Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Application Number: 2023-005

Ultra-hypofractionated adjuvant radiotherapy for breast cancer:

Evidence synthesis to support a generic justification decision

Date of decision: 16 November 2023

Date of publication: 24 November 2023

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority 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.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

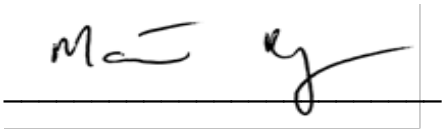
- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for 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 health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these 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 services, in conjunction with the Department of Health and the HSE.

Foreword

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 SI 256 in January 2019.[(1)] These Regulations named 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.

This report sets out a review of prior evidence synthesis which provides the evidence base to inform HIQA's generic justification decision. The report also includes the consideration of this evidence by HIQA's multidisciplinary Medical Exposure to Ionising Radiation Expert Advisory Group which is formally reported using an evidence to decision framework. The review considers the net benefit for this patient population in the context of the medical exposure to ionising radiation; the potential for occupational and public exposure is also considered.

This review was undertaken by the Ionising Radiation Evidence Review Team from the HTA Directorate in HIQA and was supported by HIQA's Medical Exposure to Ionising Radiation Expert Advisory Group who advised on the preparation of this report and participated in the evidence to decision exercise. HIQA would like to thank the Evidence Review Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.



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Deputy Chief Executive and Director of Health Technology Assessment

Acknowledgements

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The findings of the evidence review prepared by HIQA informed the deliberations of the MEIR EAG in completing the evidence to decision framework. The output of the framework reached through consensus.

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Key: * Alternate for programme/association

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Conflicts of interest

None declared.

Table of Contents

List of abbreviations used in this report

ASTRO	American Society for Radiation Oncology
BCS	breast conserving surgery
CI	confidence interval
EAG	expert advisory group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPA	Environmental Protection Agency
ESTRO	European Society for Radiation Oncology
EUSOM	European Society of Breast Cancer Specialists
GRADE	grading of recommendations, assessment, development and evaluation
Gy	gray
HIQA	Heath Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment
IR-ERT	ionising radiation evidence review team
MEIR	medical exposure to ionising radiation
NCCP	National Comprehensive Cancer Network
NCCP	National Cancer Control Programme
NCRI	National Cancer Registry of Ireland
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
PICOS	population, intervention, comparator, outcome, setting

RR	risk ratio
ROBIS	risk of bias in systematic reviews
RCR	Royal College of Radiologists
RCT	randomised controlled trial
RQ	research question
SI	statutory instrument
SIGN	Scottish Intercollegiate Guideline Network
SIOG	International Society of Geriatric Oncology
TNM	tumour nodes metastasis
UK	United Kingdom
US	United States of America

List of tables

Plain Language summary

Radiotherapy is an important part of the treatment for many people with breast cancer. Until recently, patients undergoing radiotherapy in Ireland would typically have 15 sessions over a three week period. This is known as a moderately hypofractionated regimen. However, clinical trials have been carried out to determine whether it is equally effective and safe to deliver a course of radiotherapy in a smaller number of sessions, but using a larger dose per session. For example, delivering the full course of radiotherapy in five sessions over one-week. This is known as an ultra-hypofractionated regimen.

Under Irish law, any new practices which involve the exposure of patients to ionising radiation must be justified by the Health Information and Quality Authority (HIQA). Justification means making sure that the benefits of the practice outweigh the risks involved for the kind of patients undergoing this practice. To decide if this practice is justified, HIQA has reviewed the available evidence in the medical literature, and have sought input from a group of experts, including a patient representative. As part of this evidence review, side effects, quality of life and cosmetic outcome were considered, as well as how effective ultra-hypofractionated radiotherapy is, compared with moderately hypofractionated radiotherapy. HIQA has also considered the occupational and public radiation safety issues in this review.

While ultra-hypofractionated radiotherapy is not suitable for all patients, for those for whom it is appropriate, the available evidence indicates that, it is as effective and safe as moderately hypofractionated radiotherapy as part of the treatment for breast cancer. As with all treatments, the radiation oncologist must consider the individual patient characteristics when deciding which approach to take.

An important advantage of ultra-hypofractionated radiotherapy is that patients only have to attend the hospital for five sessions over one-week, rather than 15 sessions over three weeks. There are side effects associated with both types of regimens, but the available evidence indicates that there are no important differences between them.

After reviewing the risks and benefits of the practice, and considering the recommendation from its Medical Exposure to Ionising Radiation Expert Advisory Group, HIQA decided to justify this practice of ultra-hypofractionated radiotherapy for breast cancer.

Key Points

Application

- This review was conducted in response to an application submitted by the Saint Luke's Radiation Oncology Network in Dublin for the generic justification of ultra-hypofractionated external beam radiotherapy for the treatment of breast cancer.
- Radiotherapy regimens using 5 gray (Gy) or more per fraction are typically considered ultra-hypofractionation.

Summary of evidence synthesis process

- In accordance with HIQA's Methods for generic justification of new practices in ionising radiation, a review of prior evidence synthesis was conducted to establish the evidence base for this new type of practice. This involved a targeted search of grey literature sources.
- In total, twelve guidelines from professional bodies and from country-specific organisations were identified.
- Two key clinical guidelines were identified as relevant to the research questions posed in this review:
  - A clinical guideline published by the Irish National Cancer Control Programme (NCCP) in May 2023.
  - A clinical guideline published in June 2023 by the UK's National Institute for Health and Care Excellence (NICE) – the NG101 guideline.
- As the most recent summary of evidence, the systematic review contained within the NICE clinical guideline was appraised using the risk of bias in systematic reviews (ROBIS) tool.
- From the included systematic review, six primary studies were identified of which three were relevant to this review as they included one-week ultra-hypofractionation schedules.

Clinical effectiveness evidence

- Only the results for a 26Gy in 5 fractions one-week ultra-hypofractionated schedule are summarised here as this schedule aligns with the application received by HIQA. In addition, this schedule was identified in the NICE review as the clinically relevant regimen with evidence that efficacy is non-inferior to a moderate hypofractionated schedule with similar normal tissue effects.
- The body of evidence was largely underpinned by the findings of a single randomised trial (RCT), the FAST-Forward trial (n=4,096), which had a

primary outcome of ipsilateral breast tumour relapse. An additional trial was identified by the NICE review, published by Ivanov et al. (n=60) – the results from this trial were used by NICE to report on skin toxicity and cosmetic results.

- Key secondary endpoints from the FAST-Forward trial included late normal tissue effects and disease-related and survival outcomes (locoregional relapse, distant relapse, disease-free survival and overall survival).
- Five year results from the FAST-Forward trial demonstrated that 26Gy delivered in 5 fractions over one-week (an ultra-hypofractionated regimen) is non-inferior to a 40Gy in 15 fractions delivered over three weeks (a moderately hypofractionated regimen).
  - Based on moderate certainty evidence, for local and loco-regional relapse, no difference was observed between the 40Gy and 26Gy regimens (RR: 1.48 (95% CI: 0.86 - 2.57) and RR: 1.49 (95% CI: 0.94 - 2.37), respectively).
- Pre-planned subgroup analysis by NICE could not be performed due to evidence gaps and a lack of published disaggregated data. Considering the potential applicability of the data from the FAST-Forward trial to different subgroups:
  - A sequential boost of 10Gy in 5 fractions or 16Gy in 8 fractions was given to approximately 24% of the patients in all treatment arms.
  - Individuals who underwent chest wall radiotherapy (post mastectomy) comprised a small proportion of the FAST-Forward trial population (n=264 / 4,096 patients) and were excluded from the Ivanov trial.
- NICE outlined that further research is needed to establish the safety and efficacy of one-week fractionation regimens where nodal radiation is included and following immediate breast reconstruction.
- In terms of guideline recommendations developed on the basis of systematic review of the evidence:
  - NICE recommend the use of a one-week regimen for patients having chest wall, whole breast or partial breast, without nodal radiotherapy, with or without a boost.
  - The NCCP recommend the use of a one-week adjuvant radiotherapy regimen (e.g., 26Gy in 5 fractions) for patients after breast conserving surgery, without nodal RT, but with or without a boost.

Quality of life

- The FAST-Forward trial reported quality of life, as assessed using the European Organisation for the Research and Treatment of Cancer (EORTC)

QLQ-BR23 tool to assess loss of quality of life associated with arm or shoulder pain, swollen arm or hand, difficulty raising arm, breast pain, breast swollen, breast oversensitive and skin problems in breast.

- For most outcomes, the review could not differentiate between the two fractionation schedules. While the 40Gy in 15 fractions was favoured in the assessment of breast swelling and also for breast pain, the difference between the groups was less than the defined minimum important difference (the smallest difference which is considered meaningful).

Adverse events and safety evidence

- At five years, based on evidence from the FAST-Forward trial, while evidence in relation to clinician-assessed adverse events favoured the 40Gy in 15 fraction schedule, the difference was less than the defined minimum important difference. In terms of clinician-assessed normal tissue effects in the breast or chest wall, either no meaningful difference was found between the schedules or the observed difference was less than the defined minimum important difference.
- At 18 months, Ivanov et al. (n=60) reported that the toxicity profiles for the 40Gy and 26Gy schedules were comparable overall. No significant difference was observed in the incidence of grade two acute skin or sub-cutaneous toxicity.
- The identified studies did not highlight any safety concerns for public and occupational exposure. The exposure risk associated with ultra-hypofractionation is likely to be the same as moderate hypofractionation, provided appropriate radiation protection safeguards are in place.

