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Original paper

The role of medical physics experts in clinical trials: A guideline from the European Federation of Organisations for Medical Physics

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ABSTRACT

The EFOMP working group on the Role of Medical Physics Experts (MPEs) in Clinical Trials was established in 2010, with experts from across Europe and different areas of medical physics.

Their main aims were: (1) To develop a consensus guidance document for the work MPEs do in clinical trials across Europe. (2) Complement the work by American colleagues in AAPM TG 113 and guidance from National Member Organisations. (3) To cover external beam radiotherapy, brachytherapy, nuclear medicine, molecular radiotherapy, and imaging.

This document outlines the main output from this working group. Giving guidance to MPEs, and indeed all Medical Physicists (MP) and MP trainees wishing to work in clinical trials. It also gives guidance to the wider multidisciplinary team, advising where MPEs must legally be involved, as well as highlighting areas where MPEs skills and expertise can really add value to clinical trials.

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1. Introduction

1.1. Aim

The European Federation of Organisations for Medical Physics (EFOMP) established a Working Group (WG) on the Role of the Medical Physics Expert (MPE) in Clinical Trials in 2020, with members representing clinical, academic and industry organisations as well as from a broad range of medical physics specialities (including radiotherapy, radiology and nuclear medicine). This article represents the main output from the WG and aims to give guidance, to all relevant medical professionals, on the role of medical physics in clinical trials. Specifically, it provides guidance to all MPEs working or wishing to work in clinical trials, helping to harmonise the role and opportunities across Europe.

This includes MPEs working at a national or international level with or within trial management groups; as well as MPEs working in clinical trials as part of the local team in the recruiting centres. However, recognising the multidisciplinary effort required to deliver clinical trials, it will also work as a reference and guidance for other members of the multidisciplinary team, highlighting where clinical trials may benefit from MPE involvement. It complements the guidance from colleagues in North America [1] from 2018, giving updated guidance with more relevance to MPEs working across Europe.

Recommendations for where MPEs should be involved with clinical trials are summarised in the comprehensive table (Table 1) below. It is to be noted that while the current guideline is focused on the role of MPEs, aligning it with other EFOMP guidance and policies, the diverse regulations and policies across Europe regarding the MPE nomenclature (or lack of) makes it difficult to refer to an umbrella term that does not discriminate among members of the medical physics profession. Consequently, many of the roles described in this article are suitable for MPEs as well as all Medical Physicists (MPs) and MP trainees, provided they have had suitable training and supervision from an MPE.

The WG has taken a standard approach to nomenclature throughout these recommendations:

- "Could": Roles that may be suitable for MPEs (or MPs under MPE supervision)
- "Should": Roles we recommend are carried out by MPEs (or MPs under MPE supervision)
- "Must": Roles that have to be carried out by MPEs due to a legislative requirement.

All roles described are carried out in collaboration with colleagues working in other professions (Radiographers (RTTs), dosimetrists, Physicians, nurses, trial managers etc.).

1.2. Introduction

MPEs, and indeed all MPs and MP trainees, play a fundamental role in clinical science, responsible for the safe and efficient use of radiation for diagnostic and therapeutic purposes. Most modern clinical trials involve diagnostic or interventional technologies for personalised medicine; many directly investigate technologies, such as medical imaging and Radiotherapy (RT) advances, which MPEs have helped to develop. These clinical trials rely on MPEs' skills and expertise; thus, the involvement of MPEs in the design and conduct of a trial is central for their success.

However, the role of MPEs in clinical trials varies greatly across European countries. A recent survey developed by the EFOMP WG on the Role of the MPE in Clinical Trials collated information from 31 out of 36 professional medical physics societies organised as EFOMP National Member Organisations (NMOs). It revealed a very heterogeneous landscape of MPEs' actual involvement in clinical trials. This might be due to both a lack of national and international guidelines and unequal access to specialist clinical trials training [2]. In several European countries,

Table 1
Summary of recommendations. The WG group has taken a standard approach for nomenclature for these recommendations.

Section	Recommendations
2. Design, planning and leadership of clinical trials	MPEs should have a key role in all clinical trials involving ionising radiation, including trials where standard-of-care RT is combined with novel therapies, for example immunotherapy. MPEs should be involved in protocol writing whenever relevant diagnostic or therapeutic technologies are central to the study question (either as part of the trial intervention or in defining and assessing primary or secondary endpoints), or where an existing procedure is used in a novel way. MPEs should be directly involved in trial design whenever the trial assesses relevant new medical technology (e.g. novel RT modality trials, new imaging techniques, etc.). MPEs must be directly involved in developing and writing trial-specific guidelines for any interventional or diagnostic technology for which they would normally be responsible during standard clinical use. When trials involve novel imaging, RT, or other interventional techniques, it will usually be appropriate for MPEs to (co-)lead and take on the (shared) responsibility for developing and writing such guidelines. Trials involving novel imaging, RT, or other interventional techniques (including new or modifications of existing dosimetric approaches) should have MPEs membership on the TMG. MPEs should be considered as trial PI or co-PI where relevant medical technologies are completely central to the trial question. MPEs involved in clinical trials must be offered specialised training on trial conduct and regulation.
3. Clinical trial set-up and ongoing quality assurance program	MPEs must be involved with the safety assessment and validation of clinical implementation of new diagnostic or therapeutic technologies (for which they are or would be responsible in standard clinical practice) for patients and workers, and be involved in conducting facility and knowledge-assessment questionnaires. MPEs should be involved in the trial setup phase of studies involving relevant technologies, as their link to relevant scientific knowledge and clinical workflow can ensure a vital connection to routine clinical practice. MPEs should be involved in harmonisation and standardisation of imaging and/or RT across all centres recruiting to a clinical trial. MPEs should manage trial Quality Assurance (QA) to ensure compliance to the protocol and international standardisation for all relevant technologies, including dosimetry audit design and evaluation. MPEs should be involved in running training or workshops to help assist recruiting centres in setting up the trial in terms of scientific support and logistics for all relevant technologies.
4. Research Data, Statistical Analysis and Secondary Use of Trial Data	MPEs should be involved in relevant data collection and analysis, in particular when RT and imaging data are an essential part of

(*continued on next page*)

Table 1 (*continued*)

Section	Recommendations
	the endpoints analysis. This may involve responsibility for trial design and data analysis where dedicated trial statistician support is unavailable, provided that the MPE has undertaken appropriate specialist training; however, MPEs should preferably work alongside statisticians to help link multidisciplinary members of the study team. MPEs should be involved in primary trial publications whenever RT plays a key role, to ensure that all treatment information (relevant to the MPE role) necessary to interpret the trial (and implement any positive findings in clinical practice) has been reported. MPEs should be involved in discussions and plans for data infrastructure, collection, and management in studies involving imaging or RT data. When applicable, MPEs should be involved in development, evaluation, and implementation of data processing tools; including use of AI technologies (see Section 6) for data analysis. Specialist scientific computing support provided by MPEs, including data collection and processing, should be adequately costed and covered by the funding body, in line with any other specialist trial data management and processing roles.
5. Clinical implementation	MPEs must be part of all phases of clinical implementation of new treatment strategies, tested by clinical trials, which involve new technologies for which they will be responsible in daily clinical practice. This should involve the full process from implementation strategy to validating the implementation results. When the trial intervention involves a new technology, new use of ionising radiation, etc., for which MPEs will be responsible in daily clinical practice, MPEs must lead or co-lead, with clinical colleagues, the clinical implementation process and analyse complex interactions with other clinical procedures. MPEs should identify quantitative measures of the value of the implementation of new relevant treatment strategies. Following positive clinical trial results, MPEs must set up QA procedures for safe implementation and routine clinical use of new relevant imaging or radiation therapy interventions, in a safe but timely manner, as clinical procedures are modified. MPEs should be involved in the publication of post-trial implementation as well as on-going review of clinical significance.
6. Artificial Intelligence (AI)	MPEs should be involved in the dedicated MDT of experts ensuring safe and clinically relevant use of AI in clinical trials of interventional or diagnostic technology (such as radiology and RT trials). MPEs should be involved in the team that provides training for correct use of AI and interpretation of its results in clinical trials. The MDT should be aware of any changes to the AI tool during the trial and if new changes are made (i.e. more training data is added to the model, assessing drift migration in results). In which case, concerted efforts should be made to understand the implications of any such changes to the AI tool. MPEs should evaluate if participating institutions have the capability to support and manage the desired AI tools, proposed for the clinical trial, in a scalable and sustainable manner.
7. Legislation and regulation	A dedicated MPE must handle the trial radiation safety and relevant regulatory aspects. MPEs should be key stakeholders in the review process of studies with relevant innovative medical devices. MPEs should (co-)lead to ensure that DICOM (Digital Imaging and Communications in Medicine), and other patient data is suitably de-identified / anonymised, whilst ensuring data is kept in a usable format. MPEs must be involved in all clinical trials related to radiotherapeutic practice, therapeutic nuclear medicine, radiodiagnostics or interventional radiology.

