An Roinn Sláinte
Department of Health

Diagnosis, staging and treatment of patients with prostate cancer

National Clinical Guideline No. 8

Original Publication June 2015
Radiology and Diagnosis Sections Reviewed May 2022

NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

Guideline Development Group

The National Clinical Guideline on the diagnosis, staging and treatment of patients with prostate cancer in Ireland was developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, librarians and stakeholder groups.

Reference of National Clinical Guideline

National Clinical Guideline No. 8 should be referenced as follows:

Department of Health. Diagnosis, staging and treatment of patients with prostate cancer.
National Clinical Guideline No. 8.
June 2015. ISSN 2009-6259.

National Clinical Guideline No 8. should be referenced as follows:

Department of Health. Diagnosis, staging and treatment of patients with prostate cancer.
National Clinical Guideline No. 8.
June 2015, with Radiology and Diagnosis sections retired May 2022. ISSN 2009-6259.

Update May 2022: Sections on Radiology and Diagnosis reviewed.

The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/

Notice to Health Professionals and Disclaimer

The Guideline Development Group's expectation is that health professionals will use clinical knowledge and judgment in applying the principles and recommendations contained in this guideline. These recommendations may not be appropriate in all circumstances and it may be necessary to deviate from this guideline. Clinical judgment in such a decision must be clearly documented. Care options should be discussed with the patient, his/her significant other(s), and the multidisciplinary team on a case-by-case basis as necessary.

National Clinical Effectiveness Committee

The National Clinical Effectiveness Committee (NCEC) was established as part of the Patient Safety First Initiative. The NCEC is a partnership between key stakeholders in patient safety. NCEC's mission is to provide a framework for national endorsement of clinical guidelines and audit to optimise patient and service user care. The NCEC has a remit to establish and implement processes for the prioritisation and quality assurance of clinical guidelines and clinical audit so as to recommend them to the Minister for Health to become part of a suite of National Clinical Guidelines and National Clinical Audit.

The aim of the suite of National Clinical Guidelines is to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland. The implementation of these National Clinical Guidelines will support the provision of evidence-based and consistent care across Irish healthcare services.

NCEC Terms of Reference

1. Provide strategic leadership for the national clinical effectiveness agenda.
2. Contribute to national patient safety and quality improvement agendas.
3. Publish standards for clinical practice guidance.
4. Publish guidance for National Clinical Guidelines and National Clinical Audit.
5. Prioritise and quality assure National Clinical Guidelines and National Clinical Audit.
6. Commission National Clinical Guidelines and National Clinical Audit.
7. Align National Clinical Guidelines and National Clinical Audit with implementation levers.
8. Report periodically on the implementation and impact of National Clinical Guidelines and the performance of National Clinical Audit.
9. Establish sub-committees for NCEC workstreams.
10. Publish an Annual Report.

Information on the NCEC and endorsed National Clinical Guidelines is available at: www.health.gov.ie/patient-safety/ncec.

Using this National Cancer Control Programme National Clinical Guideline

The NCCP is part of the Health Service Executive (HSE) and was established in 2007 to implement the recommendations of the National Cancer Strategy. The NCCP is responsible for national cancer control by helping to prevent cancer, treat cancer and increase survival and quality of life for those who develop cancer, by converting the knowledge gained through research and surveillance into strategies and actions. The need to follow evidence-based clinical guidelines covering a patient's journey from early detection, diagnosis, treatment, monitoring and end-of-life care is a key priority for the NCCP.

It is critical to have a range of health professionals working together to plan and deliver care for cancer patients. The target users of the guideline are the multidisciplinary clinical team caring for patients with prostate cancer.

The development of this National Clinical Guideline would not have been possible without the enormous contribution of the members of the Guideline Development Group (GDG), the NCCP Guideline Steering Group and the reviewers. We are grateful for the commitment shown by all who contributed to the development of this guideline. In particular, the invaluable input of the clinicians and the HSE/hospital librarians in this process is acknowledged and we thank them for giving generously of their time and expertise.

This National Clinical Guideline is available at:
www.health.gov.ie/patient-safety/ncec and www.hse.ie/cancer

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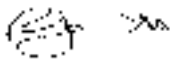

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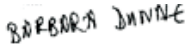

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1 Background

Cancer is a major healthcare challenge. Each year in Ireland, approximately 19,000 people are diagnosed with malignant cancer. Cancer is the second leading cause of death in Ireland after diseases of the circulatory system. Deaths from cancer averaged about 8,800 deaths per year during 2010-2012, representing about 30% of all deaths in that period (NCRI, 2014a).

Cancer incidence data from the National Cancer Registry Ireland (NCRI) and population projections from the Central Statistics Office (CSO) have been combined by the NCRI to estimate the number of new cancer cases expected in five year bands from 2015 to 2040. The total number of new invasive cancer cases (including non-melanoma skin cancer) is projected to increase by 84% for females and 107% for males between 2010 and 2040, based only on changes in population size and age distribution (demography). If trends in incidence since 1994 are also taken into account, the number of cases is expected to increase by between 86% and 125% for females (depending on the method of projection used) and by between 126% and 133% for males (NCRI, 2014b).

Prostate cancer is the most common cancer in men (excluding non-melanoma skin cancer). The annual average incidence for prostate cancer in Ireland between 2010 and 2012 was 3,384 cases per annum, accounting for a little over 30% of all newly diagnosed cases of cancer in men (NCRI, 2014a). Prostate cancer incidence in Ireland is currently one of the highest in Europe and estimated incidence rates in Ireland for 2012 are approximately 1.5 times higher than in the UK or the EU overall (NCRI, 2014c). The chances of developing prostate cancer increase as you get older. Most cases develop in men aged 70 or older. For reasons that are not understood, prostate cancer is more common in men of Afro-Caribbean or African descent, and less common in men of Asian descent. The causes of prostate cancer are largely unknown (HSE, 2014).

There are eight hospitals designated as cancer centres and one satellite breast unit (Letterkenny General Hospital). As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

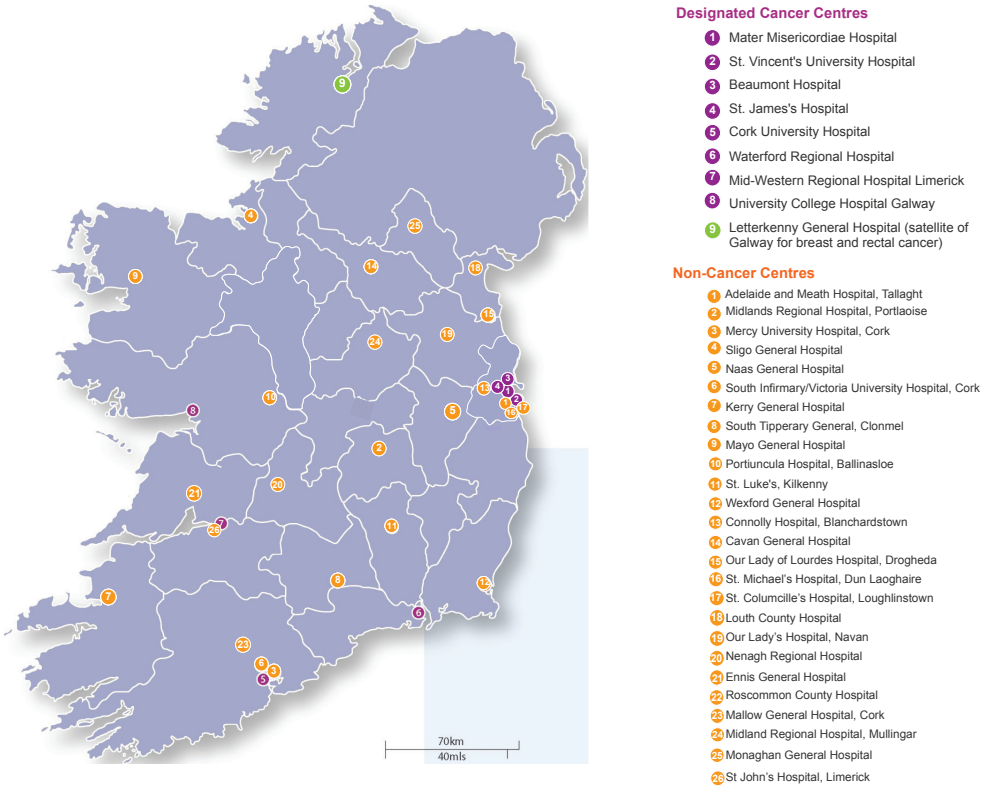

Figure 1 Cancer Services in Ireland

1.1 The rationale for a National Clinical Guideline

In 2006, the second national cancer strategy, 'A Strategy for Cancer Control in Ireland' (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:

- Improvements in the quality of clinical decisions,
- Improvement in patient outcomes,
- Potential for reduction in morbidity and mortality and improvement in quality of life,
- Promotion of interventions of proven benefit and discouragement of ineffective ones, and
- Improvements in the consistency and standard of care.

1.2 Clinical and financial impact of prostate cancer

The diagnosis, staging and treatment of patients with prostate cancer requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery, chemotherapy and radiation therapy. A proportion of patients may also require palliative care.

A recent population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer is estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). Prostate cancer is estimated to have cost the EU €8.43 billion. The healthcare costs per person varied between countries and were estimated to cost between €1 and €21 for prostate cancer (€11 per person in Ireland). With cancer incidence expected to increase by 99% by 2040 (NCRI, 2014b), there could be a significant increase seen in healthcare costs per person in Ireland, in cancers with costs that can accrue over several years (e.g. prostate cancer).

In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare costs out of a total of €619 million. Drug expenditure accounted for a further €127 million, while primary, outpatient and emergency care were estimated at €32 million, €30 million and €13 million, respectively (Luengo-Fernandez et al., 2013).

1.3 Objectives of the National Clinical Guideline

The overall objectives of the National Clinical Guideline No. 8 'Diagnosis, staging and treatment of patients with prostate cancer' are:

- To improve the quality of clinical care,
- To prevent variation in practice (Specifically Qs 2.4.2, 2.4.3, 2.4.5, 2.4.6, 2.4.9, 2.4.10, 2.5.2, 2.7.2)
- To address areas of clinical care with new and emerging evidence,
- Based on the best research evidence in conjunction with clinical expertise,
- Developed using a clear evidence-based internationally used methodology.

1.4 Scope of the National Clinical Guideline, target population and target audience

1.4.1 Scope

This National Clinical Guideline was developed to improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.

The guideline focuses on the diagnosis, staging and treatment of patients with prostate cancer. This guideline does not include recommendations covering every aspect of diagnosis, staging and treatment. This guideline focuses on areas of clinical practice:

- known to be controversial or uncertain,
- where there is identifiable variation in practice,
- where there is new or emerging evidence,
- where guidelines have potential to have the most impact.

This guideline focuses solely on the clinical management of patients with prostate cancer. The NCCP has developed general practitioner (GP) referral guidelines, standardised GP referral forms, and GP electronic referrals for patients with prostate cancer. The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme. The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and their families and healthcare professionals in relation to healthy lifestyle, disease prevention and control. It aims to promote a good quality of life and prolonged survival for people who experience cancer. There is also a range of patient information booklets covering various aspects of the cancer journey available on the NCCP website.

The NCCP has also set up a Prostate National Clinical Lead's Network with defined terms of reference. The output of this network includes the following:

- Development and agreement of Key Performance Indicators (KPIs)
- Organisation of annual multidisciplinary Cancer Quality and Audit Fora
- Focus on cancer specific issues such as:
  i. Development of a National Policy on Management of Infection Post TRUS prostate biopsy
  ii. PSA Harmonisation Project
  iii. Development of patient booklets on various topics, e.g. TRUS Biopsy, Having your prostate checked.

The NCCP have prioritised the development of clinical guidelines for those cancers that have the highest burden of illness. Prostate cancer is now the largest solid tumour diagnosed annually in Ireland.

1.4.2 Target population

Patients that are covered by this guideline are:

- Adults (18 years or older) with newly diagnosed prostate cancer
- Adults with metastases arising from prostate cancer.

1.4.3 Target audience

This guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with prostate cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

Whilst the guideline is focused on clinical care, it is expected to be of interest to patients with prostate cancer and their significant others. Cancer specific patient information has already been developed by the NCCP and is available on the NCCP website.

1.5 Governance

Governance of the guideline development process was provided by a multidisciplinary Guideline Steering Group which was chaired by the National Director of the NCCP. Membership included representatives from all relevant disciplines and the chairs of each NCCP Guideline Development Group (GDG). Details of GDG members and Guideline Steering Group members are available in appendices 2 and 3. Figure 2 outlines the stages of guideline development.

A GDG was responsible for the development and delivery of this National Clinical Guideline and included representatives from relevant groups (radiologists, histopathologists, urologists, medical oncologists, and radiation oncologists) with expertise in the diagnosis, staging and treatment of patients with prostate cancer. The GDG also included a project manager, a methodologist and clinical librarians.

1.5.1 Conflict of interest statement

A conflict of interest form (see NCCP Methodology Manual: Appendix II) was signed by all GDG members and reviewers.

The GDG was managed by the Chair to promote the highest professional standard in the development of this guideline. Where funding had been obtained to attend conferences etc., this was stated and extra care was made to ensure that no conflict arose from these situations.

1.5.2 Funding body and statement of influence

The guideline was commissioned and funded by the NCCP, however, the guideline content was not influenced by the NCCP or any other funding body. This process is fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.