Cosmetic outcome

- Ivanov et al. reported that there was no significant difference in the cosmetic effect of treatment, as assessed by both patients and radiation oncologists using an unvalidated four-point scale.

Certainty of the evidence

- The GRADE assessment of the certainty of the evidence outlined in the NICE guidelines found the certainty of the evidence to be:
  - moderate for local relapse, loco-regional relapse and distant relapse
  - low for all-cause mortality and breast cancer-related mortality
  - moderate to high for quality of life outcomes
  - moderate to high for normal tissue effects
  - moderate for clinician-assessed adverse events

- very low to moderate for acute skin toxicity
- very low to low for cosmetic outcomes
- very low for late skin toxicity and subcutaneous skin toxicity.

Clinical significance of change in ionising radiation dose

- The radiobiological basis for changing dose lies in the fact that breast cancer cells should respond favourably to hypofractionation when compared with conventional 2Gy per fraction treatments.
- While the total dose is reduced in an ultra-fractionated schedule compared with a moderate hypofractionation schedule (26Gy versus 40Gy), the dose delivered per fraction is higher (5.2Gy versus 2.67Gy).
- Based on five-year follow-up data, the evidence from this review demonstrated no clinically significant difference in outcomes or toxicity between a moderately hypofractionated schedule (40Gy in 15 fractions over three weeks) and an ultra-hypofractionated schedule (26Gy in 5 fractions over one-week) in this breast cancer cohort.

Medical Exposure to Ionising Radiation Expert Advisory Group (MEIR EAG)

- Informed by the review of the above evidence, the MEIR EAG completed judgments under a modified evidence-to-decision making framework to arrive at a recommendation to HIQA on the generic justification of ultra-hypofractionated adjuvant radiotherapy for breast cancer.
- While acknowledging that current data are limited to five-year follow-up, the MEIR EAG judged that the differences in benefit between this practice and moderately hypofractionated adjuvant radiotherapy were trivial, given the RCT data presented indicate non-inferiority in terms of oncological outcomes.
- Again acknowledging that current data are limited to five-year follow-up, the MEIR judged the overall potential for harm to be trivial given the RCT data presented indicate that ultra-hypofractionated adjuvant radiotherapy is non-inferior in terms of adverse events, toxicities and cosmetic outcomes.
- When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the practice was favoured over moderately fractionated radiotherapy, and could be used at the discretion of the treating radiation oncologist. This judgment was on the basis that available five-year follow-up data indicate that there are no differences in the outcomes discussed, but that there are positive implications for patients in terms of treatment burden (fewer required treatment attendances and for radiation oncology capacity).

- The MEIR EAG recommended that ultra-hypofractionated adjuvant radiotherapy for breast cancer should be generically justified.

Decision making

- Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.
- The practice of ultra-hypofractionated adjuvant radiotherapy for breast cancer is generically justified under SI 256/2018.
- The generic justification of this practice is effective from 16 Nov 2023.

1. Introduction

1.1 Background to the application and description of the technology

This review was conducted in response to an application submitted by the St. Luke's Radiation Oncology Network in Dublin for the generic justification of ultra-hypofractionated radiotherapy treatment in breast cancer. The target population listed in the application for generic justification was patients undergoing adjuvant radiotherapy, following breast conserving surgery or mastectomy.

Hypofractionated regimens are where the treatment course is divided into fewer fractions with a higher dose per fraction. The radiobiological basis for hypofractionation in breast cancer lies in the fact that breast cancer cells have a low α/β ratio**.** This means that breast cancer cells should respond favourably to higher doses delivered over fewer fractions when compared with conventional 2Gy per fraction treatments.[1] Moderately hypofractionated regimens (regimens using more than 2Gy per fraction) have been part of standard clinical practice for adjuvant breast radiotherapy for a number of years.[2, 3] Radiotherapy regimens using 5Gy or more per treatment are typically considered ultra-hypofractionation.[4] A key advantage of ultra-hypofractionated radiotherapy is a reduction in the number of visits that a patient is required to make to complete their treatment course. This can be more convenient for patients as well as increasing radiation service capacity. During the COVID-19 pandemic, ultra-hypofractionated radiotherapy was used to help alleviate the pressures on radiotherapy machine capacity and reduce the risk of COVID-19 exposure for both patients and staff.[5] Shorter courses of treatment are now used routinely in some countries.[6]

The initial evidence base for ultra-hypofractionation in breast cancer was established by the publication of the five-year results of the FAST-Forward randomised controlled trial (RCT) in April 2020.[7] In May 2023, the National Cancer Control Programme (NCCP) published updated clinical guidance on the treatment of breast cancer with radiotherapy, which included the findings from the FAST-Forward trial.[8] One of the recommendations of the NCCP guidelines was that the use of ultra-hypofractionation should be considered for certain patient groups. This included patients who have undergone breast conserving surgery and are having whole breast radiotherapy, with or without a boost, but with no nodal radiotherapy.

As noted, ultra-hypofractionated radiotherapy was introduced in Ireland during the COVID-19 pandemic. The St. Luke's Radiation Oncology Network in Dublin intend to continue to use ultra-hypofractionation in routine clinical practice. Therefore,

consistent with the requirements under the European Union Basic Safety Standards for the Protection Against Dangers from Medical Exposure to Ionising Radiation Regulations 2018 as amended, which were transposed into Irish law under Statutory Instrument (SI) 256 in January 2019, it requires generic justification before it can be generally adopted.

Ultra-hypofractionated radiotherapy is now an established treatment in some countries. Topic exploration performed by HIQA in advance of developing this report indicated that a number of evidence syntheses have already been conducted in relation to this practice. For this reason, and in accordance with HIQA's Methods for generic justification of new practices in ionising radiation[9] a review of prior evidence synthesis was undertaken.

1.2 Overall approach

A standing multidisciplinary MEIR expert advisory group (EAG) has been convened by HIQA comprising representation from key stakeholders. A full list of the membership of the EAG is available in the acknowledgements section of this report. The terms of reference for the EAG are published on the HIQA website.

Evidence synthesis was undertaken to inform the discussions of the MEIR EAG and its recommendation-making process as well as the subsequent decision-making by the Director of Health Technology Assessment (HTA). The following summarises the steps that were taken:

- A review of prior evidence synthesis was performed by the Ionising Radiation Evidence Review Team (IR-ERT) to provide the evidence base to inform a generic justification decision.
- This review of prior evidence synthesis identified relevant evidence which related to the clinical effectiveness and safety of ultra-hypofractionated radiotherapy for the treatment of breast cancer.
- A draft report summarising the benefits and harms associated with this practice was produced and circulated to the EAG for review.
- Following a meeting of the MEIR EAG, the draft of the report was amended as appropriate and circulated to the MEIR EAG for review.
- The final report was sent to the Director of HTA, along with a recommendation from the MEIR EAG regarding the generic justification of the practice.
- Following HIQA's decision, the final report and generic justification decision

were published on the HIQA website.

2. Description of clinical indications and epidemiology

According to the National Cancer Registry in Ireland (NCRI) data for the period 2018 to 2020, there were 3,363 cases of breast cancer diagnosed in females and 29 in males reflecting an average age-standardised annual incidence rate of 157.2 and 1.7 per 100,000 persons, for females and males, respectively.[(10)]

Excluding non-melanoma skin cancer, breast cancer is the most commonly diagnosed invasive cancer in women, comprising 29.8% of all invasive cancers during the period 2018 to 2020. It was the second most common cause of cancer death for women (17%) in the same period. The NCRI also notes a recent increasing trend in the incidence of breast cancer of 1.7% per year (95% CI: 0.6-2.9), starting around 2014, but a decreasing trend in terms of mortality.[(11)] Five-year net survival averaged 88% for women diagnosed during the period 2014 to 2018 compared with 72% for those diagnosed during the period 1994 to 1998.[(12)]

Treatment of breast cancer can include chemotherapy, hormone therapy, radiotherapy, surgery, or combinations thereof, with the choice of treatments depending on a number of factors including age and stage at diagnosis. In Ireland, of women diagnosed between 2014 and 2016, 48% received chemotherapy, 59% received hormone therapy, 71% radiotherapy and 85% underwent surgery within the first year of diagnosis.[(12)] A systematic review published by the Early Breast Cancer Trialists' Collaborative Group indicated that radiotherapy following primary surgery reduces locoregional cancer recurrence and breast cancer deaths in women with early stage cancers.[(13)] This finding was also found to apply to patients with positive lymph nodes who undergo mastectomy and axillary clearance.[(14)]

3. Methodology

3.1 Methods

3.1.1 Review questions (RQs)

The generic justification process is informed by the following four research questions (RQs):

RQ 1 In patients who have undergone breast conserving surgery and who require adjuvant radiotherapy to the breast (with or without a boost), does a one-week ultra-hypofractionated regimen provide equivalent oncological outcomes to a moderately hypofractionated regimen?

RQ 2 In patients who have undergone breast conserving surgery and who require adjuvant radiotherapy to the breast (with or without a boost), does a one-week ultra-hypofractionated regimen provide equivalent quality of life outcomes to a moderately hypofractionated regimen?

RQ 3 In patients who have undergone breast conserving surgery and who require adjuvant radiotherapy to the breast (with or without a boost), what is the risk of adverse events and toxicities associated with a one-week ultra-hypofractionated regimen compared with a moderately hypofractionated regimen?