MPEs are either not involved in clinical trials at all or have very limited involvement, which leaves considerable room for improvement.

Encouragingly, the survey demonstrated the varied roles that MPEs can undertake in clinical trials. These covered all phases of trial conduct including trial design, defining interventions, development of guidelines, radiation protection, QA, data collection, complex analysis & data processing, and management. While the involvement of MPEs in more traditional physics duties (such as QA and radiation protection) is relatively common, MPEs' contributions to aspects such as trial design and data analysis, where MPEs skillsets could add real value, are not nearly as widespread.

The roles of MPEs working in industry is also evolving, as the need to develop clinical evidence for novel technologies (through clinical trials) is becoming more critical. Therefore, an overall multidisciplinary approach will be key within medical devices industries. For imaging studies that are primarily physician driven, medical physicists can have a role in trial design and conduct, particularly in studies examining imaging biomarkers (IB), where there is a need to be reliable and precise in their clinical implementation. In all cases, collaboration between clinicians and MPEs will be important for the successful development and deployment of research activities.

EFOMP is working to harmonise the education, training, and registration of MPEs across Europe. The first steps to reach this goal are the approval of National Registration Schemes (NRS) together with the revision of the Core Curricula to reach MPE level, and to strive towards the recognition of the Medical Physics Expert profession at the European level [3]. In this regard, the recently revised Core-Curriculum for MPEs in Radiotherapy [4] highlights the strong scientific knowledge, skills, and competences of an MPE and advocates for the importance to have MPEs involved in ensuring that clinical trials are properly designed, analysed, interpreted and conducted. Being qualified as an MPE implies having reached the EQF level of 8 [5]. This corresponds to the possibility of taking decisions on matters concerning basic safety provisions and quality of care related to MPE's professional fields of expertise. This does not exclude the involvement of MPs and trainees who contribute to clinical trials under the appropriate supervision of an MPE. However, for the safety of patients, workers, and in particular young professionals and to ensure a successful outcome of clinical trials, it is important that decisions concerning basic safety provisions regarding the use of physical agents are made by professionals who have reached the highest level

of qualification in the field.

Based on the findings of the survey of NMOs, the EFOMP WG on the role of the MPE in Clinical Trials identified the need to produce guidelines for the involvement of MPEs in clinical trials. These guidelines are designed to illustrate the full spectrum of potential MPE contributions to clinical trials, thus demonstrating the value added by MPEs within the multidisciplinary trial team. The longer-term goal is to encourage the involvement of a larger number of MPEs in all stages of trial conduct, aiming for more homogenous approach across Europe.

MPEs engagement in clinical trials covers two levels of involvement:

1. Central investigator: this can be in the design, planning, leadership and/or analysis of a clinical trial as a member of the writing committee, as a principal or co-principal Investigator (PI), or as part of the central Trial Management Group (TMG). This may also cover other oversight roles, such as membership of data safety monitoring boards or ethics review committees, and the overall trial QA coordination.
2. Local investigator: local institutional involvement as part of trial setup and QA. This is typically undertaken by local site MPEs who contribute to the practical aspects of trial conduct in individual study sites (i.e. when taking part in clinical trials initiated by investigators from another institution, organisation, or company).

The sections in these guidelines highlight the range of roles that MPEs have in clinical trials, as outlined in Fig. 1. Section 2 describes the role of a central investigator, while Section 3 discusses the role in QA, with a focus on both central and local investigator roles. Section 4 discusses the implementation of the trial results into clinical practice, while Section 5 develops the input of MPEs for data analysis. Section 6 covers the emerging importance of Artificial Intelligence (AI) in clinical trials and the potential roles to be played by MPEs, and Section 7 reviews the relevant legislation. Appendices of acronyms and common terms used in these guidelines are available at the end of the document.

2. Design, planning, and leadership of clinical trials

MPEs' involvement in the central leadership of clinical trials is not widespread, as shown in our recently published survey results [2]. In only about one third of the EFOMP NMOs are MPEs PIs or members of the TMG, or they participate in the writing of the protocol (e.g. through multidisciplinary disease groups). This lack of MPEs' involvement in clinical trial leadership may be cultural or due to local regulations and guidelines impeding MPEs involvement; but it may also be a result of insufficient specialist training in clinical trials.

Fig. 1. Overview of the role of medical physics experts in Clinical Trials. Note, training is not a standalone role and is important in all aspects of clinical trials.

However, as described in this section, MPEs can provide key contributions to trial design, planning and leadership; including as PI, co-PI, or TMG member. MPEs can play a significant role in trial development, from the conception and definition of the study hypothesis, through to statistical design and protocol writing. The input level depends on how central the relevant medical technology is to the trial. MPEs can actively participate or lead the definition & standardisation of diagnostic and interventional procedures. They can also take part in the assessment of the risk, radiation exposure and ethics of the trial design, particularly when a new technology or technique is compared with current practice.

2.1 Clinical trial design and protocol writing

MPEs have advanced scientific and clinical understanding of current technology and how it may best be applied to patients in clinical practice. This allows them to formulate research hypotheses and to turn them into quantitative and testable predictions. Hence, MPEs can support trial design in collaboration with trial statisticians and other multidisciplinary colleagues (see Section 4 for the input of MPEs to the statistical aspects of study design). MPEs may help in the design of the clinical trial, which includes the development of a strategy to fulfil the trial objectives.

In addition, MPEs can contribute to writing the study protocol. Clinical trials should align with or integrate within existing clinical workflows and must be reproducible: particular care is required to define all steps in a procedure and to detail them in the clinical trial protocol and supporting documents. MPEs have a long tradition and the necessary experience for writing trial specific guidelines and accompanying documentation, based on their clinical experience and experience from previous trials. For RT trials, including external beam and brachytherapy, these guidelines include dose and fractionation regimes, treatment modalities, imaging to be used for target and OAR (Organ At Risk) delineation, as well as treatment techniques and planning details (including optimisation objectives and dose calculation methodology). Additionally, MPEs may advise on normal tissue tolerances and their achievability, as well as target and normal tissue dose constraints. MPEs are also knowledgeable of the radiobiological aspects: they can advise on novel prescriptions (such as hypo- or hyper-fractionation), strategies for missing treatment fractions, or the timing of RT in combination with other treatment modalities or agents, as well as the possible impact on their use on the trial's central question. Consequently, development and writing of trial RT guidelines should generally have MPE (co–)leadership. This includes definition of QA requirements, such as quality checks and audit requirements, trial specific benchmarking and on-trial QA, all detailed in Section 3. This is supported by the Euratom Directive [6], which states that the therapeutic use of ionising radiation shall be based on strong cooperation between competent medical doctors and MPEs, each for their experience, knowledge, and clinical competence.

MPE involvement in imaging clinical trial design is mostly related to the introduction or use of novel Imaging Biomarkers (IBs) involving a technical, clinical and cost-effectiveness validation. The technical validation, which sets out to confirm that the IB is measurable precisely and accurately, should be led by an MPE [7]. The MPE should also participate in the clinical evaluation of the IB, ensuring biologically relevant characteristics or predictors of clinical outcomes can be measured. Finally, MPEs may help evaluate the feasibility of IB use, for example whether it is widely available in all participating geographical territories.

