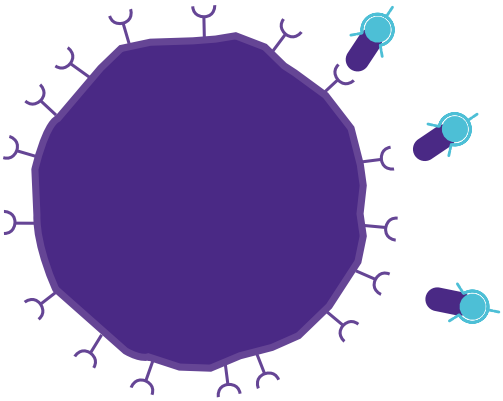

The Health Policy Partnership

Radioligand Therapy Readiness Assessment Framework

User guide

This user guide was drafted by The Health Policy Partnership, with guidance from a multi-stakeholder International Advisory Group. The group has had full editorial control. The guide is part of the readiness assessment project supported with funding from Advanced Accelerator Applications, a Novartis Company, with additional support from Nordic Nanovector.

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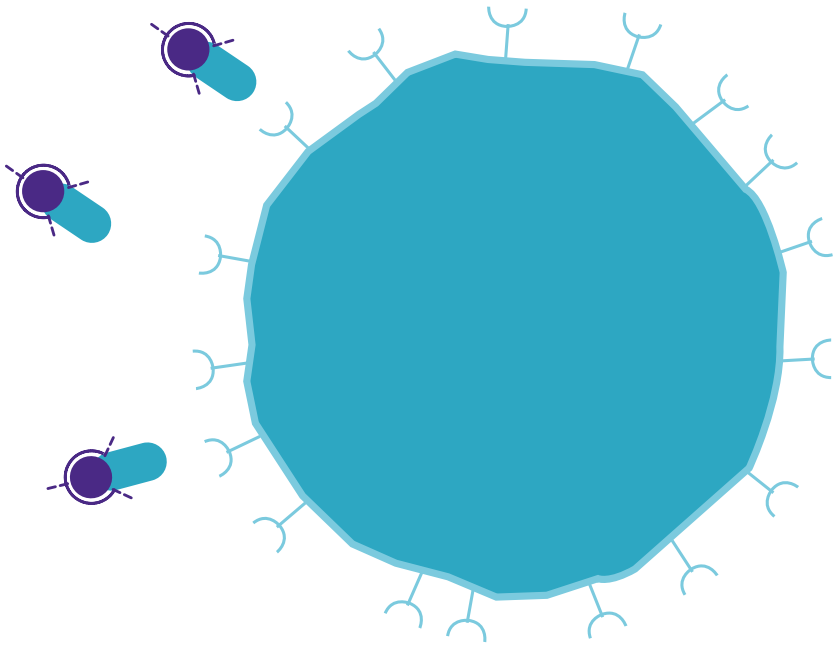

Introduction

This user guide accompanies the Radioligand Therapy Readiness Assessment Framework. It is designed to be read alongside the framework and aims to support interested parties in applying the framework to their own context.

The guide provides a standardised approach to applying the framework. It describes how to validate findings and use these to identify areas for policy action. It also includes a glossary of the main technical terms used in the framework. These terms may need to be adapted to suit each national context.

Using the framework

The framework has been designed to inform a country-level assessment of readiness for the integration of radioligand therapy into cancer care. Applying it can lead to the development of a national situation analysis, which can form the basis for shaping country-specific policy recommendations. There are four steps to applying the framework:

1	**Prepare**	• Convene a multidisciplinary expert group and research team • Clarify each member's roles and responsibilities • Identify a timeframe for performing the assessment
2	**Research**	• Explore peer-reviewed and grey literature, policy documents, expert interviews and other sources of information to answer metrics and contextual factors • Formulate responses for each framework indicator
3	**Validate**	• Seek feedback on findings from the multidisciplinary expert group • Integrate feedback and address remaining gaps in research
4	**Prioritise**	• Identify priority areas for policy action with the multidisciplinary expert group • Determine which stakeholders to reach out to, and build a dissemination and policy engagement plan accordingly

1 Prepare

Multidisciplinary expert group

We recommend convening a multidisciplinary group of experts that can provide insights into the readiness assessment. The multidisciplinary expert group is responsible for providing general oversight of the assessment, validating research findings and identifying priority areas for policy action. Accordingly, the group should ideally include:

- **patient advocates** for the clinical indications being assessed
- **healthcare professionals providing radioligand therapy**, such as those from nuclear medicine, radiation oncology, specialist nursing, radiopharmacy, medical physics and hospital administration
- **healthcare professionals representing the multidisciplinary team**, such as those from clinical/medical/radiation oncology, specialist nursing, nuclear medicine, radiology, pathology, surgery and organ specialists for the indications being assessed (*see* Table A1 in the framework)
- **energy and policy advisers**, for example those involved in radio-protection and production, and working with policymakers.