RQ 4 In patients who have undergone breast conserving surgery and who require adjuvant radiotherapy to the breast (with or without a boost), does a one-week ultra-hypofractionated regimen provide equivalent cosmetic outcomes to a moderately hypofractionated regimen?

Table 1 outlines the population, intervention, comparison, outcomes, setting (PICOS) eligibility criteria, as well as details of the eligible study designs and languages.

Table 1: PICOS

PICOS	Description
Patient/Problem:	Adults aged 18 years and older with breast cancer who have undergone breast conserving surgery
Intervention:	Ultra-hypofractionated radiotherapy regimen such as 1-week hypofractionated radiotherapy (e.g., 26Gy in 5 fractions)
Comparison:	Moderately hypofractionated radiotherapy regimen, such as 3-week hypofractionated radiotherapy (e.g., 40Gy in 15 fractions)
Outcomes:	▪ Oncological outcomes: e.g., overall survival, progression-free survival ▪ Quality of life ▪ Frequency and severity of adverse events and toxicities ▪ Cosmetic outcomes.

Study Design:	Relevant records will include: ▪ health technology assessments which incorporate a systematic review ▪ clinical guidelines which incorporate a systematic review ▪ systematic reviews. For the purpose of this evidence search, a 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, 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.[15]
Languages:	▪ Only articles for which an adequate English translation can be obtained will be included.

Key: Gy – Gray; RCT - randomised controlled trial.

3.1.2 Search Strategy

A targeted search of grey literature sources was carried out - details of this search are outlined in Table A.1 in Appendix 1. In order to streamline this review, a google and google scholar search was not undertaken.

3.1.3 Record selection and data extraction

The identified systematic reviews were compiled and ordered in accordance with their relevance to the research questions and the recency of the searches they performed. After checking for consistency of findings across all prior evidence syntheses identified, the most relevant and recent evidence synthesis was selected and appraised with the 'risk of bias in systematic reviews' (ROBIS) tool.[16]

4. Results

4.1 Search results

The targeted search of grey literature sources identified 12 relevant records from professional and international organisations.[8, 17-27] These guidelines originated from

the following countries: Australia,[18] Brazil,[19] Canada,[24] Germany,[20] Ireland,[8] Scotland,[25] the United Kingdom[23, 27] and the United States.[21, 26] With the exception of one guideline which was published in 2013, all guidelines were published between 2018 and 2023. The key findings and or recommendations, along with the level of evidence supporting the recommendation, where reported, are summarised in Table 2.

4.1.1 Record characteristics

Table 2: Results from search of grey literature sources

Professional body/organisation	Year published	Country	Key findings and recommendations
Irish guideline			
National Cancer Control Programme (NCCP)[8]	2023	Ireland	See Section 5 of this report for summary of evidence findings from this guideline. Recommendations pertaining to adjuvant radiotherapy for patients who have undergone breast conserving surgery: • Moderately hypofractionated regimen (e.g., 40Gy in 15 fractions) is recommended for breast and nodal regions • An ultra-hypofractionated regimen (e.g., 26Gy in 5 fractions) should be considered for patients having whole breast radiotherapy with or without a boost (but no nodal radiotherapy).
Guidelines and guidance from international professional bodies and organisations			
American Society for Radiation Oncology (ASTRO)[26]	2018	United States	Guidelines on radiation therapy for the whole breast recommends the use of moderate hypofractionation e.g., 40Gy in 15 fractions or 42.6Gy in 16 fractions for women with invasive breast cancer receiving whole breast irradiation with or without inclusion of the low axilla. Guidelines do not include ultra-hypofractionation.
Brazilian Society of Radiation Therapy[19]	2018	Brazil	Recommends hypofractionated whole-breast irradiation; does not include the use of ultra-hypofractionated regimens.
Canadian Agency for Drugs and Technologies[24]	2022	Canada	Summary of abstracts compared conventional fractionation with hypofractionation, so not relevant to the research question of this review.
Cancer Australia[18]	2020	Australia	Recommendations for the management of early breast cancer include offering a moderately hypofractionated course of radiation therapy to women with breast cancer who have undergone breast conserving surgery with clear surgical margins and who

			require post-operative whole breast radiation therapy.
European Society of Breast Cancer Specialists (EUSOMA) & International Society of Geriatric Oncology (SIOG)[17]	2021	N/A	Updated recommendations regarding the management of older patients with breast cancer recommend that hypofractionated schedules (40Gy in 15 fractions over 3 weeks, 42.5Gy in 16 fractions over 3.5 weeks or 26Gy in 5 fractions over 1 week) are recommended for older patients. The publication noted that this recommendation is based on level 4 evidence.
European Society for Radiation Oncology (ESTRO)[22]	2022	N/A	The ESTRO Advisory Committee in Radiation Oncology Practice published consensus recommendations on patient selection, dose and fractionation for external beam radiotherapy in early breast cancer. The consensus statement specifically addressed the following: whole breast irradiation; chest wall irradiation; nodal irradiation; partial breast selection; and partial breast dose and fractionation. With 89% consensus agreement, the group recommended that ultra-hypofractionation (5 fractions) can also be offered for non-nodal breast or chest wall (without reconstruction) radiotherapy either as standard of care or within a randomised trial or prospective cohort. The group cited that the FAST-Forward RCT demonstrated non-inferior local control rates & a similar adverse event profile for ultra-hypofractionated (26Gy in 5 daily fractions) whole breast irradiation compared with 40Gy in 15 fractions over 3 weeks.
German Guideline Program in Oncology[20]	2021	Germany	Discusses de-escalation strategies & recommends moderate hypofractionation (40Gy in 15 fractions). Notes the ongoing FAST and FAST-FORWARD studies and pending results on tumour control late toxicity expected in 2020.
National Comprehensive Cancer Network (NCCN)[21]	2022	United States	Clinical practice guidelines for breast cancer overall recommends the use of a dose of 40-42.5Gy in 15–16 fractions for all patients receiving whole breast radiation without regional nodal radiation. The role for ultra-hypofractionated regimens is recommended as: • Ultra-hypofractionated whole breast RT of 28.5Gy delivered as 5 (once weekly) fractions may be considered in select patients with pTis/T1/T2/N0 aged >50 years after breast conserving surgery, though the optimal fractionation for the

			boost delivery is unknown for this regimen. Alternatively, 26Gy in 5 daily fractions over one-week may be considered, noting that data beyond 5 years for local relapse or toxicity are not yet available for this regimen.
National Institute for Health and Care Excellence (NICE)[23, 28]	2023	United Kingdom	NICE updated the guideline on early and locally advanced breast cancer: diagnosis and management in June 2023. This guideline included an evidence review for the effectiveness of different external beam hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer. See further detail below in Section 4.1.6.
Royal College of Radiologists (RCR)[27]	2021	United Kingdom	Consensus statements regarding hypofractionation for postoperatively breast radiotherapy. Based on FAST-Forward trial data from 2020 and other literature the RCR recommends offering 26Gy in 5 fractions over one-week for whole breast, chest wall with or without reconstruction, and for partial breast radiotherapy. The use of 28.5Gy in 5 fractions over 5 weeks instead of 26Gy in 5 fractions over one-week is recommended for consideration for patients with significant co-morbidities and/or frailty that make daily radiotherapy difficult. The use of 15 fractions over 3 weeks is noted as the standard of care for breast nodal radiotherapy while awaiting results of the FAST-Forward nodal sub-study (due in 2021). For patients requiring a boost either 26Gy in 5 fractions plus sequential boost or 15 fractions simultaneous integrated boost is recommended.
Scottish Intercollegiate Guidelines Network (SIGN)[25]	2013	Scotland	Breast guideline available online was published in Sept 2013 (due for consideration for review in 2016, but not updated). Recommends 40Gy in 15 fractions as an unconventional regimen, and notes FAST, FAST-Forward are ongoing.

Key: ASTRO – American Society for Radiation Oncology; ESTRO – European Society for Radiation Oncology; EUSOMA – European Society of Breast Cancer Specialists; NCCP – national comprehensive cancer network; NCCP – National Cancer Control Programme; NICE: National Institute for Health and Care Excellence; RCT – randomised controlled trial; RCR: Royal College of Radiologist; SIGN – Scottish Intercollegiate Guidelines Network; SIOG – International Society of Geriatric Oncology

4.1.2 Record selection and data extraction

Two key clinical guidelines were identified from the targeted search of grey literature sources as relevant to this review. These were the Irish National Cancer Control Programme (NCCP) updated breast cancer radiation oncology guideline published in May 2023[8] and the 2023 update to the NG101 guideline for the diagnosis and management of early and locally advanced breast cancer from the UK's National Institute for Health and Care Excellence (NICE).[28] The NCCP updated guideline was considered key to this generic justification decision due to its national relevance and recommendations specific to the Irish setting.

The NICE guidelines included an evidence review of the effectiveness of different external beam hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer.[23] The review was carried out to underpin updated recommendations in the NICE NG101 guideline NG101.[28] The update was carried out following the publication of the five-year results of the FAST-Forward multicentre RCT which was carried out across 97 hospitals in the UK.

In accordance with the methods outlined in Section 3.1, the systematic review conducted as part of the NICE clinical guideline was selected for use in this review of prior evidence synthesis due to its relevance to the review questions and the recency of its search (December 2022).[28] The systematic review also included up-to-date GRADE tables which included an additional relevant study from Ivanov 2022 as part of the clinical effectiveness evidence.[29]

A summary table comparing the recommendations made by NICE and the NCCP for ultra-hypofractionation are outlined in Table A.2 in Appendix 1.

