Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application number 2024-001

Magnetic resonance imaging-guided radiotherapy: Protocol for an evidence review to inform generic justification

Version 1.0

May 2024

About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory body established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector of Social Services within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services** — Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social services.
- **Health technology assessment** — Evaluating the clinical and cost effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health and social care services, with the Department of Health and the HSE.

Visit www.hiqa.ie for more information.

1 Purpose and Aim

The European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation (Euratom) were initially transposed into Irish law under Statutory Instrument (SI) 256 in January 2019.[1] These regulations named the Health Information and Quality Authority (HIQA) as the competent authority for medical exposure to ionising radiation. One requirement under the regulations is that new practices involving medical exposures must be justified by HIQA before they are generally adopted — this is known as generic justification.

HIQA received an application from Elekta Limited in March 2024 requesting the justification of the following practice: external beam radiotherapy involving magnetic resonance imaging-guided radiotherapy (MRgRT) using an MR linear accelerator (MR-linac).

This protocol aims to outline the process by which the Evidence Review Team (ERT) in the Health Technology Assessment (HTA) Directorate will undertake a review of the evidence to inform this generic justification decision. The approach adopted is consistent with that outlined in HIQA's methods for the generic justification of new practices in ionising radiation.

2 Process outline

It is vital that a standardised approach to the process is developed and documented to allow for transparency, aid project management, and mitigate risks that may arise during the project. Five distinct steps in the process have been identified and will be completed. These are listed below and described in more detail in sections 3.1-3.5.

1. Identify document types of interest.
2. Search relevant sources.
3. Screen identified documents.
4. Data extraction and quality appraisal of included documents.
5. Summarise findings.

3 Review process

This review will address the following two research questions (RQs):

RQ1. In patients with cancer requiring radiotherapy, does the choice of image-guided modality (MRgRT versus other) result in a difference in clinical effectiveness?

RQ2. In patients with cancer requiring radiotherapy, does the choice of image-guided modality (MRgRT versus other) result in a difference in potential harms?

In accordance with HIQA's regulatory remit to take account of occupational and public exposure, any relevant issues identified from the included records will be narratively summarised, but a dedicated search will not be conducted. Similarly, any limitations of MRgRT delivery systems identified from the included records will be narratively summarised.

A relevant systematic review contained within a HTA published by the Canadian Agency for Drugs and Technologies in Health (CADTH) in 2019 was identified during topic exploration. The CADTH report identified one relevant study — a non-randomised, retrospective cohort study comparing the clinical effectiveness of an MRgRT delivery system to a linear accelerator delivery system for the treatment of patients with lung cancer requiring radiotherapy. The review found no relevant evidence-based guidelines for this practice. The assessment concluded that overall, given the limited availability and low quality of evidence, the effectiveness and utility of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy was uncertain. Given that MRgRT is an emerging technology and the database search date of the CADTH systematic review (January 2018) yielded only one relevant study, the search date in this review will be restricted to January 2018 onwards.

The RQs were formulated using the PICOS (population, intervention, comparator, outcome and study type) framework as detailed in Table 1.

Table 1: Population, intervention, comparator, outcome, study type (PICOS)

Population	Patients who require external beam radiotherapy for cancer treatment
Intervention	External beam radiotherapy delivered using magnetic resonance imaging-guided radiotherapy (MRgRT) delivery systems such as MR-linac, i.e., MRI combined with a radiotherapy linear accelerator, such as Elekta Unity, Viewray MRIdian, Viewray MRIdian LINAC or any other MRgRT hybrid delivery system.
Comparator	▪ External beam radiotherapy delivered with other image-guided radiotherapy systems (e.g., CT or X-ray or other image-guided modality) ▪ Studies without a comparator will be included such as before-and-after treatment comparisons
Outcome	RQ1: any measure of clinical effectiveness ▪ Overall survival, progression-free survival ▪ Quality of life or symptom control measured using a validated instrument ▪ Mortality ▪ Treatment duration

