Society for Endocrinology

Endocrine Oncology (2024) **4** e230045
https://doi.org/10.1530/EO-23-0045

Received 14 December 2023
Accepted 17 April 2024
Available online 17 April 2024
Version of Record published 10 May 2024

THEMATIC REVIEW

How to design a theranostic trial?

Dheeratama Siripongsatian[1], Quido G de Lussanet de la Sablonière[2], Frederik Anton Verburg[2] and Tessa Brabander[2]

[1]National Cyclotron and PET Centre, Chulabhorn Hospital, Bangkok, Thailand
[2]Department of Radiology & Nuclear Medicine, Erasmus MC, Rotterdam, Netherlands

Correspondence should be addressed to T Brabander: t.brabander@erasmusmc.nl

This paper forms part of a themed collection on Theranostics in Neuroendocrine Neoplasms.

Abstract

The field of nuclear theranostic clinical trials is continuously expanding as an increasing number of novel agents and treatment combinations are explored for treating advanced and metastatic cancers. Moving from 'bench-to-bedside' is oftentimes a complex and lengthy process. The objective of this overview is to explore the basic elements involved in designing clinical trials with a special focus on theranostics in nuclear medicine. The 'bench-to-bedside' journey involves translating basic scientific research into patient-effective treatments. Preclinical studies, a crucial initial step, are a complex process encompassing *in vitro* experiments, *in vivo* studies, and animal models to explore hypotheses in humans. Clinical trials follow, with predefined phases assessing safety, effectiveness, and comparisons to existing treatments. This process demands investments in data management, statistics, good clinical practice (GCP) accreditations, and collaborative efforts for funding and sustainable pricing. Theranostics, merging diagnostics and personalized treatment, is at the forefront. Continuous efforts to enhance existing agents involve reducing adverse effects, exploring new indications, and incorporating advanced imaging modalities. Radionuclide therapy, unique with non-uniform distribution and complex radiobiology, plays a distinct role. This article explores trends and challenges in each clinical trial phase in light of the emerging field of theranostics in nuclear medicine, emphasizing meticulous trial design, dosimetry optimization, and the necessity of collaborative stakeholder efforts for successful implementation.

Keywords: clinical trials; nuclear medicine; radionuclide therapy; theranostics

Introduction

Theranostics in nuclear medicine is the unique combination of radionuclide-based agents used for both diagnostic and therapeutic purposes. The first described example of a theranostic is the radio-iodine treatment in both benign and malignant thyroid disease. Since the introduction of radio-iodine-based theranostics, new theranostic agents have been explored. Some have proven their success, such as metaiodobencylguanide-based treatment for adrenal disease, peptide-receptor radionuclide therapy (PRRT) in neuroendocrine tumors, and more recently, prostate-specific membrane antigen (PSMA)-peptide-based treatment in prostate cancer. Conversely, many other potential theranostics proved unsuccessful, oftentimes in early preclinical phases, yet some failed in advanced clinical trials.

There is a growing interest in exploring novel theranostic agents for various advanced and metastatic cancers, including combination therapies and innovative targets (Bodei *et al.* 2022). Advances in hybrid imaging, such as the combination of single photon emission computed tomography (SPECT) with CT and positron emission tomography (PET) with CT or MRI, are propelling the growth of theranostics. These developments enhance

Published by Bioscientifica Ltd.
https://eo.bioscientifica.com
© 2024 the author(s)

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

Endocrine Oncology (2024) **4** **e**230045
https://doi.org/10.1530/EO-23-0045

cancer detection and monitoring, with the potential to optimize cancer diagnosis, personalized treatment, and ultimately, patient outcomes (Howlader *et al.* 2020, Markham *et al.* 2020).

Clinical trials are fundamental for assessing new treatments and follow structured phases (preclinical phase, phase 0, phase I, phase II, and phase III). These phases evaluate safety and toxicity, effectiveness, and short-term adverse events and risks associated with the treatment. Regulatory approval marks the beginning of phase IV trials, which are conducted to determine long-term safety and effectiveness and to identify adverse events that may not have been apparent in prior trials. Organizations such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) maintain strict standards for biomedical research throughout the drug development process, including clinical trials (Umscheid *et al.* 2011, Bighelli & Barbui 2012).

In this overview, we explore theranostic considerations within each phase, highlighting aspects such as patient selection, imaging modalities, therapy strategies, and outcome measures, aiming to provide tools for future theranostic trial designs.

Preclinical phase and phase 0: exploratory and 'first-in-human'

Preclinical studies play a crucial role in the development of therapeutic agents, aiming to predict their effect in humans. In the context of radionuclide therapy, these studies focus on comprehending three key aspects: biodistribution (how the drug is distributed in the body), tissue retention, and pharmacokinetics (how the drug is metabolized and excreted). These factors are critical in determining both the potential effectiveness and potential toxicity of the treatment in humans. Of note, toxicity is generally related to the absorbed dose in non-target tissue. The potential pharmacologic toxicity of the carrying agent is usually considered low as the amount of agent administered is generally in the order of just micrograms. Dosimetry studies are of utmost importance to address the absorbed dose in both target and non-target tissue and hence to evaluate the potential radiobiological effects of consequent radionuclide therapy.