Experts for the group can be identified through completion of a stakeholder mapping exercise. The Stakeholder map template that we have developed may support your efforts.

> 'We hope the framework will guide research and clinical communities aspiring to establish radioligand therapy services, as well as patient organisations seeking to generate information to encourage evidence-based planning for this approach to be available to people with cancer.'
>
> **CHRISTINE RIDOUT**
> PROGRAMME LEAD FOR HEALTH SYSTEM READINESS, THE HEALTH POLICY PARTNERSHIP

Research team

Preparing to apply the framework also involves establishing a research team who can populate the framework through evidence-based research. To be successful, the research team should be able to conduct meticulous research and have high-level understanding of the country's health system. They would be responsible for developing a comprehensive situation analysis of the current use of radioligand therapy in the national context, and drawing from these findings to develop concrete policy proposals, as outlined on page 3.

Ways of working

We recommend organising a series of meetings between the expert group and research team to discuss and validate findings. These meetings should take place at key junctions of the assessment. In the first meeting, the teams should jointly

decide on the scope of assessment (i.e. whether they will apply part or all of the framework), as well as timeframes for its completion. In later meetings, they should discuss preliminary findings, validate findings, prioritise them and, if relevant, plan for a launch of the assessment's overarching findings.

Adapting the framework

Before research can begin, the framework should be adapted to the national context. The framework has been designed for international use (*see* Appendix for methodology); therefore, there is value in adapting the terms it uses, as well as metrics, indicators and contextual factors, to reflect national nuances. Adaptation will enable a more targeted search, resulting in more meaningful findings. For example, the framework asks to investigate how funding mechanisms apply to radioligand therapy in the national context. Funding has different connotations across countries, therefore the term should be adapted as appropriate.

2 Research

Exploring data sources

Researchers should use a variety of data sources to populate the framework. This will ensure that different perspectives are taken into account, enabling a comprehensive analysis of the situation within the national context (*see* Table 1). It is equally important to obtain reliable data which are consistent and reputable. Researchers applying the framework can use the Search strategy template to help identify relevant search terms and record findings. Expert interviews may complement what can be gleaned from published sources; advice for the development of interview questions is included in the Discussion guide template.

We also recommend looking for analogues from other therapies or clinical indications that may provide concrete examples of what integration or readiness could look like. For example, it may be relevant to look at what policies and practices have been put in place to enable the integration of radiotherapy or precision medicines and emulate these for radioligand therapy.

Compiling findings

Findings from metrics and contextual factors should help formulate a response to each indicator. This should facilitate an overarching explanation of the situation for each sub-domain and, ultimately, each domain. We compiled the findings into one working paper for each domain, and subsequently developed an overarching situation analysis report. Research teams can use the Working paper template and Situation analysis template to help organise their findings.

3 Validate

Research findings should be validated by the multidisciplinary expert group. Validation can be achieved through individual review and group consultation. Following this step, the research team should integrate the multidisciplinary expert group's feedback into the research and address any remaining gaps.

4 Prioritise

Experts and researchers should reach consensus on priority areas for policy action. When the assessment is complete, the expert group and research team should jointly identify priority areas for policy action. These areas may form the basis for the development of policy asks to present to policymakers and decision-makers. The groups should also identify stakeholders who can support system-level planning of radioligand therapy services. The team can use the Policy action blueprint development template to support the selection of priority policy areas and build consensus.

Table 1. Examples of data sources to use when performing the readiness assessment for radioligand therapy

Peer-reviewed publications	Relevant to oncology, radiation oncology, endocrinology, gastroenterology, urology, haematology, nuclear medicine, healthcare policy
Government publications	National health or disease-specific plans, strategies, legislation, policies, standards
Databases	Audits, registries
Specialist publications	Clinical guidelines, best practice documents, training curriculums
Expert interviews	Representatives from government bodies, national institutions, professional societies, patient organisations, healthcare facilities, health insurance funds
Grey literature	Patient organisation websites, patient blogs, hospital news

Glossary

This glossary provides definitions of terms as they are used in the framework. They are derived from existing sources[1–5] and adapted for the purposes of this project.

ANTIBODY is a type of protein created by blood cells when they are invaded by bacteria, viruses or other foreign substances in the blood. Antibodies that are synthetically made and typically used in radioimmunotherapy and other medicinal approaches are called monoclonal antibodies.