	Surrogate outcomes: ▪ Normal tissue sparing ▪ Target coverage RQ2: Harms: ▪ Frequency and severity of radiotherapy-related adverse events and toxicities ▪ MRI-related harms: adverse events resulting from contraindications to MRI (e.g., pacemakers, neurostimulators, or from metallic objects acting as projectiles in magnetic field)
Study type	Included: ▪ High-quality systematic reviews, RCTs and non-randomised controlled trials, cohort studies, case-control studies, self-controlled case series and phantom studies. ▪ Only studies relating to external beam radiotherapy. Excluded: ▪ Case reports, cross-sectional studies, case studies, case series, non-systematic literature reviews, narrative reviews ▪ Animal studies ▪ Studies relating to brachytherapy ▪ Studies relating to MRI used only for radiotherapy simulation and planning
Languages	Only articles for which an adequate English translation can be obtained will be included.
Search period	01/01/2018 to current*

Key: MRgRT – magnetic resonance imaging-guided radiotherapy; RCT – randomised controlled trial; RQ – research question

Note: *search period selected on the basis of updating the search carried out by the Canadian Agency for Drugs and Technologies in Health (CADTH) as part of one of their assessments.[3]

3.1 Identify document types of interest

The evidence describing magnetic resonance guided radiotherapy will be identified from the following document categories:

- systematic reviews, including those contained in published HTAs
- original research studies
- clinical guidelines.

Where an existing high-quality systematic review is identified, this will be used and updated as appropriate. This reflects a pragmatic approach to evidence synthesis, consistent with the hierarchy of evidence, wherein duplication of effort is minimised. For the purpose of this evidence review, a high-quality systematic review is considered to comprise reviews reporting on at least one outcome of interest with all of the following characteristics:

- A clearly stated set of objectives with an explicit, reproducible methodology.

- A systematic search of at least two databases, carried out since January 2018, which attempts to identify all studies that would meet the eligibility criteria.
- A systematic presentation and synthesis of the characteristics and findings of the included studies.
- A critical appraisal of the available evidence.
- Ideally, the systematic review will have evaluated the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[2]

Where sufficient randomised controlled trials (RCTs) and or non-randomised controlled studies are identified, other (lower quality) studies will not be considered during critical appraisal, data extraction and synthesis of the literature.

3.2 Search relevant sources

A systematic literature search will be conducted in Medline (EBSCO), Embase (Elsevier) and CINAHL. The full search strategy for the Medline (EBSCO) search is outlined in Table A.1 in the Appendix. Forward citation searching and searching of the reference lists of included studies will also be undertaken. A separate search will be conducted using clinicaltrials.gov, the WHO's ICTRP portal and CENTRAL via the Cochrane Library to identify ongoing and completed clinical trials and research studies. A grey literature search will also be conducted; a list of grey literature sites searched is presented in Table A.2 in the Appendix. The full search strategy can be found here on Zenodo: https://doi.org/10.5281/zenodo.11244102

3.3 Screen identified documents

All potentially eligible documents identified will be exported to Covidence. For both title and abstract and full text screening, all documents will be screened against the eligibility criteria (see Table 1) by two reviewers. Disagreements identified will be resolved by discussion. Any major disagreements may lead to the involvement of a third reviewer. Documents will only be included where full texts are available. Where websites or documents are not readily available in English, titles will be screened for relevant keywords using the language of the document; full page translations will not be performed at the screening stage. Where documents are considered for inclusion in the evidence summary, they will be translated via Deepl Pro translation software.[4]

3.4 Data extraction and quality appraisal of included documents

Data extraction will be completed by one reviewer. A second reviewer will check 100% of data variables. Minor disagreements identified will be resolved by discussion. Any major disagreements may lead to the involvement of a third

reviewer. Data extraction templates will be used to aid in the identification and storage of relevant data, and are detailed in Tables A.3, A.4 and A.5 in the Appendix.

Two reviewers will independently assess the methodological quality or risk of bias of included studies or systematic reviews, using standardised critical appraisal tools, with any disagreements resolved through discussion. Any major disagreements may lead to the involvement of a third reviewer. As different study designs warrant different tools to assess methodological quality/risk of bias, Table 2 outlines the critical appraisal tools that will be used by study design. All tools will be piloted first on a small number of included studies and systematic reviews, and modifications made if needed, before standardising for the remaining studies.