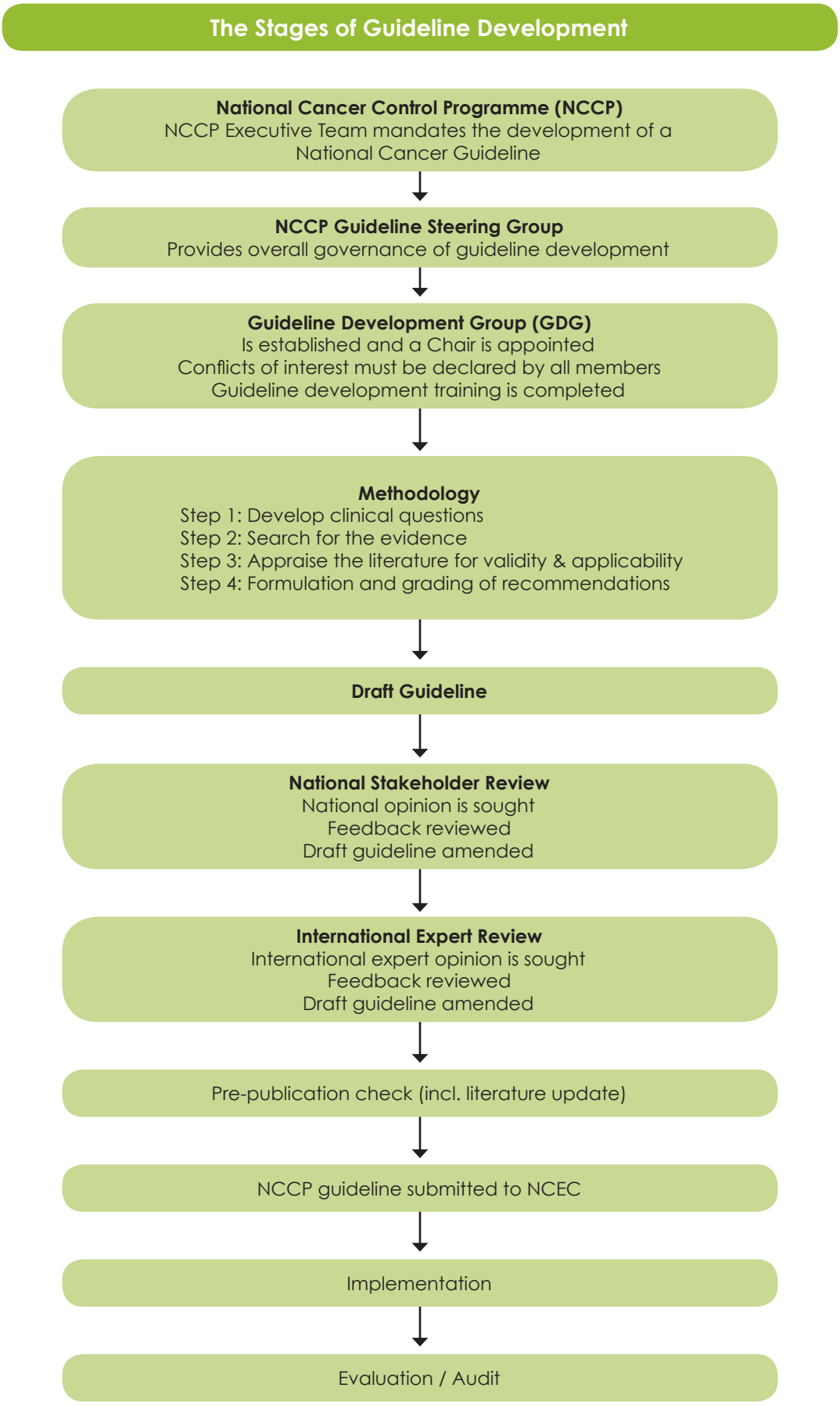

Figure 2 The Stages of Guideline Development

1.6 Guideline methodology

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

1.6.1 Step 1: Develop clinical questions

The first step in guideline development was to identify areas of new and emerging evidence or areas where there was variance in practice. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time.

This process was carried out by discipline specific sub-groups. The GDG signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 45 clinical questions are listed in appendix 4.

1.6.2 Step 2: Search for the evidence

The first step in searching for the evidence is the identification of international guidelines. Searches of the primary literature were only conducted if the answers to the clinical questions were not found in up to date evidence based guidelines.

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (appendix 5). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools
- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to September 2014. A full set of literature search strategies is available on the NCCP/NCEC website.

A literature search for the budget impact assessment was performed using an economic filter (Table 10, appendix 6). Full details of this search strategy are available in appendix 11.

1.6.3 Step 3: Appraise the literature for validity and applicability

International guidelines were appraised using an international, validated tool the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of the guideline? (external validity).

1.6.4 Step 4: Formulation and grading of recommendations

The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN; see Methodology Manual: Appendix VII) was completed for each clinical question.

The following items were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
  - What is the potential impact on the health system?
- What is the potential benefit and potential harm to the patient?
- Are there resource implications?

The evidence statements and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are documented in appendix 6.

Good practice points were based on the clinical expertise of the GDG.

For the economic literature, key messages are presented in boxes entitled 'relevance to the guideline recommendations'.

1.7 Patient advocacy

A collaborative approach is used in the development of the NCCP patient information, clinical guidelines and other national projects. All NCCP booklets are submitted to the National Adult Literacy Agency (NALA) (www.nala.ie) for the Plain English Award. This is to ensure comprehension and readability are in line with health literacy best practice standards. Service user testing is a key part of the process, and includes liaising with the HSE Patient Forum, online surveys, and engaging with other relevant patient groups e.g. Irish Cancer Society, Marie Keating Foundation.

1.8 National stakeholder and international expert review

The draft guideline was signed off by the entire GDG and the NCCP Guideline Steering Group before going to national stakeholder review. It was circulated to relevant organisations and individuals for comment between 30th May and 18th July 2014. A full list of those invited to review this guideline is available in appendix 7.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. The views and preferences of the target population were sought by inviting patient advocacy groups. Stakeholders were required to submit feedback with

supporting evidence on a form provided (NCCP Methodology Manual: Appendix VIII) along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.

All feedback received was reviewed by the project manager and research team. Suggested amendments and supporting evidence were reviewed by the discipline specific sub-group and consensus reached to accept or reject the amendments. Amendments were rejected following discussion between members of the relevant subgroup(s) and in instances where no superior evidence was provided or no conflict of interest form was provided. All modifications were documented.

The amended draft guideline was then submitted for international expert review. The GDG nominated two international bodies to review the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the national stakeholder review. The guideline was circulated for comment between 25th August and 17th October 2014.

A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process and is available on request from the GDG.

1.9 Procedure for updating the National Clinical Guideline

This guideline was published in June 2015 and will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

1.10 Implementation of the National Clinical Guideline

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual. The implementation plan outlines facilitators and barriers to implementation (appendix 8).

The National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available on the NCCP and NCEC websites.

A multidisciplinary team (MDT) is responsible for the implementation of the guideline recommendations and a lead clinician for prostate cancer has been nominated in each prostate unit in the designated cancer centres. Recommendations have been divided into the key clinical areas of radiology and diagnosis, pathology, active surveillance, surgery, medical oncology, radiation oncology and palliative care.

All priorities in relation to prostate care are agreed annually by the NCCP and are submitted to the annual HSE Service Plan, which is published on the HSE webpage. The NCCP Cancer Guidelines will be included in the annual service planning process.

1.11 Tools to assist the implementation of the National Clinical Guideline

A list of relevant tools to assist in the implementation of the National Clinical Guideline is available in appendix 9.

1.12 Audit

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care. For audit criteria see appendix 10.

1.13 Budget impact

Many recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG has identified the areas that require change to ensure full implementation of the guideline. The potential resource implications of applying these recommendations have been considered (appendix 11). In areas where additional resources are required these will be sought through the HSE service planning process.

1.14 Organisational responsibility

This National Clinical Guideline should be reviewed by the multidisciplinary clinical team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline. A Cancer Network Manager from the NCCP meets with each cancer centre on a quarterly basis for performance monitoring and service planning.

All clinical staff with responsibility for the care of patients with prostate cancer are expected to:

- Comply with this National Clinical Guideline and any related procedures or protocols,
- Adhere to their code of conduct and professional scope of practice as appropriate to their role and responsibilities, and
- Maintain their competency for the management and treatment of patients with prostate cancer.

1.15 Glossary of terms and abbreviations

A glossary of the terms and abbreviations used throughout the guideline is available in appendix 12.

1.16 Accompanying documents

The following documents are available on the NCCP and NCEC websites.

- Guideline Summary
- NCCP Methodology Manual for guideline development
- Literature search strategies.

2 National Clinical Guideline

2.1 Summary of clinical recommendations

Responsibility for implementation: While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline. Each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

There are various entry points for patients within the scope of this guideline.

Defining risk categories

2.2.1.1 It is recommended that the risk categories stated are used when interpreting and placing patients into risk groups.
- **Low-risk:** cT1-T2a and Gleason score ≤6 and prostate specific antigen (PSA) <10µg/L.
- **Intermediate-risk**: cT2b-T2c or Gleason score = 7 or PSA 10-20µg/L.
- **High-risk**: cT3a, Gleason score 8-10 or PSA >20µg/L.
- **Very-high-risk:** cT3b-T4 or any T, N1. **(C)**

Radiology and diagnosis

The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/

Pathology

2.4.1.1 A report should be generated for each designated site of biopsy. **(C)**
2.4.1.2 A maximum of three cores should be submitted per cassette. **(D)**
2.4.1.3 To optimise the detection of small lesions, blocks should be cut and examined at three levels. **(C)**
2.4.2.1 For determining tumour extent in prostate core biopsies, when there are multiple foci of prostate cancer in a single core separated by benign intervening stroma, it is suggested that the collapsing method is used (i.e. where intervening benign tissue is excluded from the measurement). **(D)**
2.4.3.1 For each biopsy site the presence of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported. The pathologists should assign a separate Gleason score to each sample core (or site) rather than an overall score for the entire biopsy session. **(C)**
2.4.3.2 Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores. **(D)**

2.4.4.1 The extent of cancer involvement in a core biopsy should be reported. This may be done in millimetres or percentage involvement. **(B)**

2.4.5.1 All prostate core biopsies should be reported with the pathological prognostic factors as outlined in Table 2. **(B)**

2.4.6.1 All radical prostatectomy specimens should be reported with the minimum dataset items as outlined in Table 3. **(B)**

2.4.7.1 Positive surgical margins are defined by microscopic tumour in touch with ink. **(B)**

2.4.7.2 A margin status is negative if tumour is very close to the inked surface of the margin or when they are at the surface of the tissue lacking any ink. **(B)**

2.4.8.1 It is optional, according to local practice, to report extent of margin positivity. This can be done either as mm of involvement or by documenting focal versus extensive involvement. **(B)**

2.4.9.1 The location of positive margins should be reported. Locations may be noted as follows: left or right and posterior, posterolateral, lateral, or anterior at either the apex, mid, or base (or bladder neck). **(D)**

2.4.10.1 Extraprostatic extension should be documented. **(B)**

2.4.10.2 Extraprostatic extension should be quantified. The method of quantification should be according to local practice. **(B)**

2.4.12.1 If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented. There is less definitive evidence at this time to specify peripheral versus transitional location. **(D)**

2.4.13.1 The reporting of pT2 substage (a, b, and c) is optional as it has not been proven to be of prognostic significance. **(B)**

2.4.14.1 There is insufficient evidence regarding the additional prognostic value of tumour volume to recommend mandatory reporting of prostate cancer volume. **(B)**

2.4.14.2 It may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate. **(D)**

Active surveillance

2.5.1.1 Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable. **(C)**

Definition for lowest risk for prostate cancer progression:
cT1c, PSA <10µg/L, biopsy Gleason score ≤6 (at least 12 cores), ≤2 positive cores, minimal biopsy core involvement (<50% cancer per biopsy).

2.5.2.1 The protocol in Figure 2 is recommended for men who have chosen active surveillance. **(D)**

2.5.3.1 Prior to enrolment in an active surveillance programme, a multiparametric MRI scan should be performed. **(B)**

2.5.4.1 Given the evidence available from large centre trials, ≤2 positive cores and a maximum of 50% involvement of one core is recommended. **(B)**

2.5.5.1 A repeat prostate biopsy is mandatory for all patients considering active surveillance and this can be done by either the transrectal or transperineal approach. **(B)**

2.5.5.2 There is emerging evidence that transperineal biopsies identify more clinically important prostate cancer. **(C)**

2.5.6.1 Criteria for conversion to active treatment include:
- Change in PSA
- Change in DRE findings
- Upgrade of disease (including increase in core volume, increase in number of positive cores and increase in Gleason grade)
- MRI findings suggestive of disease progression
- Patient preference for radical treatment. **(D)**

Surgery

2.6.1.1 Radical treatment may be an option for men with low-risk prostate cancer and life expectancy of ≥10 years. **(C)**

2.6.1.2 If radical treatment is being provided, then radical prostatectomy is a treatment option for men with low-risk prostate cancer. **(B)**

2.6.2.1 Radical treatment is recommended for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years. **(B)**
2.6.2.2 Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years. **(B)**
2.6.3.1 Radical prostatectomy may be considered as a treatment option in high-risk disease, either alone or in combination with other therapies. **(C)**
2.6.4.1 A lymph node dissection is **not** necessary in low-risk, localised prostate cancer, because the risk for positive lymph nodes does not exceed 5%. **(B)**
2.6.4.2 Extended lymph node dissection should be performed in intermediate-risk, localised prostate cancer if the estimated risk for positive lymph nodes exceeds 5%, using an available nomogram. **(B)**
2.6.4.3 Extended lymph node dissection should be performed in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15%-40%. **(B)**

Medical oncology

2.7.1.1 The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life. **(C)**
2.7.2.1 For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option. **(B)**
2.7.2.2 Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients. **(B)**
2.7.3.1 Androgen deprivation therapy should be continued indefinitely in these patients. **(D)**
2.7.4.1 For men with castration resistant prostate cancer, second line hormone therapy should be considered. **(A)**
2.7.4.2 For men with castration resistant prostate cancer in whom chemotherapy is **not** yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**
2.7.4.3 For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. **(A)**
2.7.5.1 Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy. **(A)**
2.7.5.2 Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have **not** received docetaxel. **(A)**
2.7.5.3 Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223. **(A)**
2.7.6.1 For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated. **(B)**

Radiation oncology

Patients with undetectable PSA post-operatively
2.8.1.1 Patients who are classified as margin positive or with seminal vesicle involvement after radical prostatectomy, should be considered for adjuvant radiotherapy. **(A)**
2.8.1.2 Patients who are classified as margin negative and who have no other adverse prognostic features should be monitored, pending the results of ongoing clinical trials (e.g. RADICALS, RAVES, GETUG), with early salvage radiotherapy when PSA becomes detectable using ultra-sensitive PSA assay. **(A)**

Patients with detectable PSA post-operatively
2.8.1.3 Salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease. **(B)**

The role of external beam radiotherapy (EBRT) and/or brachytherapy in:
Low-Risk Prostate Cancer

2.8.2.1 All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with low-risk prostate cancer. **(B)**

Intermediate-Risk Prostate Cancer

2.8.2.2 All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with intermediate-risk prostate cancer. **(B)**

2.8.2.3 Hormonal therapy should be considered in addition to EBRT. **(A)**

High-Risk Prostate Cancer

2.8.2.4 Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy. **(B)**

Very-High-Risk Prostate Cancer

2.8.2.5 A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **(A)**

2.8.2.6 A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **(C)**

Biochemical recurrence following curative treatment

2.8.3.1 Following radical prostatectomy, a recurrence of prostate cancer can be defined as at least two PSA readings ≥0.2µg/L. **(C)**

2.8.3.2 Following radiotherapy, a recurrence of prostate cancer can be defined as a PSA value of 2µg/L above the nadir after treatment. **(C)**

The role of hormone therapy in conjunction with radiotherapy in:
Low-Risk Prostate Cancer

2.8.5.1 There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease. **(C)**

Intermediate-Risk Prostate Cancer

2.8.5.2 Androgen deprivation therapy for four to six months should be considered in conjunction with EBRT. A pooled analysis suggests that a duration of six months is optimal. **(A)**

High-Risk Prostate Cancer

2.8.5.3 A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy. **(A)**

2.8.5.4 EBRT plus brachytherapy with or without androgen deprivation therapy. **(C)**

Very-High-Risk Prostate Cancer

2.8.5.5 A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **(A)**

2.8.5.6 A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **(C)**

Palliative Care

2.9.1.1 For patients with cancer, early provision of palliative care can improve patient outcomes. **(C)**

2.9.1.2 Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need. **(D)**

Good practice points
Recommended best practice based on the clinical experience of the Guideline Development Group.

2.2 Defining Risk Categories

Clinical question 2.2.1

What are the definitions for the following categories of prostate cancer:

- **Low-risk prostate cancer**
- **Intermediate-risk prostate cancer**
- **High-risk prostate cancer**
- **Very-high-risk prostate cancer?**

Evidence statement
The current EAU guideline (Mottet et al., 2014) and a retrospective cohort study (D'Amico et al., 1998) addressed this question.