4.1.3 Risk of bias assessment

The ROBIS tool[16] indicated that the systematic review of clinical effectiveness contained in the NICE guideline[23] would be considered at low risk of bias – see Table A.3 in Appendix 1 for details of the judgments applied.

4.1.4 Data synthesis

The NICE guideline synthesised the findings of six RCTs on the clinical effectiveness and safety of ultra-hypofractionated radiotherapy, three of which were considered most relevant to this review of prior evidence synthesis as they included a one-week hypofractionation schedule. These studies are summarised in Table 3: Fast-Forward (Brunt et al.),[7] Ivanov et al.,[29] and Shahid et al.[30].

Table 3: Summary of studies related to one-week ultra-hypofractionation regimens included in the NICE systematic review (clinical effectiveness)

Author / Country / Study design	Population	Surgery	Nodal irradiation & boost	Reconstruction	Intervention	Comparator	Outcomes	Follow-up
Brunt (2020b) FAST-Forward trial[7] **UK** **RCT**	n=4,096 participants aged 25-90 years with invasive carcinoma of the breast	Breast conserving surgery or mastectomy (n= 84 in the 26Gy in 5 fraction arm)	Nodal irradiation not allowed in the main study (sub-study ongoing) Boost allowed	Reconstru-ction allowed. (n=7 in the 26Gy in 5 fraction arm)	26Gy in 5 fractions over 1 week OR 27Gy in 5 fractions over 1 week	40Gy in 15 fractions over 3 weeks	Study aimed to demonstrate non-inferiority of 26Gy in 5 fractions in terms of local cancer control. Outcomes: ▪ All-cause mortality ▪ Breast cancer-related mortality ▪ Local relapse ▪ Locoregional relapse ▪ Distant relapse ▪ Adverse events ▪ Normal tissue effects ▪ Quality of life	10 years (only 5-year results reported)
Ivanov (2022)[29] **Serbia** **RCT**	n=60 women aged 45-83 years with early breast cancer requiring radiotherapy	Preserving breast surgery	Participants with planned sequential boost or post-mastectomy irradiation or an indication for nodal treatment were excluded	Not stated	26Gy in 5 fractions over 1 week	40Gy in 15 fractions over 3 weeks	▪ Normal tissue effects	18 months

Shahid (2009)[30] **Pakistan** **RCT**	n=300 women with breast cancer were randomised to receive different hypofractionation regimens after mastectomy	Exclusion criteria not included, but methods state patients were post mastectomy	Nodal regions were included (supraclavicular and post axillary)	Exclusion criteria not stated	27Gy in 5 fractions over 1 week OR 35Gy in 10 fractions over 2 weeks	40Gy in 15 fractions over 3 weeks	▪ All-cause mortality ▪ Disease free survival ▪ Overall survival ▪ Loco-regional relapse ▪ Disease free survival ▪ Metastatic disease ▪ Adverse events	12 months

Key: Gy – Gray; RCT – randomised controlled trial; UK – United Kingdom

4.1.5 GRADE

The NICE guideline appraised outcomes using GRADE. Evidence was graded as high, moderate, low or very low quality, the definitions of which are outlined in Table 4 below.

Table 4: Definitions of the quality rating of evidence grades

Quality rating	Definition
High	'We are very confident that the true effect lies close to the estimate of the effect.'
Moderate	'We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.'
Low	'Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.'
Very low	'We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.'

The relevant GRADE table was extracted and is reproduced in its entirety in Table 5.

The associated summary of the effectiveness evidence is included in Table A.4 in Appendix 1.

Table 5: GRADE Table

Hypofractionation regimen: 40Gy in 15 fractions over 3 weeks (whole breast) compared to 26Gy in 5 fractions over 1 week (whole-breast)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	40Gy/15 fractions	26Gy/5 fractions	Relative (95% CI)	Absolute		
All-cause mortality [MID =/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	92/1361 (6.8%)	90/1368 (6.6%)	RR 1.03 (0.78 to 1.36)	2 more per 1000 (from 14 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Breast cancer related mortality [MID =/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[5]	None	47/1361 (3.5%)	53/1368 (3.9%)	RR 0.89 (0.61 to 1.31)	4 fewer per 1000 (from 15 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
Local relapse [MID =/- 0.8 to 1.25] (follow-up 5 years)												

1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	31/1361 (2.3%)	21/1368 (1.5%)	RR 1.48 (0.86 to 2.57)	7 more per 1000 (from 2 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
Loco-regional relapse [MID =/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	43/1361 (3.2%)	29/1368 (2.1%)	RR 1.49 (0.94 to 2.37)	10 more per 1000 (from 1 fewer to 29 more)	⊕⊕⊕O MODERATE	CRITICAL
Distant relapse [MID =/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	59/1361 (4.3%)	76/1368 (5.6%)	RR 0.78 (0.56 to 1.09)	12 fewer per 1000 (from 24 fewer to 5 more)	⊕⊕⊕O MODERATE	CRITICAL
Acute skin toxicity – 1 point [MID =/- 0.8 to 1.25] (follow-up 18 months; assessed with: CTCAE)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[2]	None	17/27 (63%)	15/33 (45.5%)	RR 1.39 (0.86 to 2.22)	177 more per 1000 (from 64 fewer to 555 more)	⊕⊕⊕O MODERATE	CRITICAL
Acute skin toxicity – 2 points [MID =/- 0.8 to 1.25] (follow-up 18 months; assessed with: CTCAE)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	5/27 (18.5%)	1/33 (3%)	RR 6.11 (0.76 to 49.21)	155 more per 1000 (from 7 fewer to	⊕OOO VERY LOW	CRITICAL

										1000 more)		
Late skin toxicity [MID =/- 0.8 to 1.25] (follow-up 18 months; assessed with RESS-RTOG/EORTC)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/33 (18.2%)	9/27 (33.3%)	RR 0.55 (0.22 to 1.34)	150 fewer per 1000 (from 260 fewer to 113 more)	⨁OOO VERY LOW	CRITICAL
Sub-cutaneous tissue toxicity – 1 point [MID =/- 0.8 to 1.25] (follow-up 18 months; assessed with RESS-RTOG/EORTC)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	8/33 (24.2%)	7/27 (25.9%)	RR 0.94 (0.39 to 2.25)	16 fewer per 1000 (from 158 fewer to 324 more)	⨁OOO VERY LOW	CRITICAL
Sub-cutaneous tissue toxicity –2 points [MID =/- 0.8 to 1.25] (follow-up 18 months; assessed with RESS-RTOG/EORTC)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	0/33 (0%)	5/27 (18.5%)	RR 0.07 (0 to 1.3)	172 fewer per 1000 (from 185 fewer to 56 more)	⨁OOO VERY LOW	CRITICAL
Cosmetic results – 1 point [MID =/- 0.8 to 1.25] (follow-up 18 months)												
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Serious[2]	None	22/33 (66.7%)	14/27 (51.9%)	RR 1.29 (0.83 to 1.99)	150 more per 1000 (from 88 fewer to 513 more)	⨁⨁OO LOW	CRITICAL

Cosmetic results – 2 points [MID = / - 0.8 to 1.25] (follow-up 18 months)											
1[3]	Randomised trials	Serious[4]	No serious inconsistency	No serious indirectness	Very serious[5]	None	11/33 (33.3%)	13/27 (48.1%)	RR 0.69 (0.37 to 1.29)	149 fewer per 1000 (from 303 fewer to 140 more)	⨁OOO VERY LOW	CRITICAL
Adverse events (clinician assessed) [MID + / - 0.8 to 1.25] (follow-up 5 years)											
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	651/6121 (10.6%)	774/6327 (12.2%)	RR 0.87 (0.79 to 0.96)	16 fewer per 1000 (from 5 fewer to 26 fewer)	⨁⨁⨁O MODERATE	CRITICAL
EORTC QLQ-BR23 - Arm or shoulder pain [MID + / - 0.8 to 1.25] (follow-up 5 years)											
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	401/2537 (15.8%)	455/2599 (17.5%)	RR 0.9 (0.8 to 1.02)	18 fewer per 1000 (from 35 fewer to 4 more)	⨁⨁⨁⨁ HIGH	CRITICAL
EORTC QLQ-BR23 - Swollen arm or hand [MID + / - 0.8 to 1.25] (follow-up 5 years)											
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	101/2536 (4%)	124/2592 (4.8%)	RR 0.83 (0.64 to 1.08)	8 fewer per 1000 (from 17 fewer to 4 more)	⨁⨁⨁O MODERATE	CRITICAL
EORTC QLQ-BR23 - Difficulty raising arm [MID + / - 0.8 to 1.25] (follow-up 5 years)											

1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	338/2538 (13.3%)	417/2597 (16.1%)	RR 0.83 (0.73 to 0.95)	27 fewer per 1000 (from 8 fewer to 43 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	122/2538 (4.8%)	192/2599 (7.4%)	RR 0.65 (0.52 to 0.81)	26 fewer per 1000 (from 14 fewer to 35 fewer)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised Trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	283/2528 (11.2%)	319/2587 (12.3%)	RR 0.91 (0.78 to 1.06)	11 fewer per 1000 (from 27 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	156/2539 (6.1%)	164/2592 (6.3%)	RR 0.97 (0.79 to 1.2)	2 fewer per 1000 (from 13 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	156/2539 (6.1%)	164/2592 (6.3%)	RR 0.97 (0.79 to 1.2)	2 fewer per 1000 (from 13 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												