As for IBs, MPEs can (and should) be involved in the planning of prospective validation and use of radiobiological models in RT trials, e.g. as secondary or explorative (tertiary) trial outcomes, or as part of the

study intervention [8].

MPEs are also well placed to be key leaders in targeted radionuclide therapy (RNT) where personalised patient dosimetry to improve therapeutic efficacy has long been proposed. Recent policy statements and endeavours by professional societies such as the EANM [9] and EFOMP [10] have highlighted the role of MPEs in clinical RNT; from initial setup of gamma cameras for full quantification and acquisition protocols (i.e. SPECT or planar imaging), to eventual accurate calculation of dosimetric variables such as absorbed dose. Although these recommendations are aimed towards implementing cleared RNT agents as per clinical requirements of the site, EANM have also more recently published dosimetry guidelines for first-in-man and early phase 0 clinical trials, with the aim to optimise and standardise the information available from a wide range of imaging and analysis techniques [11].

2.2. Principal investigator, co-PI, and trial management group

The TMG is composed of people from different professions contributing to the management of the trial. Members of the TMG have specific roles, coordinating different activities during the clinical trial, including but not limited to: protocol writing & review, pharmacovigilance, pathological and radiological review, site qualification and QA assessment.

Given their key role in study development, design, and implementation, MPEs are natural members of the TMG for trials involving novel imaging, RT, or other relevant interventional techniques. MPE members may serve as the link between specialised trial statisticians (or may take the role of a trial statistician, where appropriate) or between the trial management and dedicated QA groups. MPE membership of TMGs also helps to ensure that relevant technical data required for the clinical trial are collected, as discussed further in Section 4.

Where trials specifically investigate new imaging or RT technology, it may be appropriate for an MPE to serve as PI or co-PI. This may particularly be the case for early phase or pilot studies where the main study question evolves around clinical implementation and feasibility. Here, MPEs can provide the right expertise for successful trial leadership, providing a deep understanding of the technology in question, of complex data analyses, and of the practicalities of clinical implementation. Examples of trials with MPEs as co-PIs in RT include studies of the use of Image Guided Radiotherapy (IGRT) [12] and tumour tracking [13]; use of functional imaging for dose escalation in head-and-neck cancer [14]; dose escalation [15] and on-treatment imaging [16] for organ preservation in rectal cancer; use of proton therapy for lung cancer [17]; physicist involvement in direct patient care [18]; metastatic thyroid cancer therapy with I-124 dosimetry [19]; and hepatocarcinoma selective internal RT with Y-90 micro-spheres [20]. Outside of RT, MPEs have, for example, led trials on the use of functional imaging for treatment response assessment in follicular lymphoma [21], Hodgkin lymphoma [21,22] and myeloma [23].

2.3. Ethics and safety assessment

An essential aspect of trial protocol design is to ensure that a clinical study is performed to the highest ethical standards; offering patients the best standard of care and ensuring that the proposed scientific question can be answered by the study design. MPEs play a key role in ensuring safe and ethical use of novel technology, including evaluation of its proposed use and implementation as part of the study design phase. MPEs will be part of the expertise on the TMG on the safe use of ionising and non-ionising radiation, both for patients and for the clinical staff involved. In particular, the designated MPE, as from the (European Union) EU 59/2013 Directive art 83 comma 2 [6], is the responsible person for dosimetry, including physical measurements for evaluation of the dose delivered to the patient. Additionally, MPEs should be consulted by ethics committees, e.g. as external experts, for any studies involving use of ionising radiation. They bring the scientific expertise necessary to assess a project properly as well as assist with the discussion of benefits and appropriate dose constraints. The MPE role also includes the co-review of reported or unexpected events (such as side effects) during the conduct of the trial.

2.4. The MPE role in radiation protection

EFOMP recently approved the Malaga Declaration, one of the Federation's main statements [3]. This document defines the roles that MPEs can play in different scenarios and applies in many settings, including clinical trials. In particular, depending on their specific area of expertise, MPEs can be responsible for the radiation protection of patients, workers and the general public, act as radiation safety experts, laser safety experts, magnetic resonance (MR) safety experts and MR scientists [3,24].

2.5. Current practice and potential future improvements

As demonstrated by our previously published survey [2], only a few EFOMP NMOs have established legal requirements for MPEs' official involvement in clinical trials. MPEs being part of Institutional Review Boards (IRB), Independent Ethics Committees, or TMGs is common practice in about one-third of the NMOs, but mainly for assistance in technical/technological issues. Moreover, only 12 out of 31 (39%) EFOMP NMOs reported any knowledge of MPEs taking the role of (co-)PI on clinical trials. This is demonstrated by the relatively few named MPE investigators and co-authors on trial protocols and publications, despite the examples provided in Section 2.2. This may reflect a combined lack of understanding of the benefits provided by involving MPEs in trial leadership, a lack of access to appropriate training on clinical trial conduct for MPEs, and potentially the lack of available MPEs in the workforce to provide the required level of support [3].

Only a small number of European countries have a strong tradition of MPEs participating in the design and development of clinical trials. Positive examples include RT trials in the Nordic countries [25] or the response-assessment experience in lymphoma and myeloma [21,26]. This may, as mentioned above, partly be due to a lack of training in core concepts of clinical trials: while general training on clinical trials is available in almost half of the NMOs, those specifically dedicated for MPEs are extremely scarce, with only one NMO reporting the existence of regular courses. However, many international, interdisciplinary courses or workshops exist, which MPEs are encouraged to attend. These include the week-long European Organisation for Research and Treatment of Cancer – European Society for Medical Oncology – American Association for Cancer Research (EORTC-ESMO-AACR) "Methods in Clinical Cancer Research" course, held yearly and the EORTC "Clinical Trial Statistics for Non-Statisticians" 3-day course. Additionally, the European SocieTy for Radiotherapy and Oncology (ESTRO) has several relevant courses partly covering key aspects of study design, including the "Quantitative methods in Radiation Oncology" course and "Research Course in Radiotherapy Physics." Although these courses are available, and cover many relevant skills required for working in clinical trials, there is currently a need for further specific training programmes covering specific roles suitable for MPEs, and indeed all MPs and MP trainees wanting to be involved in clinical trials.

2.6. Recommendations

MPEs should have a key role in all clinical trials involving ionising radiation, including trials where standard-of-care RT is combined with novel therapies, for example immunotherapy.

MPEs should be involved in protocol writing whenever relevant diagnostic or therapeutic technologies are central to the study question (either as part of the trial intervention or in defining and assessing primary or secondary endpoints), or where an existing procedure is used in a novel way.

MPEs should be directly involved in trial design whenever the trial assesses relevant new medical technology (e.g. novel RT modality trials, new imaging techniques, etc.).

MPEs must be directly involved in developing and writing trial-specific guidelines for any interventional or diagnostic technology for which they would normally be responsible during standard clinical use. When trials involve novel imaging, RT, or other interventional techniques, it will usually be appropriate for MPEs to (co-)lead and take on the (shared) responsibility for developing and writing such guidelines.

Trials involving novel imaging, RT, or other interventional techniques (including new or modifications of existing dosimetric approaches) should have MPEs membership on the TMG.

MPEs should be considered as trial PI or co-PI where relevant medical technologies are completely central to the trial question.

MPEs involved in clinical trials must be offered specialised training on trial conduct and regulation.

3. Clinical trial set-up and ongoing QA program

Clinical trials are designed to respond to a clinical question: the trial primary objective (e.g. is treatment A better than B? Does imaging C permit a better patient staging or re-staging respect to no imaging done?), with the aim to demonstrate the effect on specified primary endpoints (e.g. a better failure free or overall survival of patients treated with A with respect to B). The sample-size (the number of patients to be enrolled in the trial) is set to ensure sufficient data to demonstrate this primary objective without exposing too many patients to an experimental treatment or management strategy. Thus, it is essential that the study intervention is implemented into clinical practice as intended, in an affordable and reproducible manner.