Prostate Specific Antigen (PSA), Gleason score and tumour stage are predictive of cancer outcome (D'Amico et al., 1998).

Low-risk: cT1-T2a and Gleason score ≤6 and PSA <10µg/L (Mottet et al., 2014).
Intermediate-risk: cT2b-T2c or Gleason score = 7 or PSA 10-20µg/L (Mottet et al., 2014).
High-risk: cT3a Gleason score 8-10 or PSA >20µg/L (Mottet et al., 2014).
Very-high-risk: cT3b-T4 N0 or any T, N1 (Mottet et al., 2014).

Other disease classification systems are emerging, e.g. CAPRA. However, the D'Amico classification system is currently the gold standard. This will remain under review as new evidence emerges.

Recommendation 2.2.1.1	Grade
It is recommended that the risk categories stated are used when interpreting and placing patients into risk groups.	C

Good practice point
Prior to considering treatment, clinicians need to take into account individual co-morbidities, age, and life expectancy. All patients should be discussed at an multidisciplinary meeting and patients should be seen in consultation by both a urologist and a radiation oncologist.

2.3 Radiology and Diagnosis

The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/

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2.4 Pathology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.4.1

What is the optimum handling, processing, and reporting of prostate core biopsies?

Evidence statement

Current guidelines from the EAU (Mottet et al., 2014), Oncoline (2007), PCRMP (2006), RCPath (2006) and a review (Fine et al., 2012) addressed this question.

There is consistency in international guidelines regarding the handling, processing, and reporting of prostate core biopsies (Mottet et al., 2014, Oncoline, 2007, RCPath, 2009). When prostate cores are submitted separately or assigned a clear site designation by container, the pathology report should reflect this (Fine et al., 2012).

As a minimum requirement, cores should be identifiable according to the side (right/left) of the gland that they originated from. This information is of paramount importance as it may enable a unilateral nerve sparing prostatectomy to be performed when a cancer involves only one side of the gland. (PCRMP, 2006)

In addition, a number of studies have correlated the presence and amount of cancer in different regions with risk of higher pathologic stage and margin positivity (Zhou and Epstein, 2003). (Fine et al., 2012)

To achieve optimal flattening and alignment of individual cores, one should embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat (Van der Kwast et al., 2003, Rogatsch et al., 2000). To optimise the detection of small lesions, blocks should be cut at three levels (Pelzer et al., 2005). It is helpful to mount intervening tissue sections in case additional immunostaining is needed. (Mottet et al., 2014)

Recommendation 2.4.1.1	**Grade**
A report should be generated for each designated site of biopsy.	**C**

Recommendation 2.4.1.2	**Grade**
A maximum of three cores should be submitted per cassette.	**D**

Recommendation 2.4.1.3	**Grade**
To optimise the detection of small lesions, blocks should be cut and examined at three levels.	**C**

Good practice point

Intervening spare sections should be cut and retained at each of three levels per block.

Clinical question 2.4.2

What is the best method of determining percentage core involvement or tumour length in prostate biopsies?

Evidence statement
Two retrospective studies (Brimo et al., 2008, Karram et al., 2011) addressed this question.

There is no consensus as to the optimal method of measuring tumour length or percentage core involvement, especially when there are two or more foci of prostate cancer in a single core separated by benign intervening stroma (Karram et al., 2011). Discontinuous foci can be measured as if there were a single continuous focus, i.e. measure from the start of one focus to the end of the last focus (end-to-end method) or they can be measured as individual foci and each focus added together excluding the areas of intervening benign tissue (collapsed method). Both methods are almost equally commonly used (Egevad et al., 2006).

Karram et al., (2011) suggests that including benign prostate tissue in the measurement is more predictive of stage and margins than ignoring the intervening benign tissue.

Brimo et al., (2008) suggests the prognostic significance of estimating cancer lengths may not differ whether one considers separate foci of cancer on a single core as separate or as one focus, as long as the intervening stroma is ≤5mm.

For the benefit of uniformity and data collection, it is suggested by the GDG that the collapsed method be used. When multiple foci of carcinoma are separated by intervening benign prostatatic glands and stroma, pathologists will collapse the tumour by disregarding the intervening benign prostate tissue (Brimo et al., 2008). (Fine et al., 2012)

It is not possible to draw a definitive conclusion at this time.

Recommendation 2.4.2.1	**Grade**
For determining tumour extent in prostate core biopsies, when there are multiple foci of prostate cancer in a single core separated by benign intervening stroma, it is suggested that the collapsing method is used (i.e. where intervening benign tissue is excluded from the measurement).	**D**

Clinical question 2.4.3

How should Gleason score be calculated and reported in prostate core biopsies?

Evidence statement

Current guidelines from the EAU (Mottet et al., 2014), RCPath (2009) and a review (Fine et al., 2012) addressed this question.

The International Society of Urological Pathology (ISUP) 2005 modified Gleason Score should be reported (Mottet et al., 2014, RCPath, 2009).

There are certain circumstances in which reporting primary plus secondary Gleason grades may be inexact, as the traditional Gleason Score is unlikely to be representative of cancer in the gland (Table 1).(Fine et al., 2012)

The pathologist should assign a separate Gleason Score to each sampled core (or site), rather than an overall score for the entire biopsy session (Epstein et al., 2005a, Rubin et al., 2004, Kunju et al., 2009). (Fine et al., 2012)

Table 1 Reporting recommendations for special Gleason grading scenarios

Clinical setting	Recommendation
Only one grade present (e.g. GG 3)	This grade is doubled (GS 3+3 = 6)
Abundant high-grade cancer (e.g. GG 4) with <5% lower-grade cancer	The lower grade cancer is ignored (GS 4+4 = 8)
Smaller focus with mostly GG 4 and few glands of GG 3	Since GG 3 occupies >5%, the lower grade cancer will be included (GS 4 + 3 = 7)
Abundant GG 3 with any extent of GG 4	The higher grade will be included (GS 3+4 = 7)
Three grades (e.g. GG 3, 4, and 5) present	Classify as high grade (assign most common plus highest grade)
NB: Multiple cores showing different grades – cores submitted separately and/or with designated location	Each core or site will be assigned a separate GS
NB: Multiple cores showing different grades – all cores were submitted in one container or cores are fragmented	An overall GS will be assigned to the specimen
GG = Gleason grade, GS = Gleason score, NB = Needle biopsy	

Adapted from Fine et al., (2012)

ISUP recommends assigning a Gleason score to every 'specimen' but recognises the difficulties particularly if multiple biopsies are submitted in a single cassette and have fragmented. However, it also gives the option of creating a 'global' or composite Gleason score for the case. It defers to the clinician whether the global Gleason score or the 'highest' Gleason score should be used. Discordance between composite and highest Gleason scores is relatively infrequent, and usually occurs because one core contains only high grade Gleason (e.g. 4+4) whereas all the other cores contain a lower grade (e.g. 3+4).(RCPath, 2009)

Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores.

Individual Gleason scores should be assigned to each individual site. If multiple cores are submitted per site, it may be useful to highlight the presence of a higher Gleason score if this is present in an individual core. Similarly, the extent of the most involved core per site can be given.

Recommendation 2.4.3.1	**Grade**
For each biopsy site, the presence of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported. The pathologists should assign a separate Gleason score to each sample core (or site) rather than an overall score for the entire biopsy session.	**C**

Recommendation 2.4.3.2	**Grade**
Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores.	**D**

Clinical question 2.4.4

Should extent of cancer in a prostate biopsy core be measured in millimetres (mm) or percent?

Evidence statement
Guidelines from the EAU (Mottet et al., 2014), Oncoline (2007), RCPath (2009) and a review (Fine et al., 2012) addressed this question.

The international guidelines are consistent that extent of cancer (either mm or percent) should be reported.

There is a potential clinical impact of reporting the extent of cancer in a prostate core biopsy, because of the size criteria, >50% or >5mm might trigger treatment versus active surveillance.

There are numerous studies which have addressed this topic and there is equal evidence to suggest that the extent of cancer in a core biopsy may be measured in either mm or percentage involvement (Mottet et al., 2014, Oncoline, 2007, RCPath, 2009, Fine et al., 2012).

Recommendation 2.4.4.1	Grade
The extent of cancer involvement in a core biopsy should be reported. This may be done in millimetres or percentage involvement.	B

Clinical question 2.4.5

For men who have had a prostate biopsy, what are the pathological prognostic factors?

Evidence statement
The CAP (2012) guideline and a review (Fine et al., 2012) addressed this question.

The literature is largely in agreement on pathological prognostic factors (Table 2), which include Gleason score, number of positive cores and tumour quantification (CAP, 2012, Fine et al., 2012).

Table 2 Pathological prognostic factors

Ideally the following clinical data would be provided:
PSA Clinical stage (DRE) Number of prostatic biopsies Side +/- site of prostatic biopsies History of previous treatment History of previous biopsies Imaging findings (if any)
Macroscopic pathology data (per site submitted):
Number of cores or fragments Length of cores
Microscopic pathology data:
Modified Gleason score Number of positive cores per site Total percentage/mm of cancer per site Perineural invasion, if present Seminal vesicle invasion, if present Vascular invasion, if present Involvement of adipose tissue if present If no carcinoma is present, any features that should lead to consideration of re-biopsy, including: – High grade prostatic intraepithelial neoplasia – Foci suspicious for but not diagnostic of carcinoma
Others features which could be reported:
Presence of rectal mucosa (optional) Presence of inflammation (optional)

Recommendation 2.4.5.1	**Grade**
All prostate core biopsies should be reported with the pathological prognostic factors as outlined in Table 2.	**B**

Good practice point
Pathologists reporting prostate biopsies should participate in external quality assurance programmes.

Clinical question 2.4.6

For men who have had a radical prostatectomy what are the essential reporting items?

Evidence statement
The current EAU guideline (Mottet et al., 2014) addressed this question.

There is a large body of consistent evidence in the international guidelines, on reporting items for radical prostatectomy.

Radical prostatectomy specimen report
The pathology report provides essential information on the prognostic characteristics relevant for clinical decision-making (see Table 3) (Mottet et al., 2014).

Minimum dataset for reporting radical prostatectomy specimens

- Typing (>95% of prostate cancer represents conventional (acinar) adenocarcinoma)
- Grading according to the modified Gleason score

(Sub) Staging and surgical margin of the tumour

- If appropriate, location and extent of extraprostatic extension, location and extent of positive surgical margins, presence of bladder neck invasion, laterality of extraprostatic extension or seminal vesicle invasion.
- Additional information may be provided on multifocality, diameter of the dominant tumour and zonal location (transition zone, peripheral zone, anterior zone) of the dominant tumour.

As a result of the complex information provided on each radical prostatectomy specimen, the use of synoptic (-like) or checklist reporting is recommended. (Mottet et al., 2014)

Table 3 Example reporting proforma of radical prostatectomy

Macroscopy	
Weight of prostate:	_____ g (indicate if weight is with or without seminal vesicles)
Dimensions of prostate:	_____ mm apex-base, _____ mm anterior-posterior, _____ mm lateral
External Surface:	Description (i.e. smooth, incisions, etc) _____
Visible tumour:	location(s)_____ dimension(s) _____
Seminal Vesicles:	Right, dimensions _____ x _____ x _____ mm, vas _____ mm Left, dimensions _____ x _____ x _____ mm, vas _____ mm
Lymph Nodes: Measurement of lymph node packet, right and left (optional) Right: _____ Indicate number of lymph nodes identified grossly Left: _____ Indicate number of lymph nodes identified grossly	
Approximate volume of gland embedded: 100% /75-99% / 50-74% etc.	
Tissue withheld for bio banking: Yes/No	

Microscopy

Tumour type: **Acinar / Other (specify)** _____ **/ no tumour**

Gleason Grade:
Primary _____
Secondary _____
Sum score _____ **(Primary plus secondary)**
Tertiary _____

Tumour volume/size (optional): _____ (indicate either approximate tumour volume or size of largest tumour nodule)

Location (size, zone) of dominant tumour nodule _____

Stage: as follows; pT2 *sub staging is optional*

≤½ of one lobe involved – pT2a
>½ of one lobe involved – pT2b
Both lobes involved – pT2c
pT3 Extraprostatic extension: indicate if p3a extraprostatic extension, without seminal vesicle involvement pT3b seminal vesicle involvement
Site(s) of extraprostatic extension _____
Extent of extraprostatic extension (focal vs. non-focal or mm of involvement)*: _____
(Note: microscopic bladder neck invasion constitutes pT3a disease)
pT4 Tumour involving adjacent organs or pelvic wall _____ (indicate organ etc.)

Margins

Positive / Negative
If positive, indicate site(s) of margin positivity _____

Margin positive at site of intraprostatic incision _____Yes/No_____ Site(s)

Extent of margin involvement (focal vs. non-focal or mm of involvement)*:

Vascular Invasion

Present / Absent

Perineural Invasion

Present / Absent *(optional)*
High grade prostatic intra-epithelial neoplasia: Present / Absent *(optional)*

Treatment Effect

Present / Absent

Nodal Status

Lymph nodes submitted: Yes ❒ No ❒

Right:
No. of positive nodes/ No. of nodes submitted AND size of largest lymph node metastasis _____ mm

Left:
No. of positive nodes/ No. of nodes submitted AND size of largest lymph node metastasis _____ mm

Pathologic stage (AJCC/UICC 7th Edition): pT__ N__

*****Measurement methods should be in accordance with local practice, as there are currently no agreed methodologies.

Synoptic reporting of surgical specimens results in more transparent and complete pathology reporting (Chan et al., 2008). (Mottet et al., 2014)

Recommendation 2.4.6.1	Grade
All radical prostatectomy specimens should be reported with the minimum dataset items as outlined in Table 3.	B

Clinical question 2.4.7

How do we determine margin status?

Evidence statement
Current guidelines from the EAU (Mottet et al., 2014) and RCPath (2009) addressed this question.

The international guidelines are in agreement that margin positivity is an independent prognostic parameter for prostate cancer. Positive surgical margins are defined by microscopic tumour in touch with ink (Mottet et al., 2014, RCPath, 2009).

A margin status is negative if tumour is very close to the inked surface of the margin (Epstein et al., 2005b) or when they are at the surface of the tissue lacking any ink. (Mottet et al., 2014)

Recommendation 2.4.7.1	**Grade**
Positive surgical margins are defined by microscopic tumour in touch with ink.	**B**

Recommendation 2.4.7.2	**Grade**
A margin status is negative if tumour is very close to the inked surface of the margin or when they are at the surface of the tissue lacking any ink.	**B**

Clinical question 2.4.8

Should margin positivity be quantified?

Evidence statement

A meta-analysis (Stephenson et al., 2009) addressed this question.

Positive surgical margins increase the risk of biochemical recurrence after radical prostatectomy by 2-to 4-fold. The risk of biochemical recurrence may be influenced by the anatomical location and extent of positive surgical margins. In a multicentre study of 7,160 patients treated with radical prostatectomy alone at 1 of 3 institutions between 1995 and 2006, Stephenson et al., (2009) analysed the predictive usefulness of several subclassifications of positive surgical margins.

Positive surgical margins were analysed as solitary vs. multiple, focal vs. extensive and apical location versus other. The usefulness of these subclassifications was assessed by the improvement in predictive accuracy of nomograms containing these parameters compared to one in which the surgical margin was modelled simply as positive vs. negative.