In the preclinical phase, experiments start *in vitro* with cell cultures and tissues, enabling researchers to observe processes at the cellular level using imaging. Following this, *in vivo* model systems come into play, typically in small animal rodents, which can include cell-line-based models, patient-derived xenograft models, and genetically engineered mouse models, for example (Langdon 2012, Tentler *et al.* 2012). Small animals can be evaluated with imaging techniques that are comparable to those routinely applied in clinical settings, such as animal PET, SPECT, CT, and/or MRI (Timpson *et al.* 2011).

In nuclear medicine, small-animal imaging is required to assess the biodistribution and pharmacokinetics of therapeutic agents in preclinical studies. However, it is essential to note that nuclear medicine imaging cannot distinguish between intact carrier-associated radioactive agents and dissociated free radioactive agents. Therefore, complementary *in vitro* and *in vivo* competitive inhibition and control studies are needed (Sgouros *et al.* 2014).

As phase 0 progresses to the initiation of phase I clinical trials, the activities to be administered are calculated based on the absorbed dose to the dose-limiting organ and the tolerance absorbed dose values. Currently, these dosimetry approaches are based on experiences and models for external beam radiotherapy in humans for that particular organ. As experiences with targeted radionuclide therapy increase, important differences with respect to external beam therapy-based dosimetry are being discovered, however. Preclinical studies serve as the critical foundation that ensures a safe and effective transition from the laboratory to the clinical application of radionuclide therapy (Emami *et al.* 1991, Bentzen *et al.* 2010).

Methodological requirement for radionuclide therapy

Quality control of radiopharmaceuticals

In Europe, both diagnostic and therapeutic radiopharmaceuticals, including investigational medicinal products used in clinical trials, are required to adhere to good manufacturing practices (GMP) during the production process (Decristoforo *et al.* 2021). These GMP guidelines are essential to ensure the safety, efficacy, and consistency of radiopharmaceuticals. To produce radiopharmaceuticals in line with GMP, several critical requirements must be met (Elsinga *et al.* 2010).

Moreover, the final radiopharmaceutical must undergo a thorough analysis to ensure it meets pharmacopoeial standards. This analysis involves verifying the identity of materials and checking the certificate of analysis for sterility, radioactivity, purity, stability, and other factors such as batch size, appearance, and shelf-life (Verbruggen *et al.* 2008).

Stability assays play a vital role in this process, as they help determine a radiopharmaceutical's stability under typical storage conditions for a specified shelf life. It is crucial for a radiopharmaceutical formulation to retain its properties, including purity and its affinity for the intended target. Over time, radiopharmaceuticals may aggregate, deteriorate, undergo radiolysis, experience changes in their properties during storage, or (when used *in vivo*) undergo enzymatic degradation. A lack of stability can significantly impact both scientific results, clinical effectiveness, and safety (e.g. adverse

Endocrine Oncology (2024) **4** **e**230045
https://doi.org/10.1530/EO-23-0045

events) of these products (International Atomic Energy Agency 2023).

Dosimetry

The International Atomic Energy Agency has formulated basic safety standards requiring the optimization of protection and safety for each medical exposure, including the administration of radiopharmaceuticals for therapeutic purposes. The type and activity of the radiopharmaceutical administered to each patient have to be appropriate. The dosimetry calculations performed should account for patient-to-patient variation in pharmacokinetics and anatomy. In radionuclide therapy, dosimetry can be divided into two main aspects: pretherapy and posttherapy, as well as target (e.g. tumor) and non-target (e.g. healthy tissue/organs and bone marrow). Pretherapy dosimetry is crucial for treatment planning and predicting biodistribution, while post-treatment dosimetry can quantify the actual effective half-life and absorbed target- and non-target doses. In fractionated therapies, dosimetry guides (personalized) subsequent cycles, adjusting doses or stopping the treatment. Lesional dosimetry aims to deliver a predetermined radiation dose to a tumor while maintaining a safe absorbed dose in non-target tissue. The rationale behind lesional dosimetry is that the absorbed dose by the tumor may have a direct relationship with the response. Currently, the most commonly utilized lesional dosimetry is performed in locoregional radionuclide therapies, such as selective intra-arterial liver-directed radionuclide therapy. On the other hand, systemically administered radionuclide therapies may not consistently achieve the desired absorbed dose in every tumor without causing toxicity to non-target organs. The maximum targeted activity dosimetry aims to administer the highest safe activity while avoiding toxic dose concentrations, especially in organs at risk (Lawhn-Heath *et al.* 2022).

The absorbed radiation dose, as measured in the SI unit Gray (Gy, J/kg), relies on factors such as the rate of radioactive decay, the energy emitted, tissue retention time, tissue volume, and the energy deposited in the tumor or organ. To calculate the absorbed dose, multiple measurements in time are generally necessary for evaluating pharmaceutical uptake, retention, and washout. These measurements result in time–activity curves for which the area-under-the-curve is used for estimating the cumulated activity per selected volume of tissue. As these curves generally follow an exponential course, ideally, a minimum of three data points is required. In practice, this means that measurements must be performed, for example, on the day of administration (between the first and fourth hours after administration) and in the following days up to day 7 (depending on the radiopharmaceutical used) (Sjögreen Gleisner *et al.* 2022).

In clinical trials and the evaluation of novel therapeutics, dosimetry is vital, especially in phase I ‘dose-escalation’ assessments and pre-therapeutic planning. Dosimetry helps establish organ-specific doses, determine the maximum tolerated activity, and recommend phase II doses. In the case of a dose escalation study, dosimetry assessments must occur at each level and should be correlated with safety laboratory data.