The role of MPEs in trial conduct may be crucial in trials of interventional or diagnostic technologies for assessing the feasibility of the trial itself, as well as defining the level of pre- and on-trial QA required, based on the complexity of the trial [27,28]. Delivery of high-quality RT becomes even more pertinent for the increasing number of trials exploring novel drugs in combination with or adjuvant to RT, such as immunotherapy, targeted agents, or radiosensitisers. For such trials, the question of drug efficacy can be masked by variation in RT techniques and quality across institutions [29,30]. Finally, high quality trial QA for novel technologies can help improve general practice and implementation, thus benefitting patients beyond the specific clinical trial [31–35].

Locally, MPEs play a crucial role in ensuring that trials can be run at study sites: they conduct multiple tasks, depending on the complexity of the trial, such as dummy runs and dosimetry audits for RT or verification of imaging equipment as described later in this paper. Challenges and opportunities related to this role have previously been described in detail. But multiple studies [22,23] have demonstrated that local MPEs tend to be informed of their site's participation in a clinical trial only at a late stage when their direct help will be needed.

3.1. Feasibility of trial

Feasibility should be considered, including the cost-effectiveness for the specific trial, assessing how many sites shall be opened and the resource requirements to enrol patients. The workload, qualification and availability of staff, training needs and also the technical resources needed (such as the required resources for dosimetry audit) should be assessed. This should be relevant to the equipment required for the trial; for example, if specialist equipment is used, specific imaging protocols or techniques may be required (such as whole-body diffusion Magnetic Resonance Imaging (MRI)), or specialist radiopharmaceutical expertise may be needed (such as in kinetic analysis) [36]. MPEs participate in defining the assessment of required qualifications, resources and training of institutions wishing to participate in the clinical trial.

An important step in the analysis of the trial feasibility is to write a clinical trial protocol that can be followed strictly by the sites participating in a multi-centre clinical trial [37]. To do so, a thorough program of standardisation and harmonisation is usually carried out. Examples in RT include work by Task Group 263 [38], European Association of Nuclear Medicine (EANM) [39], Global QA of RT clinical trials harmonisation [37], SQUIRE 2.0 [40] and RATING [41]. In imaging, this usually involves following guidelines of international scientific societies [42,43].

To illustrate, feasibility assessment may include (but is not restricted to) the development of a questionnaire by the trials team, including the MPE, and distribution to all participating sites. The questionnaire should be completed by the local multidisciplinary team, including the MPE, and work as an aid to give assurance that the participating sites are able to meet the protocol requirements. This may, for example, include an evaluation of whether they have the required resources to perform the RT or imaging procedures specified in the trial protocol.

3.2. Clinical trials QA

The QA within a clinical trial has one overall key concept: the TMG must ensure that participating sites demonstrate the ability to use equipment in line with the basic requirements of the clinical trial. This is demonstrated by the sites performing pre- and on-trial QA, a set of tests that are specific to the trial.

Trial QA design must be pragmatic and adapted to the trial's level of complexity, especially with respect to the imaging or therapeutic technologies involved. Considering their expertise in patient radioprotection, treatment planning, medical imaging information for treatment and dose measurement and evaluation, MPEs have the comprehensive understanding essential to determine the complexity and needs of the QA for the trial. Sections 3.2.1-3.2.4 give details of key requirements for QA programmes.

3.2.1. Design of a QA programme

MPEs are involved in defining valid and suitable QA and Quality Control (QC) for the entire trial pathway [44]. If needed, end-to-end tests (Appendix 1 for definition) with customised protocol-specific phantoms can be designed by the MPE team. The methodology should be defined to ensure optimisation and appropriate implementation of protocols and QA procedures specific to each medical application, whilst considering the entire workflow, from acquisition to post-processing or treatment:

- In RT, the design of a QA programme encompasses (but is not restricted to) immobilisation evaluation, motion management, contouring, treatment planning, quantifying contour uncertainties, treatment delivery, absorbed dose measurement and patient plan verification [45].
- In imaging trials, the aim is to ensure software compliance (i.e. correct interpretation of DICOM tags) and image quality in order to assess the accuracy of each IB used for subsequent analysis.

3.2.2. Pre-trial QA

Pre-trial QA ensures that individual centres or healthcare professionals can adhere to the trial protocol. This process is often overseen by the MPE team. Pre-trial QA is designed to gain an understanding of local practice in terms of imaging and treatment practice; it helps to ensure that compliance to the protocol is achievable at each participating centre. MPEs may be involved in the definition of the number and type of accrual centres, as part of the trial strategy. MPEs have a good understanding of what techniques are currently possible across institutions, and they can identify if training may be required for trial implementation at individual sites.

Dosimetry and calibration are detailed in local centre protocols and procedures. Relevant information is shared with the central QA team in the clinical trials technical questionnaire and reviewed to ensure that

adherence to the trial protocol is possible at the centre. The central trial MPE team should be involved in dummy or dry runs (Appendix 1); the relevance of results compared to the trial aim should be assessed. Requirements and complexity of benchmark cases for RT trials (outlining and planning cases, consideration for multiple plans if multiple RT dose arms, dose summation etc.) should be evaluated. For imaging trials, certain pre-trial imaging tasks may need to be performed, most typically benchmarking the scanner(s) with phantom measurements. Examples include scanner benchmarking using the 'COPDGene phantom' in a 20-year longitudinal multicentre lung CT study [46], implementation of multicentre quantitative SPECT-CT in radionuclide dosimetry studies [47], and multicentre phantom benchmarking with calibration phantoms for quantitative MRI (qMRI) [48].

3.2.3. On-trial QA

MPEs should be involved in defining the on-trial QA (prospective, timely retrospective, retrospective or data collection only) for analysis during and/or at the end of trial. This should include the definition and frequency of QA tests, the number of patients to be analysed and how to evaluate any trends.

MPEs should be involved in determining and defending action levels. For example, when errors or inconsistencies or unacceptable variations from protocol are substantial enough to be corrected for an individual patient, or when the correction is on an institutional level and only required for future enrolled patients. The timing of on-trial QA is highly important, as non-compliance to the trial protocol needs to be able to be corrected while still relevant for the conduct of the trial.

3.2.4. Post-trial QA

Post-trial QA is typically centred on data curation, where specific data are identified as outliers and must be validated. The curation process is often handled best by the MPE team at each institution, in collaboration with the central trial MPE, and wider multidisciplinary team. They have in-depth knowledge of local treatment procedures and can identify incorrect or problematic data through data processing and pattern recognition, prior to central data analysis.

3.3. Examples of current practice

In our published survey, just over half (51 %) of NMOs responded that MPEs are involved in or lead on QA programmes in clinical trials in their respective countries.

In RT, an example of strong MPE involvement in trial QA can be found in the United Kingdom, where the RTTQA (Radiotherapy Trials Quality Assurance Group) [49] co-ordinates trial QA for almost all multi-centre RT trials (those on the NIHR (National Institute for Health & Care Research) portfolio). Its role is to design and implement QA programmes; the RTTQA team includes MPEs working alongside a MultiDisciplinary Team (MDT), all working to ensure consistency in QA across institutions and clinical trials. For every trial they work on, a bespoke QA programme is designed, based on the complexity of the RT technique as well as imaging and dosimetry requirements.

On a European level, the EORTC RT QA team has MPEs as key members [50,51], alongside other multidisciplinary experts, and they are involved in all steps of a study lifecycle. They have, for example, co-ordinated international dosimetry audits as part of trial set-up and credentialing (Appendix 1) [52,53], published on the importance of clinical trial radiotherapy QA [54,55] and explored the relationship between pre-trial QA [56] and delivered treatment [57]. Retrospective post-trial QA has been performed in the Danish Head and Neck Cancer group (DAHANCA): the negative trial result of using EPO (Erythropoietin) to improve the survival chance meant that there was a need to ensure baseline RT was of a high standard [58].