The authors found the 7-year progression-free probability was 60% in patients with positive surgical margins. A positive surgical margin was significantly associated with biochemical recurrence (HR 2.3, $P<0.001$) after adjusting for age, prostate specific antigen, pathological Gleason score, pathological stage and year of surgery. An increased risk of biochemical recurrence was associated with multiple versus solitary positive surgical margins (adjusted HR 1.4, $P=0.002$) and extensive versus focal positive surgical margins (adjusted HR 1.3, $P=0.004$) on multivariable analysis. However, neither parameter improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modelled as positive vs. negative (concordance index 0.851 vs. 0.850 vs. 0.850) (Stephenson et al., 2009).

The authors concluded the number and extent of positive surgical margin significantly influence the risk of biochemical recurrence after radical prostatectomy. However, the empirical prognostic usefulness of sub-classifications of positive surgical margins is limited (Stephenson et al., 2009).

Recommendation 2.4.8.1	Grade
It is optional, according to local practice, to report extent of margin positivity. This can be done either as mm of involvement or by documenting focal versus extensive involvement.	**B**

Clinical question 2.4.9

For patients undergoing radical prostatectomy, should location of the positive surgical margin be reported?

Evidence statement
A consensus statement from the ISUP (Tan et al., 2011) addressed this question.

While location of positive surgical margin does not predict prostate cancer recurrence, it is recommended internationally that the location of positive surgical margins is reported.

This is one of the tools necessary to audit the quality of surgery and provide feedback to urologists.

The locations of positive margins should be noted as occurring on the left or right and posterior, posterolateral, lateral or anterior at either the apex, mid, or base (or bladder neck) (Tan et al., 2011).

Recommendation 2.4.9.1	**Grade**
The location of positive margins should be reported. Locations may be noted as follows: left or right and posterior, posterolateral, lateral or anterior at either the apex, mid, or base (or bladder neck).	**D**

Clinical question 2.4.10

Should we document, quantify, and specify the location of extraprostatic extension (EPE)?

Evidence statement

An RCPath guideline (2009), three cohort studies (Epstein et al., 1993, Marks et al., 2007, Sung et al., 2007) and a retrospective analysis (Wheeler et al., 1998) addressed this question.

EPE is the recommended term for the presence of tumour beyond the confines of the prostate. EPE is defined as carcinoma mixed with periprostatic adipose tissue, or bulging out beyond the contours of the prostate gland (e.g. at the neurovascular bundle or the anterior prostate). Bladder neck invasion is also considered to be an EPE. At the apex of the prostate gland, tumour mixed with skeletal muscle does not constitute EPE.

There is consensus in the literature that EPE should be documented, as extension is related to the risk of recurrence.

There is no agreement in the literature on the optimum method to measure EPE (Fine et al., 2012, RCPath, 2009). Accepted methods include focal versus extensive (Epstein et al., 1993), <1 high-power field versus >1 high-power field (Wheeler et al., 1998, Marks et al., 2007), and radial measurement in mm (Sung et al., 2007).

Pathologists usually report the location or locations of EPE. This parameter has no known prognostic significance unless there is a positive margin at this site.

Recommendation 2.4.10.1	**Grade**
Extraprostatic extension should be documented.	**B**

Recommendation 2.4.10.2	**Grade**
Extraprostatic extension should be quantified. The method of quantification should be according to local practice.	**B**

Good practice point

It may be useful to give the location of extraprostatic extension (EPE), as it can be used for audit purposes for clinical, radiology and pathology.

Clinical question 2.4.11

How do we define a dominant tumour nodule in radical prostatectomy specimens?

Evidence statement

There is no consensus as to how a dominant tumour nodule should be defined, e.g. largest nodule vs. nodule with highest Gleason Score (Van Der Kwast, et al., 2011).

Good practice point

A dominant tumour nodule, where identifiable, may be defined according to local practice e.g. largest nodule or nodule with the highest Gleason Score.

Clinical question 2.4.12

Is it necessary to give the location of a dominant tumour nodule in radical prostatectomy specimens?

Evidence statement
A review (Fine et al., 2012) addressed this question.

There is some evidence to suggest that anterior located prostatic tumours have a worse prognosis (Al-Ahmadie et al., 2008). If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented (Al-Ahmadie et al., 2008). There is less definitive evidence at this time to specify peripheral vs. transitional location. (Fine et al., 2012)

Recommendation 2.4.12.1	Grade
If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented. There is less definitive evidence at this time to specify peripheral versus transitional location.	D

Clinical question 2.4.13

Should reporting of pT2 substage (a, b, and c) be optional?

Evidence statement
An ISUP consensus statement (Van der Kwast et al., 2011) addressed this question.

At the 2009 ISUP consensus the validity of the current pT2 substaging system was discussed after the presentation of background data. The majority (65.5%) of participants felt that the current pT2 substaging of prostate cancers should be discontinued. If the pT2 category was to be maintained, the majority of participants preferred to see a return to a two-tier subcategorisation for pT2 (unilateral versus bilateral prostate cancer) as defined in the 1992 TNM classification. A consensus was achieved for the view that a minimum size or volume measure should be employed as a cutpoint to distinguish unilateral (pT2a) from bilateral (pT2c) cancers, although no agreement was reached as to the defining value of such a cutpoint. It was proposed that for a tumour to be classified as pT2c, the contralateral tumour should be at least 1 cm in diameter (approximately equal to 0.5 ml). It was argued that this would be consistent with the criteria employed for clinical T2 substaging; however, no consensus was reached on this proposal. The conference concluded that consensus was reached to discontinue the use of the current pT2 substaging system. In view of the lack of clinical significance of the current (TNM 2002/2010) pT2 subcategories, there was general agreement in the subsequent discussion for the recommendation that the reporting of pT2 substaging of prostate cancers should be optional. (Van der Kwast et al., 2011)

Recommendation 2.4.13.1	**Grade**
The reporting of pT2 substage (a, b, and c) is optional as it has not been proven to be of prognostic significance.	**B**

Clinical question 2.4.14

For men who have had a radical prostatectomy, should we document prostate cancer volume?

Evidence statement
Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) addressed this question.

The independent prognostic value of the volume of prostate cancer in radical prostatectomy specimens has not been established (Marks et al., 2007, Stamey et al., 2000, Epstein et al., 2005b, Kikuchi et al., 2004, Van Oort et al., 2008). (Mottet et al., 2014)

Calculating tumour volume is labour-intensive and is unlikely to provide additional benefit beyond that of Gleason score, pT-stage, and surgical margin status (Epstein et al., 2004). Reporting tumour dimensions is sufficient. Multiple studies have shown that the maximum tumour diameter correlates well (significantly) with not only tumour volume but also Gleason score, percentage of positive surgical margins, stage, and biochemical recurrence (Renshaw et al., 1998, Eichelberger et al., 2005). (Oncoline, 2007)

It can therefore be recommended that the greatest dimension of the dominant tumour nodule be assessed (if identified), or that a rough estimate of the percentage of cancer tissue in the prostate be provided. (Mottet et al., 2014)

Recommendation 2.4.14.1	**Grade**
There is insufficient evidence regarding the additional prognostic value of tumour volume to recommend mandatory reporting of prostate cancer volume.	**B**

Recommendation 2.4.14.2	**Grade**
It may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate.	**D**

2.5 Active surveillance

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.5.1

For men with a histological diagnosis of prostate cancer, what are the inclusion criteria for being offered active surveillance?

Evidence statement
The current EAU guideline (Mottet et al., 2014) and a consensus statement (Montironi et al., 2014) addressed this question.

Choo and co-workers were the first to report on a prospective active surveillance protocol (Choo et al., 2002, Choo et al., 2001). A series with a long follow-up was reported by Klotz et al., (2010). A total of 452 patients with clinical stage T1c or T2a and a PSA of <10µg/L were enrolled. Patients aged 70 years or younger had a Gleason score of <6; patients that were >70 years had a Gleason score of <7 (3+4). Initially, six biopsies were performed, but in recent years the usual extended 12-core protocol was introduced. At a median follow-up of 6.8 years, the 10-year overall survival was 68%. At 10 years, the disease-specific survival was 97.2%, with 62% of men still alive on active surveillance. A total of 30% of patients had, in the end, undergone a radical treatment for the following reasons:

- 48% for a PSA doubling time of <3 years
- 27% for Gleason score progression on repeat biopsies
- 10% because of patient preference. (Mottet et al., 2014)

A variety of additional studies have now been published on active surveillance in clinically organ-confined disease (Dall'Era et al., 2008, Van As et al., 2008, Soloway et al., 2010, Tosoian et al., 2011, Adamy et al., 2011, Bul et al., 2013). Disease-specific survival in low-grade disease in the pre-PSA era was 87% at 10 years with delayed non-curative treatment. However, longer follow-ups are necessary to obtain definitive results. (Mottet et al., 2014)

Active surveillance might mean no treatment at all for patients older than 70 years, while in younger patients it might mean delaying treatment by possibly as long as years. The repeated biopsies that are part of active surveillance might then become important for their potential side-effect on nerve preservation if surgery is subsequently considered. Repeat biopsies may result in an increase in erectile dysfunction observed during active surveillance (Braun et al., 2014). Infectious complications increased after repetitive biopsies with a factor of 1.3 for each set of earlier biopsies in an active surveillance programme (Ehdaie et al., 2014). (Mottet et al., 2014)

Specific inclusion criteria for active surveillance vary across institutions (Dall'Era et al., 2008). Patients are selected for active surveillance on the basis of their age, PSA density (PSA/prostate volume), measures of PSA kinetics, such as PSA velocity, percent of positive biopsy cores, the extent of prostate cancer in any core, and Gleason score 3+3=6 (Dall'Era et al., 2008). Some institutions include patients with intermediate-risk clinical parameters, allowing for inclusion of patients with PSA at diagnosis greater than 10 µg/L or including select men with Gleason score 3+4=7 prostate cancer. (Montironi et al., 2014)

A multicentre clinical trial of active surveillance versus immediate treatment was opened in the USA in 2006. Its results are expected in 2025. (Mottet et al., 2014)

Recommendation 2.5.1.1	**Grade**
Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable.	**C**

Definition for lowest risk for prostate cancer progression:
cT1c, PSA <10µg/L, biopsy Gleason score ≤6 (at least 12 cores), ≤2 positive cores, minimal biopsy core involvement (<50% cancer per biopsy).

Clinical question 2.5.2

What should active surveillance entail?

Evidence statement
No studies were identified comparing the effectiveness of various active surveillance protocols.

A recent consensus statement (Montironi et al., 2014) concluded that the clinical parameters for patient selection and definition of progression for active surveillance protocols are evolving as data from several large cohorts become mature.

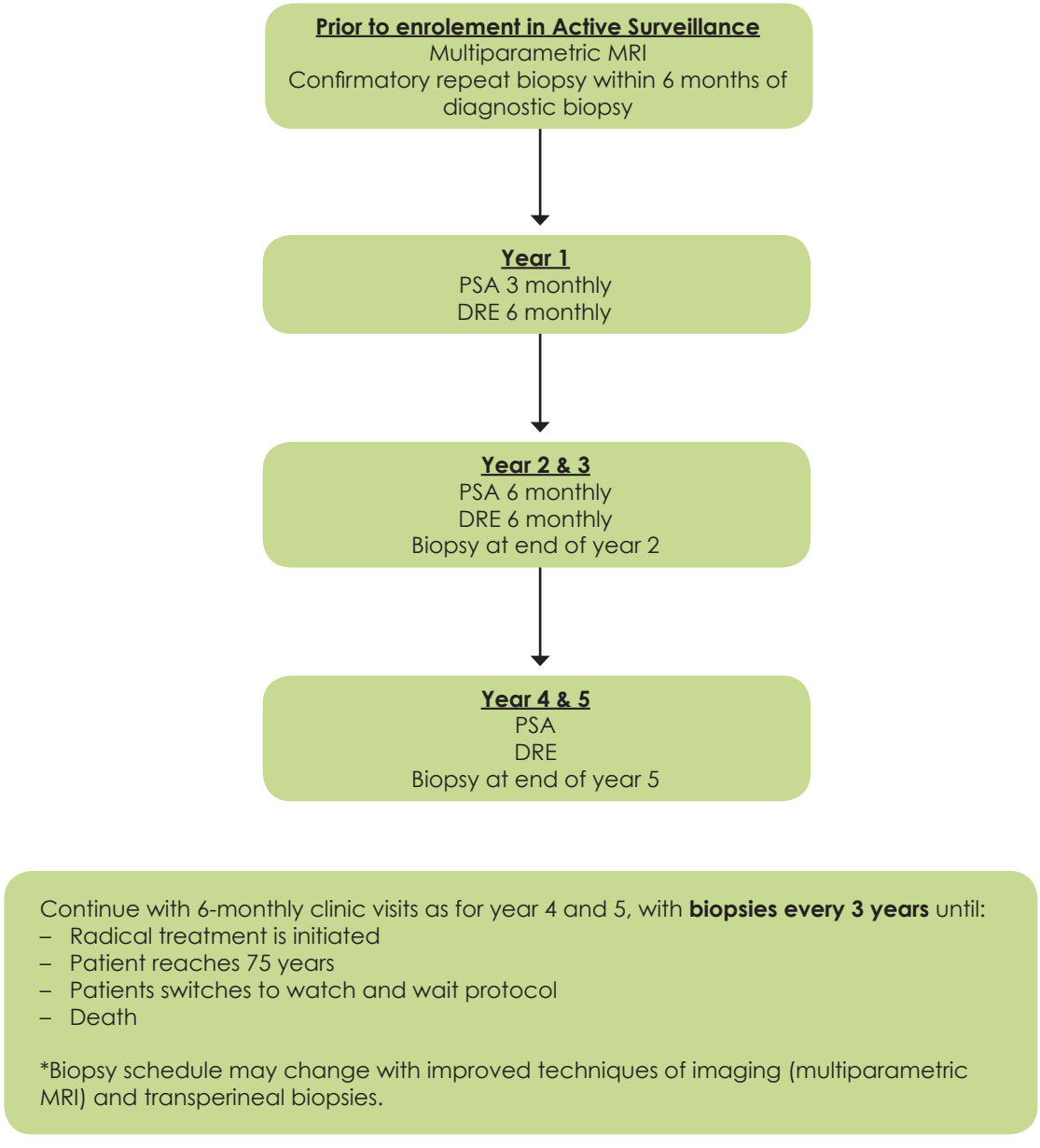


Figure 3 Protocol for men who have chosen active surveillance

Recommendation 2.5.2.1	**Grade**
The protocol in Figure 3 is recommended for men who have chosen active surveillance.	**D**

Clinical question 2.5.3

Prior to enrolment on active surveillance, should an MRI be performed?

Evidence statement

The current NICE guideline (2014), a systematic review (Dall'Era et al., 2012) and two cohort studies (Margel et al., 2012, Vargas et al., 2012) addressed this question.