The upcoming use of alpha-emitting radionuclides imposes a new challenge in dosimetry. While traditionally used beta-emitting radionuclides are reliably measured using SPECT or PET cameras. Alpha emitters, such as Ac-225, have typically very few (gamma) emissions in their decay scheme, making dosimetry quite difficult. The dosimetry of other alpha-emitting isotopes, such as Ra-223 or Th-227, is more feasible (Staudacher *et al.* 2014).

Phase I: safety and dosage

Phase I studies have two primary objectives: ensuring the safety of the drug and finding the most effective dose for later phases of research. In these trials, researchers might work with healthy volunteers, but with radionuclides, it is preferred to include individuals with the specific disease under investigation, such as cancer patients. The main goal of phase I trials is to evaluate how the drug interacts with the human body and identify the maximum tolerated dose (MTD) without causing severe side effects.

To establish the MTD in radionuclide therapies, various approaches are employed. The choice of a dose-escalation methodology, whether predetermined or adjusted based on toxicity, depends on specific trial considerations and requirements, such as dose–toxicity and dose–efficacy curves of the drugs, rate of dose escalation, or interpatient variability (Le Tourneau *et al.* 2009). A traditionally used dose-escalation study is the ‘3 + 3 design’. In this design, three patients are initially enrolled in a specific dose cohort (Le Tourneau *et al.* 2009, Ivy *et al.* 2010). If none of the patients experience dose-limiting toxicities (DLTs) according to the Common Toxicity Criteria from the National Cancer Institute (CTCAE), the trial progresses to the next higher dose cohort. In cases where one patient in a specific dose level experiences a DLT, three additional individuals are enrolled in that cohort to collect more data. If two or more out of the total six patients exhibit DLTs, further dose escalation is halted, indicating that the MTD has been exceeded.

Another commonly used method involves a fixed percentage increase per dose group, typically around 20–25%. Predetermined approaches often utilize a modified Fibonacci series to determine dose increments, while toxicity-adjusted escalation plans take into account the highest toxicity grade observed in the prior dose level. For instance, no toxicities may trigger a 100% escalation, Grade I toxicities may lead to a 50% increase, Grade II to a 25% increase, and Grade III or higher

Endocrine Oncology (2024) **4** **e**230045
https://doi.org/10.1530/EO-23-0045

toxicities result in halting the escalation and expanding the cohort. If less than one-third of patients experience Grade III or higher toxicities, a further 25% escalation may be implemented. The choice of dose-escalation methodology is ultimately guided by trial considerations and specific requirements (Kurzrock *et al.* 2021).

Throughout the phase I study, participants are closely monitored, and data on the drug's pharmacological behavior and immediate and short-term side effects are collected. While phase I studies may assess therapeutic effectiveness, their primary focus is on establishing safety, determining the appropriate dosage, and comprehending the drug's pharmacokinetics. The results obtained from phase I studies provide essential insights that guide subsequent phases of clinical development (Meredith 2002).

Phase II: efficacy and side effects

Phase II studies are the next step in the process of evaluating new radiopharmaceuticals. The primary goal of phase II trials is to assess the effectiveness of the treatment while ensuring patient tolerability and safety. To achieve this, a common approach is to use a dose set at about 80% of the highest dose that patients can tolerate without severe side effects, also known as the MTD, as established in phase I studies. The secondary goal of Phase II trials is to consider factors like the duration of the response, progression-free survival, and overall survival rates after treatment (overall survival).

To make the trial process efficient, a two-stage design is often used. This design allows for an early stop to the trial if no responses are observed within an initial group of 14 patients, indicating a low likelihood of achieving a response rate of 20% or more. Conversely, if promising responses are observed, researchers can adjust the required number of patients needed to confirm a response rate of at least 20%, based on the fraction of patients who respond positively.

It is important to note that in phase II trials, personalized dosing strategies are considered. These strategies take into account factors like a patient's body weight, race, and other biological characteristics. These considerations are carefully factored into the trial's design and implementation.

Patient selection

Patients are typically recruited for theranostic trials when they have reached the advanced or end-stage of their disease. These are often individuals with conditions that cannot be treated with surgery, and they may have experienced suboptimal outcomes or side effects from previous treatments. Nevertheless, ongoing trials aim to evaluate the effectiveness and safety of theranostic approaches, like PSMA radioligand therapy, in earlier stages of diseases such as prostate cancer, including hormone-naive prostate cancer and hormone-sensitive metastatic prostate cancer (Zhang *et al.* 2021).

The use of diagnostic tools is essential for patient selection in theranostics. PET/CT is generally inherent in theranostics for assessing whether radionuclide treatment is appropriate. For example, if the pathology to be treated does not show sufficient targeted uptake on the PET images, the patient is generally not an appropriate candidate for targeted radionuclide treatment. In addition, diagnostic CT and/or MRI may be used for response assessment in terms of radiologic imaging-based Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Patient characteristics also play a significant role in the selection process. Factors like a patient's overall health, World Health Organization (WHO) performance status, medical history, and comorbidities are essential when determining their eligibility for theranostic trials. Generally, patients with a good performance status, indicating their ability to cope with potential side effects and treatment demands, are preferred. Patients with a fast rate of progression and relatively short life expectancy (e.g. <3–6 months) are generally not suited for targeted radionuclide therapy because the treatment is generally given in multiple cycles with an interval of multiple weeks (e.g. PRRT and PSMA 6–8 weeks interval) and need time for the treatment to take effect.

