MEDICAL PHYSICS AND CLINICAL TRIALS

W.A. Beckham[1,2], K.H. Ng[3,4]

[1] British Columbia Cancer/Medical Physics, Victoria, Canada
[2] Physics and Astronomy Department, University of Victoria, Victoria, Canada
[3]Department of Biomedical Imaging, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
[4] Faculty of Medicine and Health Sciences, UCSI University, Negri Sembilan, Malaysia

Abstract— **This paper underscores the vital, yet often under-recognized, role of medical physicists in clinical trials, particularly in radiation oncology and imaging. Medical physicists contribute significantly across all stages of clinical trials, from trial design and protocol development to quality assurance, data analysis, and outcome assessment. Their expertise is integral in managing high-cost, high-technology interventions, ensuring the precise application of advanced medical technologies, and addressing critical safety and dosimetric concerns. In radiation oncology, medical physicists ensure the accuracy of treatment delivery, especially in trials involving advanced techniques like Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), which pose complex challenges in radiation distribution and patient safety. Medical physicists play a crucial role in pre-clinical research, particularly in the development of small animal irradiation platforms used to test new therapies that complement radiation treatment. These platforms are vital for obtaining regulatory approval for clinical trials involving human subjects. The paper also emphasizes the importance of medical imaging in radiation oncology clinical trials, which aids in target delineation, treatment monitoring, and compliance assessment, ultimately ensuring the integrity of trial results.**

The complexity of medical imaging technologies makes it difficult to assess and improve their clinical efficacy. Clinical imaging trials are often impractical due to ethical and logistical challenges. Virtual clinical trials (VCTs), which simulate patients and imaging systems, offer an alternative. VCTs have advanced significantly, with key components such as computational phantoms, simulators, and interpretation models, applied across various imaging techniques. As the demand for high-quality clinical trials increases, it is a priority for the international medical physics community to better recognize the pioneers who have contributed significantly in clinical trials.

Keywords— **clinical trials, radiation oncology, medical imaging, medical physicist, modelling**

I. INTRODUCTION

Medical physics practice is diverse and covers many domains in medicine. The conduct of clinical trials is a very important area of medicine that influences medical practice around the world. Clinical trials especially randomised controlled ones provide some of the highest quality evidence that evolves how patients with specific disease profiles are managed. There are some extremely high cost/high technology interventions that industry makes available to the healthcare market, and proving the benefits and deciding which patients are likely to see improved outcomes is a critical step in providing cost effective medical care where resources can be scarce. Some of the interventions involve technology that necessitates medical physics expertise to understand how it can be used and what the limitations and safety concerns are such that trial design and conduct would be impossible without such expertise. Medical physicist involvement with clinical trials is often overlooked and therefore under-recognised. To the knowledge of the authors there are no awards available to medical physicists specifically from medical physics only organisations that recognise excellence in work that supports clinical trials. An excellent editorial by physicist Tomas Kron from 2013 nicely summarises the extent of medical physicist's roles in clinical trials [1].

II. ROLE OF MEDICAL PHYSICISTS IN CLINICAL TRIALS

There are many activities related to clinical trials that provide opportunities for medical physicist involvement. These range from trial conception, pilot studies to prove practicability of trial methodology, protocol development, statistical power calculations to determine subject accrual targets, components of research ethics board submissions, quality assurance requirements to ensure trial conduct consistency, investigator and institutional credentialing, real-time review of adherence of investigators to trial protocol requirements, data analysis to develop conclusions of the trial and publication of results in the literature.

Ensuring consistency and adherence to clinical trial protocols is key to any trial that is seeking to show whether a significant difference exists between a standard arm of treatment and a new experimental arm [2, 3]. This paper will focus mostly on examples from radiation oncology, but medical physics input in clinical trials generally comes from medical physicists employed in radiation oncology, nuclear medicine, magnetic resonance imaging, diagnostic imaging, academics, and industry.

