONSORT) guidelines can be used for evaluating randomized trials, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies, Standards for Reporting Diagnostic accuracy studies (STARD) for diagnostic or prognostic studies, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for systematic reviews and meta-analyses. An additional way to assess appropriateness of design would be to evaluate how the manuscript you are currently reviewing compares to other published articles on similar topics in the field. Additionally, registration of prospective trials is recommended by the International Committee of Medical Journal Editors (ICMJE), which helps facilitate transparency, validity, and dissemination of results [13]. The World Health Organization (WHO) has further provided guidance on acceptable registries and trial data that are important to report [14]. Additionally, ethical and safety considerations should be addressed including a statement on ethical approval, if applicable. Further details are discussed in the institutional review board (IRB) section below.

In addition to the above, descriptions of methods should be written to allow for reproducibility [15]. Sample sizes and statistical analyses should be clearly stated and justified. For laboratory science experiments, assays, controls (positive and

negative), and outcomes are important to include. As well, deposition of materials, data, and protocols into accessible databases (e.g., genetic sequence in GenBank) are recommended to further facilitate transparency and reproducibility.

Analysis and Interpretation of Data

A proper study design will facilitate interpretation of data. Some common pitfalls in analysis have been previously described including inadequate controls, indirect comparisons, multiple comparisons, reporting correlation versus causation, p-hacking, and poor interpretation of nonsignificant data.

Firstly, the purpose of a control in a study is to account for effects of an intervention that are unrelated to the research question [16]. Inappropriate controls or inadequate controls can prevent researchers from making certain claims regarding the results of an intervention. Conclusions derived from analysis of a single group is an example where there is a missing second experimental control group [16]. Should this be the case in a manuscript, limitations in the study should be stated as well as a rationale as to why a control group was not included.

Making inferences without performing a statistical analysis has been another commonly identified pitfall [17]. For example, Makin et al. [16] describe a scenario whereby there is a significant effect measured before and after an intervention in one group, but a nonsignificant effect in another group. Does this mean that there is a greater effect in the former group? To make a firm claim, a statistical analysis must be made between groups rather than in each group individually. Additionally, in the scenario of many comparisons taking place, an astute reviewer should note the number of independent variables measured and the number of analyses performed, and recommend correction for multiple testing if this were not already addressed by the authors [16]. Otherwise the study could suffer from an increased risk of a Type I error (false positivity) [18].

Confusing correlation with causation is another classic misstep by investigators [19]. Reviewers should suggest rewording of claims if no interventional experiment was performed to help facilitate clarity of results. Randomized controlled trials have long been perceived as an approach that is amenable to causal conclusions compared to other types of clinical studies [20, 21].

Furthermore, p-hacking is a bias in the literature that occurs when there is selective reporting of significant results [22]. P-hacking has been described as an issue particularly when studies are not registered or preplanning on an analysis is not completed [23]. In these scenarios, it is recommended that the selection of variables to analyze be justified in the text. In the vein of p-value interpretation, another issue is that nonsignificant p-values are often disregarded or assumed to have no effect [16]. However, insufficient evidence to conclude an effect is not necessarily the same as providing support for a null hypothesis. In these scenarios, suggesting additional testing (e.g., Bayesian statistics [24] or equivalence tests [25]) may help the author decipher the difference between those two possibilities.

Lastly, knowing the limits of your own knowledge is very important. Commonly, researchers are asked to review a paper based on their expertise of specific subject matter. Nevertheless, the statistical analysis can be a crucial part of the paper and your role as a reviewer could be recommending that a manuscript to undergo additional review by a statistics expert [5]. Greenwood et al. [26] have put together a helpful checklist of general questions to ask to assess the methods, presentation, and interpretation of data; this framework can help decide whether an additional statistical review by an expert in the field may be helpful.

Understanding Publication Rules

Some additional strategies to assist in the peer review process in a timely fashion is to respond to peer review invitations quickly [27], complete your review as soon as possible, and take the time to familiarize yourself with the publication requirements. In particular, identifying any missing elements or formatting errors can help streamline the publication process and reduce time to publication [7]. For example, understanding the number of tables or figures permissible by the journal will allow you to comment on the appropriateness of the selected display items in supporting the main message of the article. Additionally, it would help you as the reviewer to provide precise and constructive suggestions on how the authors could incorporate additional main or supplementary figures to support their research claims. Depending on the audience of the journal, you could also suggest how the investigators could improve or tailor their writing to most effectively communicate with the target audience of the journal (e.g., clinicians, scientists, educators, or administrators).