Table 2: Critical appraisal tools

Study design	Critical appraisal tool
Systematic reviews or HTA	ROBIS
RCTs	RoB 2
Cohort studies and case-control studies	ROBINS-I

Key: HTA health technology assessment; RCT – randomised controlled trial; RoB 2 – risk of bias tool for randomized trials; ROBIS – risk of bias in systematic reviews.

3.5 Summarise findings

A preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the identified documents will be presented and a summary of the evidence for the effectiveness and potential harms associated with MRgRT will be compiled.[5]

The study design and baseline characteristics for all included studies will be presented, followed by the outcome results; these will be grouped per indication. Using GRADE, a summary of findings table, including the certainty of the evidence for the primary outcomes, will be prepared. This will assist in populating the evidence to decision table outlined in HIQA's methods document.[6]

4 Quality assurance process

This review will be undertaken in accordance with HIQA's HTA Quality Assurance Framework and led by an experienced member of staff. The relevant equipment manufacturers will be provided an opportunity to confirm the accuracy of the description of technology outlined in the report. The report will be reviewed by two senior members of the team, to ensure processes are followed and quality maintained. Additionally, draft outputs from the evidence synthesis will be circulated

to HIQA's Medical Exposure to Ionising Radiation (MEIR) Expert Advisory Group (EAG) for review and will be presented and discussed at a meeting of the MEIR EAG.

5 Review and update

This protocol will be regarded as a live document and amended when required to ensure it reflects any changes made to the outlined processes. Amendments will be captured in the published report.

Appendix

A.1 Full search strategy - Medline

Database name		**Medline Complete via Ebscohost**		
Date search was run		**22 May 2024**		
#	**Query**	**Limiters/Expanders**	**Last Run Via**	**Results**
S12	S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	Limiters - Publication Date: 20180101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	3,637
S11	TX MRIdian	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	255
S10	TX "Elekta Unity"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	224
S9	AB (MRIgRT OR MRgRT OR MRgART OR MR-gRT MRg-A-SBRT OR MRgSBRT) OR TI (MRIgRT OR MRgRT OR MRgART OR MR-gRT OR MRg-A-SBRT OR MRgSBRT)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	394

S8	AB ((MR OR MRI) N3(Radiotherap* OR radiation OR RT OR ART OR SBRT)) OR TI ((MR OR MRI) N3 (Radiotherap* OR radiation OR RT OR ART OR SBRT))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	4,288
S7	AB ((MR OR MRI) N2 linear accelerator) OR TI ((MR OR MRI) N2 linear accelerator)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	268
S6	AB (MR OR MRI) N2 linac* OR TI (MR OR MRI) N2 linac*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	880
S5	AB Magnetic Resonance linear accelerator OR TI Magnetic Resonance linear accelerator	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	62
S4	AB (Magnetic Resonance N3(radiotherapy OR radiation OR RT OR ART OR SBRT)) OR TI (Magnetic Resonance N3(radiotherapy OR radiation OR RT OR ART OR SBRT))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	1,650
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	2,443

S2	(MH "Radiotherapy, Image-Guided") OR (MH "Radiotherapy Planning, Computer-Assisted")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	28,395
S1	(MH "Magnetic Resonance Imaging")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE Complete	486,290

Table A.2 Grey literature search

Organisation type	
Health Technology Assessment agencies	
Organisation	**Link to URL**
Canada's Drug and Health Technology Agency	www.cadth.ca
Choices In Health Care (COHERE) Finland	https://palveluvalikoima.fi/en/cohere-finland
Health Quality Ontario	https://www.hqontario.ca
Health Technology Wales	https://healthtechnology.wales/
International HTA database	https://database.inahta.org/
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/
NIHR Health Technology Assessment programme	Health Technology Assessment | NIHR
Norwegian Institute of Public Health (NIPH)	https://www.fhi.no/en/qk/HTA/
Scottish Health Technologies Group	https://shtg.scot/
Swedish Agency for Health Technology Assessment and Assessment of Social Services	https://www.sbu.se/en/