BUILT ENVIRONMENT includes the rooms, space and equipment within a healthcare facility. The built environment needs to enable the safe and effective delivery of treatments.

CANCER COMMUNITY includes people with cancer or those who have survived cancer, cancer patient organisations, and all healthcare professionals working in cancer care.

CARE PATHWAY is a term that describes the clinical processes that patients go through, from eligibility for treatment to follow-up after treatment has been completed.

CLINICAL INDICATION is a health condition that could benefit from a specific test, therapy or procedure. If a therapy has been established and approved by regulatory bodies, it is said to be approved for a specific clinical indication.

COMPUTED TOMOGRAPHY (CT) SCANS use X-rays to create images of the body at different angles. A computer develops these into a 3D image. X-rays identify changes in bones and tissue caused by cancer or other disease.

ELIGIBILITY ASSESSMENT is used to evaluate whether radioligand therapy is a suitable treatment option for a particular individual based on the outcome of specific, often imaging, tests.

ENDOCRINOLOGIST is a medical specialist involved in the diagnosis and treatment of people who have hormone-related disorders. This includes people with neuroendocrine neoplasms as they arise from the cells of the endocrine and nervous systems.

GASTROENTEROLOGIST is a medical specialist involved in the diagnosis and treatment of people who have disorders of the digestive system. This may include people with neuroendocrine neoplasms that affect the pancreas or gastrointestinal tract.

GOVERNANCE refers to a range of policies, standards and ways of working that directly impact the availability, accessibility and standards of delivery for any therapy, ultimately influencing health outcomes.

HAEMATOLOGIST is a medical specialist involved in the diagnosis and treatment of people who have disorders of the blood, bone marrow and lymph nodes, including lymphoma.

HAEMATO-ONCOLOGIST is a medical specialist involved in the diagnosis and treatment of people with cancers affecting the blood, bone marrow and lymph nodes, including lymphoma.

HALF-LIFE is the time it takes for unstable atoms of a radioisotope to decay by half. Different isotopes have different half-lives. Some radioisotopes have a short half-life, meaning they decay quickly and must be used quickly once created.

HEALTH INFORMATION refers to data that are collected, analysed and synthesised to support health-related decision-making.

IDENTIFIED NEED is the potential need and demand for a specific healthcare intervention.

INPATIENT CARE refers to overnight care provided to a patient in a hospital setting.

INTEGRATION is the adoption and assimilation of an intervention into every aspect of a health system (e.g. governance, regulation, reimbursement, service delivery) to ensure its availability to all people who may benefit from it.

INVESTIGATIONAL THERAPY relates to a drug or medical procedure being assessed in clinical trials to evaluate its safety and efficacy, but not yet licensed for clinical use.

LIGAND is a small molecule that selectively binds to another specific molecule. Examples are a hormone binding to a receptor on a cell, or an antibody binding to an antigen.

METASTATIC CANCER is cancer that has spread to different parts of the body from where it first originated.

METASTATIC CASTRATION-RESISTANT PROSTATE CANCER is an advanced type of prostate cancer that has spread to the bone and become resistant to hormonal cancer therapy.

MULTIDISCIPLINARY TEAM is a group of healthcare professionals who work closely together to deliver comprehensive patient care. The team are responsible for each patient's diagnosis, management plan and assessment of treatment. It may include medical and radiation oncologists, surgeons, pathologists, nurses and other healthcare professionals.

NATIONAL LEVEL relates to a country as a whole.

LYMPHOMA is a type of blood cancer that affects the lymphatic system. It develops when white blood cells grow uncontrollably. There are over 60 types of lymphomas, each requiring different treatment.

NEUROENDOCRINE NEOPLASMS (NENs), also known as **NEUROENDOCRINE CANCERS**, are a group of cancers which occur in neuroendocrine cells. NENs arise from cells of the hormonal and nervous systems that can develop in many different organs of the body. They include neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs).

NUCLEAR MEDICINE is a medical discipline that involves the application of radioactive substances to assess bodily functions, as well as to diagnose and treat disease.

OUTPATIENT CARE is care provided to a patient in a healthcare facility that does not involve an overnight stay.

POSITRON-EMISSION TOMOGRAPHY (PET) SCANS use radioactive tracers to produce 3D images of the inside of the body. The scan shows how organs and tissues function, and can provide evidence of the presence or absence of cancer.

PRECISION MEDICINE takes the variability of an individual's genes and proteins into account to prevent, diagnose or treat disease.

RADIATION is the emission of energy as electromagnetic waves or subatomic particles. This energy can be emitted by radioisotopes and used to diagnose or treat disease.

RADIATION PROTECTION are measures aimed to reduce radiation exposure and minimise the harmful effects of ionising radiation among patients and healthcare professionals.