Multiparametric MRI may add additional information and can help to gauge suitability for active surveillance. (NICE, 2014)

Multiple investigators have evaluated MRI for prostate cancer, as this modality offers advantages over other imaging modalities, including enhanced delineation of pelvic anatomy as well as the opportunity for functional assessment. (Dall'Era et al., 2012)

Vargas et al., (2012) assessed adding endorectal MRI to the initial clinical evaluation of 388 men with clinically low-risk prostate cancer. At multivariate analysis patients with higher MRI scores were more likely to have disease upgraded on confirmatory biopsy. The authors concluded that adding endorectal MRI may help predict findings on confirmatory biopsy and assess eligibility for active surveillance.

Margel et al., (2012) investigated the impact of multiparametric endorectal MRI on disease reclassification among 60 active surveillance candidates. The authors concluded that MRI appears to have a high yield for predicting reclassification (18 cases (32.14%)) among men who elect for active surveillance and MRI may be used to better select and guide patients before active surveillance.

Recommendation 2.5.3.1	Grade
Prior to enrolment to an active surveillance programme, a multiparametric MRI scan should be performed.	B

Clinical question 2.5.4

For men being considered for active surveillance what is the maximum number of positive cores, and the greatest percentage of any one core that should allow inclusion in active surveillance?

Evidence statement
A cohort study (Ploussard et al., 2013) and short-term data from the PRIAS study (Bul et al., 2013) addressed this question.

The selection of candidates for active surveillance depends on various factors such as the biopsy and clinical criteria but also the biopsy core number, the prostate volume, and surgeon experience in performing biopsies. Published active surveillance series use different criteria largely based on centre experiences and preferences with no hard data. The most common clinical data used to define active surveillance criteria are a Gleason score ≤6, PSA ≤10µg/L, and a clinical stage T1c disease. The PSA density and thus indirectly the prostate volume, is noted in inclusion criteria in some studies with different reported cut-offs for active surveillance inclusion. Other characteristics to consider include pathologic biopsy parameters with a wide variation concerning the active surveillance inclusion criteria. Various active surveillance programs include cancers involving <3 cores only and with an extent of cancer in any core <50% or involving <33% of positive cores. (Ploussard et al. 2013)

Ploussard et al., (2013) used insignificant prostate cancer criteria defined by Epstein et al., (1994) for the selection of active surveillance patients from the Johns Hopkins cohort. Detailed biopsy data at baseline provided additional information on the initial risk of reclassification and significantly predicted initial unfavourable disease in strictly selected active surveillance patients. Patients eligible for active surveillance and having a total tumour length <5 mm and positive cores at midline zone are more likely to have favourable pathologic characteristics at diagnosis. These variables can be used for selection and monitoring improvement in active surveillance programmes. Others variables such as bilaterality, multifocality, or number of positive cores, in this series failed to predict adverse pathologic features in radical prostatectomy specimens in strictly selected low-risk prostate cancer patients.

The PRIAS study found that the strongest predictors for reclassification and switching to deferred treatment were the number of positive cores (two cores compared with one core) and PSA density. The disease-specific survival rate was 100%. Follow-up was too short to draw definitive conclusions about the safety of active surveillance. Limitations of using surrogate end points and markers in active surveillance should be recognised. (Bul et al., 2013)

Recommendation 2.5.4.1	**Grade**
Given the evidence available from large centre trials, ≤2 positive cores and a maximum of 50% involvement of one core is recommended.	**B**

Clinical question 2.5.5

After initial biopsy, what type of prostate biopsy should be offered to men before being offered active surveillance?

Evidence statement
The current AUA guidelines (2013), two cohort studies (Ayres et al., 2012, Taira et al., 2010), a literature review (Ukimura et al., 2013) and an UpToDate review (Benway and Andriole, 2014) addressed this question.

Ultrasound-guided transrectal biopsy (TRUS)
The transrectal ultrasound approach has the ability to guide the physician to obtain specimens in the suspicious areas using a biopsy gun. A template or grid is not used during a TRUS biopsy (AUA, 2013). Twelve cores are taken.

Template-guided transperineal biopsy
A template-guided transperineal approach combines transrectal ultrasound with transperineal biopsy, guided by a brachytherapy template (Moran and Braccioforte, 2009, Symons et al., 2013, Kuru et al., 2013). This enhanced localisation augments the biopsy technique and may prove especially beneficial for repeat biopsy when pre-malignant pathology is found on initial biopsy. (Benway and Andriole, 2014)

Prospective randomised trials using extended 12-core schemes revealed no differences between the transrectal and transperineal approach in terms of cancer detection in initial prostate biopsy (Hara et al., 2008, Takenaka et al., 2008). Similarly, in the repeat biopsy setting, both approaches have a similar detection rate in men undergoing saturation biopsy (Abdollah et al., 2011). A retrospective analysis of 1,132 radical prostatectomy specimens revealed that cancers previously detected by transrectal (n = 718) or transperineal (n = 414) prostate biopsy are similar in tumour size (2.0 vs. 1.8 cm^3, respectively). Furthermore, the rate of insignificant cancer (defined as size <0.5 cm^3, Gleason ≤6, organ confined) is 5.1% for both (Hossack et al., 2012). Both methods identify the majority of clinically significant cancers (94.9%). Nevertheless, the transperineal approach detected more anterior tumours (16.2%) than the transrectal approach (12%) (Hossack et al., 2012). (Ukimura et al., 2013)

Transperineal template-guided mapping biopsy (TTMB) provides as high a rate of cancer detection as initial biopsy (75.9%) and as repeat biopsy (46.9%). Over half of all cancers found were Gleason ≥7; and only a small minority of cancers were potentially insignificant (11.1%). The distribution of cancers identified in men with multiple prior transrectal biopsies suggests that a template-guided transperineal approach allows better access to the anterior and apical aspects of the gland, in which clinically significant prostate cancer is often located. Increased ability to diagnose apical and anterior disease has implications for men undergoing active surveillance, those who are considering subtotal prostate gland treatment, those with initial negative biopsy but persistently elevated PSA, and those considering minimally invasive treatment options. (Taira et al., 2010)

Ayres et al., (2012) found 34% of men had more significant prostate cancer on restaging transperineal template biopsies compared with their transrectal biopsies. Of these men, 44% had disease predominantly in the anterior part of the gland, an area often under-sampled by transrectal biopsies. In the group of men who had their restaging transperineal template biopsies within six months of commencing active surveillance 38% had more significant disease. There was no correlation with PSA velocity or PSA doubling time. In total, 33% of men stopped active surveillance and had radical treatment. Around one-third of men had more significant prostate cancer on transperineal template biopsies. This probably reflects under-sampling by initial transrectal biopsies rather than disease progression.

Recommendation 2.5.5.1	**Grade**
A repeat prostate biopsy is mandatory for all patients considering active surveillance and this can be done by either the transrectal or transperineal approach.	**B**

Recommendation 2.5.5.2	**Grade**
There is emerging evidence that transperineal biopsies identify more clinically important prostate cancer.	**C**

Clinical question 2.5.6

For men undergoing active surveillance what are the triggers for conversion to radical treatment?

Evidence statement
The current NICE guidelines (2014) addressed this question.

No trigger factors for conversion to active treatment have been validated. There is broad agreement around a rapidly rising PSA, Gleason score progression, increased tumour volume (core number and/or core percentage involvement), DRE changes and patient preference.

Four analyses (Selvadurai et al., 2013, Klotz et al., 2010, Khatami et al., 2009, Khatami et al., 2007) from three studies were found which reported on the effectiveness of relevant prognostic factors to predict biochemical progression or conversion-free survival. (NICE, 2014)

Predictive Prognostic Factors
- PSA velocity (Selvadurai et al., 2013)
- PSA level at diagnosis (Klotz et al., 2010, Khatami et al., 2009)

Non Predictive Prognostic Factors
- PSA density (Selvadurai et al., 2013)
- Free-to-total PSA (Selvadurai et al., 2013, Khatami et al., 2007)
- Total cancer length at biopsy (Khatami et al., 2007)
- Tumour volume (Khatami et al., 2009)

Equivocal Prognostic Factors
- PSA doubling time (Klotz et al., 2010, Khatami et al., 2009, Khatami et al., 2007)
- Gleason score at diagnosis (Selvadurai et al., 2013, Klotz et al., 2010, Khatami et al., 2009)
- Clinical stage at diagnosis (Selvadurai et al., 2013)

Recommendation 2.5.6.1	Grade
Criteria for conversion to active treatment include: - Change in PSA - Change in DRE findings - Upgrade of disease (including increase in core volume, increase in number of positive cores and increase in Gleason grade) - MRI findings suggestive of disease progression - Patient preference for radical treatment	**D**

2.6 Surgery

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.6.1

Is radical prostatectomy a treatment option for men with low-risk prostate cancer (cT1-T2a and Gleason score ≤6 and PSA less than 10µg/L)?

Evidence statement
Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) addressed this question.

Radical prostatectomy is a treatment option for men with low-risk prostate cancer (Mottet et al., 2014).

Based on the available evidence on the treatment of patients with localised prostate cancer, no recommendations can be made regarding which treatment is preferred. Based on the reported adverse events and complications, a specific treatment cannot be recommended. (Oncoline, 2007)

The choice of treatment is determined after consultation with the patient whom the clinician should inform thoroughly and as objectively as possible regarding the efficacy and toxicity of each treatment modality. The patient's age and general condition are taken into account in the decision, particularly when considering the option of withholding treatment.

There is a potential for overtreatment.

Recommendation 2.6.1.1	**Grade**
Radical treatment may be an option for men with low-risk prostate cancer and life expectancy of ≥10 years.	**C**

Recommendation 2.6.1.2	**Grade**
If radical treatment is being provided, then radical prostatectomy is a treatment option for men with low-risk prostate cancer.	**B**

Clinical question 2.6.2

Is radical prostatectomy a treatment option for patients with intermediate-risk prostate cancer and a life expectancy of greater than 10 years?

Evidence statement
Guidelines from the EAU (Mottet et al., 2014) and Oncoline (2007) and an RCT (Bill-Axelson et al., 2014) addressed this question.

Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of >10 years (Mottet et al., 2014).

Bill-Axelson et al., (2014) report that the number needed to treat (NNT) to avert one death was 8 overall and 4 for men younger than 65 years of age.

Results are dependent on T stage, initial PSA (iPSA), Gleason score, and the level of surgical experience. It should be noted that the results from large studies were all derived from patients treated in the era prior to PSA assessment, Gleason classification, and adequate staging using advanced imaging techniques. (Oncoline, 2007)

There is evidence that the rate of complications following radical prostatectomy is lower when the operation is performed in a high-volume hospital and by an urologist who has performed this procedure regularly (Ellison et al., 2000, Hu et al., 2006, Begg et al., 2002). (Oncoline, 2007)

However, no relationship has been demonstrated between cancer specific survival and the number of procedures performed (open or laparoscopic). (Oncoline, 2007)

Recommendation 2.6.2.1	**Grade**
Radical treatment is recommended for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years.	**B**

Recommendation 2.6.2.2	**Grade**
Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years.	**B**

Good practice point
All surgery should be performed in high-volume hospitals to reduce complications.

Clinical question 2.6.3

Is radical prostatectomy a treatment option for patients with high-risk localised and locally advanced prostate cancer?

Evidence statement
The current EAU guideline (Mottet et al., 2014) addressed this question.

Patients classified with high-risk prostate cancer are at an increased risk of PSA failure, the need for secondary therapy, metastatic progression and death from prostate cancer. Nevertheless, not all high-risk prostate cancer patients have a uniformly poor prognosis after radical prostatectomy (Yossepowitch et al., 2007). (Mottet et al., 2014)

There is no consensus regarding the optimal treatment of men with high-risk prostate cancer. Decisions on whether to elect surgery as local therapy should be based on the best available clinical evidence. Provided that the tumour is not fixed to the pelvic wall, or that there is no invasion of the urethral sphincter, radical prostatectomy is a reasonable first step in selected patients with a low tumour volume. Management decisions should be made after all treatments have been discussed by a multidisciplinary team (including urologists, radiation oncologists, medical oncologists and radiologists), and after the balance of benefits and side effects of each therapy modality has been considered by the patients with regard to their own individual circumstances. (Mottet et al., 2014)

Surgery can be carried out with curative intent or to achieve local control. The potential side effects of surgery must be weighed against the potential benefits.

Radical prostatectomy will be curative in a select group of high-risk patients with prostate cancer. It should be considered either singularly or as a component of combined therapy.

Although still controversial, it is increasingly evident that surgery has a place in treating locally advanced disease (Gerber et al., 1997, Ward et al., 2005, Hsu et al., 2007). (Mottet et al., 2014)

Recommendation 2.6.3.1	**Grade**
Radical prostatectomy may be considered as a treatment option in high-risk disease, either alone or in combination with other therapies.	**C**

Clinical question 2.6.4

During a radical prostatectomy, is an extended lymph node dissection (lymphadenectomy) indicated over a standard (limited) lymph node dissection in all patients?

Evidence statement
The current EAU guideline (Mottet et al., 2014) addressed this question.

Extended lymph node dissection (eLND) includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. (Mottet et al., 2014)

If a lymph node dissection is being performed then an extended lymph node dissection is recommended. A limited lymph node dissection (LND) is not recommended. (Mottet et al., 2014)

Patients with PSA <10µg/L and biopsy Gleason score <7 have a low-risk of lymph node metastasis and therefore eLND might not be beneficial. (Mottet et al., 2014)

If the risk for lymph node metastases exceeds 5%, according to the EAU nomogram, then an extended lymph node dissection is necessary.

Recommendation 2.6.4.1	**Grade**
A lymph node dissection is not necessary in low-risk, localised prostate cancer, because the risk for positive lymph nodes does **not** exceed 5%.	**B**

Recommendation 2.6.4.2	**Grade**
Extended lymph node dissection should be performed in intermediate-risk, localised prostate cancer if the estimated risk for positive lymph nodes exceeds 5%, using an available nomogram.	**B**

Recommendation 2.6.4.3	**Grade**
Extended lymph node dissection should be performed in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15%-40%.	**B**

Good practice point
Limited lymph node dissection should no longer be performed, because it misses at least half of the nodes involved.

2.7 Medical oncology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.7.1

In men with prostate cancer who have biochemical/clinical relapse following definitive treatment, when should you commence hormonal therapy?

Evidence statement
Guidelines from the NCCN (2014) and Oncoline (2007) addressed this question.

The question whether hormone therapy should be started immediately after a diagnosis of metastatic prostate cancer or delayed until subjective, biochemical, or objective progression occurs has been a point of discussion for years (Newling, 2001). The number of studies addressing this topic is limited, and the available studies have reported conflicting results and have methodological flaws (Nesbit and Baum, 1950, Byar and Corle, 1988). (Oncoline, 2007)

The timing of androgen deprivation therapy (ADT) for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long-term effects of ADT. (NCCN, 2014)

Most patients will have a good 15 year prognosis. Their prognosis is however best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy. (NCCN, 2014)

Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualised until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier. (NCCN, 2014)

Recommendation 2.7.1.1	**Grade**
The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life.	**C**

Clinical question 2.7.2

Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?

Evidence statement
The current NICE guideline (2014) addressed this question.

