The role of medical physicists in clinical trials: More than quality assurance

All healthcare workers aspire to do the best for patients in their care. However, it is not always clear what 'the best' actually is. It depends on many issues and is at times controversial. Clinical trials play an important role in defining the evidence of what can be considered 'best' in certain well-defined circumstances. While it is often perceived that clinical trials are designed for drugs, they also can test technology and this editorial argues that medical physicists who are responsible for the optimal use of technology need to engage with trials early and on several different levels.

According to the World Health Organization (WHO) a clinical trial is defined as: "… any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (http://www.who.int/ictrp/en/). For any clinical trial to be successful, the 'health-related intervention' must be clearly, concisely, and unambiguously defined. This is also the case for radiation oncology and the requirements for imaging, treatment planning, and technology use need to be clearly specified. This makes a good clinical trial protocol a valuable resource for all practitioners.

It is common to distinguish clinical trials into three different phases ranging from I (establishing the correct dose) to II (testing efficacy) and III (comparing to current standard) (http://www.nih.gov/). Sometimes a fourth phase is considered which refers to studies that are conducted after the intervention has been marketed and is widely available. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use. These phase IV trials are necessary to demonstrate the effectiveness of an intervention in a real world scenario as clinical trials are conducted in a well-controlled environment with only motivated (and possibly selected) centers participating.

Access this article online	
Quick Response Code:	Website: www.jmp.org.in
	DOI: 10.4103/0971-6203.116360

For medical physicists clinical trials can be a useful resource. The technical details of the protocols are of general interest as they are usually written with a wide range of equipment in mind to maximize the chances of clinics to contribute and increase accrual. It is also not surprising that many clinical trial protocols which require the use of complex technology have medical physicists as co-investigators and co-authors. Their input is essential in defining the technological approaches allowed and specifying exactly what a particular procedure must achieve. Another valuable resource in many trial protocols for radiation oncology is contouring guidelines for targets and critical structures. They are often accompanied by planning objectives that can inform treatment planning and provide useful benchmarks. The Radiation Therapy Oncology Group (RTOG) trial protocols, which are freely available at http://www.rtog.org/, are an excellent example for this.

As trial protocols are a result of interdisciplinary collaboration, they are also useful to stimulate discussion amongst professions. Even if a center is not interested in participating in the trial, the information provided can be used to review one's own procedures. Through the technical requirements for trial participation, the protocol also supports physicists in their attempt to ensure high levels of confidence in the technical process. This also implies allocation of adequate resources to implement new technology.

The costs of clinical trials can be enormous even if the time of the investigators is not taken into consideration. This is well-known and publicized for pharmaceuticals where we accept that a considerable part of the purchase cost for a drug is covering development, clinical research, and testing. However, it equally applies to radiotherapy and a phase III randomized controlled trial with several hundred participants typically costs many millions of dollars. As such it is important to minimize risks that can affect the ability of a trial to answer its question.

Risk management is a well-established activity in industry to minimize the likelihood of not achieving a given objective. The International Standards Organization (ISO) has published a group of standards that deal with risk management.[1] In medicine, these concepts are also taking hold with laboratory-based specialties such as pathology

being particularly active.[2] In radiation oncology, many concepts of risk management are quite familiar through the fostering of a safety culture, incident reporting, and quality assurance (QA) activities.[3,4]

Medical physicists are typically familiar with risk management concepts from their involvement in radiation protection. This places them in a good position to provide risk management advise also for clinical trials in particular as it pertains to technological aspects. It is important to note that clinical trial risk management is not necessarily ensuring good treatment: It merely ensures that the trial question can be answered with the data collected. However, best patient care is still applicable and there is some evidence that participants in clinical trials fare better than other patients even if they are randomized to the control arm.[5] While this could not be proven in a structured review[6] many potential reasons are cited for this. The increased level of and documentation is likely to contribute to any such effect.

As demonstrated recently by Peters *et al*., in a head and neck clinical trial of a hypoxic sensitizer for radiotherapy, protocol adherence and good quality control can have a huge impact on patient outcome.[7] The effect was so strong that it obscured any actual effect of the drug to be tested.[8]

Given the significant impact of high quality treatment planning and delivery, it is essential that clinical trials are accompanied by QA. The set-up of appropriate procedures and the conduction of technical quality control activities are tasks for medical physicists. For trials typically two phases of physical QA are required:

- Credentialing of centers to ensure they have the technical capabilities and resources to participate in the trial.[9] This can be further broken down in a planning exercise and a physical test of dose delivery. The planning study ensures that participating centers can successfully plan patients using the required technique and may include a test of contouring to verify that targets and critical structures are contoured according to protocol.[10] The physical test of dose delivery consists in many circumstances of participation in a dose auditing program, but other more complex procedures could require the irradiation of customized phantoms.[11-13]
- Review of all or selected treatment plans remotely to ensure they comply with the protocol. In cases where this is critical and potentially affects safety of patient treatment, such as stereotactic ablative radiation therapy (SABR), these checks can be performed 'real-time', which requires review of the plans prior to the patient receiving treatment. In some cases, this review may also include a review of the patient specific QA measurements.