Side effects

Radionuclide therapy, while effective, has potential inherent adverse effects, particularly affecting non-targeted normal tissues. To assess and manage these adverse effects during clinical trials, standardized scoring systems are utilized. Two common systems are the CTCAE (Dueck *et al.* 2015) and the grading system associated with the WHO (Franklin *et al.* 1994). These systems use a grading scale ranging from 0 (no significant toxicity) to 4 (potentially life-threatening toxicity) to categorize the severity of side effects. Other indicators that may be monitored include the time it takes for moderate to severe side effects to develop, how long severe side effects last, and the impact of side effects on factors like a patient's performance.

In radionuclide therapy, the bone marrow often plays a crucial role as a dose-limiting organ for many systemic treatments. Patients undergoing radionuclide therapy may experience transient subacute bone marrow compromise, leading to temporary anemia, leukopenia, and/or thrombocytopenia. Chronic adverse events are of particular concern as they are often permanent. The occurrence of chronic adverse events may vary depending on the specific organs involved. Some events, such as renal failure or salivary gland impairment, exhibit a dose-dependent relationship, meaning the risk increases with higher radiation doses. Conversely,

Endocrine Oncology (2024) **4** **e**230045
https://doi.org/10.1530/EO-23-0045

certain events, like therapy-related myeloproliferative syndrome, can occur randomly without a clear dose-dependent relationship, although the probability of such events tends to increase with higher radiation doses and pretreatment with chemotherapy.

Phase III: efficacy and monitoring of adverse reaction

Phase III studies are designed to determine the true benefits of a new treatment for a specific group of patients. These trials offer essential insights into both the effectiveness and safety of a new treatment, particularly in uncovering less common side effects that might have been missed in earlier phases. Phase III trials differ from phase II by their larger scale (i.e. more patients) and longer follow-up duration, to capture longer-term and possibly less frequent side effects. In this context, a phase III trial typically undergoes evaluation by means of a head-to-head comparison with the current standard of care or the established treatment. The aim is to discern whether the new radionuclide treatment surpasses the standard in terms of effectiveness or offers other advantages, such as diminished side effects, all while delivering equivalent therapeutic benefits.

Response evaluation

Evaluating treatment response in theranostics presents unique challenges, primarily because established criteria for assessing response with modern hybrid imaging techniques are lacking. Although the reduction in tumor size is a widely recognized indicator of treatment response, clinical experience has shown that stable disease can also be indicative of a positive response. This stability may result from tumoral volume being replaced by fibrotic tissue, often going unnoticed by conventional imaging methods like the RECIST (van Vliet *et al.* 2013).

Moreover, specific non-measurable lesions complicate the assessment process. These include small tumors with diameters less than 10 mm, bone metastases lacking distinct soft-tissue components, pleural tumor seeding, lymphangitic tumor spread, and peritoneal or leptomeningeal tumor diseases (Ruchalski *et al.* 2022).

To overcome these issues, molecular imaging techniques and biologic markers, such as PET, come into play. Criteria like Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.1 provide valuable tools for evaluating these non-measurable lesions. PERCIST involves assessing changes in the tumor's standardized uptake value (SUV). For example, a significant decrease in metabolic intensity in terms of standardized SUV measurements or relative uptake with respect to other organs such as the liver, spleen, or blood pool may signify a more favorable treatment outcome. However, an ongoing debate exists in the field regarding the applicability of PERCIST to various PET tracers (Wahl *et al.* 2009). This debate arises from fundamental differences in the uptake mechanisms between tracers like [18F]FDG and other tracers, such as PSMA or DOTATATE PET, which assess glucose metabolism versus PSMA or SSTR expression. As a result, many experts in molecular imaging exercise caution when applying PERCIST and often restrict its use to predefined thresholds for progressive disease and partial response (Grubmüller *et al.* 2019, Huizing *et al.* 2020, Rosar *et al.* 2022).

Tracer-specific response criteria are in development, however. One example is early response evaluation in men with mCRPC treated with 177Lu-PSMA, which has shown higher prognostic value and inter-reader reliability as compared to conventional CT assessment or other imaging modalities: response evaluation criteria in PSMA PET/CT (RECIP) 1.0 (Gafita *et al.* 2022). Additionally, artificial intelligence is making strides in assisting radiologists by automating the segmentation of PET images to obtain prognostic parameters (Kendrick *et al.* 2023). Recent advancements in radiomics and quantitative PET techniques hold the promise of providing more refined parameters for assessing tumor heterogeneity, phenotypes, and overall tumor burden. These developments aim to establish PET as a significant prognostic biomarker across various cancers, thereby improving treatment response assessment in theranostics (Schöder & Moskowitz 2016, Winther-Larsen *et al.* 2016).