Overall survival
Moderate quality evidence from six randomised trials shows no significant difference in overall survival between men treated with intermittent hormone therapy and those treated with continuous hormone therapy (*P*=0.17; only five included in meta-analysis). However, the most recent randomised study (Hussain et al., 2013) suggested an inferior overall survival outcome for the intermittent ADT approach (5.8 vs. 5.1 years). (NICE, 2014)

Progression-free survival (not biochemical)
Low quality evidence from two randomised trials found no significant difference in progression-free survival between intermittent and continuous therapy. However, both trials included both clinical and biochemical progression in their definition of disease progression. Three studies also provided very low quality evidence of no significant difference in progression-free survival between intermittent and continuous treatment groups for clinical progression. (NICE, 2014)

Adverse events
One moderate quality study found the incidence of treatment-emergent adverse events to be borderline significantly higher in the continuous treatment group (*P* = 0.042) (Mottet et al., 2009, Mottet et al., 2012). However, two further studies provided low quality evidence of no significant difference in the rates of adverse events between groups but provided no figures. Crook et al., (2012, 2011) and Duncan et al., (2011) also reported no significant difference between treatment arms in the rate of cardiovascular events or osteoporotic fractures (but did not provide figures). Hering et al., (2000) observed fewer mild adverse events (gastrointestinal, gynaecomastia and fatigue) and severe adverse events (severe nausea/vomiting and oedema of the lower limb) with intermittent than with continuous therapy (relative risk (RR) 0.29 and 0.15, respectively). (NICE, 2014)

Low quality evidence from two randomised trials suggests that hot flushes are significantly less likely with intermittent than with continuous hormone therapy. While both studies reported fewer hot flushes with intermittent therapy (RR 0.66 and 0.97, respectively) there is uncertainty about the size of the effect due to heterogeneity. (NICE, 2014)

Moderate quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) shows gynaecomastia is less likely in men treated with intermittent than with continuous hormone therapy (RR 0.64, 95% CI 0.43-0.93). The evidence suggests that for every 100 men treated with intermittent instead of continuous therapy, there would be seven fewer cases of gynaecomastia. Crook et al., (2012, 2011) and Duncan et al., (2011) also reported patients receiving intermittent therapy had significantly less gynaecomastia than those receiving continuous therapy but no effect size was reported (*P*<0.001). (NICE, 2014)

Low quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) suggests sexual activity within the previous month was more likely during intermittent therapy than during continuous therapy (RR 2.90, 95% CI 1.52-5.53). The evidence suggests for every 100 men treated with intermittent instead of continuous therapy there would be an additional 18 reporting sexual activity within the previous month. Low quality evidence from another randomised trial (Hering et al., 2000) found impotence was much less likely in men receiving intermittent than in those on continuous therapy (RR 0.06, 95% CI 0.01-0.28). While Crook et al., (2012, 2011) and Duncan et al., (2011) reported that patients receiving intermittent therapy had significantly greater desire

for sexual activity and better erectile function than those receiving continuous therapy but no effect sizes were reported (*P*<0.001). Miller et al., (2007) also found self-assessed sexual activity to be better with intermittent therapy but no effect sizes were reported. (NICE, 2014)

Health-related quality of life
Very low quality evidence from five randomised trials suggests better quality of life with intermittent than with continuous therapy. The studies reported that patients receiving intermittent therapy had significantly better physical function (*P*<0.001), overall self-assessed health (*P*<0.001), and physical and emotional scores, but did not report the actual figures. (NICE, 2014)

However, one moderate quality study did not find any significant difference between the treatment groups using the QLQ-C30 but did not provide figures (Mottet et al., 2009). Another study found that those in the intermittent group were significantly less likely to report impotence (*P*<0.001) or poor mental health (*P*=0.003) at 3 months (Hussain et al., 2013). At 9 months patients in the intermittent group were more likely to report high libido (*P*=0.01) and less likely to report impotence (*P*<0.001). However, at 15 months there remained no significant difference between groups in any of the quality of life outcomes. Salonen et al., (2013) found significant differences in sexual functioning but not activity limitation or physical capacity, favouring intermittent treatment at a median follow-up of 65 months, but did not report individual scores or outcomes of other domains. (NICE, 2014)

Evidence on treatment-related morbidity and mortality and patient acceptability was not reported by any of the included studies.

Recommendation 2.7.2.1	**Grade**
For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option.	**B**

Recommendation 2.7.2.2	**Grade**
Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients.	**B**

Clinical question 2.7.3

Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?

Evidence statement
The current EAU guideline (Mottet et al., 2014) addressed this question.

Eventually men with prostate cancer show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in castration resistant prostate cancer (CRPC) is debatable, as suggested by Manni et al., (1988). (Mottet et al., 2014)

These data have been challenged by two trials that showed only a marginal survival benefit for patients remaining on luteinising hormone-releasing hormone (LHRH) analogues during second- and third-line therapies (Taylor et al., 1993, Hussain et al., 1994). However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition nearly all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients. (Mottet et al., 2014)

Recommendation 2.7.3.1	**Grade**
Androgen deprivation therapy should be continued indefinitely in these patients.	**D**

Good practice point
When men with prostate cancer develop biochemical evidence of castration resistant prostate cancer, their treatment options should be discussed by the urological cancer multidisciplinary team with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.

Clinical question 2.7.4

Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?

Evidence statement

The current NCCN (2014) guideline and four RCTs (Beer et al., 2014, Logothetis et al., 2012, Ryan et al., 2013, Scher et al., 2012) addressed this question.

In the setting in which patients are docetaxel naïve and have no or minimal symptoms, administration of secondary hormonal manipulations including the addition of, or switching to, a different antiandrogen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole or abiraterone (+ predisone)), or use of an oestrogen, such as diethylstilbestrol (DES), can be considered. (NCCN, 2014)

Ryan et al., (2013) found that abiraterone improved radiographic progression-free survival (16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone; hazard ratio for abiraterone-prednisone vs. prednisone alone, 0.53; 95% confidence interval [CI], 0.45 to 0.62; *P*<0.001), showed a trend toward improved overall survival (25% decrease in the risk of death in the abiraterone-prednisone group, median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; *P*=0.01), and significantly delayed clinical decline (time to decline, 12.3 vs. 10.9 months; hazard ratio for decline, 0.82; 95% CI, 0.71 to 0.94; *P*=0.005) and initiation of chemotherapy in patients with metastatic CRPC (mCRPC) (median time to the initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone–prednisone group vs. 16.8 months in the prednisone-alone group; hazard ratio, 0.58; 95% CI, 0.49 to 0.69; *P*<0.001).

In a double-blind, phase 3 study, Beer et al. (2014) randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The co-primary end points were radiographic progression-free survival and overall survival.

The study was stopped after a planned interim analysis showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% CI, 0.15 to 0.23; P<0.001). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; P<0.001). The benefit of enzalutamide was shown with respect to all secondary end points, including time to initiation of cytotoxic chemotherapy (hazard ratio, 0.35), time to first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), time to PSA progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) (P<0.001 for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment. These results showed enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy in men with metastatic prostate cancer.

Scher et al. (2012) concluded that enzalutamide significantly prolonged the survival of men with mCRPC after chemotherapy (18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; *P*<0.001).

In patients with mCRPC previously treated with docetaxel, Logothetis et al. (2012) found abiraterone (+ prednisone) offer significant benefits compared with prednisone alone in terms of pain relief (157 of 349 [45%] patients vs. 47 of 163 [29%] respectively; *P*=0.0005), delayed pain progression, and prevention of skeletal-related events (time to first skeletal related event: 25.0 months [95% CI 25.0-not estimable] vs. 20.3 months [16.9-not estimable] respectively; *P*=0.0001).

Recommendation 2.7.4.1	Grade	Resource Implications
For men with castration resistant prostate cancer, second line hormone therapy should be considered.	**A**	–

Recommendation 2.7.4.2	Grade	Resource Implications
For men with castration resistant prostate cancer in whom chemotherapy is **not** yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	**A**	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Recommendation 2.7.4.3	Grade	Resource Implications
For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	**A**	–

Clinical question 2.7.5

Which treatment options are beneficial for patients with castration resistant prostate cancer?

Evidence statement
Six high quality phase III RCTs on the treatment for CRPC, with many therapeutic options in this setting (Beer et al., 2014, De Bono et al., 2011, Logothetis et al., 2012, Parker et al., 2013, Ryan et al., 2013, Scher et al., 2012) addressed this question.

Where there is no evidence of metastases, second-line hormonal options would be preferred to chemotherapy.

Where there is evidence of metastases (mCRPC):
- In patients with no symptoms, second-line hormonal options may be preferred to chemotherapy.
- In patients with symptoms, chemotherapy may be prioritised in order to produce a rapid response. It is recognised that certain patients may not be suitable for chemotherapy. The optimal sequencing of the newer agents is yet to be determined.

Third or further lines of treatment may be considered in patients who have maintained performance status. Choice would depend on previous treatment.

A phase III, randomised, double-blind, placebo-controlled study for the treatment of adults with castration resistant prostate cancer, symptomatic bone metastases and no known visceral metastases (Parker et al., 2013), which was terminated for efficacy at the pre-specified interim analysis concluded that radium-223 improved overall survival (median, 14.9 months versus 11.3 months; hazard ratio, 0.70; 95% CI, 0.58 to 0.83; $P<0.001$).

Recommendation 2.7.5.1	**Grade**	**Resource Implications**
Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy.	**A**	–

Recommendation 2.7.5.2	**Grade**	**Resource Implications**
Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have **not** received docetaxel.	**A**	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH and the HSE with the pharmaceutical industry.

Recommendation 2.7.5.3	**Grade**	**Resource Implications**
Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223.	**A**	–

Clinical question 2.7.6

Is treatment with bisphosphonates beneficial in patients with castration resistant prostate cancer?

Evidence statement
A recent UpToDate review (Sartor and DiBiase, 2014) addressed this question.

The benefit of zoledronic acid in men with bone metastases and CRPC was demonstrated in a trial in 643 men whose disease was progressing while on ADT (Saad et al., 2002). Men were randomly assigned to one of two doses of zoledronic acid (4mg or 8mg) or placebo, each given every three weeks. The 8 mg dose of zoledronic acid was reduced to 4mg early in the trial because of an increased risk of renal toxicity. At an average follow-up of 24 months, there was a significant reduction in the frequency of skeletal related events in men receiving zoledronic acid compared to placebo (38% vs. 49%), and the median time to develop a skeletal related events was significantly longer with zoledronic acid (488 days vs. 321 days) (Saad et al., 2004). Pain and analgesic scores were significantly higher in men who received the placebo than in those who received zoledronic acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups. (Sartor and DiBiase, 2014)

In a double-blind phase III trial 1901 men with CRPC and at least one bone metastases were randomly assigned to denosumab (120mg) or zoledronic acid (4mg), each given every four weeks (Fizazi et al., 2011). Patients on both treatment arms were advised to use calcium and vitamin D supplements. The primary objective of the study was time to first skeletal-related event (pathologic fracture, need for radiation therapy or surgery, or spinal cord compression). (Sartor and DiBiase, 2014)

At a median follow-up of approximately 12 months, results included the following:

- The time to first skeletal-related event was significantly delayed with denosumab compared to zoledronic acid (median 20.7 vs. 17.1 months, HR 0.82, 95% CI 0.71-0.95).
- There was no statistically significant difference in either overall survival (19.4 vs. 19.8 months, HR 1.03) or time to disease progression (8.4 months with both regimens, HR 1.06).
- Both treatments were well tolerated. Osteonecrosis of the jaw tended toward being more frequent with denosumab compared with zoledronic acid (2.3% vs. 1.3%) although these differences were not statistically significant. Hypocalcaemia was also significantly more frequent with denosumab (13% vs. 6%). (Sartor and DiBiase, 2014)

The main side effects of denosumab are fatigue, nausea and hypophosphataemia (BCCA, 2012). Post marketing experience suggests a small risk of significant hypocalcaemia especially in vulnerable patients (e.g. elderly, frail, renal impairment, at risk of non compliance with calcium supplements).

The toxicity of bisphosphonates and denosumab includes osteonecrosis of the jaw and electrolyte disturbance. Bisphosphonates can also cause nephrotoxicity. Serum creatinine and electrolytes including calcium should be obtained prior to each dose with appropriate dose modification or omission if results are abnormal.

Recommendation 2.7.6.1	Grade	Resource Implications
For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated.	**A**	In 2011, the NCPE considered denosumab a cost-effective therapy for the prevention of skeletal-related events in adults with bone metastases from solid tumours as compared with zoledronic acid. The cost of zoledronic acid has changed considerably in the interim. The market price of zoledronic acid is estimated to be below €50. The HSE high tech reimbursed price of denosumab (Xgeva®) is €356.99. In the absence of a formal re-appraisal of the cost effectiveness of denosumab the drug acquisition cost changes would suggest that zoledronic acid is likely to be the most cost effective treatment option in this patient cohort.

2.8 Radiation oncology

Responsibility for the implementation of recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

Clinical question 2.8.1

Which subgroup of patients will benefit from adjuvant radiotherapy after radical prostatectomy?

Evidence statement

The current EAU guideline (Mottet et al., 2014) and a cohort study (Stephenson et al., 2007) addressed this question.

Three prospective randomised trials have assessed the role of immediate postoperative radiotherapy (RT) (Bolla et al., 2012, Swanson et al., 2008, Wiegel et al., 2009a). (Mottet et al., 2014)

They were well conducted clinical trials. There were methodological differences in the Wiegel et al., (2009a) trial, in that patients had undetectable PSA at point of randomisation.

The updated results of the SWOG 8794 trial, with a median follow-up of more than 12 years, which randomly assigned 425 pT3 patients, showed that adjuvant radiation significantly improved metastasis-free survival, with a ten year metastasis-free survival of 71% vs. 61% (median prolongation of 1.8 years, *P*=0.016) and a ten year overall survival of 74% vs. 66% (median: 1.9 years prolongation; *P*=0.023) (Swanson et al., 2008). (Mottet et al., 2014)

EORTC 22911 (Bolla et al., 2012), with a target sample size of 1005 patients, compared immediate postoperative radiotherapy (60 Gy) with radiotherapy delayed until local recurrence (70 Gy) in patients classified as pT3 pN0 with risk factors R1 and pT2R1 after retropubic radical prostatectomy. Immediate postoperative radiotherapy was well tolerated. Grade 4 toxicity was not observed. The rate of grade 3 genitourinary toxicity was 5.3% versus 2.5% in the observation group after 10 years. For patients younger than 70, the study concluded that immediate postoperative radiotherapy after surgery significantly improved the 10-year biological progression free survival (PFS): 60.6% vs. 41.1%. A difference observed in the clinical progression rates for the entire cohort that favoured adjuvant RT after 5 years was not sustained after 10 years, although locoregional control was better in the long-term follow-up after immediate irradiation (hazard ratio, HR = 0.45, P <0.0001). However, adjuvant RT patients with pT2-3 R1 also showed an improved clinical PFS after 10 years (HR = 0.69; P = 0.008). Overall survival did not differ significantly between the treatment arms. After re-evaluation using a central pathological review, the highest impact of adjuvant RT was found to be on the biochemical progression (HR down to 0.3) seen in patients with positive margins, but there was also a positive effect of 10% after 5 years for pT3 with negative margins and other risk factors (Van der Kwast et al., 2007, Wiegel et al., 2009a). (Mottet et al., 2014)

It should be noted that the rate of salvage radiotherapy (SRT) was much greater in the EORTC study than the SWOG study, potentially diluting the benefit of adjuvant radiotherapy (ART) in the EORTC study. In the EORTC 47.5% (95% CI 42.7%-52.4%) of the wait-and-see group receiving salvage treatment with 30.8% of the wait-and-see group receiving radiotherapy as the first salvage treatment.