Collaborative oncology trial groups outside of Europe also operate extensive QA programmes, including the Japan Clinical Oncology Group–RT Study Group [59], the National Clinical Trials Network in the United States (IROC – Imaging and Radiation Oncology Care) [60] and TROG (Trans-Tasman Radiation Oncology Group) in Australia & New Zealand [61]. Furthermore, the Global Harmonisation Group has representatives from all key national/regional RT QA groups and aims to "promote harmonization of radiotherapy quality assurance for clinical trials between groups globally" [37].

MPE are also frequently involved in imaging trials, e.g. in the definition of the rules and metrics for inter-observer variability when a central review is carried out [62–64] and in the harmonisation of the procedure for image acquisition [65,66]. Harmonization and QA should be carried out to equalise equipment though clinical sites in multi-centre clinical trials. There are examples of MPE involvement in PET [65,67–69] and Single Photon Emission Computed Tomography (SPECT) [70,71] studies, as well as in trials utilising and evaluating a variety of MRI techniques such as Spectroscopy [72–74], Arterial Spin Labelling [75] and Diffusion Weighted Imaging [76,77].

3.4. Recommendations

MPEs must be involved with the safety assessment and validation of clinical implementation of new diagnostic or therapeutic technologies (for which they are or would be responsible in standard clinical practice) for patients and workers, and be involved in conducting facility and knowledge-assessment questionnaires.

MPEs should be involved in the trial setup phase of studies involving relevant technologies, as their link to relevant scientific knowledge and clinical workflow can ensure a vital connection to routine clinical practice.

MPEs should be involved in harmonisation and standardisation of imaging and/or RT across all centres recruiting to a clinical trial.

MPEs should manage trial Quality Assurance (QA) to ensure compliance to the protocol and international standardisation for all relevant technologies, including dosimetry audit design and evaluation.

4. Research data, statistical analysis and secondary use of trial data

As discussed in previous sections, MPEs play an important role in clinical trial design and conduct. This is especially true for trials for which imaging or interventional technologies are central to the study question, where MPEs are core members of the TMG from the design phase into data analysis and reporting. MPEs are often essential for turning research hypotheses into quantitative and testable predictions as part of the trial design process. They may be a crucial part of the data analysis process as a natural corollary.

Where specialised trial statisticians are available and involved in the design and study analysis process, they will ideally be part of the multidisciplinary trial team, with MPEs and other specialists. However, dedicated trial statisticians are a scarce and expensive resource in many countries. In such situations, MPEs, given their training in data analysis and biostatistics, have in the past stepped up and taken responsibility for study designs and data analysis plans. This will likely continue as an important role for MPEs in clinical trials but requires that they have undertaken appropriate specialist training (see below).

Importantly, MPEs ensure that complex imaging and RT data get analysed and reported comprehensively and robustly, as appropriate for the trial in question. Reporting of treatment data in RT trials has been notoriously patchy, with trials reporting on pure RT questions missing essential treatment information [78–82]. This lack of proper reporting severely limits the interpretability of trial results and the opportunity for timely clinical implementation, as per Section 5. However, there are also numerous examples of the converse, i.e. trials where MPEs have played a central role in study analysis and reporting, generally with robust reporting of relevant technical details [14,83–86].

Historical issues with reporting of multifaceted (diagnostic or treatment) information may be partly due to the complexities of data

collection and management for such data. MPEs have essential specialist knowledge of data formats and structures (such as DICOM data), of the challenges in sourcing and collating these data, and of the problems imposed by the lack of appropriate metadata [87]. MPEs can thus support or lead the design and management of imaging and RT trial data infrastructure. This may involve development, evaluation, and implementation of data processing tools; for example, tools for validation of radiomics data extraction, image processing, and image biomarker calculation. Our survey of EFOMP NMOs, showed 29 % of respondents listed participation in data collection as a normal role for MPEs.

MPEs taking on such roles should ensure that they follow best practices; including storing raw data whenever possible, having robust metadata, describing each data item and data origin, and storing data linkage between different data components, particularly when data is de-identified or anonymised. In general, RT and imaging data should be collected, annotated, and stored at the 'time of production,' as post-hoc collection is notoriously difficult. This can be facilitated by ensuring that the data collection process is as automated as possible, to reduce errors and workload in the daily clinic. MPEs are essential to ensure that this happens, it should therefore be adequately costed and covered by the funding body, in line with any other specialist trial data management and processing roles.

Imaging and RT data (as well as data from other diagnostic and interventional technologies) represent a rich source of information from clinical trials, which seldomly gets fully utilised. RT data are complex, and many nuances are lost in simple endpoint reporting. This is unfortunate, given the potential from combining the high-quality clinical data available in prospective trials, such as toxicity and treatment outcome information, with complex dose data. There are numerous good examples of additional knowledge gained from secondary analyses of trial dose and imaging data, particularly in RT, where the field has a long track record of data modelling and mining studies. One such illustrative case is the secondary analysis of dose data from the randomised phase III PARSPORT trial [88]. Detailed Dose Volume Histogram (DVH) analysis demonstrated a correlation between dose to central nervous system structures and the reporting of acute fatigue, thereby explaining the increased rate of fatigue observed in the IMRT (Intensity-Modulated RadioTherapy) trial arm [89]. Other examples from RT include the relationship between heart dose and overall mortality reported in a secondary analysis of the Radiation Therapy Oncology Group (RTOG) 0617 trial [90–94] and multiple publications exploring dose-toxicity relationships in data from prostate cancer trials [91–94].

Additionally, MPEs' high level of mathematics and knowledge of clinical pathways and technologies, as well as their inherent multidisciplinary practice, make them strong candidates for leading, interpreting and/or implementing health economic evaluations in clinical trials; including prospective and retrospective sub-studies and data analyses, especially when secondary data is abundant. Two good examples are the use of data from the SMaRT trial [95] in Radiology and ARTSCAN 2 trial [96] in RT.

Where MPEs take on the responsibility for trial design, sample size calculation and trial data analysis, this should be supported by appropriate training [2]. Limited high-level training is available specifically for MPEs, however, and specialist external modules may instead have to be sought out, e.g. from postgraduate programmes. Shorter introductory courses include the yearly EORTC "Clinical Trial Statistics for Non-Statisticians" 3-day course and relevant parts of the EORTC "Methods in Clinical Cancer Research" course (as mentioned above). For secondary data analysis, ESTRO offers the "Quantitative methods in Radiation Oncology" course, which covers many aspects of data modelling. The EFOMP school course "Statistics in Medical Physics" also introduces some topics relevant to trial data analysis (such as general hypothesis testing, survival analysis and general outcome modelling).

Best practice for trial design and reporting should always be followed, irrespective of the specific roles played by MPEs and other MDT members. The EQUATOR network [97] provides relevant guidelines and checklists; these include the SPIRIT statement for clinical trial protocols [98], the CONSORT checklist [99] and extensions for randomised controlled trial reporting [100] and guidelines for the content of statistical analysis plans [101]. Further guidelines and reporting checklists are available for data management & analysis, including the FAIR principles for data [102] and TRIPOD checklist for prediction model reporting [103].

4.1. Recommendations

MPEs should be involved in relevant data collection and analysis, in particular when RT and imaging data are an essential part of the endpoints analysis. This may involve responsibility for trial design and data analysis where dedicated trial statistician support is unavailable, provided that the MPE has undertaken appropriate specialist training; however, MPEs should preferably work alongside statisticians to help link multidisciplinary members of the study team.

MPEs should be involved in primary trial publications whenever RT plays a key role, to ensure that all treatment information (relevant to the MPE role) necessary to interpret the trial (and implement any positive findings in clinical practice) has been reported.

MPEs should be involved in discussions and plans for data infrastructure, collection, and management in studies involving imaging or RT data. When applicable, MPEs should be involved in development, evaluation, and implementation of data processing tools; including use of AI technologies (see Section 6) for data analysis.

Specialist scientific computing support provided by MPEs, including data collection and processing, should be adequately costed and covered by the funding body, in line with any other specialist trial data management and processing roles.