1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	778/2480 (31.4%)	770/2563 (30%)	RR 1.04 (0.96-1.13 to)	12 fewer per 1000 (from 13 fewer to 13 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	585/2445 (23.9%)	515/2542 (20.3%)	RR 1.18 (1.06 to 1.31)	36 more per 1000 (from 12 more to 63 more)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	499/2446 (20.4%)	626/2534 (24.7%)	RR 0.83 (0.74 to 0.92)	42 fewer per 1000 (from 20 fewer to 64 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25] (follow-up 5 years)												
1[1]	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	345/2505 (13.8%)	338/2576 (13.1%)	RR 1.05 (0.91 to 1.21)	7 more per 1000 (from 12 fewer to 28 more)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] FAST-Forward (Brunt et al. 2020b)
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] Ivanov et al. 2022
[4] Study at moderate risk of bias. Quality of the outcome downgraded once.
[5] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice

4.1.6 Summary of included records

Three trials identified in the NICE review considered two different one-week ultra-hypofractionation schedules (26Gy in 5 fractions and 27Gy in five fractions) as an alternative to a three-week moderate hypofractionation (40Gy in 15 fractions) schedule. Two RCTs (FAST-Forward[31] (n=4,096) and Ivanov et al.[29](n=60)) compared a schedule of 26Gy in 5 fractions over one-week with 40Gy in 15 fractions. The results for this comparison are discussed below in the context of the RQs of interest to this evidence synthesis (oncological outcomes; quality of life; adverse events and toxicities; and cosmetic outcomes). Two RCTs (Fast-Forward trial[7]) and Shahid et al.[30] (n=300) presented evidence for the comparison of 27Gy in 5 fractions with 40Gy in 15 fractions.[7] On the basis of the this evidence, the NICE review deemed that the 26Gy in 5 fractions over one-week regimen was the clinically relevant regimen with evidence of non-inferiority of efficacy and similar normal tissue effects to a moderate hypofractionation schedule. Given this, and the application for generic justification received by HIQA stating that the new practice consisted of the use of 26Gy in 5 fractions, only the results for this comparison are included in the below summary.

RQ1: oncological outcomes

Comparative effectiveness data were considered in relation to the following outcomes: all-cause and breast-cancer related mortality, local relapse and distant relapse (Table 5). Evidence to inform these comparisons was all based solely on the five-year follow-up data from the FAST-Forward trial, which aimed to demonstrate the non-inferiority of a one-week ultra-hypofractionated regimen compared with the three-week standard of care.[31]

The NICE review found the two regimens (40Gy in 15 fractions over 3 weeks and 26Gy in 5 fractions over 1 week) to be comparable and could not differentiate between them in terms of all-cause mortality (relative risk (RR):1.03, 95% CI: 0.78–1.36). Similarly, no difference was found with respect to breast-cancer related mortality (RR: 0.89, 95% CI: 0.61 - 1.31). For both outcomes, the certainty of the evidence was noted to be low. In terms of distant relapse, based on moderate certainty evidence, again the NICE review could not differentiate between the two regimens (RR: 0.78, 95% CI 0.56 – 1.09). In terms of local and loco-regional relapse, again based on moderate certainty evidence, no difference was observed between the 40Gy and 26Gy regimens (RR: 1.48 (95% CI: 0.86 - 2.57) and RR: 1.49 (95% CI: 0.94 - 2.37), respectively).

While noting that the longest follow up available in any of the studies was five years, the NICE review concluded that the body of evidence indicated no difference

between the effectiveness of the two hypofractionation regimens for the following outcomes: mortality, local recurrence and distant recurrence. This indicated non-inferiority of the 26Gy in 5 fraction schedule. However, it was highlighted that longer term data will provide more information about distant relapse and disease-free survival associated with each treatment regimen.

RQ2: quality of life

The NICE review considered evidence from the FAST-Forward trial[31] in relation to quality of life. The European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-BR23 tool was used in this study to assess patient-reported quality of life outcomes with respect to: arm or shoulder pain, swollen arm or hand, difficulty raising arm, breast pain, breast swollen, breast oversensitive and skin problems in breast. For most outcomes, based on moderate to high certainty evidence, the review found the fractionation schedules to be comparable (Table 5) While, based on moderate certainty evidence, the relative risk of reduced quality of life due to breast swelling and also due to breast pain was lower with the 40Gy in 15 fractions schedule, the difference between the groups was less than the defined minimum important difference.

RQ3: adverse events and toxicities

The NICE review considered the results of the Ivanov trial (n = 60) in relation to acute and late skin and sub-cutaneous tissue toxicity noting the maximum follow-up reported was at 18 months.[29] Overall, the study found the two fractionation regimens to be comparable. No significant difference was observed in the incidence of grade two sub-cutaneous toxicity between the 40Gy and 26Gy schedules (RR: 0.07, 95% CI: 0 – 1.3 or for grade two acute skin toxicity (RR: 6.11, 95% CI: 0.76-49.21), noting very low certainty evidence for both outcomes.

At five years, the FAST-Forward trial reported a lower incidence of clinician reported adverse events with the 40Gy schedule (RR: 0.87, 95% CI: 0.79 to 0.96). While statistically significant, the differences were less than the defined minimum important difference. However, it was highlighted that longer term data will provide more information about long-term adverse events associated with each treatment regimen.

At five years, the FAST-Forward trial reported the prevalence of any moderate or marked clinician-assessed normal tissue effects in the breast or chest wall. [31] Assessment of normal tissue effects (breast smaller) favoured 26Gy (RR: 1.18, 95% CI: 1.06-1.31) and for breast harder or firmer favoured the 40Gy regimen (RR: 0.83 95% CI: 0.74-0.92), noting moderate certainty evidence for both outcomes.

However, the differences was less than the defined minimum important difference. No difference was observed between the regimens in terms of the outcome 'breast appearance changed' (RR=1.04, 95% CI: 0.96- 1.13). Overall, the 26Gy in 5 fractions over a week regimen was deemed the clinically relevant regimen with non-inferiority of efficacy and similar normal tissue effects.

RQ4: cosmetic outcomes

Evidence in relation to cosmetic results were derived from the RCT by Ivanov et al. (n=60) in the NICE review.[29] The cosmetic effect of treatment was assessed by both patients and radiation oncologists using an unvalidated four-point scale. Based on low and very low certainty evidence, no difference was found in cosmetic results found between the 40Gy and 26Gy schedules for one point and two points of difference in cosmesis (RR:1.29 (95% CI: 0.83-1.99) and RR 0.69 (95% CI 0.37-1.29), respectively. The NICE review downgraded the certainty of evidence for this outcome by two levels due to imprecision.

Sub-groups

The NICE review protocol outlined the prospective intention to carry out sub-group analysis by type of breast reconstruction surgery (breast-conserving surgery or mastectomy, which could include reconstruction), type of radiotherapy (whole breast, chest wall, partial breast with or without regional node radiotherapy), and if a radiotherapy boost was or was not given. However, sub-group analysis was not presented in the review for clinical effectiveness due to the evidence gaps for each sub-group population. The text below summarises the number of patients in specific subgroups from the relevant studies to support interpretation of the evidence and the potential applicability of the evidence to various subgroups.

Type of surgery

Eligibility for the FAST-Forward RCT was initially limited to individuals who had undergone breast conserving surgery who would undergo whole breast radiotherapy; however, the protocol was subsequently extended to include individuals who were post-mastectomy who would receive radiotherapy to the chest wall. Out of the 4,096 number of patients in the FAST-Forward trial, 264 patients were post-mastectomy (n = 84 in the 26Gy arm and n = 91 in the 40Gy arm). The trial[7] results did not present disaggregated results for this post mastectomy cohort in their findings. The publication in 2020 noted that a small cohort of patients who received radiotherapy to the chest wall after mastectomy were recruited into a photographic sub-study for patient-reported outcomes, but these results were not

published. In the Ivanov et al. trial[29], post-mastectomy irradiation was an exclusion criterion.

As noted, a small number of participants (84 out of the 1,368 patients randomised to the 26Gy in 5 fractions arm) had undergone mastectomy in the FAST-Forward study, and an even smaller number had immediate reconstruction (n = 7 in the 26Gy in five fractions arm). The trial results outlined the types of reconstruction included: autologous reconstruction (n=5) and with implant-based reconstruction (n=2). However, disaggregated data for the group with immediate reconstruction were not presented.

Nodal irradiation

Patients requiring local regional lymph node irradiation were excluded from both the main FAST-Forward RCT[31] and the trial reported by Ivanov et al.[29] An ongoing sub-study as part of the FAST-Forward RCT is testing the same fractionation schedules for patients requiring nodal irradiation (axilla or supraclavicular fossa). The results are not reported as the follow-up data are not yet mature.

Boost

Patients whose treatment schedule included a planned sequential boost were excluded from the Ivanov et al. study. However, in the FAST-Forward study, a sequential boost was delivered via electrons or photons in 24.3% of the 26Gy cohort and 25.1% of the 40Gy cohort. The boost dose was 16Gy in 8 fractions or 10Gy in 5 fractions. The publication noted that concurrent or synchronous boost regimens were avoided despite current interest in such approaches.