III. RADIOTHERAPY CLINICAL TRIALS SUPPORT AND EXAMPLES OF MEDICAL PHYSICIST CONTRIBUTIONS

Clinical trials involving radiation therapy (phase I, II or II) are relatively common and may be international or national multi-centre studies as well as single institution investigator-initiated trials. Some trials involving new technology, for example, Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc therapy (VMAT) where the trial objective is to evaluate the highly conformal dose distribution intervention against a 3-dimensional conformal technique, can be difficult to perform. This is because prior to consent to the study patients have to understand that they could receive a treatment that will naturally cause radiation to be delivered to much larger organ volumes. These kinds of challenges to health technology assessment were highlighted in a publication by medical physicist Søren Bentzen in 2008 [4]. Bentzen also has made fundamental contributions in the literature that helped to improve quality and integrity of randomised clinical trials [5, 6, 7, 8].

Fundamental to the success of clinical trials where the primary intervention involves radiotherapy is the accuracy of the delivered ionising radiation dose. There have been many physics led initiatives over the years that provide analysis and infrastructure to assess dosimetric accuracy across many institutions that may be geographically distributed locally, nationally and internationally. 30 years of experience of this in the United Kingdom was published by several medical physicists in 2015 [9] and followed the initial work by medical physicists David Thwaites et. al. [10]. The review article [9] offers an historical chronology of dosimetry audits by various groups around the world. The International Atomic Energy Agency (IAEA) in 1966 started a mail-in thermoluminescent dosimetry (TLD) service to assess the accuracy of dose delivered globally for Cobalt-60 treatment machines. The work was led by medical physicists Svensson et. al. [11] and in 1968 the group was joined by the World Health Organisation and that program still operates today.

In Europe, some of the earliest dosimetry audit and quality assurance work was pioneered by medical physicist Andrée Dutreix [12, 13] and led to the establishment in 1998 of the European Society for Radiotherapy and Oncology (ESTRO) Quality Assurance Network for radiotherapy (EQUAL). Medical physicist Stefano Gianolini was involved in developing the software package known as Visualization and Organization of Data for Cancer Analysis (VODCA) that allows data to be collected from multiple clinical trial sites treatment planning computers and centrally analyzed for quality assurance purposes. The European Organisation for Research and\Treatment of Cancer (EORTC) have implemented VODCA to support RT quality assurance involving several trials.

Medical physicists in the USA have also made significant contributions in several areas that have led to world class support for conducting high quality radiotherapy clinical trials. One of the notable pioneers was Robert Shalek, Chair of the Physics Department at MD Anderson Cancer Centre. In 1968, following a successful funding proposal to the National Cancer Institute (NCI), he established the Radiological Physics Centre (RPC) that was responsible for monitoring radiation treatment facilities involved in NCI clinical trials [14]. This legacy endures today (RPC is now known as the Imaging and Radiation Oncology Core—Houston [IROC-H]) with mail-in dose monitoring, postal phantom services to credential centres to participate in advanced technology clinical trials and carrying out site visits. In addition, data exchange platforms that can receive RT planning data for clinical trials quality assurance were developed by physicists James Purdy [15], Joseph Deasy [16] and Jatinder Palta and James Dempsey [17].

In Australia, medical physicist Martin Ebert was responsible for developing a software platform called SWAN [18]. This software allows upload and review of complex radiation treatment planning data for patients participating in multi-centre clinical trials. It facilitates rigorous quality assurance review of treatment plans thus minimising the likelihood of protocol deviations that could affect outcomes and hence trial results. This software is widely used to support quality assurance efforts in clinical trials conducted by the Trans-Tasman Radiation Oncology Group (https://trog.com.au/). Of note in Australasia in 1996 there was an early multi-centre phantom assessment of expected and measured doses in mantle radiotherapy treatments for Hodgkin's lymphoma that was spearheaded by three medical physicists (Amies, Rose and Metcalfe) and a radiation oncologist colleague (Barton) [19]. In 2000 medical physicist and co-author of this paper (WB) and radiation oncologist colleagues published a study involving 10 Australian radiation oncology centres treating an anthropomorphic phantom with two different breast sizes and looking at the variation in planned versus delivered dose at multiple points [20]. In 2002, a further study led by Kron used an anthropomorphic phantom at 18 Australian and New Zealand radiation treatment centres assessing clinical trials dosimetry of tonsil and prostate [21].

