WORKING TOGETHE(RT): A UNIQUE NEED FOR AN ETHICAL FRAMEWORK FOR GLOBAL RADIOTHERAPY RESEARCH

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I. INTRODUCTION

The recent recognition of Global Oncology as a formal academic discipline has given birth to innovative research [1]. This has led to an increased push to eradicate exploitative research activities and instead pursue equitable research practices [2]. It wasn't until the 1970s that ethical frameworks made their way into academic global health [3] Ethical frameworks assist clinicians and scientists by providing a plan and approach to balancing moral values in line with research and clinical activities. With the rising burden of cancer seen in low- and middle-income countries (LMICs) but the disproportionate publication of research coming from high income countries, the impetus for an ethical framework of research in global oncology has never been greater [4]. In this commentary, we discuss a brief history of ethical frameworks in global health and introduce a new ethical framework, specifically applicable to global radiotherapy research: TOGETHE(RT).

II. BRIEF HISTORY OF GLOBAL HEALTH ETHICAL FRAMEWORKS

According to the World Health Organization (WHO), global health ethics covers a spectrum of topics that range from the issues surrounding "brain drain," equitable distribution of health services, and proper informed consent for clinical trial [5]. Global health ethics researchers also make a plea in their research to elevate global health education so that students are equipped with the correct framework, that focuses on developing humility, awareness of limitations, and how involvement in developing countries without sustainability can create harm even with the best of intensions [6].

Particularly relevant in global health ethical research is a need to prevent against "parachute" research, exploitative research by high income countries about the state of health in low-and-middle-income countries (LMICs), without proper acknowledgement of expertise and knowledge of local partners [3]. Prior global health mostly focused on communicable diseases [7], however the need for an ethical framework for non-communicable and chronic diseases is paramount [8].

The pursuit of a framework to encompass global health ethics has been complicated and at times political. In a recent editorial, Dr. Cancedda and colleagues describe challenges in this new age of global health. Even with the knowledge that sustainability is critical and that priorities of chronic disease come into focus, funders and donors may be driven by an agenda of favoring disease-specific initiatives that are HIV or infectious focused or opt to provide funding through NGOs and academic institutions rather than the communities themselves [9].

Historically, traditional ethical health frameworks utilized include the preference utilitarianism of Peter Singer, which states that "the more affluent should support the least privileged whenever this can be achieved without costing anything of comparable moral significance." or the cosmopolitanism of Thomas Pogge which suggests that "the manipulation of the global structure has advantaged, and continues to advantage, the affluent whilst disadvantaged the underprivileged and, therefore, perpetuates global inequity" [5]. These theories represent an ethical baseline, but certainly do not encompass the nuances from which a framework in global health ethics for radiation oncology are needed.

III. WHY IT'S IMPORTANT FOR A SPECIFIC FRAMEWORK FOR RADIATION ONCOLOGY

While there has been a push for ethical frameworks in various disciplines of medicine and global health research with select examples seen in Table 1, there is currently no guiding ethical framework in global radiotherapy. In a 2014 editorial published by Zietman [8], the case was made for increased participation of radiation oncology professionals (physicians, medical physicists, dosimetrists, radiation oncology nurses, radiation therapists and social workers at all levels) in improving health and achieving equity globally. Over the years there has been a growing interest (Figure 1) in radiation oncology research in LMICs where radiation presents unique challenges and opportunities to provide cancer care.

Ethics in Global Surgery [10, 11] encompass components including clinical care delivery education and exchange of trainers and engagement in collaborations and partnerships.

Table 1. Examples of frameworks in other global health disciplines

Ethical considerations in infectious disease [12].
Ethics in obstetrics and gynecology [13].
Ethics in Oncology [14-16].

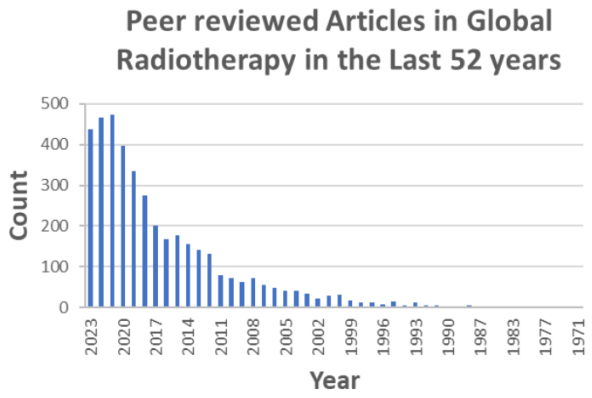

Figure 1. Publications on Global Radiotherapy on PubMed database from 1971-2023

In a comprehensive search of MEDLINE databases, there were almost 20,000 articles containing the phrase "global oncology," that had been published between 1973 and 2023 as shown in Figure 2. Out of these only 517 that contained the phrase "global oncology" and "ethics," and none that contained the phrase "global health" and "radiation oncology" and "ethics."