Quality of life

Improving the quality of life (QOL) for oncology patients stands as a paramount objective with profound implications for treatment decisions. QOL, in this context, encompasses the holistic impact of a disease on a patient's physical, psychological, and social well-being, as perceived by the patient themselves. Measuring QOL, however, presents several notable challenges. These include selecting appropriate tools, determining the frequency and timing of measurements, simplifying data interpretation and comparison, and identifying the minimum clinically important difference. While generic measures offer a broad perspective on QOL issues, they might lack the sensitivity to capture the specific changes in how cancer affects individual patients. Nonetheless, many studies now recognize the importance of incorporating QOL indicators into clinical trials, spanning from generic to cancer-specific and site-specific measures (Soni & Cella 2002, Khan *et al.* 2011, Strosberg *et al.* 2018).

Phase IV: post-marketing surveillance

Phase IV trials play a crucial role in the post-market safety monitoring of approved drugs or devices, following their clearance by regulatory authorities such

Endocrine Oncology (2024) **4** **e**230045
https://doi.org/10.1530/EO-23-0045

as the FDA or EMA. These trials are aimed at identifying and assessing any potential side effects or adverse events that may not have been observed in earlier phases of clinical testing.

Moreover, phase IV trials offer a unique opportunity to scrutinize the long-term effectiveness and sustainability of a new treatment approach. During this phase, researchers and healthcare professionals examine the real-world impact of the treatment beyond the controlled environment of clinical trials. This extended view allows for the detection of any unexpected or rare side effects that may emerge in a larger patient population, providing crucial insights into the safety profile of theranostic agents.

Phase IV trials generally generate large sets of data that require professional data management and vast financial investments in personnel, analyses, and storage, which might sometimes be better outsourced to professional organizations.

Beyond safety considerations, phase IV trials also provide essential data from a financial perspective in terms of cost-effectiveness and economic implications. This aids healthcare providers and decision makers in making informed assessments of the treatment value and impact on healthcare and healthcare costs, which is vital for financially sustainable healthcare.

Overall, phase IV trials serve as a bridge between clinical research and real-world implementation, contributing to the ongoing improvement of patient care. By continuously monitoring the safety and effectiveness of approved treatments, we can enhance patient outcomes, refine healthcare practices, and make informed decisions about the allocation of healthcare resources.

Special considerations

Combination therapies

The integration of theranostic agents with established systemic therapies represents a compelling and emerging approach that holds great potential in improving patient outcomes. This strategy involves exploring various combinations, such as chemotherapy, radiosensitizers, external beam radiation therapy, and immunotherapies, to harness synergistic effects and develop more effective and comprehensive treatment strategies. This field of research has garnered significant interest and has been the subject of studies. (Nonnekens *et al.* 2016, Cullinane *et al.* 2020, Huang & Zhou 2020, Czernin *et al.* 2021, Satapathy *et al.* 2021).

Nuclear theranostic agents primarily induce DNA damage as part of their mode of action. To amplify their effectiveness, they can be combined with chemotherapy or radiosensitizers. These combinations obstruct crucial processes, like DNA damage repair and immune checkpoints. For instance, PARP-1, involved in repairing both single-stranded and double-stranded DNA breaks, is a potential target for radiosensitization. Immune checkpoint blockers that target programmed death receptor 1 (PD-1) ligand 1 (PD-L1) have significantly improved survival across various cancer types. Employing targeted radionuclide therapy to deliver systemic radiation to tumors can potentially transform the tumor microenvironment across all metastatic sites and enhance the effectiveness of immune modulators. However, it is important to note that combining these therapies can lead to increased adverse events, possibly due to overlapping toxicities (Chan *et al.* 2020). Nonetheless, the results of studies combining radionuclide therapy with other therapies are promising for improving patient outcomes and broadening our understanding of synergistic treatment modalities.

Discussion

Clinical trials are the gold standard for establishing the safety and efficacy of new treatments, including new radionuclide therapies. These trials require highly controlled variables and a well-defined patient population, in order to determine the 'true' effect of the medical intervention on patients. However, one should acknowledge that these controlled conditions may not fully mirror real-world scenarios.

Clinical trials and the real world

The advancement of radionuclide therapies has leaned significantly on 'compassionate use programs at academic centers and single-center trials. Regulatory agencies such as the EMA provide recommendations with respect to compassionate use, but these do not create a legal framework, and different countries set their own rules and procedures. Nonetheless, compassionate use pathways have played a crucial role in development in theranostics. However, when it comes to official approval of new drugs, including radiopharmaceuticals, formal clinical trials are mandated.

As thorough as clinical trials may be, a shortcoming is that the results from these trials may not always perfectly match what happens in the real world, where patients have varying disease burdens, other health issues, different ages, and ethnic backgrounds. To address this gap, surveys of large patient groups that collect real-world evidence or 'real-world data' are becoming of increasing importance.

Access to theranostics

Ensuring global access to theranostics financial aspects must be taken into account. Affordability and reimbursement of these agents are pivotal in ensuring equitable access. It is imperative for stakeholders, including governments, insurers, and healthcare