4.1.7 Additional benefits or harms

The applicant noted a number of advantages of the one-week course of radiotherapy. Suggested advantages included convenience for patients, greater cost effectiveness and increased service capacity for both patients with breast cancers and patients generally. The applicant noted that the ultra-hypofractionated regimen was initially introduced as part of the COVID-19 pandemic emergency response, as a one-week course was felt to reduce risk of infection due to lower numbers of hospital visits.[5]

In terms of potential harms, the NCCP guideline noted that with hypofractionation, any treatment error will affect a great proportion of treatment. While in radiotherapy, it is sometimes possible to compensate for accidental or unintended exposures, with an ultra-hypofractionated regimen there would be less opportunity for compensation.

4.1.8 Public and occupational exposure

In Ireland, public and occupational exposure is primarily the responsibility of the Environmental Protection Agency (EPA). However, the Regulations require HIQA to consider public and occupational exposure as part of the justification of medical exposures.

In accordance with Regulation 12(5) of S.I. No. 30 of 2019, all practices involving the use of ionising radiation must be authorised in advance by the Environmental Protection Agency (EPA).[32] All undertakings carrying out a radiological practice must fully comply with the relevant provisions of the S.I. No. 30 of 2019 and any conditions attached to an authorisation.

In the context of Ireland, exposure to staff, the public, carers and comforters can be minimised through a carefully considered prospective risk assessment and use of a well-developed quality management system. The design stage of the risk assessment must be completed prior to the installation and commissioning of all sources of ionising radiation.

Local policies, procedures and guidelines must be in place to protect staff and members of the public. Procedures to be followed in the event of an incident liable to have radiation safety implications for workers and members of the public must be developed. It must be ensured that dose constraints and limits for occupational and public exposure as set out in Part 3, Sections 1 and 2 of SI 30 of 2019 are adhered to.[32] In assessing compliance with the dose constraints for medical applications, account should be taken of the principles and approach set out in the EPA's guidance document "The Design of Diagnostic Medical Facilities Where Ionising Radiation Is Used" (2009).[33]

Further information on the EPA requirements is provided in their guidance for undertakings on the application of the IRR19.[34] Information on the dose constraints for carers and comforters, and individuals participating in medical or biomedical research is also available in guidance issued by HIQA.

No change in risk of radiation exposure to staff, the public, carers and comforters is anticipated from the use of an ultra-hypofractionated radiotherapy regimen, compared to a moderately hypofractionated regimen, provided the usual safeguards are in place.

5. Discussion

The purpose of this review was to carry out evidence synthesis to compare ultra-hypofractionated and moderately hypofractionated external beam radiotherapy in the management of breast cancer.

Summary of NICE Guidelines

The NICE review[28] reported findings from two RCTs which are relevant to the research questions of this report: the FAST-Forward trial[7] and the RCT by Ivanov et al.[29] Both RCTs reported that 26Gy in 5 fractions delivered over one-week (ultra-hypofractionation) is non-inferior to 40Gy in 15 fractions over three weeks (moderate hypofractionation) in terms of oncological outcomes. While there were some differences reported for normal tissue effects and adverse events in the FAST-Forward study, the NICE review noted that these differences were less than the minimal important difference, therefore no clinically meaningful differences were observed. The NICE review examined a range of fractionation schedules including a comparison of two one-week ultra-hypofractionation schedules with a moderate hypofractionation schedule. Non-inferiority was noted not to have been demonstrated in the FAST-Forward trial for the 27Gy in 5 fraction schedule. The NICE review therefore deemed that the 26Gy in 5 fractions over one-week regimen was the clinically relevant regimen with non-inferiority of efficacy and similar normal tissue effects.

Summary of NCCP Guidelines

The NCCP published updated breast cancer radiation oncology guidelines in May 2023.[8] Clinical question 3 (new to 2023) addressed the use of hypofractionation, including a one-week ultra-fractionation regimen in breast cancer patients who have undergone breast conserving surgery. Five meta-analyses from 2010 to 2019 addressing hypofractionation were reviewed.[35-39] The fractionation schedules considered included conventional fractionation and hypofractionation, and data from the FAST [31] and FAST-Forward trials.[7] The guideline stated that based on clinical evidence, there was no significant difference in local recurrence rate, overall survival and cosmetic outcome between standard fractionation and hypofractionation schedules. In terms of toxicity and cosmetic outcomes, there was no significant difference between 40Gy and 26Gy regimens from the FAST-Forward trial. The guideline detailed the following recommendations, specifying both the strength of the recommendations and the assessment of quality of the underpinning evidence:

Recommendation 1: In patients with breast cancer who have undergone breast

conserving surgery and who require adjuvant radiotherapy to breast and nodal regions, a moderately hypofractionated regimen e.g. 40Gy in 15 fractions is recommended.

- Quality of evidence: High
- Grade of recommendation: Strong

Recommendation 2: In patients with breast cancer who have undergone breast conserving surgery, and are having whole breast radiotherapy only (with no boost or nodal radiotherapy) an ultra-hypofractionated regimen e.g. 26Gy in 5 fractions should be considered.

- Quality of evidence: Moderate
- Grade of recommendation: Strong

Recommendation 3: In patients with breast cancer who have undergone breast conserving surgery, and are having whole breast radiotherapy with a boost (but no nodal radiotherapy) an ultra-hypofractionated regimen e.g. 26Gy in 5 fractions may be considered.

- Quality of evidence: Low
- Grade of recommendation: Weak

Sub-groups to consider

The application received by HIQA for justification of ultra-hypofractionation as a practice was requested for broad categories of breast cancer patients, including patients post breast conserving surgery and mastectomy. The NICE review protocol outlined the prospective intention to carry out sub-group analysis by type of radiotherapy (whole breast, chest wall, partial breast with or without regional node radiotherapy), breast reconstruction surgery and if a boost was given or not given. However, it was noted that it was not possible to complete these due to the current evidence gaps for each sub-group population, so these data were not presented in the review of clinical effectiveness.

The recommendations made by NICE and the NCCP were mostly aligned in favour of ultra-fractionation, however, there were some differences pertaining to patient sub-groups, such as whether ultra-hypofractionation is to be considered after mastectomy. While the NICE guidelines recommend the use of ultra-hypofractionation after breast conserving surgery and mastectomy, the evidence considered by NICE was largely derived from populations who had undergone breast conserving surgery. In the FAST-Forward study, only 6.1% of included patients in the 26Gy arm were post mastectomy and disaggregated outcome results for this

sub-population were not reported. The NCCP guideline however, adopted a slightly more conservative approach and recommended consideration of ultra-hypofractionation for patients post breast conserving surgery, and did not include post mastectomy radiotherapy in the recommendations.

Both NICE and the NCCP guidelines make recommendations in relation to the use of a sequential boost with different fractionation schedules, including ultra-hypofractionation. While disaggregated oncological outcome data for patients who received a boost were not presented in the NICE review, it was noted that similar numbers of patients had a boost in the various treatment arms of the FAST-Forward study.

Of note, the data presented in the NICE review specifically related to patients with invasive breast cancer. Furthermore, the data presented did not include outcome data for those receiving regional lymph node irradiation due to the limited evidence currently available. Given this, both the NICE and NCCP guidelines recommend moderately hypofractionated radiotherapy (e.g., 40Gy in 15 fractions) where regional node radiotherapy is included. NICE specifically notes that ultra-hypofractionation (26Gy in 5 fractions) should not be offered for regional node radiotherapy until results from ongoing trials are published.

The NICE review also highlights gaps in the current evidence to support the use of ultra-hypofractionation for patients with immediate reconstruction. The NICE review noted the need to further explore the effectiveness of the 26Gy in 5 fractions regimen in this patient group. The NICE committee recommends that clinical judgment should be used to decide on the most suitable option for such patients.

Furthermore, the NICE review noted that there are other circumstances where a moderately hypofractionated regimen may be more suitable than a one-week regimen and that clinical judgment should be used. This included, for example, patients at increased risk of side effects due to presence of other comorbidities such as high body mass index. The NCCP guideline recommends that the dosimetric parameters from FAST-Forward should be adhered to when using ultra-hypofractionation. Similarly, the NICE guideline recommends the use of 15 fractions where dosimetry is outside the FAST-Forward constraints.

Considerations

The NCCP guideline development group, which included patient representatives considered patient values and preferences in their decision-making.

The guideline group considered hypofractionation less burdensome for patients, that patients would value the time saved from a shorter course of treatment. Similarly,

the applicant also noted convenience for patients as an advantage of the one-week regimens with the potential that this may make treatment more accessible. The applicant also noted that from a service perspective, hypofractionation has the potential to be cost saving and to increase service capacity which benefits both patients with breast cancers and other patients needing radiotherapy. The applicant noted that the ultra-hypofractionated regimen was initially introduced as part of the COVID-19 pandemic emergency response, as a one-week course was felt to reduce risk of infection due to lower numbers of hospital visits.[5]

Limitations

While the NCCP and NICE guideline recommendations in favour of a one-week hypofractionation regimen are primarily based on the FAST-Forward RCT, it should be noted that, thus far, only five-year follow-up data are published. Given this, there is some variation in the international guidance regarding the use of ultra-hypofractionation schedules. While some countries and organisations outside the NCCP and NICE including the European ESTRO group[22] have adopted the findings of the FAST-Forward trial into recommendations, other countries and organisations are taking a more cautious approach and awaiting the 10 year follow-up data.[20, 21, 24] Longer term data will provide further evidence about the distant recurrence of tumours, disease free survival and the long-term adverse events associated with ultra-hypofractionation regimens.