Figure 2. Publications on Ethics in Global Health on PubMed database from 1977-2023

By creating a framework for global health research, the goal is to ensure that partnerships are equitable and that for research conducted, there is consensus on a compass and rubric for funding organizations like the National Institutes of Health (NIH) or National Cancer Institute (NCI) to grade and assess projects to be applied globally.

IV. UNIQUE CHALLENGES AND OPPORTUNITIES PRESENTED BY RADIOTHERAPY

Radiation oncology as a discipline is unique, involving continuous technical progress as evidenced by innovation that led to adoption of linear accelerators, high dose rate brachytherapy (HDR), low-dose (LDR) brachytherapy, Cyberknife, and relatively newer technologies like proton therapy.

This technological wave, however, is not always universally and equitably adopted. Indeed, global progress requires that collaborative research between institutions is guided by a framework that provides a solution in combating parachute research in global health. There are limited regulations governing consensus in international training of radiation oncologists, physicists, and radiation therapists. There is also a dependency on vendors and supply chains of governments to acquire the appropriate equipment to deliver radiation safely and effectively. This begs the question: in this era of global health research in radiation oncology, how are these decisions being made and by whom?

V. TOGETHE(RT)

The TOGETHE(RT) framework will allow institutions (academic and private), non-profits, and vendors that manufacture and supply radiation oncology equipment, to carefully consider if their research activities and collaborations in less resourced facilities fit into this framework. Our proposed TOGETHE(RT) is shown in Figure 3. framework has the following tenants:

Technology

The first tenant of this framework draws on the specific nature of radiation oncology as a field dependent on the delivery of photon energy and radionuclides. Technology highlights the importance for institutions and industry to ensure that the machines, computer software, and supplies all meet the needs of the provider and patients. As intensity modulated radiation therapy (IMRT) and stereotactic body radiation (SBRT) have made their way into academic medical centers in the Global North, there is an important need to discuss best practices of implementing these tools, globally. Even with current technology, including linear accelerators and CT simulators, regular maintenance and on-the-ground trouble shooting is challenging in many countries.

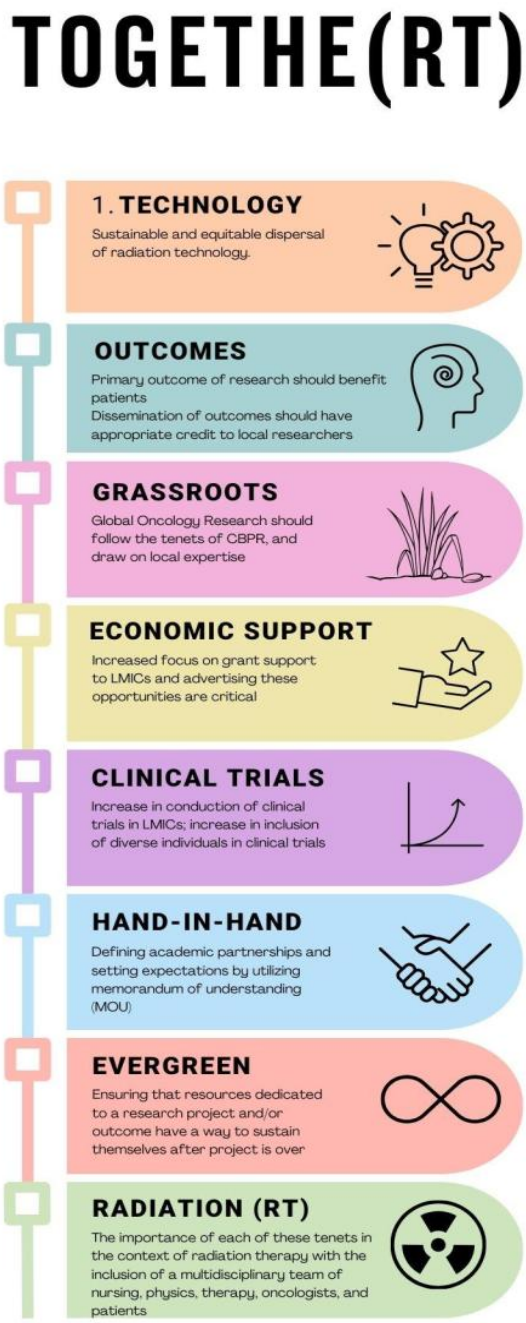

Figure 3. Diagrammatic Representation of TOGETHE(RT)

In a summary of four decades of experience, Reichenvater and dos S. Matias [10] described the importance of providing regular maintenance and repair plans for sustainable linear accelerator use. Traditionally, in higher income countries maintenance was completed with contracts with suppliers, while within Africa, it was conducted by in-house maintenance. While material costs and availability of hard currency were available in higher income countries, in Africa, there are exorbitant material costs and hard currency restrictions. Physicists are often the first line personnel who execute maintenance and repair of linear accelerators, whereas in High income countries, the labor is divided among engineers, hospital engineers, or contracted out by the vendor.