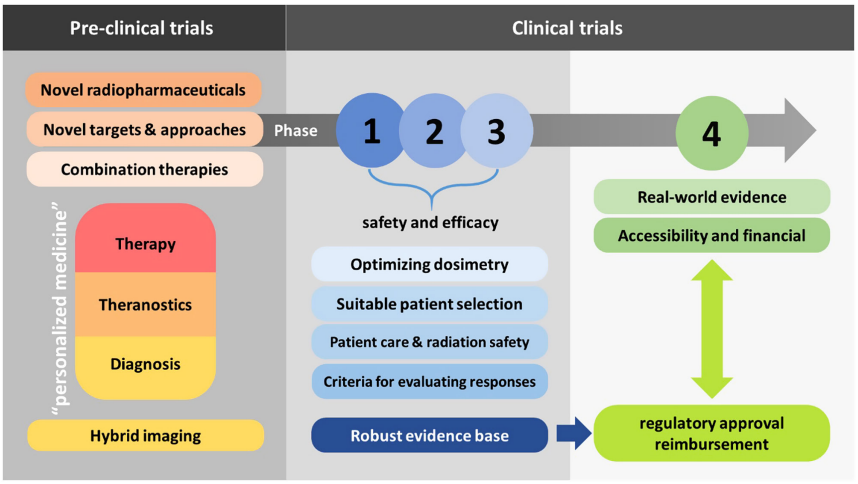

Figure 1

Key elements of theranostics development across preclinical and clinical trials.

providers, to come together and develop sustainable pricing models and reimbursement strategies. This collaborative approach can help alleviate the financial burden on patients and healthcare systems, ultimately making theranostics accessible to a broader population.

Building and fortifying nuclear medicine facilities in various countries is essential for the effective implementation of theranostics. This encompasses training healthcare professionals, establishing the necessary infrastructure, and ensuring the availability of required equipment and radiopharmaceuticals. International collaborations, knowledge sharing, and technology transfer can provide crucial support for developing these facilities in regions where they are currently limited.

How to handle the results of trials

Effectively handling the results of trials, even when they are negative, plays an important role in drug discovery, especially in the realm of novel theranostic approaches. Sharing these outcomes through established platforms can minimize waste, promote transparency, and stimulate innovation, leading to sustainable and beneficial solutions.

Conclusion

In conclusion, theranostics combines diagnostics and treatment for personalized cancer care. Clinical trials are an essential part of moving promising targeted radionuclide treatment from 'bench-to-bedside' (Fig. 1). This article explores trends and challenges in each clinical trial phase in light of the emerging field of theranostics in nuclear medicine.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

Funding

The authors declare that there is no funding for this study.

References

Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK & Yorke ED 2010 Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *International Journal of Radiation Oncology, Biology, Physics* **76**(Supplement) S3–S9. (https://doi.org/10.1016/j.ijrobp.2009.09.040)

Bighelli I & Barbui C 2012 What is the European Medicines Agency? *Epidemiology and Psychiatric Sciences* **21** 245–247. (https://doi.org/10.1017/S2045796012000170)

Bodei L, Herrmann K, Schöder H, Scott AM & Lewis JS 2022 Radiotheranostics in oncology: current challenges and emerging opportunities. *Nature Reviews. Clinical Oncology* **19** 534–550. (https://doi.org/10.1038/s41571-022-00652-y)

Chan TG, O'Neill E, Habjan C & Cornelissen B 2020 Combination strategies to improve targeted radionuclide therapy. *Journal of Nuclear Medicine* **61** 1544–1552. (https://doi.org/10.2967/jnumed.120.248062)

Cullinane C, Waldeck K, Kirby L, Rogers BE, Eu P, Tothill RW & Hicks RJ 2020 Enhancing the anti-tumour activity of 177Lu-DOTA-octreotate radionuclide therapy in somatostatin receptor-2 expressing tumour models by targeting PARP. *Scientific Reports* **10** 10196. (https://doi.org/10.1038/s41598-020-67199-9)

Czernin J, Current K, Mona CE, Nyiranshuti L, Hikmat F, Radu CG & Lückerath K 2021 Immune-checkpoint blockade enhances 225Ac-PSMA617 efficacy in a mouse model of prostate cancer. *Journal of Nuclear Medicine* **62** 228–231. (https://doi.org/10.2967/jnumed.120.246041)

Decristoforo C, Neels O & Patt M 2021 Emerging radionuclides in a regulatory framework for medicinal products – how do they fit? *Frontiers in Medicine* **8** 678452. (https://doi.org/10.3389/fmed.2021.678452)

Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, Atkinson TM, Bennett AV, Denicoff AM, O'Mara AM, *et al.* 2015 Validity and reliability of the US National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *JAMA Oncology* **1** 1051–1059. (https://doi.org/10.1001/jamaoncol.2015.2639)

Elsinga P, Todde S, Penuelas I, Meyer G, Farstad B, Faivre-Chauvet A, Mikolajczak R, Westera G, Gmeiner-Stopar T, Decristoforo C, *et al.* 2010

Guidance on current good radiopharmacy practice (cGRPP) for the small-scale preparation of radiopharmaceuticals. *European Journal of Nuclear Medicine and Molecular Imaging* **37** 1049–1062. (https://doi.org/10.1007/s00259-010-1407-3)

Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ & Wesson M 1991 Tolerance of normal tissue to therapeutic irradiation. *International Journal of Radiation Oncology, Biology, Physics* **21** 109–122. (https://doi.org/10.1016/0360-3016(91)90171-y)

Franklin HR, Simonetti GP, Dubbelman AC, ten Bokkel Huinink WW, Taal BG, Wigbout G, Mandjes IA, Dalesio OB & Aaronson NK 1994 Toxicity grading systems. A comparison between the WHO scoring system and the common toxicity criteria when used for nausea and vomiting. *Annals of Oncology* **5** 113–117. (https://doi.org/10.1093/oxfordjournals.annonc.a058760)