Conclusion

The evidence identified in this review of prior evidence synthesis relevant to this justification of practice is based on two RCTs. The certainty of evidence for ultra-hypofractionation in adjuvant breast radiotherapy varied across outcomes, with low certainty evidence in relation to mortality outcomes, moderate certainty evidence for local tumour control and evidence ranging from low to high certainty evidence for many outcomes evaluating treatment side effects and toxicity. Based on these trials, there is evidence based on a maximum of five year follow-up data that ultra-hypofractionated radiation (for example, 26Gy in 5 fractions over one-week) is non-inferior in terms of efficacy and has similar normal tissue effects to moderate fractionation schedules (40Gy in 15 factions) for the treatment of breast cancer. The recommendations in national guidelines in favour of external beam ultra-hypofractionation were derived from the available evidence mindful also of patient preference and service capacity implications.

6. Evidence to decision

A draft of this report was submitted to the MEIR EAG for their consideration and feedback. Following this, a discussion was held on 19 October 2023, in which the evidence summary and additional contextual factors were considered. As per the HIQA Methods for Generic Justification Of New Practices In Ionising Radiation, a modified version of the GRADE evidence to decision (EtD) framework was used to support the MEIR EAG in coming to a recommendation regarding the generic justification of ultra-hypofractionated radiotherapy for the treatment of breast cancer.[2]

6.1 Overview of MEIR EAG GRADE EtD discussion

Informed by the review of the above evidence, the MEIR EAG completed judgments under a modified evidence-to-decision (EtD) making framework to arrive at a recommendation to HIQA on the generic justification of ultra-hypofractionated adjuvant radiotherapy for breast cancer. The full EtD framework including a summary of the panel discussion and the final judgments can be found in Appendix 2 and Table 6, respectively. In terms of potential benefits and harms, the MEIR EAG considered the evidence for the outcomes listed in terms of both the magnitude of the effect and the certainty of the evidence.

While acknowledging that current data are limited to five-year follow-up, the MEIR EAG judged that the differences in benefit between this practice and moderately hypofractionated adjuvant radiotherapy were trivial, given the RCT data presented indicate non-inferiority in terms of oncological outcomes. Again acknowledging that current data are limited to five-year follow-up, the MEIR judged the overall potential for harm to be trivial given the RCT data presented indicate that ultra-hypofractionated adjuvant radiotherapy is non-inferior in terms of adverse events, toxicities and cosmetic outcomes.

When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the practice was favoured over moderately fractionated radiotherapy, and could be used at the discretion of the treating radiation oncologist. This judgment was on the basis that available five-year follow-up data indicate that there are no differences in the outcomes discussed, but that there are positive implications for patients in terms of treatment burden (fewer required treatment attendances and for radiation oncology capacity).

The MEIR EAG recommended that ultra-hypofractionated adjuvant radiotherapy for breast cancer should be generically justified.

Table 6: Modified evidence to decision table for generic justification of ultra-hypofractionated radiotherapy for the treatment of breast cancer

	SUMMARY OF JUDGMENTS						
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large	Varies	Don't know	
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**	Varies	Don't know	
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High		No included studies	
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

6.2 HIQA Decision

Having considered the application, the evidence review and the recommendation from the MEIR EAG, HIQA is satisfied that on consideration of the balance between the benefits and harms, this practice should be generically justified.

The practice of ultra-hypofractionated adjuvant radiotherapy for breast cancer is generically justified under SI 256/2018.

The generic justification of this practice is effective from 16 Nov 2023. Under the Regulations, HIQA may review the generic justification of this practice if new and important evidence about the practice emerges. HIQA may also review this practice if new and important evidence about alternative techniques and technologies (including non-ionising practices) emerges.

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Appendix 1

Table A.1 Details of grey literature search

Organisation, country Description	URL link
International organisations	
World Health Organization	www.who.int/en
European Network for Health Technology Assessment (EUnetHTA)	https://www.eunethta.eu/
International HTA database (INAHTA)	https://database.inahta.org/
Guidelines International Network (G-I-N) (International guidelines library)	https://g-i-n.net/international-guidelines-library
Country specific organisations (only examples from selected countries)	
Australia	
Australian National Health and Medical Research Council	https://nhmrc.gov.au/about-us/publications
Imaging Pathways (government Western Australia)	http://imagingpathways.health.wa.gov.au/index.php/imaging-pathways
Canada	
Canadian Agency for Drugs and Technology in Health (CADTH)	http://www.cadth.ca
Canadian Medical Association Infobase	https://joulecma.ca/cpg/homepage

Canada safe imaging	
Objective Health Canada	https://objectivehealth.ca/
Germany	
German Institute of Medical Documentation and Information	www.bfarm.de
Association of the Scientific Medical Societies Germany	https://www.awmf.org/
Ireland	
Department of Health (including National Clinical Guidelines)	health.gov.ie
Health Service Executive (HSE)	www.hse.ie
National Cancer Control Programme HSE	https://www.hse.ie/eng/services/list/5/cancer/
Faculty of Radiologists Ireland	www.radiology.ie/
United Kingdom	
COMARE	https://www.gov.uk/government/groups/committee-on-medical-aspects-of-radiation-in-the-environment-comare
The Royal college of Radiologists	https://www.rcr.ac.uk
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/
Department of Health and Social Care	https://www.gov.uk/government/organisations/department-of-health-and-social-care
Health Technology Wales	https://healthtechnology.wales/
SHTG, Scotland	https://shtg.scot/about-us/
United States	

Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/
Food and Drug Administration (FDA)	http://www.fda.gov/cder/guidance/index.htm
American College of Physicians	https://www.acponline.org/
National Academy of Medicine	https://nam.edu/

Table A.2: Recommendations for patient sub-groups in the NCCP and NICE guidelines

	Surgery	Partial breast irradiation	Boost	Nodal irradiation	Reconstruction
NCCP guideline recommends one-week regimen	After BCS	Whole breast only	With or without a boost	Moderately hypo regimen recommended 40Gy in 15 fractions	Not stated
NICE guideline recommends one-week regimen	After BCS or mastectomy	Whole breast or partial breast irradiation	With or without a boost	Use 40Gy in 15 fractions if nodal irradiation included	40Gy in 15 fractions where implant based reconstruction used

Key: BCS - breast conserving surgery; NCCP – National Cancer Control Programme; NICE – National Institute for Health and Care Excellence

Table A.3: ROBIS Judgments

Review	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
NICE guideline June 2023[23]	Low concern	Low concern	Unclear concern	Low concern	Low concern

Table A.4 Summary of the effectiveness evidence

Hypofractionation regimen: 40Gy in 15 fractions over 3 weeks (whole breast) compared to 26Gy in 5 fractions over 1 week (whole-breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
All-cause mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.03 (0.78 to 1.36)	66 per 1000	2 more per 1000 (from 14 fewer to 24 more)	Could not differentiate (low quality evidence)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.89 (0.61 to 1.31)	39 per 1000	4 fewer per 1000 (from 15 fewer to 12 more)	Could not differentiate (low quality evidence)
Local relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.48 (0.86 to 2.57)	15 per 1000	7 more per 1000 (from 2 fewer to 24 more)	Could not differentiate (moderate quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.49 (0.94 to 2.37)	21 per 1000	10 more per 1000 (from 1 fewer to 29 more)	Could not differentiate (moderate quality evidence)
Distant relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.78 (0.56 to 1.09)	56 per 1000	12 fewer per 1000 (from 24 fewer to 5 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 1 point [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 1.39 (0.86 to 2.22)	455 per 1000	177 more per 1000 (from 64 fewer to 555 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 2 points [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 6.11 (0.76 to 49.21)	30 per 1000	155 more per 1000 (from 7 fewer to 1000 more)	Could not differentiate (very low quality evidence)
Late skin toxicity [MID +/- 0.8 to 1.25	60 (1 study[3]) 18 months	RR 0.55 (0.22 to 1.34)	333 per 1000	150 fewer per 1000 (from 260 fewer to 113 more)	Could not differentiate (very low quality evidence)
Subcutaneous tissue toxicity - 1 point [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.94 (0.39 to 2.25)	259 per 1000	16 fewer per 1000 (from 158 fewer to 324 more)	Could not differentiate (very low quality evidence)