5. Clinical implementation

Implementation of clinical trial results is a vital step, as this is where the trial results are put into routine clinical use. The benefits of the trialled intervention are being disseminated to healthcare professionals and, ultimately, to the patients. Ensuring that clinical trial results can be implemented into clinical practice is a significant role for the multidisciplinary trial team. This includes MPEs who are responsible for leading on the technical parts of the implementation process. Naturally, specific tasks, like safety assessment, are part of the MPE role and are highly important. The MPEs' analytical, scientific, and problem-solving skills are generally required in complex implementation tasks in a busy healthcare environment.

Implementation science is an emerging and rapidly evolving field [104]. It studies methods to promote the systematic uptake of evidence-based interventions into clinical practice and policy to advance healthcare [105]. The role of MPEs is often linked to specific tasks (i.e. requirements for ancillary equipment, new QC measures, availability of additional processing software etc.), and they are healthcare professionals who have knowledge of the whole healthcare chain. Through an analytical approach, MPEs are able to identify the potential pitfalls in the implementation process [106]. This includes the effects of potentially increased radiation dose to healthy tissues, additional time required for new processes, effective dissemination of updated information and any required training. MPEs may also aid with assessing the cost of new procedure implementation, given that a new procedure may be more or less cost effective depending on its complexity.

Well-conducted implementation starts with an implementation strategy. Key elements of the implementation are: legal requirements, patient and staff radiation safety, equipment and staffing resources, the applicability of the new intervention or procedure, and interaction with current clinical practice. These elements can seem simple; however, some can have wide-ranging implications on other clinic procedures, which must be identified and handled. Here, the knowledge and skill of the MPEs to identify, analyse and understand complex interactions are

important.

Describing new procedures for implementation as a result of a trial may involve concurrent review from many members of the clinical service team (e.g. radiologists, oncologists, specialist surgeons, nuclear medicine experts, radiographers, medical physicists, dosimetrists, clinical service managers and the administration team); the procedures need to be tested before being set into practice. These tests are often performed by or with the MPEs, who fine-tune the procedures to set as the local standard.

The final step in a successful clinical implementation is to validate that it resulted in the desired outcome. Implementation science has recommendations on measuring and quantifying the implementation success, which can be a useful tool irrespective of whether it is the intention to publish the results or not [104,105]. As all implementations are unique in their local setting, some of the questions in the checklist may not be applicable to each and every site; however, all of the items need to be considered [104,105].

5.1. Published guidance and examples of current practice

MP' involvement in clinical implementation of technical developments is widely demonstrated in the literature. Examples include the clinical implementation of respiration-gated IMRT at Virginia Commonwealth University, United States [107]; the recently published AAPM (American Association of Physicists in Medicine) Task Group guidelines to inform and aid development and safe clinical implementation of MLC (MultiLeaf collimator) tracking [107]; the applications and clinical implementation of machine learning (ML) in RT [108]; and the IAEA (International Atomic Energy Agency) publication of strategies for clinical implementation of PET tracers [109]. Although these examples are not trial specific, they all represent technologies either previously tested in clinical trials or under current evaluation. In general, there is currently a lack of studies specifically for post-trial implementation in areas relevant to the MPE role and this should be a priority for future research.

5.2. Recommendations

MPEs must be part of all phases of clinical implementation of new treatment strategies, tested by clinical trials, which involve new technologies for which they will be responsible in daily clinical practice. This should involve the full process from implementation strategy to validating the implementation results.

When the trial intervention involves a new technology, new use of ionising radiation, etc., for which MPEs will be responsible in daily clinical practice, MPEs must lead or co-lead, with clinical colleagues, the clinical implementation process and analyse complex interactions with other clinical procedures.

MPEs should identify quantitative measures of the value of the implementation of new relevant treatment strategies.

MPEs should identify quantitative measures of the value of the implementation of new relevant treatment strategies.

Following positive clinical trial results, MPEs must set up QA procedures for safe implementation and routine clinical use of new relevant imaging or radiation therapy interventions, in a safe but timely manner, as clinical procedures are modified.

MPEs should be involved in the publication of post-trial implementation as well as on-going review of clinical significance.

6. Artificial intelligence

Artificial intelligence is currently emerging in many domains of human activities and medicine is no exception. Although a review of uses of AI in the various specialities that comprise Medical Physics is outside the scope of this work, excellent reviews on the topic are available [110–113]. Briefly, medical physics and its primary domains, RT and imaging, have many examples of AI applications holding considerable promise for improved diagnostics, treatment and prevention, as well as improved workflows and more cost-efficient health care. As of January 2023, there are almost 400 FDA (Food and Drug Administration) cleared AI algorithms for use in radiology, with 300 of these being approved within the last 4 years [113] and 214 CE (European Conformity) marked algorithms for use within the EU [114].

Clinical AI solutions have been most prominent in image post-processing and analysis, but many other uses exist; for example, for accurate patient positioning, biopsy guidance, suppression, image reconstruction (i.e. such as image de-noising), real-time motion management and clinical report generation. In RT, the primary uses of AI have been geared towards automated organ and tumour segmentation from CT images. However, other AI solutions include the optimal dose prediction and optimisation for streamlining the planning process, expediting plan QA, and prediction of the response to a treatment and radiation-induced toxicities [115]. Finally, there are AI solutions for clinical decision support that combine clinical, genomic, and imaging data to support patient management [116]; although they may not require specific MPE support, MPEs may need to be aware of their uses.

AI is implemented in clinical practice using software that perform a specific task and can be implemented from a variety of pathways: some are developed in-house at a hospital/clinic, some are developed in partnership with an external company, and others are commercially purchased from a vendor. Recent research has pointed out that 40 out of 154 applications used in RT were homemade [117]. AI that is intended to be used for diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease falls within the scope of the Medical Device Regulation (MDR) as described in Section 7.2. As such, use of AI in clinical trials will often fall within the domain and responsibilities of trial MPEs.

6.1. Published guidance and examples of current practice

Clinical trials may either have AI as an integral part of the scientific question (e.g. testing a novel technology or intervention fully or partly AI-based) or as a supporting technology (e.g. supporting key trial operations, such as trial QA). Recent examples of the former with key medical physics involvement include prospective clinical implementation of ML-based auto planning for prostate cancer [118] and the ARCHERY trial (Artificial Intelligence Based Radiotherapy Treatment Planning for Cervical, Head and Neck and Prostate Cancer) which explores the benefit of AI for RT in low-resource settings [119]. For the latter, AI-based auto-contouring solutions have been proposed as a consistent and efficient way to QA radiotherapy target and OAR volumes [120–123] as well as treatment plans [123–126] in clinical trials. A prospective, MPE-led trial sub-study of the TROG15.03 FASTRACK II trial of stereotactic ablative body radiotherapy (SABR) for kidney cancer demonstrated the potential of automated, ML based automated planning for real-time radiotherapy plan QA [126]. Synthetic CT generation from MR images through deep learning to enable MR only based dose planning is also an active area of clinical trial investigation such as the AuToMI trial [127].

As mentioned above, AI based initiatives in imaging are primarily employed in either generation of images (i.e. noise-reduction reconstruction), automated post-processing of images to improve diagnostic readability, or in the direct calculation of quantitative biomarkers. Examples of AI initiatives involving MPEs are manifold and include: a clinical trial aiming to diagnose cardiomyopathy and predict complications, the AID-MRI (International Study of AI-based Diagnosis of Cardiomyopathy Using Cardiac MRI) trial [128]; evaluation of gadolinium-based contrast agent reduction in brain MRI in the MAGNET (Multi-centre Study of AI Model for Gadolinium-based Contrast Agent Reduction in Brain MRI) trial [129]; and the Singaporean APOLLO (AI Driven National Platform for CT cOronary Angiography for clinicaL and industriaL applicatiOns Registry) trial aiming at automating coronary

artery stenosis, calcium scoring pericardial adipose tissue and plaque quantification [130]. Furthermore, machine and deep learning in the developing field of radiomics, coupled with genomic data, require highly skilled scientific expertise when used in predictive models. The aim of these models is to generate personalised treatment plans or predict survival, for example in the international RADIOVAL (Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer Treatment Planning) trial [124] and in the ATENA (Artificial inTelligence in eNdometriosis-related ovArian Cancer and Precision Surgery in eNdometriosis-related ovArian Cancer) study [131].