Gafita A, Rauscher I, Fendler WP, Murthy V, Hui W, Armstrong WR, Herrmann K, Weber WA, Calais J, Eiber M, *et al.* 2022 Measuring response in metastatic castration-resistant prostate cancer using PSMA PET/CT: comparison of RECIST 1.1, aPCWG3, aPERCIST, PPP, and RECIP 1.0 criteria. *European Journal of Nuclear Medicine and Molecular Imaging* **49** 4271–4281. (https://doi.org/10.1007/s00259-022-05882-x)

Grubmüller B, Senn D, Kramer G, Baltzer P, D'Andrea D, Grubmüller KH, Mitterhauser M, Eidherr H, Haug AR, Wadsak W, *et al.* 2019 Response assessment using 68ga-PSMA ligand PET in patients undergoing 177Lu-PSMA radioligand therapy for metastatic castration-resistant prostate cancer. *European Journal of Nuclear Medicine and Molecular Imaging* **46** 1063–1072. (https://doi.org/10.1007/s00259-018-4236-4)

Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, Mariotto AB, Lowy DR & Feuer EJ 2020 The effect of advances in lung-cancer treatment on population mortality. *New England Journal of Medicine* **383** 640–649. (https://doi.org/10.1056/NEJMoa1916623)

Huang R-X & Zhou P-K 2020 DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. *Signal Transduction and Targeted Therapy* **5** 60. (https://doi.org/10.1038/s41392-020-0150-x)

Huizing DMV, Aalbersberg EA, Versleijen MWJ, Tesselaar MET, Walraven I, Lahaye MJ, de Wit-van der Veen BJ & Stokkel MPM 2020 Early response assessment and prediction of overall survival after peptide receptor radionuclide therapy. *Cancer Imaging* **20** 57. (https://doi.org/10.1186/s40644-020-00335-w)

International Atomic Energy Agency 2023 *Guidance for Preclinical Studies with Radiopharmaceuticals*. Vienna, Austria: International Atomic Energy Agency. (available at: https://www.iaea.org/publications/14818/guidance-for-preclinical-studies-with-radiopharmaceuticals)

Ivy SP, Siu LL, Garrett-Mayer E & Rubinstein L 2010 Approaches to phase 1 clinical trial design focused on safety, efficiency, and selected patient populations: a report from the clinical trial design task force of the National Cancer Institute investigational drug steering committee. *Clinical Cancer Research* **16** 1726–1736. (https://doi.org/10.1158/1078-0432.CCR-09-1961)

Kendrick J, Francis RJ, Hassan GM, Rowshanfarzad P, Ong JS, McCarthy M, Alexander S & Ebert MA 2023 Prognostic utility of RECIP 1.0 with manual and AI-based segmentations in biochemically recurrent prostate cancer from [68ga]Ga-PSMA-11 PET images. *European Journal of Nuclear Medicine and Molecular Imaging* **50** 4077–4086. (https://doi.org/10.1007/s00259-023-06382-2)

Khan S, Krenning EP, Essen M van, Kam BL, Teunissen JJ & Kwekkeboom DJ 2011 Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. *Journal of Nuclear Medicine* **52** 1361–1368. (https://doi.org/10.2967/jnumed.111.087932)

Kurzrock R, Lin C-C, Wu T-C, Hobbs BP, Pestana RC & Hong DS 2021 Moving beyond 3+3: the future of clinical trial design. *American Society of Clinical Oncology Educational Book* **41** e133–e144. (https://doi.org/10.1200/EDBK_319783)

Langdon SP 2012 Animal modeling of cancer pathology and studying tumor response to therapy. *Current Drug Targets* **13** 1535–1547. (https://doi.org/10.2174/138945012803530152)

Lawhn-Heath C, Hope TA, Martinez J, Fung EK, Shin J, Seo Y & Flavell RR 2022 Dosimetry in radionuclide therapy: the clinical role of measuring radiation dose. *Lancet. Oncology* **23** e75–e87. (https://doi.org/10.1016/S1470-2045(21)00657-4)

Le Tourneau C, Lee JJ & Siu LL 2009 Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute* **101** 708–720. (https://doi.org/10.1093/jnci/djp079)

Markham MJ, Wachter K, Agarwal N, Bertagnolli MM, Chang SM, Dale W, Diefenbach CSM, Rodriguez-Galindo C, George DJ, Gilligan TD, *et al.* 2020 Clinical cancer advances 2020: annual report on progress against cancer from the American Society of Clinical Oncology. *Journal of Clinical Oncology* **38** 1081. (https://doi.org/10.1200/JCO.19.03141)

Meredith R 2002 Clinical trial design and scoring of radionuclide therapy endpoints: normal organ toxicity and tumor response. *Cancer Biotherapy and Radiopharmaceuticals* **17** 83–99. (https://doi.org/10.1089/10849780252824109)

Nonnekens J, van Kranenburg M, Beerens CEMT, Suker M, Doukas M, van Eijck CHJ, de Jong M & van Gent DC 2016 Potentiation of peptide receptor radionuclide therapy by the PARP inhibitor olaparib. *Theranostics* **6** 1821–1832. (https://doi.org/10.7150/thno.15311)