Detectable PSA postoperatively
Men with detectable PSA postoperatively should be considered for postoperative radiotherapy in the adjuvant setting (Stephenson et al., 2007, Siegmann et al., 2012).

Early SRT provides possibility of cure for patients with an increasing or persistent PSA after radical prostatectomy. More than 60% of patients who are treated before the PSA level rises to >0.5 µg/L will achieve an undetectable PSA level again (Stephenson et al., 2007, Pfister et al., 2014, Siegmann et al., 2012, Ohri et al., 2012), providing patients with an ~80% chance of being progression-free 5 years later (Wiegel et al., 2009b). A retrospective analysis based on 635 patients who underwent radical prostatectomy in 1982-2004, followed up through December 2007, who experienced biochemical and/or local recurrence and received no salvage treatment (n = 397) or SRT alone (n = 160) within 2 years of biochemical recurrence, showed that SRT was associated with a threefold increase in the prostate cancer-specific survival relative to those who received no salvage treatment (P<0.001). SRT has also been effective in patients with a rapid PSADT (Trock et al., 2008). Despite the indication of SRT also a "wait and see"-strategy is an option in patients with a long PSADT of more than 12 months (Boorjian et al., 2011). (Mottet et al., 2014)

The addition of hormone therapy to SRT (n = 78) was not associated with any additional increase in the cancer specific survival; compared with SRT alone (Trock et al., 2008). So far, adding ADT to SRT has shown only some benefit in terms of biochemical progression free survival after 5 years in retrospective series (Goenka et al., 2012, Choo et al., 2009) and for PFS for "high-risk"-tumours (Soto et al., 2012), but data from prospective randomised trials are missing. Results are awaited from a recently completed randomised controlled phase III study from the Radiation Therapy Oncology Group (RTOG-9061) comparing RT + placebo vs. a combination of RT + bicalutamide (150 mg daily) in the postoperative setting. To date there is no recommendation for patients with primary pN0-stage at radical prostatectomy for a combination of SRT plus additional ADT. (Mottet et al., 2014)

Both approaches (ART and SRT) together with the efficacy of neoadjuvant hormone therapy are currently being compared in three prospectively randomised clinical trials: the Medical Research Council (MRC) Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) in the United Kingdom, the Trans-Tasman Oncology Group (TROG) Radiotherapy Adjuvant Versus Early Salvage (RAVES), and Groupe d'Etude des Tumeurs Uro-Génitales (GETUG). (Mottet et al., 2014)

Decision making on whether to proceed with adjuvant RT for high-risk prostate cancer (pT3-4 pN0 M0 with undetectable PSA) after radical prostatectomy, or to postpone RT as an early salvage procedure in case of biochemical relapse, remains difficult. In everyday practice, the urologist should explain to the patient before radical prostatectomy that adjuvant radiotherapy may be administered if the patient has negative prognostic risk factors. Ultimately, the decision on whether to treat requires a multidisciplinary approach that takes into account the optimal timing of radiotherapy when it is used and provides justification when it is not, and this will help the discussion between the physician and the patient. (Mottet et al., 2014)

While awaiting the results of ongoing randomised controlled trials, salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease (Stephenson et al., 2007).

Recommendation 2.8.1.1	Grade
Undetectable PSA postoperatively Patients who are classified as margin positive or with seminal vesicle involvement after radical prostatectomy, should be considered for adjuvant radiotherapy.	**A**

Recommendation 2.8.1.2	**Grade**
Undetectable PSA postoperatively Patients who are classified as margin negative and who have no other adverse prognostic features should be monitored, pending the results of ongoing clinical trials (e.g. RADICALS, RAVES, GETUG), with early salvage radiotherapy when PSA becomes detectable using ultrasensitive PSA assay.	**A**

Recommendation 2.8.1.3	**Grade**
Detectable PSA postoperatively Salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease.	**B**

Good practice point
Patients with detectable PSA postoperatively should be considered for postoperative radiotherapy in the adjuvant setting.

Clinical question 2.8.2

Is external beam radiation therapy (EBRT) and/or brachytherapy a treatment option for the following categories of prostate cancer:

- **Low-risk prostate cancer**
- **Intermediate-risk prostate cancer**
- **High-risk prostate cancer**
- **Very-high-risk prostate cancer**

Evidence statement

Twelve RCTs (Armstrong et al., 2011, Bolla et al., 2002, Crook et al., 2004, D'Amico et al., 2011, Dearnaley et al., 2007, Denham et al., 2011, Jones et al., 2011, Lawton et al., 2005, Pilepich et al., 2001, Pisansky et al., 2013, Warde et al., 2011, Widmark et al., 2009), five cohort studies (Alicikus et al., 2011, D'Amico et al., 2004, Eade et al., 2007, Kuban et al., 2011, Zelefsky et al., 2008) and two narrative reviews (Grimm et al., 2012, Schulz and Kagan, 2011) addressed this question.

Low-risk

All radiotherapy treatment options (EBRT and/or brachytherapy) are appropriate to be considered for patients with low-risk prostate cancer. Presently, high-intensity focused ultrasound (HIFU) and cryotherapy should be considered experimental, pending the results of future trials.

Intermediate-risk

All radiotherapy treatment options (EBRT and/or brachytherapy) are appropriate to be considered for patients with intermediate-risk prostate cancer. Hormonal therapy should be considered in addition to EBRT (D'Amico et al., 2004, Jones et al., 2011, Pilepich et al., 2001, Denham et al., 2011, D'Amico et al., 2011, Crook et al., 2004, Armstrong et al., 2011, Pisansky et al., 2013).

High-risk

Randomised trials have shown a benefit for active treatment in this group of patients (Warde et al., 2011, Widmark et al., 2009).

Combination treatment (EBRT and hormonal therapy) has a survival advantage over either modality alone (Warde et al., 2011, Widmark et al., 2009, Bolla et al., 2002, Lawton et al., 2005).

Retrospective results have shown good long-term results with a combination of EBRT, hormonal therapy and brachytherapy (Grimm et al., 2012).

There are no randomised data to suggest that radiotherapy and hormonal therapy is superior to surgery (with or without ART/SRT) for high-risk patients. Dose escalation has been shown to improve outcomes for intermediate- and high-risk prostate cancer (Kuban et al., 2011, Dearnaley et al., 2007, Zelefsky at al., 2008, Eade et al., 2007, Alicikus et al., 2011, Schulz and Kagan, 2011).

Very-high-risk

Two large randomised controlled trials have demonstrated a survival benefit for the combination of radiotherapy and hormonal therapy compared to hormonal therapy alone (Warde et al., 2011, Widmark et al., 2009).

Recommendation 2.8.2.1	**Grade**
Low-risk All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with low-risk prostate cancer.	**B**

Recommendation 2.8.2.2	**Grade**
Intermediate-risk All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with intermediate-risk prostate cancer.	**B**

Recommendation 2.8.2.3	**Grade**
Intermediate-risk Hormonal therapy should be considered in addition to EBRT.	**A**

Recommendation 2.8.2.4	**Grade**
High-risk Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy.	**B**

Recommendation 2.8.2.5	**Grade**
Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients.	**A**

Recommendation 2.8.2.6	**Grade**
Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	**C**

Good practice point
Treatment options should be individualised for very high-risk patients.

Good practice point
Prior to considering treatment, clinicians need to take into account individual co-morbidities, age, and life expectancy. All patients should be discussed at a multidisciplinary meeting and patients should be seen in consultation by both a urologist and a radiation oncologist.

Clinical question 2.8.3

For men with prostate cancer what is defined as a biochemical recurrence after curative treatment?

Evidence statement
International guidelines (NICE, 2014, Oncoline, 2007) are largely in agreement and reference the ASTRO 2005 definition as the most commonly used criteria for biochemical failure post radiotherapy.

A recurrence of prostate cancer can be defined as:
- Following radical prostatectomy, at least two PSA readings ≥0.2µg/L; and
- Following radiotherapy, a PSA value of 2µg/L above the nadir after treatment.

The reduction in PSA after brachytherapy is often slow, and it can take more than five years to reach the PSA nadir (Grimm et al., 2001). The ASTRO criteria for PSA recurrence also apply to brachytherapy. Although the PSA nadir is an important factor, no absolute value can be established that indicates treatment success. PSA bounce after brachytherapy is often more pronounced than that seen after EBRT, and it can take up to 18 months before the PSA decreases again, often to a level lower than what was previously considered the nadir (Reed et al., 2003). (Oncoline, 2007)

Kuban et al., (2006) reported the most sensitive and specific practical definitions of biochemical recurrence after brachytherapy were the current nadir + 1µg/L and the current nadir + 2µg/L, respectively (ASTRO 2005). The sensitivity and specificity of the ASTRO 2005 definition were comparable to those seen in the radiotherapy cohort (Kuban et al., 2005, Horwitz et al., 2005). The ASTRO 2005 definition had a false call rate of 2% due to PSA bounce in a large series of men after EBRT or brachytherapy for prostate cancer (Pickles, 2006). (NICE, 2014)

It is important not to misinterpret PSA bounce as a biochemical recurrence following radiation especially brachytherapy. This phenomena tends to occur within two years after radiotherapy.

Recommendation 2.8.3.1	**Grade**
Following radical prostatectomy, a recurrence of prostate cancer can be defined as at least two PSA readings ≥0.2µg/L.	**C**

Recommendation 2.8.3.2	**Grade**
Following radiotherapy, a recurrence of prostate cancer can be defined as a PSA value of 2µg/L above the nadir after treatment.	**C**

Good practice point
It is important not to misinterpret PSA bounce as a biochemical recurrence following radiation especially brachytherapy. This phenomena tends to occur within one to two years after radiotherapy.

Clinical question 2.8.4

For men with prostate cancer with a biochemical recurrence after curative treatment (in the absence of obvious metastatic disease), what additional treatments should be offered?

Evidence statement
Guidelines from NICE (2014) and Oncoline (2007) addressed this question.

Randomised trials regarding the benefits of salvage radiotherapy and hormone therapy are ongoing. Retrospective data have shown a benefit for salvage radiation treatment.

Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed. There is a range of evidence to support this recommendation. (NICE, 2014)

Brachytherapy can also be used for the treatment of local recurrence following EBRT. Initial results suggest that the incidence of adverse events, such as irritative and obstructive micturition disorders, was low (Grado et al., 1999, Battermann, 2000). Results are likely optimal with an originally low PSA, Gleason score <7, stage ≤cT2 and a long interval between primary treatment and confirmation of local recurrence (>4 years). Long-term results, however, were not found and comparative studies have not been published. (Oncoline, 2007)

Hormonal therapy may control symptomatic, progressive or metastatic disease following either surgery or radiation. There are variations in practice with regard to the indications for, and the timings of, hormonal therapy in these situations. Other systemic therapies are being investigated in continuing clinical trials. (NICE, 2014)

Meta-analysis showed a small, but not statistically significant improvement in overall and disease specific survival at one, two and five years, in favour of early salvage EBRT. The review concluded that there was insufficient evidence about the use of androgen suppression in men with clinically localised disease, who experience biochemical recurrence without other signs or symptoms. Moul et al., (2004) considered the timing of hormonal therapy in a large case series of men with biochemical recurrence. There was no difference between the metastasis free survival of early and delayed hormonal therapy groups. A subgroup analysis, however, showed significantly better metastasis free survival for high-risk patients treated with early hormonal therapy. (NICE, 2014)

Good practice point
Salvage therapies should be considered when PSA rise is evident. Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed.

Good practice point
Salvage brachytherapy should be considered for selected patients with biopsy proven local recurrence.

Good practice point
Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have symptomatic local disease progression, or any proven metastases, or a PSA doubling time of <3 months.

Clinical question 2.8.5

Which patients with prostate cancer will benefit from neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy?

Evidence statement

A systematic review (D'Amico et al., 2012), eleven RCTs (Armstrong et al., 2011, Bolla et al., 2002, Bolla et al., 2009, Crook et al., 2004, D'Amico et al., 2011, Denham et al., 2011, Hanks, et al., 2003, Jones et al., 2011, Lawton et al., 2005, Pilepich et al., 2001, Pisansky et al., 2013) and a cohort study (D'Amico et al., 2004) addressed this question.

There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease (Jones et al., 2011). For patients with intermediate-risk prostate cancer, ADT for four to six months should be considered in conjunction with EBRT (D'Amico et al., 2004, Jones et al., 2011, Pilepich et al., 2001, Denham et al., 2011, D'Amico et al., 2011, Crook et al., 2004, Armstrong et al., 2011, Pisansky et al., 2013). A pooled analysis suggests that a duration of six months is optimal (D'Amico et al., 2012). The options for patients with high-risk prostate cancer include a combination of radiation therapy and consideration for long term hormone androgen deprivation therapy (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005) or EBRT plus brachytherapy with or without ADT. A combination of EBRT and long-term androgen deprivation therapy is recommended for patients with very high-risk disease (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005).

Recommendation 2.8.5.1	Grade
Low-risk There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease.	**C**

Recommendation 2.8.5.2	Grade
Intermediate-risk Androgen deprivation therapy for four to six months should be considered in conjunction with EBRT. A pooled analysis suggests that a duration of six months is optimal.	**A**

Recommendation 2.8.5.3	Grade
High-risk A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy.	**A**

Recommendation 2.8.5.4	Grade
EBRT plus brachytherapy with or without androgen deprivation therapy.	**C**

Recommendation 2.8.5.5	Grade
Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients.	**A**

Recommendation 2.8.5.6	Grade
A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	**C**

2.9 Palliative care

There is a HSE Clinical Programme for Palliative Care and a Needs Assessment Guide was published in 2014. Palliative care recommendations are included as a generic set of recommendations for the National Clinical Guideline.

Clinical question 2.9.1

When should palliative care be introduced for patients with cancer?

Evidence statement

Palliative care is an approach that improves the quality of life of people and their families facing the problems associated with life-limiting illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (World Health Organisation, 2014). It is a vital and integral part of all clinical practice.

When combined with standard cancer care or as the main focus of care, palliative care leads to better patient and caregiver outcomes. These include improvement in symptoms, quality of life (QOL), and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care (Smith et al., 2012).

No trials to date have demonstrated harm to patients and caregivers from early involvement of palliative care (Smith et al., 2012).

A 2013 literature review on the cost and cost-effectiveness of palliative care found that despite wide variation in study type, characteristic and study quality, there are consistent patterns in the results. Palliative care is most frequently found to be less costly relative to comparator groups, and in most cases, the difference in cost is statistically significant. (Smith et al., 2014)

Good clinical practice dictates that assessment of palliative care needs should be an ongoing process throughout the course of a patient's illness; assessments should be carried out at key transition points in the patient pathway, for example:

- At diagnosis of a life-limiting condition
- At episodes of significant progression/exacerbation of disease
- A significant change in the patient's family/social support
- A significant change in functional status
- At patient or family request
- At end of life. (HSE, 2014)

Palliative care services should be structured in three levels of ascending specialisation according to the expertise of the staff providing the service (Department of Health, 2001):

- **Level one (Palliative Care Approach):** Palliative care principles should be appropriately applied by all healthcare professionals.
- **Level two (General Palliative Care):** At an intermediate level, a proportion of patients and families will benefit from the expertise of healthcare professionals who, although not engaged full time in palliative care, have had some additional training and experience in palliative care.
- **Level three (Specialist Palliative Care):** Specialist palliative care services are those services whose core activity is limited to the provision of palliative care.