Clinical trials rely on well-defined and standardized procedures in order to determine the effect on a similarly well-defined patient group. A successful trial must feature both: Adherence to the protocol procedures as well as to inclusion and exclusion criteria for participants. As clinical trials rely often on only few events to demonstrate that a new treatment approach is effective and possibly better than conventional treatment any breach in protocol compliance will adversely affect the number of patients required in a trial.[14]

When designing a trial QA protocol it is useful to distinguish different levels of radiotherapy QA needs for different trials. In trials that probe a non-radiotherapy question (such as radiotherapy with and without a certain drug) the radiotherapy QA requirements are less stringent than in trials where radiation delivery is essential for the outcome or potentially even part of the trial question. Examples for the latter where radiotherapy QA must be most stringent are dose escalation trials and feasibility studies of new technology.[15,16]

An important aspect of radiotherapy clinical trials is ensuring that technology is consistently used in participating centers. This has two implications: It can help to ensure safe and efficient role out of new technology and it can test if and how a new technology can be used in a variety of different clinical settings. The latter leads to a whole number of new questions concerning issues, such as feasibility, safety, resource requirements, training needs, and cost effectiveness, that can be assessed in clinical trials. Medical physicists would be interested in these outcomes and would be the key professionals to help formulating the correct questions and methods to answer them.

Virtually all questions can be much more efficiently answered if they are posed prospectively, that is before the trial commences. While retrospective analysis is possible, it is usually prone to many biases and it is common that essential parts of information are not collected. As such, it is important for medical physicists to engage with a trial as early as possible. Often technological questions can be introduced as secondary objectives and endpoints. For example, in any trial that allows the use of 3D conformal and Intensity Modulated Radiation Therapy (IMRT) it is possible to probe the value of IMRT directly by recording relevant parameters and planning for a subgroup analysis.

A different way to address technical endpoints is the introduction of sub-studies. This would allow for example to probe particular aspects of helical tomotherapy in a multicentric trial that includes the use of IMRT. Not all participating centers will use tomotherapy, but one can test a specific question by collecting data only for patients who are treated at particular centers. This is common practice for example when collecting quality of life (QoL) data only from a certain group of patients or when collecting tissue samples only from patients treated in centers with

appropriate facilities. Whatever the question it can be more effectively answered if posed prospectively and medical physicists would be in the best position to define a technology related question and the data required to answer it.

A particular challenge for example is the assessment of image guidance in radiotherapy.[17] The increasing specialization of medical physicists (ROMPs) provides radiation oncology medical physicists only with a basic understanding of diagnostic procedures. This makes it difficult for medical physicists to specify technical requirements for diagnostic tools such as Magnetic Resonance Imaging or develop a sound metric to assess the quality of cone beam computed tomography '(CBCT). One important problem with the assessment of technology in general is that new technology by its very nature is designed to improve treatment quality. Clinical endpoints depend on this but are not a very sensitive indicator of this.[18] As planning studies usually demonstrate better dose distributions in the design phase it is often unrealistic to expect that randomized phase III trials can be conducted because it appears unethical to randomize people to old technology. The use of sharp versus bland scalpels or the introduction of parachutes is often used as an example where the outcome of a trial would have been obvious.[19] There also is often no equipoise (perceived balance between different options) when comparing new and old technology, in particular if the new technology results in better treatment plans. Proton radiotherapy and the discussion associated with it is an excellent example for this.[20]

Another problem faced by trials in radiation oncology is that meaningful clinical outcomes such as survival or late toxicity are typically only assessable very late. In addition to the high cost of collecting data for many years, this may render the final outcome of a trial of new technology irrelevant by the time it is published as technology has moved on. Registries and post-market research ("phase IV trials") may help to address this problem and validate the surrogate endpoints such as dose distribution that we use at present to justify the use of a particular treatment technique.

Even if a new technology or technique proves to be beneficial in a clinical trial, there is no guarantee that it will actually be widely implemented, in particular if the costs are high. The assessment of resource requirements and/or costs is an interesting and relevant endpoint in modern societies. Clinical trials with very clearly defined procedures are an effective means to collect relevant data from centers with a variety of different equipment and procedures. As a trial probes at the same time clinical outcomes, it is possible to link cost and outcomes; provided cost information is collected as part of the protocol. Therefore, clinical trials increasingly include health economic endpoints to inform this discussion. Medical physicists are required not only to define the technology in question in the first place, but also to assess associated costs such as life time, maintenance, replacement, training, and of course the cost of QA to ensure patients receive safe and optimal treatments.

Conclusion

Clinical trials are conducted to determine what the best treatment modality is for a given group of patients. They do this with clearly defined procedures and medical interventions often linked to the use of particular technology. Trials offer a great opportunity for medical physicists to probe technology related questions ranging from feasibility to safety and cost effectiveness. This can be done most effectively if physicists are involved at the trial conception and design phase. Collecting all relevant data prospectively and ensuring all data is of high quality will provide a valuable opportunity to answer many important questions which physicists and societies need answers for.

Acknowledgement

Annette Haworth for helpful comments.

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How to cite this article: Kron T. The role of medical physicists in clinical trials: More than quality assurance. J Med Phys 2013;38:111-4.
Source of Support: Nil, **Conflict of Interest:** None declared.