Finally, reviewer comments should summarize the importance of the work being reviewed, the strengths and weaknesses of the study, and major/minor suggestions for improvement. Reviews should be written in a collegial manner [28]. As some have stated, "*you should review for others as you would have others review for you*" [4]. Together, we can work collaboratively to advance the field of radiation oncology through peer-reviewed publications.

Writing and Publishing a Manuscript

Academic radiation oncologists have the duty and privilege to contribute to the advancement of knowledge for our field. A major component of this endeavor is through writing and publishing of manuscripts. Manuscripts can take many different forms. New study results, meta-analyses, comprehensive reviews, and commentaries each have their place in the scientific process. It is of the utmost importance that scientific findings and opinions are communicated in a clear and balanced manner when disseminated to the research community. Equally important is execution

of a plan for manuscript writing and strategy to get manuscripts published in an appropriate venue. This section will address important topics in scientific writing, including tips for effective communication, collaborative manuscript writing, and submission strategy.

How to Communicate Science through Writing

Writing skills do not always come naturally to clinicians and scientists. High-quality formal instruction in scientific writing is hard to come by during postgraduate training. Instead, it is often left to the individual to teach oneself the tricks of the trade of effective scientific writing. Authors must balance many competing demands when writing manuscripts. They must adhere to rigid formats without seeming dry. Technical details need to be conveyed, but the message should be accessible to a broader audience. While this can seem daunting, a few guiding principles can ensure the maximum possible impact of scientific manuscripts.

Authors should write with the reader in mind. By taking into account how manuscripts are read, authors are better able to communicate their findings as opposed to simply presenting results [29]. A focus on clarity, narrative structure, and creativity improves the impact of scientific writing. The first-person active voice is more direct and easier for the reader to follow. Appropriate use of punctuation and conjunctions can help the reader navigate the meaning of otherwise complex concepts. If executed effectively, the reader will come away with a clearer understanding of the author's research, which will ultimately lead to more citations and wider recognition in the field [30].

The reader expects to encounter information in a certain order. Forcing the reader to seek information in unexpected locations introduces unnecessary barriers to straightforward interpretation. This pertains to multiple aspects of manuscript writing including data presentation, manuscript organization, paragraph structure, and sentence structure [29]. Clear presentation of experimental data within manuscripts is critical for proper interpretation. Likewise, when a manuscript is structured with sections for introduction, methods, results, and discussion, misplacing components in the wrong section increases the workload for readers.

Appropriate paragraph structure can be challenging for beginning writers. Effective writing creates clear divisions between paragraphs. Paragraphs should be able to stand alone to communicate a point or group of points around a common theme [31]. The opening sentence of each paragraph gives an overview of the theme to be explored in the remainder of the paragraph. If multiple points are made in the same paragraph, it should be apparent how they relate to one another.

Proper sentence structure helps the reader find the desired information where he/she expects it. For instance, readers expect to find the subject and predicate in close proximity in the sentence. If, instead, the predicate is placed at the end of the sentence far away from the subject, the reader is forced to do extra work to link the two. Other important considerations in sentence structure include where the topic of the

sentence is introduced (*topic position*) and where the emphasis is placed (*stress position*) [29]. The *topic position* provides the reader with context that is necessary for interpreting the point of the sentence. The reader expects the topic of a sentence to appear at the beginning, so any deviation from this can lead to misinterpretation by the reader. Conversely, the reader expects the emphasis to appear at the end of the sentence. The stress position should provide the reader with closure with respect to the point made by the sentence. In general, the topic position includes information that the reader is already familiar with, whereas the stress position introduces new information that the reader is meant to take away as important.

To summarize, scientific writing is among the most important tasks of an academic radiation oncologist. A useful framework for guiding authors is to focus on assisting readers interpret their writing. To this end, we find it helpful to read one's own writing after stepping away from a draft for a period of time. This allows an author to approach the writing fresh and from the reader's perspective. Authors can employ rhetorical devices that assist readers to link concepts across sentences and paragraphs. Parallel sentence structures can guide the reader by emphasizing common points. Special attention should be placed on transitions between sentences and paragraphs to guide the reader through the manuscript. With these concepts in mind, authors should feel confident that they can communicate their research findings to a broad audience of clinicians and scientists, thus augmenting the impact of their academic product.

The Abstract

The abstract is the most important means for efficiently communicating the content and impact of a scientific study. It is often the basis on which the work is judged by journal editors and other audiences [32–34]. Many scientific journals have specific guidelines for abstracts that must be abided. Some require structured abstracts with distinct headers (e.g., background, methods, results, and conclusions), but even unstructured abstracts should follow a similar formula. The most effective abstracts summarize abstract the study rationale, methods, and results, and then place the findings in a broader context to highlight the overall impact.