RADIOACTIVE WASTE includes radioactive materials, equipment and bodily fluids which have received exposure to radiation.

RADIOIMMUNOTHERAPY is a treatment that uses a cancer-targeting antibody to deliver a radioisotope directly to cancer cells and kill them. It is used to treat certain types of lymphoma.

RADIOISOTOPE is an unstable form of a chemical element that emits radiation as it breaks down to a stable form. Radioisotopes may occur naturally or be made in a laboratory. Their properties and applications differ, e.g. different radioisotopes would be used for diagnosing and treating cancer.

RADIOLIGAND is a cancer-targeting molecule, or ligand, attached to a radioisotope. By choosing different radioisotopes to attach to the same type of ligand, the process can be tailored to either diagnose or treat different types of cancer.

READINESS is the ability of the health system to rapidly and sustainably adapt policies, infrastructure and processes to support integration of a new intervention.

RECEPTORS are molecules on the surface of a cell that can receive certain substances in the blood.

REGIONAL LEVEL relates to provinces/regions/states of a country.

REGULATION defines why and when a healthcare intervention should be provided and how it can be delivered safely to patients, including the appropriate rules and safeguards that need to be in place.

SERVICE PROVISION encompasses the inputs (such as the health workforce, infrastructure and equipment) and outputs (such as diagnostic, therapeutic and follow-up services) required for the provision of healthcare.

TARGETED THERAPY is a category of cancer treatment that exploits differences between healthy and cancerous cells. It can be used to target and kill cancer cells and stop cancer growth.

THERANOSTICS is an approach to treat cancer using highly targeted and personalised therapy based on specific diagnostic tests.

UROLOGIST is a medical specialist who focuses on the function and disorders of the genito-urinary system.

URO-ONCOLOGIST is a medical specialist involved in the diagnosis and treatment of people with cancer of the urinary tract and the male reproductive organs, such as metastatic castration-resistant prostate cancer. Cancer can be located in the bladder, kidneys, prostate, penis and testicles.

Appendix

Readiness assessment framework methodology

We took a comprehensive look at all factors that needed to align to ensure system readiness for the integration of radioligand therapy. We evaluated several existing readiness and integration assessment tools and frameworks in cancer and other fields. Our research included resources developed by the World Health Organization,[6 7] Harvard University,[8] the International Atomic Energy Agency,[9-11] the European Society for Radiology,[12 13] the International Cancer Control Partnership,[14] the Economist Intelligence Unit,[15 16] and individual researchers including Professor Rifat Atun (Harvard University)[17] and Professor Brandon Maser (University of Toronto).[18]

None of the existing frameworks were found to be entirely applicable to radioligand therapy, therefore we developed a dedicated tool. We built on Rifat Atun's and Brandon Maser's work and outlined five domains through which a systemic and holistic analysis of integration of a health intervention can be conducted. We adapted these five domains to radioligand therapy, and they form the backbone of the framework.

The readiness assessment framework was assessed for feasibility, validity and reliability. The development of the framework has been an iterative process. We convened an advisory group of international experts in nuclear medicine, gastroenterology, haematology, urology and respective patient advocates to guide development and validate the preliminary framework across a series of meetings. In addition, we pilot tested the framework in the UK and the US, using NENs, lymphoma and advanced prostate cancer as example clinical indications (*see* Table A). We used the findings to ground the framework in the data. We recognise that cancer care is rapidly evolving, therefore the framework will need to be adapted over time to reflect continuous improvement, broader applications and new challenges.

There are various limitations to the framework's application. First, data may be incomplete or lacking in some countries, complicating completion of some of the framework's questions. The quality of available data may also vary, possibly leading to bias. Finally, there may be limited information as to whether policies, processes and protocols are actually implemented and have an impact, which could affect accuracy of the overarching situation analysis.

Table A: Licensed and investigational radioligand therapies considered in this framework

Cancer type	Licensed radioligand therapy	Radioligand therapy in phase III clinical trials[a]	Radioligand therapy in phase II clinical trials[a]
Unresectable or metastatic neuroendocrine neoplasms	Lutetium-177 oxodotreotide		
Lymphoma	Yttrium-90 ibritumomab tiuxetan		Lutetium-177 lilotomab satetraxetan
Metastatic castration-resistant prostate cancer		Lutetium-177 prostate-specific membrane antigen-617	

a. At the time of research (March 2021).

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If you have any questions about using the framework in your country, please visit www.radioligandtherapy.com or contact info@radioligandtherapy.com

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The Health Policy Partnership is a specialist health policy consultancy with longstanding experience in research and the coordination of policy leadership networks.

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