Rosar F, Wenner F, Khreish F, Dewes S, Wagenpfeil G, Hoffmann MA, Schreckenberger M, Bartholomä M & Ezziddin S 2022 Early molecular imaging response assessment based on determination of total viable tumor burden in [68ga] Ga-PSMA-11 PET/CT independently predicts overall survival in [177Lu]Lu-PSMA-617 radioligand therapy. *European Journal of Nuclear Medicine and Molecular Imaging* **49** 1584–1594. (https://doi.org/10.1007/s00259-021-05594-8)

Ruchalski K, Dewan R, Sai V, McIntosh LJ & Braschi-Amirfarzan M 2022 Imaging response assessment for oncology: an algorithmic approach. *European Journal of Radiology Open* **9** 100426. (https://doi.org/10.1016/j.ejro.2022.100426)

Satapathy S, Mittal BR, Sood A, Sood A, Kapoor R, Gupta R & Khosla D 2021 177Lu-DOTATATE plus radiosensitizing capecitabine versus octreotide long-acting release as first-line systemic therapy in advanced grade 1 or 2 gastroenteropancreatic neuroendocrine tumors: a single-institution experience. *JCO Global Oncology* **7** 1167–1175. (https://doi.org/10.1200/GO.21.00103)

Schöder H & Moskowitz CH 2016 Metabolic tumor volume in lymphoma: hype or hope? *Journal of Clinical Oncology* **34** 3591–3594. (https://doi.org/10.1200/JCO.2016.69.3747)

Sgouros G, Hobbs RF & Abou DS 2014 The role of preclinical models in radiopharmaceutical therapy. *American Society of Clinical Oncology Educational Book* e121–e125. (https://doi.org/10.14694/EdBook_AM.2014.34.e121)

Sjögreen Gleisner K, Chouin N, Gabina PM, Cicone F, Gnesin S, Stokke C, Konijnenberg M, Cremonesi M, Verburg FA, Bernhardt P, *et al.* 2022 EANM dosimetry committee recommendations for dosimetry of 177Lu-labelled somatostatin-receptor- and PSMA-targeting ligands. *European Journal of Nuclear Medicine and Molecular Imaging* **49** 1778–1809. (https://doi.org/10.1007/s00259-022-05727-7)

Soni MK & Cella D 2002 Quality of life and symptom measures in oncology: an overview. *American Journal of Managed Care* **8**(Supplement) S560–S573.

Staudacher AH, Bezak E, Borysenko A & Brown MP 2014 Targeted α-therapy using 227th-APOMAB and cross-fire antitumour effects: preliminary in-vivo evaluation. *Nuclear Medicine Communications* **35** 1284–1290. (https://doi.org/10.1097/MNM.0000000000000199)

Strosberg J, Wolin E, Chasen B, Kulke M, Bushnell D, Caplin M, Baum RP, Kunz P, Hobday T, Hendifar A, *et al.* 2018 Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177Lu-Dotatate in the phase III NETTER-1 trial. *Journal of Clinical Oncology* **36** 2578–2584. (https://doi.org/10.1200/JCO.2018.78.5865)

Tentler JJ, Tan AC, Weekes CD, Jimeno A, Leong S, Pitts TM, Arcaroli JJ, Messersmith WA & Eckhardt SG 2012 Patient-derived tumour xenografts as models for oncology drug development. *Nature Reviews. Clinical Oncology* **9** 338–350. (https://doi.org/10.1038/nrclinonc.2012.61)

Timpson P, McGhee EJ & Anderson KI 2011 Imaging molecular dynamics in vivo--from cell biology to animal models. *Journal of Cell Science* **124** 2877–2890. (https://doi.org/10.1242/jcs.085191)

Umscheid CA, Margolis DJ & Grossman CE 2011 Key concepts of clinical trials: a narrative review. *Postgraduate Medicine* **123** 194–204. (https://doi.org/10.3810/pgm.2011.09.2475)

van Vliet EI, Krenning EP, Teunissen JJ, Bergsma H, Kam BL & Kwekkeboom DJ 2013 Comparison of response evaluation in patients with gastroenteropancreatic and thoracic neuroendocrine tumors after treatment with [177Lu-DOTA0,Tyr3]octreotate. *Journal of Nuclear Medicine* **54** 1689–1696. (https://doi.org/10.2967/jnumed.112.117408)

Verbruggen A, Coenen HH, Deverre J-R, Guilloteau D, Langstrom B, Salvadori PA & Halldin C 2008 Guideline to regulations for radiopharmaceuticals in early phase clinical trials in the EU. *European Journal of Nuclear Medicine and Molecular Imaging* **35** 2144–2151. (https://doi.org/10.1007/s00259-008-0853-7)

Wahl RL, Jacene H, Kasamon Y & Lodge MA 2009 From RECIST to PERCIST: evolving Considerations for PET response criteria in solid tumors. *Journal of Nuclear Medicine* **50**(Supplement 1) 122S–50S. (https://doi.org/10.2967/jnumed.108.057307)

Winther-Larsen A, Fledelius J, Sorensen BS & Meldgaard P 2016 Metabolic tumor burden as marker of outcome in advanced EGFR wild-type NSCLC patients treated with erlotinib. *Lung Cancer* **94** 81–87. (https://doi.org/10.1016/j.lungcan.2016.01.024)

Zhang H, Koumna S, Pouliot F, Beauregard J-M & Kolinsky M 2021 PSMA theranostics: current landscape and future outlook. *Cancers* **13** 4023. (https://doi.org/10.3390/cancers13164023)