Bear in mind that the readership of the abstract often comes from a broad range of disciplines. Thus, emphasis should be placed on keeping the abstract accessible. To deliver the primary message of the manuscript in a clear and concise manner, authors should use present tense and pay close attention to sentence structure [35]. In place of long compound sentences, shorter sentences are generally easier to follow. Technical jargon and excessive use of adjectives and adverbs should be avoided if possible.

The reader abstract should come away from the abstract with a clear understanding of the impact of the study. This can be achieved by having a consistent message reiterated in the background and conclusion of the abstract. Alignment with keywords used throughout the manuscript can also be helpful. Finally, authors should

avoid words that introduce vagueness or that minimize impact. Direct and confident language will help the reader take away the most important points of the manuscript.

Data Presentation

Science is driven by data. It is critical that data is presented in a manner that can be appropriately interpreted by the reader. In scientific manuscripts, data can be presented within the text of the results section as well as within standalone display items (i.e., tables and charts). Authors should be cognizant of readers who consume information in different manners. Some readers focus primarily on the text of the manuscript, whereas others focus primarily on the display items. Therefore, a robust manuscript will be able to communicate the major findings in both forms. This layer of redundancy also helps to reinforce important messages of the manuscript.

Display items (with their associated captions) must be able to stand alone in conveying the research findings. Jargon and abbreviations (if necessary) should be explained in the caption or footer. For tables, information that is familiar to the reader should appear on the left, and new information introduced to the reader should appear on the right. This organization of data aligns with the expectation of readers and allows for ease of interpretation. For graphs, titles of axes should be labelled, and the number of observations and results of statistical tests should be specified. Axes should be scaled appropriately without distortion.

As you prepare your data, you may wonder which elements need to be made available to peer reviewers. This depends on the nature of the data (clinical vs. non-clinical, proprietary, consent) and any restrictions on its use. It is important to understand policies of specific journals with regard to data publication. The academic mission depends on the veracity of published data and honesty of its analysis and interpretation. By adhering to the above principles, authors can avoid misleading presentation of data. Data transparency is garnering increasing attention across all health research fields [36], leading many journals to require datasets and analysis methods to be made available to the research community at the time of publication. This movement underscores the importance of clear and accurate communication of science across disciplines and highlights the need for specialized training on this topic for academic radiation oncologists.

Strategy in Manuscript Writing, Submission, and Peer Review

Before embarking on writing a manuscript, plan ahead for each step of the process, including: (1) data collection and analysis, (2) collaborative writing, and (3) manuscript submission. Strategizing for each of these steps will help ensure a smooth process and ultimate success for journal publication.

For any manuscript that includes primary data, consider how data is to be managed during manuscript preparation as well as after publication. A data management plan ensures that collaborators have access to and agree upon the main data elements and their use [37]. Ideally, the plan should be put in place prior to or early on during the writing process if not beforehand. If there are specific requirements for data handling and publication by ethics boards or funding agencies, this should be explicitly addressed in the plan.

The vast majority of manuscripts in our field include multiple authors. Collaborative manuscript writing has never been easier due to digital platforms specifically geared toward this purpose. Despite the technical ease, collaborative manuscript writing can still present some delicate issues. To avoid confusion, it is best to agree on authorship criteria and order before manuscript writing commences [38]. All authors must contribute meaningfully to manuscript writing and/or supervision, and lead authors may have extra responsibilities in drafting the manuscript, adhering to timelines, and assigning tasks to coauthors. While there is no singular approach to collaborative manuscript writing, the most important principle is transparency and open communication between coauthors, as without this, misunderstandings can lead to disagreements and conflict.

The manuscript is written, and you are ready for submission to journals. While this may seem like the end of the process, publishing original research in peer-reviewed journals has become increasingly complex. There are more journals than ever, so selecting the appropriate journal for the manuscript can be challenging. In addition to the scope and audience of the journal, one must consider article format, journal impact factor, listing on public servers, open access options, and author processing charges. Some journals have formal mechanisms for pre-submission inquiry to gauge the editor's interest, which can be useful even before the manuscript has been finalized for submission. Preprint server submission is increasingly popular, and some journals even have their own preprint servers for articles undergoing peer review. The decision to post a preprint may depend on many factors including the desire to create a public record of ongoing research or the need to cite the work for grant applications [39]. Once the appropriate venue is selected, include a concise cover letter to highlight the importance of your work. After feedback from reviewers is received, you will hopefully have the opportunity to respond and resubmit your work. If so, it is highly likely your manuscript will be accepted if you follow some simple rules. Be sure to be respectful in your response-to-reviewers by considering each and every comment and request [40]. Organize the responses in such a way that the editor and reviewers can easily navigate the document. The responses should be self-contained and include any new results that may also be included in the revised manuscript. As with the writing of the manuscript, be sure to engage collaborators and coauthors on the response-to-reviewers when appropriate.