Any experimental use of AI in clinical trials, including studies applying AI as a clinical intervention, will require ethical review. For example, an AI tool that decides on the patient pathway or which automatically decides radiation exposure settings for imaging or RT will likely require institutional ethics approval, while, for example, patient positioning aides and image reconstruction will likely not. The clinical trial team (involving an MPE) will have to consider the specific situation and liaise with their local ethics board.

Although there are efforts to have AI included in MPE/MPE post-graduate education [132], there is currently no clear allocation of the role or responsibility for AI tools used within a trial. Instead, it is common practice to have a dedicated MDT of relevant experts to share their expertise as to how the tool should work, the underlying workings and the logistics of its implementation, cybersecurity issues, cloud-based implementation and regulatory/local policy issues (e.g. physician, medical physicist, information technology (IT) specialist, governance specialist) with the overall aim to ensure its safe and clinically relevant use. This team should have a basic knowledge of AI in general and an understanding of the particular model, including the patient cohorts for which it is applicable, to evaluate the strengths and possible limitations. MPEs will often play a key part of such a team, given their general clinical and trial responsibilities with respect to technology implementation and evaluation.

As in routine clinical practice, any new AI software being used for a trial should undergo scrutiny by the clinical trials team, including MPEs, before its use. Published recommendations for introducing new AI technology can be found, for example in RT clinical practice [117]. Similarly in the imaging field, ad hoc expert recommendations and professional society guidance have been published to aid in the selection, understanding and implementation of AI tools, as well as specific requirements of certain roles within the process [133–138].

For routine clinical use, as well as in clinical trials, there remain open questions in the use of AI tools, such as the ambiguity of who controls AI and who is ultimately responsible for its actions. Decision making based on the output of AI tools should be consistent and have an auditable trail of material. MPEs have a role to play in guiding this process and ensuring there is sufficient integrity and understanding of the AI software during all phases of the clinical trial.

6.2. Recommendations

MPEs should be involved in the dedicated MDT of experts ensuring safe and clinically relevant use of AI in clinical trials of interventional or diagnostic technology (such as radiology and RT trials).

MPEs should be involved in the team that provides training for correct use of AI and interpretation of its results in clinical trials.

The MDT should be aware of any changes to the AI tool during the trial and if new changes are made (i.e. more training data is added to the model, assessing drift migration in results). In which case, concerted efforts should be made to understand the implications of any such changes to the AI tool.

MPEs should evaluate if participating institutions have the capability to support and manage the desired AI tools, proposed for the clinical trial, in a scalable and sustainable manner.

7. Legislation and regulation

In this section, we summarise the role of the MPE in relation to the most common regulations that are applicable in the development and operation of a clinical trial. MPEs must be involved/advise on these aspects, given their training in relevant legislation applied to diagnostic imaging and RT technologies, alongside radiation safety experts and the wider MDT.

The legislation is based on the principles of Good Clinical Practice (GCP), an international quality standard provided by the International Council on Harmonization (ICH). Governments can transpose GCP into regulations for all phases of clinical trials involving human subjects. GCP applies to the trial sponsor team, the IRBs, Research Ethics Committees (RECs) and the investigator site teams [138].

The recent EU regulations on clinical trials on medicinal products (2014/536) and on medical devices (2017/745) represent an evolution, with respect to the previous EU directive. As regulations, they are immediately applicable in all member states, overruling national laws and give an advantage for stakeholders (e.g. sponsors and investigators) by helping to make Europe a homogeneous place for research and development of medicines and medical devices.

Besides these specific regulations, the conduct of a clinical trial should respect all local laws and regulations involving the subjects both as patients and as members of the general population. Among the regulations that are particularly relevant in clinical trials is the protection of personal data explicated in the Regulations on General Data Protection (GDPR, see Section 7.3).

The exposure of subjects to radiation is the object of specific EU Directives that are translated to each country with different delineation of the role and responsibilities. EUD 2013/59/EURATOM lays down basic safety standards for protection against the dangers arising from exposure to ionising radiation while EUD 2004/40/EC and Directive 2013/35/EU rule the exposure to electromagnetic fields.

7.1. Regulations on clinical trials on medicinal products

The rules for the conduct of clinical trials are defined by EU Regulation 2014/536 on Clinical Trials on medicinal products for human use (CTR) [139]. It entered into application on 31 January 2022. The goal of the CTR is to create an environment favourable to conducting clinical trials in the EU by harmonising the assessment, supervision, and processes of clinical trials. MPEs can help guarantee the highest standards of safety for participants, with regards to ethics and radiation protection; they can also improve transparency of information, through the publication of information concerning the conduct and results of clinical trials.

7.2. Medical device regulation

Medical devices are products or equipment intended for a medical purpose. Medical devices may be placed on the European market if they bear a CE marking. A manufacturer may affix the CE mark if it has demonstrated compliance with the requirements in the recent EU MDR 2017/745 [140].

In general, MDR increases the clinical information needed to apply and keep the CE marking. One requirement is that there is sufficient clinical evidence on the safety and effectiveness of the device for market authorisation. The MDR also promotes post-marketing studies to confirm the positive benefit-risk ratio over time during marketing.

The rules for conducting clinical investigations on medical devices are laid down in the MDR. Some aspects of GCP are named in the MDR. For detailed elaboration, the MDR refers to ISO 14155:2020 Clinical investigation of medical devices for human subjects.

The legal requirements for clinical evaluation also apply to software. In the case of self-created applications (see Article 5.5 of the MDR for requirements), CE marking does not apply. However, it is required that

the health institution using the software justifies its use in the documentation and carries out a priori risk analysis before any use on patients. They must demonstrate that the intended use, to meet the needs of a specific patient group, cannot be met at the appropriate level of performance by an equivalent device available on the market [141].

The introduction of MDR is likely to lead to an increase in preclinical and clinical research on medical devices. With their expertise between physics, informatics, and medicine, MPEs should become key stakeholders in the review process of studies with innovative medical devices in imaging and RT clinical trials. Recently, EFOMP published "EFOMP policy statement 17" describing the potential role and competences of MPs and MPEs at different stages of the medical device life cycle [142].

7.3. Regulations on general data protection

Clinical trials use a large amount of sensitive data, and public access to clinical trials data has now increased considerably. Clinical trial data transparency implies that decisions and data from clinical studies are widely shared with other researchers, clinicians, and the public. Therefore, it is of utmost importance to secure patients' privacy and confidentiality.

The EU GDPR 2016/679 applies to EU and foreign companies, authorities and other stakeholders who process the personal data of subjects residing in the EU. Its goal is to setup a mechanism to safeguard the rights of individuals to have reasonable control and be better informed about how their data is being used.

The clinical trial sponsor must identify what data are being processed, who will or can process the data, where it should and may be transferred to, what it will be used for, any risks related to the processes and finally ensure that all personnel involved in the clinical trial are trained to meet these objectives [143]. It is also its duty to maintain records of data processing activities and perform data processing impact assessments in the interest of protecting the rights of clinical trial participants.

Those developing a clinical trial must consider challenges related to informed consent, the use of publicly available data, (pseudo-)anonymisation, and international data transfer. MPEs actively participate in all these areas and must be aware of GDPR regulations and co-ordinate with other personnel involved in the clinical trial to fulfil it.

In particular, MPEs have significant expertise in managing DICOM data. DICOM objects contain extensive information on patients, as well as on personnel, such as the referring physician or technician acquiring images, which shall not be disclosed. It is compulsory that DICOM objects shared in clinical trials are correctly de-identified using proper software. Care must be taken when using such de-identification tools to ensure a sufficient de-identification (e.g. screening for the presence of private fields which might contain unexpected identifiable information) without deleting needed data (e.g. the acquisition time in PET data used to calculate SUV).