Another area of activity that medical physicists have contributed to is the development of radiation therapy treatment platforms that allow precision irradiation of small animals. These systems are vital to enable pre-clinical work that is often necessary to get regulatory approval to open clinical trials involving human subjects. Such trials can involve testing efficacy of new generations of drugs that can be used to compliment traditional radiation therapy and show promise of improving treatment outcomes. Irradiation platform development examples involving medical physicists were led by John Wong [22], David Jaffray [23] and Strahinja Stojadinovic [24]. Some of these systems are now commercially available and widely employed in pre-clinical studies.

IV. VIRTUAL CLINICAL TRIALS IN MEDICAL IMAGING

The importance of imaging in radiation oncology clinical trials is fundamental from being able to delineate targets and normal tissue structures before the treatment of trial subjects to monitoring treatment beam placement during the treatment and after treatment for outcome assessment [25]. Moreover, assessing compliance to clinical trial protocols using imaging as a tool has shown compromises to clinical trials outcomes and a significant example of this is highlighted in the paper by peters from 2010 [3].

The increasing complexity and variety of medical imaging technologies have surpassed the ability to effectively assess and improve their clinical applications. This presents a growing challenge for both researchers and clinical practitioners. Ideally, these evaluations would take place through clinical imaging trials, but such studies are often impractical due to ethical concerns, high experimental costs, time constraints, or lack of definitive reference data.

Virtual clinical trials (VCTs), also known as *in silico* imaging trials, provide an alternative by simulating patients, imaging systems, and interpreters to assess imaging technologies in a virtual environment. The field of VCTs has made significant advancements over recent decades. A recent review paper discusses the common components of VCTs, including computational phantoms, imaging simulators, and interpretation models, while also highlighting their applications in various imaging techniques [26].

Some Common Methodologies in Virtual Clinical Trials

1. Computational Modelling and Simulation: VCT rely on the usage of computational models of human anatomy, physiology and pathology. These models apply techniques such as finite element analysis (FEA), Monte Carlo simulations to simulate the dynamic nature of human health and the effects of medical interventions. They are used in the assessment of dose distribution and protocol optimisation. Thus, researchers can simulate various clinical conditions and treatment protocols, providing valuable insights into the effectiveness of imaging systems.

2. Digital Phantoms and Virtual Patients: Digital phantoms are utilised for simulating medical imaging protocols. These phantoms can represent various tissue types, pathological conditions and patient demographics, enabling highly accurate simulation of imaging modalities such as CT, MRI and ultrasound. Virtual patients are more sophisticated, computing-intensive models that incorporate both anatomical and physiological information, enabling the simulation of disease progression, treatment responses, dosimetry studies and image acquisition protocols.

3. Radiomics and Data Analytics: Radiomics plays a central role in VCT. By applying M and DL techniques to radiomic data, researchers can develop predictive models for diagnosis, prognosis and response to therapy. Virtual trials can integrate radiomic features with patient models to evaluate the performance of imaging systems in real-world clinical scenarios.

4. ML and AI Integration: ML and AI are incorporated into VCTs to analyse large datasets, optimise imaging protocols and predict clinical outcomes. AI models can potentially help to identify patterns within virtual patient data, refine imaging protocols and even predict outcomes. In virtual trials, AI systems can assist in the evaluation of imaging modalities and protocols in enhancing both accuracy and efficiency.

V. IMAGING VCT APPLICATIONS

Abadi et al [26] published an excellent review on “Virtual clinical trials in medical imaging”. We present a few selected examples here.