Scientific publishing is a prerequisite for a career as an academic radiation oncologist. The process may seem overwhelming at first, but with practice, you can learn to refine your writing style and become an effective communicator. Thankfully, the cycle of academic activities – from grants to peer review to manuscript writing – is mutually reinforcing such that your skills in one domain will benefit all others.

IRB Process

History of Research Ethics

The origins of medical ethics began as early as the fifth to third centuries BC with the Hippocratic Oath to "*first do no harm*," from which the principle of non-maleficence was derived [41]. Later in 1620, the *Novum Organon* was published by Francis Bacon, introducing the idea that research should be beneficial to society [42]. However, it was the mistreatment of human subjects through experimentation on wartime prisoners during the twentieth century that led to the formalization of a code of ethics. In the 1947 Nuremberg trials (i.e., "the Doctors' Trial"), Nazi physicians and medical administrative personnel were found guilty of murder and torture [43]. This led to the Nuremberg Code mandating research to adhere to certain principles including voluntary consent of subjects, experimental validity with societal benefits, scientifically qualified researchers, avoidance of harm, and proper termination principles [44]. In 1964, the Declaration of Helsinki was created by the World Medical Association, which provided specific guidance on consent in therapeutic research [45]. Additionally, in 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published the Belmont Report. This report outlined three foundational ethical principles including respect for persons, beneficence, and justice, which govern the field of biomedical research [46].

Of note, during the 1940s to 1970s, past human experimentation with radiation occurred in vulnerable persons from lower socioeconomic status, mental retardation, a terminal illness, or from minority groups or prisons. Experiments included feeding or injecting radioactive materials (minerals [47], plutonium [48]) and irradiating body parts (testicles [49], brain [50]) to examine their effects on the human body. These past historical events as well as those mentioned in the previous paragraph necessitate diligence in maintaining high standards of research ethics in radiation oncology.

Principles of Human Research

The purpose of human subject research is to obtain knowledge relevant to science or medicine through systematic investigation. To perform this, careful scientific review is required. In the modern era, Institutional Review Boards (IRBs in the US) and Research Ethics Boards (REBs in Canada) are the research ethics committees that help examine the benefits and harms of the proposed research. These reviews are based on the guidelines in the Belmont Report [46]. Depending on the jurisdiction, US Federal Regulations or Canadian Tri-Council Policy may be additionally considered [51].

Consent in Human Research

One of the foundational aspects of the Belmont Report focuses on respect for the autonomy of participants [46]. This is addressed through research consent, which is the communication and decision-making that occurs between a participant and the researcher proposing the study. This requires the ability for the patient (or substitute decision maker) to understand the information presented, appreciate the benefits and drawbacks of participating, and communicate that decision.

Valid consent includes being informed and deciding voluntarily [52]. Informed consent requires the researchers to communicate in lay language what is required in the study, the rationale behind the requirements, and when the study procedures will occur in addition to responding fully to all the questions posed by the eligible participants [53]. Participants need to be able to weigh the study risks, benefits, and alternatives as they relate to their own values, how the research could affect their quality of life, and be cognitively intact to be able to understand and remember the information during the decision-making time period [54]. Voluntary consent occurs in the absence of coercion or misrepresentation of the study information; the patient must also be capable to perform the steps of the decision-making process described above [55, 56].

The informed and voluntary nature of consent allows for reduction of harm and support of patient's rights in personal decision-making. It is important to note that consent is an ongoing process and should be obtained each time there is a change in a condition, treatment, or if research findings arise that could affect the decision to participate in the research [51]. The consent form documents the consent process, but is not the only aspect of the process [57]. Consent forms are reviewed by IRB/REBs; they commonly outline the investigators involved, purpose of research, potential harms and benefits, alternatives to participation, procedures for confidentiality, reimbursement, sponsorship, and conflicts of interest [51].