The authors delineate four areas of improvement:

1) Governmental support for experienced personnel who are taking on additional roles to support their radiation facility

2) Decrease in prohibitive training course prices offered by the manufacturers after the purchase of new equipment

VI. OUTCOMES

The primary beneficiary and center of global health oncologic research should be our patients. As researchers in global health, outcomes for global health research must be focused on mitigating disparities in inequitable access to resources or in unacceptably high morbidity and mortality rates. Finally, outcomes must impact those who need it (i.e., conducting a trial on utilization of stereotactic body radiation therapy (SBRT) for spinal metastasis when there is no sustained commitment to support SBRT via training of radiation therapists, physicists, nurses, and physicians), or provide the infrastructure to promote advanced technology in places that do not have it An example of outcomes stratified to the resources and what is available in the country is the development of the National Comprehensive Cancer Network Resource Stratified Guidelines [14]. Further, publishing and disseminating outcomes must be done equitably. Authorship of research publication and grant proposals should be fairly and respectfully discussed with due credit given to authors from lower-resource settings with active input where there is a critical need to disseminate knowledge.

VII. GRASSROOTS

This pillar identifies the importance of being present and capacity building from the ground up. The concept of grassroots embraces the knowledge and experience of experts already working in a location. Within the established framework of Community Based Participatory Research (CBPR), creating and answering a research question is done alongside the community [15]. In the fields of medical anthropology and implementation science, CBPR has long held that if a researcher is not local or native to a community, experts from that community work with the researchers to develop and answer questions. The same holds true for global radiation oncology. Developing professional relationships between departments of radiation oncology, ministries of health, or hospitals, is critical to ethically provide the right question and solution. When proposing a new research question, the group should pause and ask where the questions originated from the community it impacts

VIII. ECONOMIC SUPPORT

Funding for cancer research has increased greatly in recent years. A recent publication shows that over 60,000 grants totaling almost 25 billion dollars were awarded between 2016 to 2020 [16]. Considering the global cancer burden and the over 10 million deaths attributed to cancer in 2020, it is important that a healthy portion of these grants are awarded to cancer research in LMICs if we want to make tremendous progress towards reducing global disparities in cancer outcomes. Additionally, this tenet also discusses grant bias against research conducted in LMICs. Grant reviewers should evaluate the outcome of the research proposal and its magnitude of effect and although the trendiest topics in the field may be worth researching, this might not be beneficial to the targeted population. Currently, some professional organizations give grant funding purposely for global oncology efforts (Table 2).

It is worth mentioning that although the NIH currently utilizes the categories of: Significance, Investigator, Innovation, Approach and Environment to score an application, there are limited guidelines on equity and its weight in grant scoring projects.

Table 2: Above are examples of grants offered by professional organizations to support global health research. It should be noted that this is not an exhaustive list.

AAPM International Council collaborative microgrants which provide up to 6,000 USD to research projects focused on conducting needs assessment on technologies to advance care, research and education and address global health disparities.
AAPM International Council Global Health seed funding. Support early career researchers in Global health with $25,000
ASTRO- Association of Residents in Radiation Oncology (ARRO) Global Health Scholars (GHS) provides a stipend of $2,500 dollars to residents who are interested in global health work to pursue their research.
ASTRO Radiation Oncology Institute (ASTRO ROI) provides grant funding to investigators whose research aims to advance radiotherapy care for all patients and improve access to care. A total of $50,000 is awarded over a span of 2 years.
The Beginner Investigator Grants for Catalytic Research (BIG Cat) which is a collaborative effort between the American Association for Cancer Research (AACR) and the African Organization for Research and Training in Cancer (AORTIC) which offers a two-year $55,000 USD to support early-career African investigators (https://aortic-africa.org/big-cat/)
The ASCO and Conquer Cancer Global Oncology Young Investigator Award (GO YIA) provides research funding to early-career investigators whose research aims to improve health equity and champions diversity and inclusion in oncology. The grant is aimed at investigators from underrepresented populations in medicine and low and middle-income countries.
The NIH International Research Career Development Award (K43) was instituted to support research scientists from LIMCs who hold junior faculty positions at academic or research institutes with the aim of improving research sustainability and helping these individuals develop into independent researchers.
Similarly, the NIH D43 grants support for pre- and post-doctoral researchers who are citizens of LMICs.