Breast Imaging

One of the earliest applications of VCTs was in breast imaging for investigations of image quality, dosimetry, optimization, and technology evaluation. [27]

In another example, VCTs were used in the optimum projection to evaluate the smallest detectable diameter of various lesions, showing that digital breast tomosynthesis (DBT) is superior to digital mammography (DM) for masses detection.

CT Imaging

VCTs can simulate dose studies using computational phantoms and Monte Carlo-based CT simulators. These studies enable assessment of organ doses for various imaging protocols.

Zhang et al. [28] investigated uncertainties in organ dose estimations across different computational phantoms, revealing that variations in organ location and anatomy can lead to significant differences in dose estimates

Another study by Sahbaee et al. [29] assessed the effect of iodinated contrast agents on organ dosimetry in CT. The results showed that the presence of iodine increased the dose, highlighting the need to balance image quality with patient dose when optimizing contrast-enhanced CT protocols.

VI. CONCLUSIONS

Medical physicists play a vital yet often under-recognized role in clinical trials, particularly in radiation oncology and medical imaging. Their expertise is crucial in trial design, quality assurance, and data analysis, ensuring

the accuracy and safety of interventions. Through their contributions, they help improve the reliability of trial outcomes and advance patient care. As the demand for high-quality clinical trials increases, it is a priority for the international medical physics community to better recognize the pioneers who have contributed significantly in clinical trials.

ACKNOWLEDGMENT

We thank the members of the Awards and Honours Committee of IOMP for their contribution. They are Kwan Hoong Ng (Chair), Erato Stylianou Makridou, Jeannie Wong, Meshari Al-Nuaimi, Barbara Chanda M'ule, Jose Luis Rodriguez Perez, Roger Price, Cynthia McCollough, Wayne Beckham.