In general, a patient is presumed to be capable unless there are reasonable grounds to believe otherwise [58]. However, capacity is not static and can change over time, and depend on the complexity of decision-making. It is the responsibility of the researcher proposing the study to evaluate that capacity. One tool that can help with capacity assessment is the Aid to Capacity Evaluation (ACE) Tool [59]. This tool contains questions that can help decipher if the participant understands the proposed intervention, alternative options, consequences of accepting the intervention, and whether comorbid conditions may affect their judgement [59]. The need for research in vulnerable populations (e.g., children, elderly, mentally ill) or incapable persons have additionally allowed for the introduction of substitution decision maker to act on behalf of a participant in the decision-making process [60].

The Regulatory Environment

International Conference on Harmonization Tripartite Guideline: Good Clinical Practice (GCP) is an ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials of new healthcare interventions for human subjects [61]. Clinical trials are also registered after IRB/REB approval, prior to starting the research activity. Furthermore, there is an International Compilation of Human Research Standards that outline laws, regulations, and guidelines on protection of human subjects across 133 countries [62]. This document discusses principles for drugs and devices, clinical trial registries, research injury, social behavioral research, privacy/data protection, human biological materials, genetic, embryos, stem cells, and cloning.

National and international guidelines on membership of the review board recommend a minimum of five members with expertise to review the research including a scientist, a person with knowledge of the relevant law, and a non-scientist [51]. The research protocol is reviewed for scientific merit and equipoise of the research question [63]. More invasive research will require increased examination at review based on the concept of proportional review [51, 64]. The board will also review procedures of ongoing research including adverse event reporting, annual reports, and monitoring of research (data safety monitoring boards, audits of research documents, consents and results, monitoring of informed consent process) [65].

Conflicts of Interest

There are three types of conflicts of interest in research: conflict of interest, obligation, and bias [66]. Conflicts of interest include personal or financial interests of a researcher that can prevent them from satisfying their obligations to the participant [67]. Conflicts of obligation include two or more moral or legal responsibilities that inherently prevent fulfilment of the other responsibility(ies) without compromise [67]. Conflict of bias are psychological factors that stop a researcher from fulfilling their obligation toward a participant [68].

To manage conflicts of interest, conflicts must first be identified. Conflicts can be actual, potential, or perceived [51]. Once identified, they are to be disclosed to institutions, sponsors, peer reviewers, co-investigators, and/or research participants; this may lead to withdrawal from a role that is creating the conflict [51]. The goal of conflict-of-interest management is to support informed decision-making and participant welfare, ensure transparency and accountability, and minimize legal risks [51]. These principles are outlined by Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) in Canada and other documents [51].

Special Issues Relevant to Radiation Oncology

In the field of radiation oncology, two common questions that are scientifically asked include: "Which is the better dose and fractionation of radiotherapy to administer?" and "What modality of radiotherapy is better?" As part of the scientific process, radiation doses that might lead to inferior disease control could be delivered to a proportion of patients during early-phase dose escalation studies. To reduce harm (or suboptimal benefit), early phase studies should limit the number of such participants and also directly inform the design of later studies. This situation has been described by Koyfman et al. [69], in relation to an example of a Phase 1 trial for stereotactic body radiotherapy for early-stage non-small cell lung cancer directly informing the dose used in a subsequent Phase 2 trial [70, 71]. Additionally, radiation oncology is a highly technological and dynamic discipline with quick adoption of new techniques of enhanced conformality or improved dosimetry. Koyfman et al. [69] remarked that trials comparing older to newer technologies are rare. Due to perceived lack of equipoise, questions on the superiority of new treatments or their cost–benefit compared to standard treatments may not be definitively answered in this field prior to proceeding with novel treatments.

Progress in radiation oncology requires careful consideration of the ethical principles of study design and consent similar to other fields of medical research. In particular, historical ethical violations in human experimentation with radiation in the twentieth century underscore the importance of continued diligence in providing ethical management of research in this discipline.

Conclusion

This chapter summarizes some foundational activities that all academic researchers in radiation oncology will engage in during their careers, including how to write grants, budgets, and manuscripts; review manuscripts; and how to navigate the ethics and review board process. We hope that our overview of these essential topics will facilitate a greater understanding of not only how to perform each of these activities well, but also provides the context on why these activities are important. We encourage you to use this text to help improve your academic research skillsets. Regular engagement in these activities with guidance and feedback on your performance by trusted advisors will help develop a basis for a successful academic career.

For Discussion with a Mentor or Colleague

- What are the critical elements to a successful research grant application?
- How do I build a budget for my upcoming grant application?

- How do I submit an REB application for my upcoming project?
- How do I structure my first major research paper for publication?
- What are the key steps in reviewing a manuscript?

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