IX. (CLINICAL) TRIALS:

From the onset of clinical trial design to patient recruitment, the importance of utilization of community informed participation is critical. Recent publications have emphasized the importance of diversity and inclusion in clinical trials. However, critically important is that as new technologies or fractionation patterns (i.e., hypofractionation for breast and prostate cancer) allow for improved resource utilization, these practices must also be tested in international settings. The major clinical trials for hypofractionation of breast cancer were all completed in North America and Europe (reference); yet the burden of breast cancer mortality falls unequally in low-and-middle-income countries. In order to improve resource utilization in these countries, an emphasis on the broader application and conduction of clinical trials must be undertaken. An article in 2018 PLOS medicine examined the clinical trial density in all fields in a span of 7 years. Between 2006 to 2012, 83% of the trial sites operated in 25 high-income countries, and only 5% were conducted in 91 LMICs [17]. In the years since there's been ongoing clinical trials in LMICs specifically in sub-Saharan Africa (Table 3).

Table 3: A few examples of ongoing clinical trials in Africa

Pediatric Oncology Clinical Trials and Collaborative Research in Africa: Current Landscape and Future Perspectives. van Heerden et al.
ARETTA: Assessing Response to Neoadjuvant Taxotere and Subcutaneous Trastuzumab in Nigerian Women with HER2-Positive Breast Cancer: A Study Protocol Ntekim et al.
Working Together to Build a Better Future for Children with Cancer in Africa Chitsike et al.
Challenges of HIV Lymphoma Clinical Trials in Africa: Lessons from the AIDS Malignancy Consortium 068 Study Strother et al.
Clinical Trials for Treatment and Prevention of HIV-Associated Malignancies in Sub-Saharan Africa: Building Capacity and Overcoming Barriers Lin et al.
Challenges and opportunities for implementing hypofractionated radiotherapy in Africa: lessons from the HypoAfrica clinical trial. Olatunji and Swason, et al.

X. HAND-IN-HAND/PARTNERSHIPS:

As the field of global radiotherapy grows, academic institutions and non-profits organizations recognize the need to support global health cancer research that improves health systems and outcomes in less resourced areas. This has spurred interest in academic partnerships like the one between the University of Pennsylvania and Botswana, University of North Carolina - Chapel Hill and Malawi, Emory University and Ethiopia, University of Washington - AIIMs Institute in India, Uganda Cancer Institute and Komfo Anokye Teaching Hospital in Ghana, Moffitt Cancer Center – University of Ghana to name a few. As such we must be careful not to repeat activities of historical colonialism but undertake research collaborations and

educational training and interventions tailored towards their needs. A recent publication recommends that while collaborative work is often desirable, misunderstandings are inevitable hence one method used to minimize misunderstandings having pre-defined terms of engagement in a memorandum of understanding (MOU) [18]. In the space of global health research this is highly recommended and key elements specified should include scope of the research, leadership and the team, time commitment of each team member and methods or approach, review process and finally how to disseminate and publish results [4]. It is also important to mention that working hand-in-hand means equitably sharing authorship and in the case of clinical trial enrollment, equal enrollment of patients [9].

XI. EVERGREEN

Finally, in the advent of a new intervention or a new technology adoption, it is important to make sustainability a central theme. In the field of global health research, the gong of sustainability is often chimed and yet it seems to be very challenging to achieve this mark. Studies shows that these challenges could be due to attempting to address issues in geographic isolation, siloed by the regions that experience them [9]. There is also the issue of time and resources allocated to improve health outcomes and reducing health inequalities require longer commitments to see sustainable impacts. Another challenge is the power structure within the global health ecosystem and the behavior of outside actors which has often been seen as undermining the pursuit of sustainability in less resourced environments. In the context of global radiotherapy, some of the questions to ask will be how sustainable or self-sufficient is an intervention or technology? What is the guarantee that the findings of a research will make their way to impact the community long after the research funding support ends? How will these studies be monitored and evaluated and improved?

XII. RADIATION (RT)

The last tenet aims to bring the framework back to radiation. These 7 criteria we have laid out and the examples provided can prove to assist departments looking to expand their global health reach, or companies interested in mitigating inequities in cancer research, globally.

Thus, these 7 tenets directly to radiation oncology with specific examples, data, and case scenarios. Radiation Oncology's unique requirements of equipment, technology, technique, imaging, and personnel, all underline the urgent need for a framework to guide our field ethically in this space.

Our hope is that by building this framework it can be used to evaluate and guide, future research proposals, studies, trials, partnerships, and memorandums of understanding. We urge funding agencies and academic institutions alike to evaluate proposals based on these ethical principles. The tenets listed here are by no means exhaustive, but we do believe they prioritize important fundamentals of ethical research in global radiation oncology to promote future equitable access to radiotherapy.

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