REFERENCES

1. Kron T (2013) Editorial: The role of medical physicists in clinical trials: More than quality assurance. Journal of Medical Physics 38:111-114
2. Khalil A, Bentzen S, Bernier J et al (2003) Compliance to the prescribed dose and overall treatment time in five randomized clinical trials of altered fractionation in radiotherapy for head-and-neck carcinomas. International Journal of Radiation Oncology Biology and Physics 55:568-575
3. Peters L, O'Sullivan B, Giralt J et al (2010) Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results from TROG 02.02. Journal of Clinical Oncology 28:2996-3001
4. Bentzen S (2008) Randomized Controlled Trials in Health Technology Assessment: Overkill or Overdue? Radiotherapy and Oncology 86:142-147
5. Bentzen S (1994) Radiobiological considerations in the design of clinical trials. Radiotherapy and Oncology 32:1-11
6. Bentzen S (1998) Towards evidence-based radiation oncology: improving the design, analysis, and reporting of clinical outcome studies in radiotherapy. Radiotherapy and Oncology 46:5-18
7. Bentzen, S (2003) A user's guide to evidence-based oncology. European Journal of Cancer Supplements 1:77-91
8. Bentzen S, Wasserman T (2008) Balancing on a knife's edge: evidence-based medicine and the marketing of health technology. International Journal of Radiation Oncology Biology and Physics 72:12-14; discussion 14-18
9. Clark C, Aird E, Bolton S et. al. (2015) Radiotherapy dosimetry audit: three decades of improving standards and accuracy in UK clinical practice and trials. British Journal of Radiology 88: DOI: 10.1259/bjr.20150251
10. Thwaites D, Williams J, Aird E (1992) A dosimetric intercomparison of megavoltage photon beams in UK radiotherapy centres. Physics in Medicine and Biology 37:445-461
11. Svensson H, Hanson G, Zsdanszky K (1990) The IAEA/WHO TL Dosimetry Service for Radiotherapy Centres 1969–1987. Acta Oncologica 29:461-467
12. Dutreix A (1984) When and how can we improve precision in radiotherapy? Radiotherapy and Oncology 2:275-292
13. Dutreix A (1993) Preliminary results of a quality assurance network for radiotherapy centres in Europe. Radiotherapy and Oncology 29:97-101
14. Ibbott G, Ma C, Rogers D et.al. (2008) Anniversary Paper: Fifty years of AAPM involvement in radiation dosimetry. Medical Physics 35:1418-1427
15. Purdy J, Harms W, Michalski J et. al. (1998) Initial experience with quality assurance of multi-institutional 3D radiotherapy clinical trials. A brief report Strahlentrherapie und Onkologie 174:41-42
16. Deasy J, Blanco A, Clark V (2003) CERR: a computational environment for radiotherapy research. Medical Physics 30:979-985
17. Palta, J, Frouhar V, Dempsey (2003) Web-based submission, archive, and review of radiotherapy data for clinical quality assurance: a new paradigm. International Journal of Radiation Oncology Biology and Physics 57:1427-1436
18. Ebert M, Haworth A, Kearvell et.ai. (2008) Detailed review and analysis of complex radiotherapy clinical trial planning data: Evaluation and initial experience with the SWAN software system. Radiotherapy and Oncology 86:200-210
19. Amies C, Rose A, Metcalfe P, Barton M (1996) Multicentre dosimetry study of mantle treatment in Australia and New Zealand. Radiotherapy and Oncology 40:171-180
20. Delaney G, Beckham W, Veness M et al (2000) Three-dimensional dose distribution of tangential breast irradiation: results of a multicentre phantom dosimetry study. Radiotherapy and Oncology 57:61-68
21. Kron T, Hamilton C, Roff M et al (2002) Dosimetric intercomparison for two Australasian clinical trials using an anthropomorphic phantom. International Journal of Radiation Oncology Biology and Physics 52:566-579
22. Wong J, Armour E, Kazanzides P et al (2008) High-resolution, small animal radiation research platform with x-ray tomographic guidance capabilities. International Journal of Radiation Oncology Biology and Physics 71:1591-1599
23. Clarkson R, Lindsay P, Ansell S et al (2011) Characterization of image quality and image-guidance performance of a preclinical microirradiator. Medical Physics 38:845-856
24. Stojadinovic S, Low D, Hope et al (2007) MicroRT—Small animal conformal irradiator. Medical Physics 34:4706-4716
25. Fitzgerald T, Jodoin M, Laurie F (2018) The Importance of Imaging in Radiation Oncology for National Clinical Trials Network Protocols. International Journal of Radiation Oncology Biology and Physics 102:775-782
26. Abadi E, Segars WP, Tsui BMW, Kinahan PE, Bottenus N, Frangi AF, Maidment A, Lo J, Samei E. (2020) Virtual clinical trials in medical imaging: a review. Journal of Medical Imaging (Bellingham). Jul;7(4):042805.
27. Barufaldi B, Higginbotham D, Bakic PR, Maidment, ADA, "OpenVCT: a GPU-accelerated virtual clinical trial pipeline for mammography and digital breast tomosynthesis," Proc. SPIE 10573, 1057358 (2018).
28. Zhang Y, Li X, Segars WP, Samei E. Organ doses, effective doses, and risk indices in adult CT: comparison of four types of reference phantoms across different examination protocols. Med Phys. 2012 Jun;39(6):3404-23. doi: 10.1118/1.4718710.
29. Sahbaee P, Abadi E, Segars WP, Marin D, Nelson RC, Samei E. The Effect of Contrast Material on Radiation Dose at CT: Part II. A Systematic Evaluation across 58 Patient Models. Radiology. 2017 Jun;283(3):749-757. doi: 10.1148/radiol.2017152852.

Contacts of the corresponding author:

Author:	W.A. Beckham
Institute:	British Columbia Cancer
Street:	2410 Lee Avenue
City:	Victoria
Country:	Canada
Email:	wbeckham@bccancer.bc.ca