International guideline groups/professional organisations	
Organisation	**Link to URL**
European Society for Radiology (ESR)	Guidelines & Recommendations | European Society of Radiology (myesr.org)
European Society for Medical Oncology (ESMO)	https://www.esmo.org/guidelines
European Society for Radiotherapy and Oncology (ESTRO)	ESTRO - Guidelines
Guidelines International Network	https://g-i-n.net/)
International Atomic Energy Agency (IAEA)	https://www.iaea.org/
International Commission on Radiological Protection (ICRP)	https://www.icrp.org/

Country specific guideline groups/professional organisations		
Organisation	**Country**	**Link to URL**
ACR-AAPM	US	https://www.aapm.org/pubs/ACRAAPMCollaboration.asp
Agence Fédérale de Contrôle Nucléaire	Belgium	https://afcn.fgov.be/
Agency for Healthcare Research and Quality	US	https://www.ahrq.gov/
American College of Radiology (ACR)	US	https://www.acr.org/
American Society for Clinical Oncology (ASCO)	US	https://old-prod.asco.org/practice-patients/guidelines
American Society for Radiation Oncology (ASTRO)	US	https://www.astro.org/

Autorité de Sûreté Nucléaire (ASN)	France	https://www.asn.fr/
Haute Autorité de santé (HAS)	France	https://www.has-sante.fr/jcms/r_1455134/en/about-has
Health Products Regulatory Authority (HPRA)	Ireland	https://www.hpra.ie/
National Cancer Control Programme (NCCP)	Ireland	https://www.hse.ie/eng/services/list/5/cancer/
National Centre for Pharmacoeconomics (NCPE)	Ireland	https://www.ncpe.ie/
National Comprehensive Cancer Network (NCCN)	US	https://www.nccn.org
Objective Health Canada	Canada	https://objectivehealth.ca/
Royal College of Radiologists (RCR)	US	https://www.rcr.ac.uk/guidelines
Scottish SIGN	Scotland	https://www.sign.ac.uk
Swiss Federal Office of Public Health	Switzerland	https://www.bag.admin.ch

Summary of web search	**Key words searched**
Google and Google Scholar	The first five pages of each were checked. Key words: ("MRI guided radiotherapy" OR "MRI guided radiation therapy" OR "magnetic resonance radiotherapy" OR "MR-linac" OR "MR guided linear accelerator")

Table A.3 Data extraction table: summary of characteristics of included HTAs & systematic reviews

Year published Title of document (Organisation)	Date of Search	PICO components	Number of studies (Total number of participants) Relevant to which RQ Treatment dose and site (where reported)	Funding statement Author conflicts of interest	Author conclusions

Table A.4 Data extraction table: summary of characteristics of included clinical trials & research studies

Author and Year (Trial name and identification number) Country Sponsor/ Funding	Study Design Number of patients Median age of patients (range)	Population, indications and inclusion criteria	Intervention Comparator Treatment dose and site (where reported)	Follow-up	Outcome(s)

Table A.5: Data extraction table: summary of ongoing clinical trials & research studies

Study: Reference (name.CT.gov number), country	Design (RCT; retrospective comparative study; prospective comparative study; case control study)	Control & intervention Treatment dose and site (where reported)	No of participants/target recruitment	Planned completion date	Status as reported

References

1. European Union (Basic Safety Standards for Protection Against Dangers Arising from Medical Exposure to Ionising Radiation) Regulations 2018 as amended. Dublin: The Stationary Office, (2019).
2. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2022. : [Available from: https://gradepro.org.
3. CADTH. Magnetic Resonance Imaging-Guided Radiotherapy Delivery Systems for Cancer Treatment: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines. 2019 March 2019. Report No.
4. DeepL Translator. Germany: Available from: www.deepl.com.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264-9.
6. Health Information and Quality Authority (HIQA). Methods for Generic Justification of New Practices in Ionising Radiation. 2022.

Published by the Health Information and Quality Authority (HIQA).

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