7.4. Ionising radiation legislation, Directive EU 2013/59

The role of the MPE is clearly defined in the European Directive 2013/59/EURATOM [144]. It concerns the MPE involvement in the following applications, as from Art. 58: (i) involved in the radiotherapeutic practice, (ii) involved in therapeutic nuclear medicine, radiodiagnostics and interventional radiology and (iii) involved or available for consultation in radiation protection in medical radiological applications. MPEs' responsibilities apply to routine medical practice and to clinical trials (as mentioned in Section 2). Considering that clinical trials regulation is equivalent across the EU, we shall consider that the role of an MPE in the case of clinical trials management shall be the one described in the Directive.

Art 5 enforces the fact that justification of a "medical exposure for medical or biomedical research [is] examined by an ethics committee, set up in accordance with national procedures and/or by the competent authority". Art 56 on Optimisation define specifically that: "Member States shall ensure that for each medical […] research project involving medical exposure:

(a) the individuals concerned participate voluntarily;
(b) these individuals are informed about the risks of exposure;
(c) a dose constraint is established for individuals for whom no direct medical benefit is expected from exposure
(d) in the case of patients who voluntarily accept to undergo an experimental medical practice and who are expected to receive a diagnostic or therapeutic benefit from this practice, the dose levels concerned shall be considered on an individual basis by the practitioner and/or referrer prior to the exposure taking place."

Within a clinical trial using ionising radiation, it is also necessary to verify that the use of radiation does not expose the workers to an excess of radiation risk and their exposure is optimised. As discussed in Section 2.4, EFOMP's position on radiation protection is described in the Malaga Declaration [3].

7.5. RP 99 – Guidance on medical exposures in medical and biomedical research

In 1998, the European Commission published the Radiation Protection (RP) 99 Guidance on medical exposures in medical and biomedical research to deal with research programs involving the use of radiation. Even if most of the principles were included in 2013/59/EU, there is additional information that is useful in the conduct of clinical trials.

In particular, RP 99 contains a framework for the risk assessment due to radiation exposure: when designing a study, an assessment of predictable risks compared with the foreseeable benefits for the subject or to others must be carried out. RP 99 also mentions the obligation of tissue dose calculation in case of RT (both external and internal) and interventional procedures; it states that justification must be made, and that methods and procedures must be compliant with GCP. Given their training, MPEs are well suited to complete risk assessments and dose calculations.

The role of the Ethical Committee is also delineated, since the aims, outline methods, justification, optimisation, and detailed plans of the clinical trial should be evaluated by the ethics committee and/or competent authority before a project is started, including input from an MPE.

7.6. Electromagnetic field legislation, Directive 2013/35/EU, and 2006/25/EC

Health care workers must be protected against the risks of electromagnetic field and optical radiation, as specified in the European directives 20013/35/EU [145] and 2006/25/EC [146]. It is the role of the MPE to advise on such matters. The use of such radiation in clinical trials requires the understanding of its potential risk since the exposure of patients may exceed the limits for the general population or for workers, potentially harming the patient. Their use in clinical trials shall be weighed, by the MPE and wider MDT, against the potential health risks also considering their interference with medical devices, a well-known issue in MRI [24].

7.7. Recommendations

A dedicated MPE must handle the trial radiation safety and relevant regulatory aspects.

MPEs should be key stakeholders in the review process of studies with relevant innovative medical devices.

MPEs should (co-)lead to ensure that DICOM (Digital Imaging and Communications in Medicine), and other patient data is suitably de-identified / anonymised, whilst ensuring data is kept in a usable format.

MPEs must be involved in all clinical trials related to radiotherapeutic practice, therapeutic nuclear medicine, radiodiagnostics or interventional radiology.

8. Summary

This document provides guidance on the varied roles MPEs should and must have within clinical trials. Table 1 summarises the recommended roles and responsibilities of MPEs across the whole clinical trial pathway, from conception to recruitment, through to dissemination and implementation of results. These guidelines should help to harmonise these roles across Europe.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix 1. Definition of common terms used in these guidelines

- Benchmark case(s): anonymised planning and/or delineation test on a common CT dataset. They are completed by all recruiting centres wanting to participate in a clinical trial.
- Coordinating Committee/Trial Management Group: a committee that a sponsor may organise to coordinate the conduct of a multicentre trial.
- Coordinating/Principal Investigator/Chief Investigator: an investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.
- Credentialing is the process of establishing the qualification and assessing the capability of a healthcare facility to produce/deliver the treatment or the imaging protocol according to the clinical trial procedures. It includes an examination and review of the institution and/or its staff to determine whether they meet certain criteria for participating in a specific clinical trial. The duration of credentialing depends on the trial; it may have to be renewed. It may be extended to other trials with shared specifications (streamlined) or withdrawn if the conditions are no longer met. By definition, it represents the green light to begin trial's patient inclusion; it may be obtained pre-accrual or may use the first patient's data and is a streamlined process. It may consist of a questionnaire and/or a phantom analysis.
- Dummy-run/Dry run (with or without delineation exercise): Using imaging data of an in-house patient, this procedure is either a protocol compliance treatment plan test or a simple connectivity check.
  - o A set of images/test patients or phantoms is sent to every centre to evaluate the possibilities of a centre to respect clinical trial requirements (e.g., contours, absolute dose, dose constraints, image quality, data transfer), simulating a specified part of the workflow, this may include all imaging and RT procedures. It is assessed by an expert or a group of experts.
- End-to-end test: methodology to assess the working order of a complex process in a start-to-finish process.
- Imaging biomarker: A special example of biomarkers where the indicator is derived from in vivo medical images. It provides an attractive choice for clinical use as IBs can be implemented and used as a real-time, non-invasive, cost effective option.
- Institutional Review Boards/Independent Ethics Committees: administrative group of persons from outside an institution that is responsible to protect the rights, the welfare and the privacy of clinical trial participants. Prior to initiate a clinical trial, an IRB/IEC reviews and monitors the research on a regulatory and ethical basis.
- Medical technology: Technology using ionising radiation, or used in the fields of radiotherapy, nuclear medicine or radiology
- Medical Physics Expert (MPE): An individual or, if provided for in national legislation, a group of individuals, having the knowledge, training and experience to act or give advice on matters relating to radiation physics applied to medical exposure, whose competence in this respect is recognised by the competent authority
- On-trial QA: Quality verification reviewed during ongoing trial. It could include, for example, the verification of image quality, target and OAR contour delineation and treatment planning. The On-trial QA can also be a set of QC tests that are done automatically during a trial (e.g. verification of DICOM compliance).
- Pre-trial QA: Quality verification realised before the inclusion of the first patient. It may consist of a facility questionnaire (designed to ask the right question expected to define if a centre may be included or not) and a dry run or dummy run.
- Protocol: A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol usually gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.
  - o Radiotherapy Guidelines or RT Protocol: a document that describes the RT specific components of the trial. This may include imaging protocols, immobilisation and localisation, target and OAR delineation, clinical target volume and planning target volume margins, dose prescription(s), treatment modalities, planning parameters (including dose objectives), planning priorities, on-treatment verification.

Appendix 2. Acronyms

AAPM	American Association of Physicists in Medicine
AI	Artificial Intelligence
CE	European Conformity
CT	Computed Tomography
CTR	Clinical Trials on medicinal products for human use
DAHANCA	Danish Head and Neck Cancer group
DICOM	Digital Imaging and Communications in Medicine
DVH	Dose Volume Histogram
EANM	European Association of Nuclear Medicine
EFOMP	European Federation of Organisations for Medical Physics

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AAPM	American Association of Physicists in Medicine
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
ESTRO	European SocieTy for Radiotherapy and Oncology
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IAEA	International Atomic Energy Agency
IB	Imaging biomarker
ICH	International Council on Harmonization
IGRT	Image Guided Radiotherapy
IMRT	Intensity-Modulated RadioTherapy
IEC	Independent Ethics Committees
IRB	Institutional Review Board
IT	Information Technology
MDR	Medical Device Regulation
MDT	MultiDisciplinary Team
ML	Machine Learning
MP	Medical Physicist
MPE	Medical Physics Expert
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NMOs	National Member Organisations
OAR	Organ At Risk
PET	Positron Emission Tomography
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RP	Radiation Protection
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group (United States)
SPECT	Single Photon Emission Computed Tomography
TMG	Trial Management Group
WG	Working Group

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