Subcutaneous tissue toxicity - 2 points [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.07 (0 to 1.3)	185 per 1000	172 fewer per 1000 (from 185 fewer to 56 more)	Could not differentiate (very low quality evidence)
Cosmetic results - 1 point [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 1.29 (0.83 to 1.99)	519 per 1000	150 more per 1000 (from 88 fewer to 513 more)	Could not differentiate (low quality evidence)
Cosmetic results - 2 points [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 0.69 (0.37 to 1.29)	481 per 1000	149 fewer per 1000 (from 303 fewer to 140 more)	Could not differentiate (very low quality evidence)
Adverse events (clinician assessed) [MID +/- 0.8 to 1.25]	12448 (1 study[1]) 5 years	RR 0.87 (0.79 to 0.96)	122 per 1000	16 fewer per 1000 (from 5 fewer to 26 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	RR 0.9 (0.8 to 1.02)	175 per 1000	18 fewer per 1000 (from 35 fewer to 4 more)	No meaningful difference (high quality evidence)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5128 (1 study[1]) 5 years	RR 0.83 (0.64 to 1.08)	48 per 1000	8 fewer per 1000 (from 17 fewer to 4 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5129 (1 study[1]) 5 years	RR 0.93 (0.76 to 1.14)	72 per 1000	5 fewer per 1000 (from 17 fewer to 10 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	RR 0.83 (0.73 to 0.95)	161 per 1000	27 fewer per 1000 (from 8 fewer to 43 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5137 (1 study[1]) 5 years	RR 0.65 (0.52 to 0.81)	74 per 1000	26 fewer per 1000 (from 14 fewer to 35 fewer)	Favours 40 Gy in 15 fractions (moderate quality evidence)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5115 (1 study[1]) 5 years	RR 0.91 (0.78 to 1.06)	123 per 1000	11 fewer per 1000 (from 27 fewer to 7 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5131 (1 study[1]) 5 years	RR 0.97 (0.79 to 1.2)	63 per 1000	2 fewer per 1000 (from 13 fewer to 13 more)	Could not differentiate (moderate quality evidence)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5043 (1 study[1]) 5 years	RR 1.04 (0.96 to 1.13)	300 per 1000	12 more per 1000 (from 12 fewer to 39 more)	No meaningful difference (high quality evidence)

Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	4987 (1 study[1]) 5 years	RR 1.18 (1.06 to 1.31)	203 per 1000	36 more per 1000 (from 12 more to 63 more)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	4980 (1 study[1]) 5 years	RR 0.83 (0.74 to 0.92)	247 per 1000	42 fewer per 1000 (from 20 fewer to 64 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5081 (1 study[1]) 5 years	RR 1.05 (0.91 to 1.21)	131 per 1000	7 more per 1000 (from 12 fewer to 28 more)	No meaningful difference (high quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **CTCAE:** Common terminology criteria for adverse events scale; **EORTC-QLQ BR23:** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer; **RESS:** Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Scoring Schema; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 FAST-Forward (Brunt et al. 2020b)
2 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
3 Ivanov et al. 2022
4 Study at moderate risk of bias. Quality of the outcome downgraded once.
5 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Appendix 2

Evidence to Decision Framework Desirable Effects How substantial are the desirable anticipated effects?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Oncological outcomes** (based on five-year follow-up data from FAST-Forward n= 4,096) All-cause mortality • NICE review could not differentiate between 40Gy and 26Gy regimens • Relative risk (RR): 1.03, (95% CI: 0.78–1.36) Breast-cancer related mortality • No difference was found between the regimens • RR: 0.89, (95% CI: 0.61-1.31) Local and loco-regional relapse • No difference was found between the regimens • Local relapse RR: 1.48, (95% CI: 0.86-2.57) • Loco-regional relapse RR: 1.49, (95% CI: 0.94-2.37). Distant relapse • No difference was found between the regimens • RR: 0.78, (95% CI 0.56 – 1.09)	
Panel discussion: The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. While bearing in mind that only five-year data are available, it was noted that the RCT data presented indicate that ultra-hypofractionated adjuvant radiotherapy is non-inferior in terms of oncological outcomes. A judgment of 'trivial' was recorded by the EAG for this criterion.		

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	**Quality of Life:** (based on five-year follow-up data from FAST-Forward n= 4,096) • The 40Gy schedule was favourable for breast swelling and also due to breast pain, however, but the difference between the groups was less than the defined minimum important difference. • Breast pain RR: 0.83 (0.73 to 0.95) • Breast swollen RR: 0.65 (0.52 to 0.81) • For all other QoL outcomes the schedules were comparable. **Adverse events and toxicity:** Toxicity (based on Ivanov 2022 n=60 with maximum of 18 month follow-up). • No significant difference was observed in the incidence of grade two sub-cutaneous or skin toxicity between the 40Gy and 26Gy schedules • Sub-cutaneous grade two toxicity (RR: 0.07, (95% CI: 0–1.3). • Grade two acute skin toxicity (RR: 6.11, 95% CI: 0.76- 49.21). Normal tissue effects (based on five-year follow-up data from FAST-Forward n= 4,096) • Assessment of normal tissue effects (breast smaller) favoured 26Gy (RR: 1.18, 95% CI: 1.06-1.31) • Assessment of normal tissue effects breast harder or firmer favoured the 40Gy regimen (RR: 0.83 95% CI: 0.74-0.92), • However, the differences for both of these outcomes were less than the defined minimum important difference and there were no meaningful differences for other normal tissue effects outcomes. Adverse events • The FAST-Forward trial reported a lower incidence of clinician reported adverse events with the 40Gy schedule (RR: 0.87, 95% CI: 0.79 to 0.96).	

	Cosmetic outcomes: (based on Ivanov 2022 n=60 with maximum of 18 month follow-up). • Cosmetic effect of treatment was assessed by both patients and radiation oncologists using an unvalidated four-point scale. Based on low and very low certainty evidence, no difference was found in cosmetic results found between the 40Gy and 26Gy schedules for one point and two points of difference in cosmesis • One point of difference in cosmesis RR: 1.29 (95% CI: 0.83-1.99) • Two points difference in cosmesis RR: 0.69 (95% CI 0.37-1.29)	

Panel discussion:

The EAG considered the evidence for the outcomes listed, both in terms of the magnitude of the effect and the certainty of the evidence. Again, bearing in mind that the evidence is limited to five-year follow-up data, it was noted that the RCT data presented indicate that ultra-hypofractionated adjuvant radiotherapy is non-inferior in terms of adverse events, toxicities and cosmetic outcomes.

A judgment of 'trivial' was agreed upon by the EAG.

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The GRADE assessment of the certainty of the evidence outlined in the NICE guidelines found the certainty of the evidence to be: • moderate for local relapse, loco-regional relapse and distant relapse • low for all-cause mortality and breast cancer-related mortality • moderate to high for quality of life outcomes • moderate to high for normal tissue effects • moderate for clinician-assessed adverse events • very low to moderate for acute skin toxicity • very low to low for cosmetic outcomes	GRADE approach is to give overall rating as per lowest certainty of all outcomes, however, overall considered certainty low due to: 1. Importance of outcomes. Considered local relapse, loco-regional relapse, distant relapse, all-cause mortality and breast

	• very low for late skin toxicity and subcutaneous skin toxicity.	cancer related mortality as most important outcomes. 2. In FAST-Forward normal tissue effects included breast distortion, shrinkage, induration and telangiectasia; and breast or chest wall oedema and discomfort. Certainty of evidence was moderate to high for these outcomes. Skin toxicity scoring was very low based on Ivanov, however, there was overlap between these outcomes and so an overall very low may not encompass findings from FAST-Forward, so determined low overall, to reflect the overlap in toxicity outcomes.

Panel discussion:

The certainty for the outcomes as assessed by the NICE guideline, based on standard GRADE methodology ranged from 'moderate' to 'very low'. Based on the available data (limited to five-year follow-up), the certainty of evidence for all-cause mortality and breast cancer related mortality were designated to be of 'low' certainty. It was acknowledged that the evidence for a number of the outcomes considered in the small trial by Ivanov et al. (n=60) which was limited to 18 month follow-up, were assessed to be of very low certainty. However, it was recognised that the outcomes from this trial overlapped with those assessed in the much larger FAST-Forward RCT (n=4,096). It was agreed that when considering the overall certainty of evidence, this judgment should be limited to the certainty of the evidence for outcomes relating to the FAST-Forward trial (range moderate to low).

A judgment of 'low' was recorded by the ERT for this criterion.

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	• NCCP guideline considered patient values and preferences and concluded hypofractionation less burdensome for patients, and that patients would value the time saved from shorter courses of treatment. • The applicant noted convenience for patients as an advantage of the one-week regimens with the potential that this may make treatment more accessible. • The applicant also noted that from a service perspective, hypofractionation has the potential to be cost saving and to increase service capacity which benefits both patients with breast cancers and other patients needing radiotherapy.	
Panel discussion: The EAG considered the relevant outcomes, as outlined in the report and also the potential benefits for both patients with breast cancer (fewer treatment attendances) and service providers (increased capacity) with ultra-hypofractionated adjuvant radiotherapy. A judgment of 'no important uncertainty or variability' was recorded by the ERT for this criterion.		
Balance of effects **Does the balance between desirable and undesirable effects favour the intervention or the comparison?**		
JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the	See GRADE Table 5, page 31 of HIQA's evidence synthesis report. A judgment of 'probably favours the intervention' was recorded by the EAG for this criteria.	

intervention or the comparison ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		

Panel discussion:

The EAG considered the balance between the desirable and undesirable effects. It was noted that late results (10-year data) are not yet available for ultra-hypofractionated adjuvant radiotherapy for this population. When considering the balance between the desirable and undesirable effects, the MEIR EAG agreed that the practice was favoured over moderately fractionated radiotherapy, and could be used at the discretion of the treating radiation oncologist. This judgment was on the basis that available five-year follow-up data indicate that there are no differences in the outcomes discussed, but that there are positive implications for patients in terms of treatment burden (fewer required treatment attendances) and for radiation oncology capacity.

A judgment of 'probably favours the intervention' was recorded by the EAG for this criterion.

Recommendation

On consideration of the balance between the benefits and harms, the EAG found that the intervention is probably favoured compared to the available alternative(s). The MEIR EAG have recommended to HIQA that the practice of ultra-hypofractionated adjuvant radiotherapy for breast cancer is generically justified.

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