All patients should be able to engage easily with the level of expertise most appropriate to their needs.

Recommendation 2.9.1.1	Grade
For patients with cancer, early provision of palliative care can improve patient outcomes.	C

Recommendation 2.9.1.2	Grade
Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	D

2.10 Recommendations for research

There was insufficient evidence to make recommendations on a number of clinical questions. The following areas have been identified as requiring further research:

- The role of ^{18}F-Fluorocholine/^{11}C-Choline imaging in patients with prostate cancer
- The optimal method of measuring tumour length or percentage core involvement
- How to define and report the location of a dominant tumour nodule
- The prognostic value of reporting tumour volume
- The efficacy of individual active surveillance protocols
- The identification of valid trigger factors for conversion to active treatment

In addition, a number of international clinical trials are ongoing, and the guideline will be updated as required, based on the publication of new evidence.

3 Appendices

Appendix 1: Epidemiology of prostate cancer

Incidence

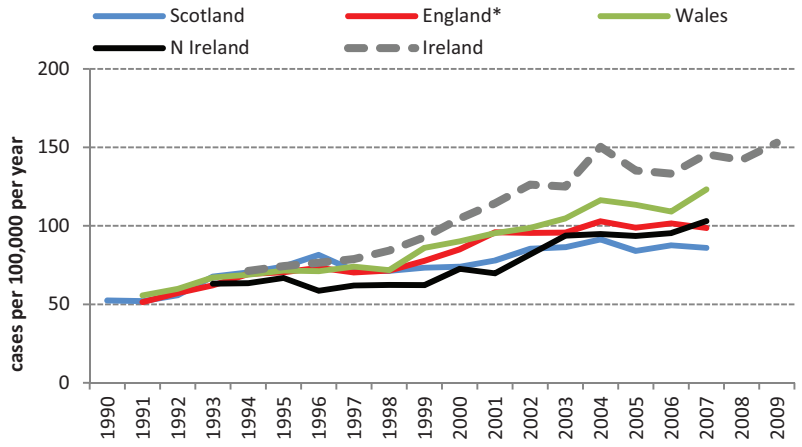
The annual average incidence for prostate cancer in Ireland between 2010 and 2012 was 3,384 cases per annum (table 4), which represents 31.5% of all invasive cancers for men (excluding non-melanoma skin cancer) (NCRI, 2014a). The incidence rate per 100,000 was 157.3. Most cases of prostate cancer occur in men aged over 70 years.

Table 4 Annual average incidence of prostate cancer in Ireland (NCRI, 2014a)

Prostate Cancer C61	
Males	3,384

The incidence rate for prostate cancer increased dramatically, by nearly 8% annually, between 1994 and 2004, and then by 1.6% annually from 2004 to 2012. The increased incidence over the last two decades probably largely reflects large-scale PSA testing of asymptomatic men. The number of PSA tests carried out increased five-fold between 1995 and 2004 (Carsion et al., 2010).

Prostate cancer incidence in Ireland is currently one of the highest in Europe and estimated incidence rates in Ireland for 2012 are approximately 1.5 times higher than the UK (Figure 4) or the EU overall (NCRI, 2014c).



TREND 1994–2007	APC	95%CI	Trend
1 IRELAND	6.2	[5.0,7.5]	↑
2 ENGLAND	3.5	[2.6,4.5]	↑
3 SCOTLAND	1.8	[0.9,2.6]	↑
4 WALES	4.9	[4.1,5.7]	↑
5 NORTHERN IRELAND	4.6	[3.5,5.8]	↑

Source: ECO EUREG [7]. APC: annual percentage change trend:
⟷ no change; ↓ significant decrease; ↑ significant increase, at the 95% level

* England represented by 8 individual registries combined, all other countries represented by national cancer registries

Figure 4 Prostate cancer incidence and trends: UK and Ireland (1990-2009) (NCRI, 2014c)

Figure 5 shows the relative frequencies of the most common invasive cancers diagnosed in men in Ireland from 2010–2012, including non-melanoma skin cancer. Prostate cancer made up 21% of all male invasive cancers.

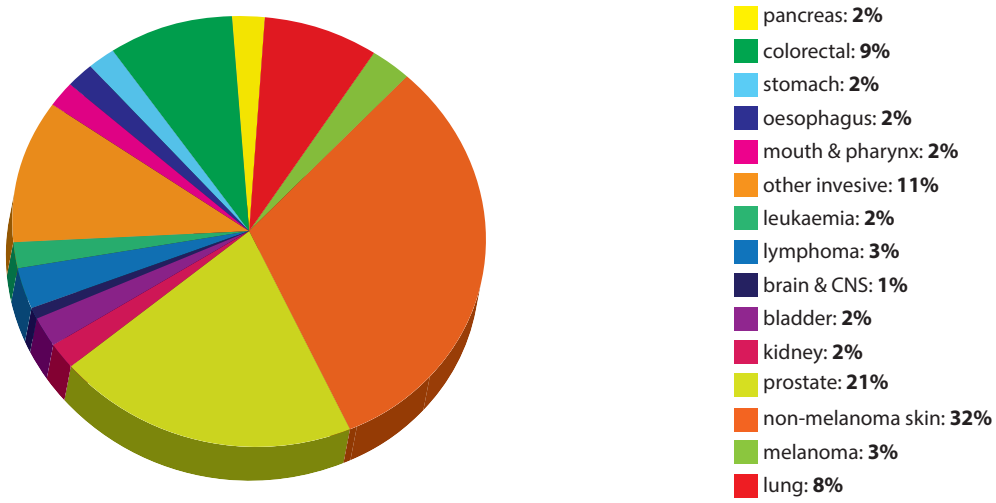


Figure 5 Relative frequencies of the most common invasive cancers diagnosed in men in Ireland, 2010-2012 (NCRI, 2014a)

Table 5 shows the ranking of the most commonly diagnosed invasive cancers among males in Ireland from 2010–2012, excluding non-melanoma skin cancer (NCRI, 2014a). Prostate cancer was the most commonly diagnosed invasive cancer among males.

Table 5 Ranking of the most commonly diagnosed invasive cancers among males in Ireland, 2010-2012 (excluding non-melanoma skin) (NCRI, 2014a)

	Male	
	%	Rank
Prostate	31.5	1
Colorectal	13.4	2
Lung	12.1	3
Lymphoma	4.4	4
Melanoma of Skin	3.6	5

Mortality

Table 6 shows the mortality from prostate cancer in Ireland in 2011. The number of deaths from prostate cancer was 549, representing 25.3 deaths per 100,000 population (NCRI, 2014a).

Table 6 Average number of deaths and mortality from prostate cancer, 2010-2012 (NCRI, 2014a)

	Deaths		Rate/100,000	
	Male	**Total**	**Male**	**Total**
Prostate	549	549	25.3	11.9
Rate: number of deaths per 100,000 population per year (European standard population)				

Figure 6 shows the relative frequency of the most common cancer deaths among males in Ireland during the period 2010-2012. Prostate cancer deaths accounted for 12% of the total male deaths from cancer (NCRI 2014a).

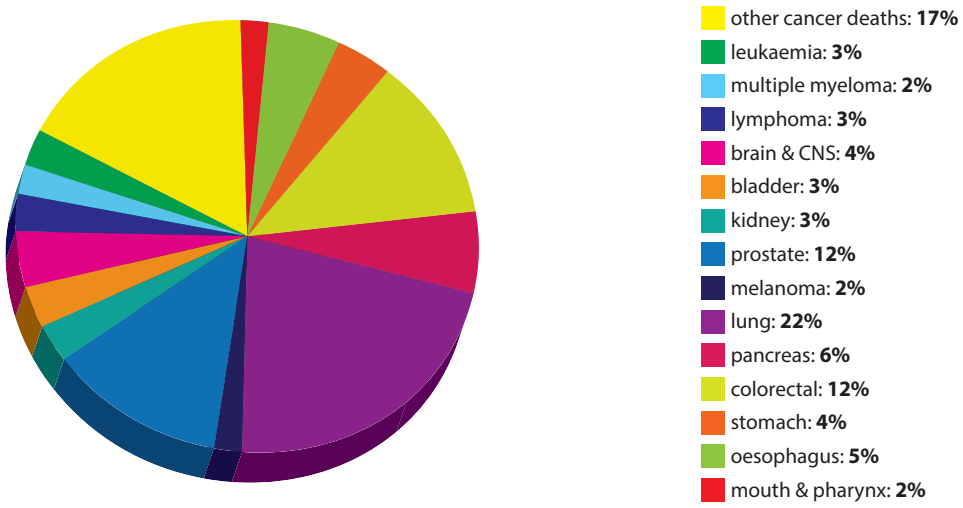


Figure 6 Relative frequency of the most common cancer deaths among males in Ireland, 2010-2012 (NCRI, 2014a)

Table 7 shows the ranking of the most common cancer deaths among males in Ireland in 2011 (NCRI, 2014a). Prostate cancer was the third most common cancer death among males.

Table 7 Ranking of the most common cancer deaths among males in Ireland, 2010-2012 (NCRI, 2014a)

	Males	
	%	**Rank**
Lung	22.4	1
Colorectal	12.4	2
Prostate	11.9	3
Pancreas	5.6	4
Oesophageal	5.0	5

Survival

Prostate cancer is now a very treatable disease, which is reflected in the increase in survival rates over the period. Five year net survival has improved from 69% to 91% between 1994-1999 and 2006-2011 (figure 7) (NCRI, 2014a). At least some of this improvement in survival may be accounted for by "lead time bias" effects, where more men are diagnosed at a very early stage through PSA screening, now common in many European countries (NCRI, 2014c).

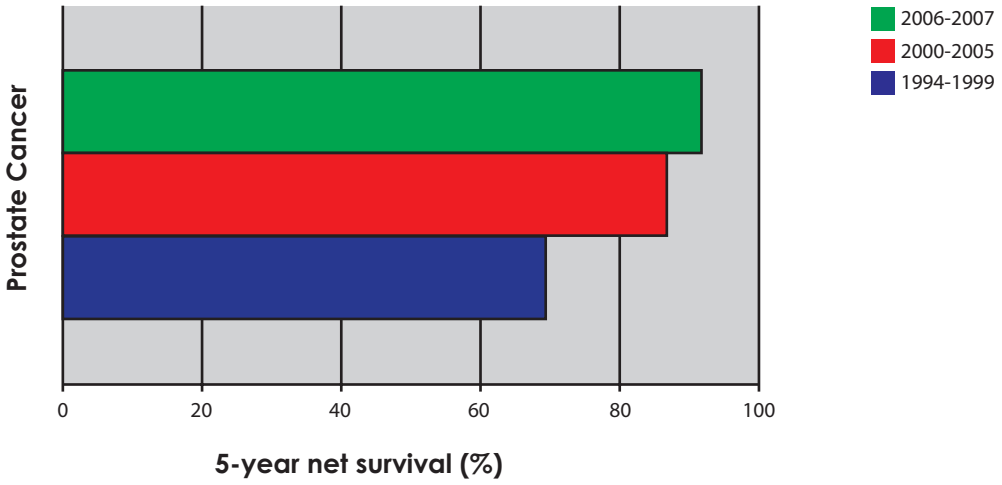


Figure 7 Five year net survival: Prostate Cancer in Ireland (NCRI, 2014a)

Cancer projections 2015-2040

There was a significant upward trend in prostate cancer numbers of 9.1% annually between 1994 and 2004 and of 4.4% annually between 2004 and 2010. Table 8 shows the projected numbers of incident cases of prostate cancer up to the year 2040, estimating a 99% increase in incidence by the year 2040, based on demographic changes only.

Table 8 Projected numbers of incident cases 2015-2040 (with % increase/decrease compared to 2010): prostate cancer (NCRI, 2014b)

Prostate Cancer		
Year	(based on demography only)	% increase/decrease compared to 2010
2010	3,222	-
2015	3,541	10
2020	4,091	27
2025	4,687	45
2030	5,307	65
2035	5,908	83
2040	6,426	99

Appendix 2: NCCP Guideline Development Group membership

Terms of reference
To develop a national evidence-based clinical guideline for the diagnosis, staging and treatment of patients with prostate cancer. Full terms of reference are available in the NCCP Methodology Manual for guideline development.

Membership of the Guideline Development Group
Chair

Mr. David Quinlan	Consultant Urologist, SVUH

Members
Radiology and Diagnosis

Dr. Conor Collins	Consultant Radiologist, SVUH
Dr. Colin McMahon (c)	Consultant Radiologist, SVUH
Mr. Paul Sweeney	Consultant Urologist, MH (to Q4 2013)

Pathology

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Dr. Christian Gulmann	Consultant Histopathologist, BH
Dr. Nick Mayer	Consultant Histopathologist, CUH
Dr. Teresa McHale	Consultant Histopathologist, GUH

Active Surveillance

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Mr. Richie Power	Consultant Urologist, BH
Dr. Brian O'Neill (c)	Consultant Radiation Oncologist, SLRON
Dr. Margaret Hanan	Consultant Microbiologist, MMUH

Surgery

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Mr. Frank O'Brien	Consultant Urologist, CUH (to Q1 2014)
Mr. Richie Power	Consultant Urologist, BH
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Prof. Frank Sullivan	Consultant Radiation Oncologist, GUH

Palliative Care

Dr. Norma O'Leary	Palliative Care Consultant, OLH
Dr. Karen Ryan	Clinical Lead of National Clinical Programme for Palliative Care, HSE and Palliative Care Consultant, SFH

(c)-Chair of sub-group

NCCP

Ms. Eileen Nolan	Project Manager, Prostate Tumour Group
Dr. Eve O'Toole	Guideline Methodologist

Librarians

Ms. Maria Carrigan	Librarian, SLH
Mr. Gethin White	Librarian, HSE East

Conflict of Interest

Dr. David Gallagher received travel expenses from Sanofi for attending the Genito-Urinary ASCO symposium and travel expenses from Roche-Pfizer for attending the ASCO symposium.

Additional contributors

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Dr. Conor Teljeur	Senior Statistician, HIQA

Methodology Expert Advisor

Prof. Mike Clarke	Director of MRC Methodology Hub, QUB

Acknowledgments

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Dr. Susan O'Reilly	National Director, NCCP (until Nov 2014)
Dr. Mary Hynes	Deputy Director, NCCP
Ms. Mary McCann	Publishing & Artwork Editor, NCCP

American Urological Association (AUA)
Centre for Behaviour Change, University College London
College of American Pathologists (CAP)
Dutch Urological Association (Oncoline)
European Association of Urology (EAU)
National Cancer Registry Ireland (NCRI)
National Comprehensive Cancer Network® (NCCN®)
National Institute for Health and Care Excellence (NICE)
Royal College of Pathologists (RCPath)

Appendix 3: NCCP Guideline Steering Group membership

Terms of reference
To set strategic direction regarding the development of multidisciplinary/interdisciplinary evidence-based clinical practice guidelines for the diagnosis, staging and treatment of cancer. Full terms of reference are available in the NCCP Guideline Methodology Manual for guideline development.

Membership of the NCCP Guideline Steering Group
The NCCP Guideline Steering Group provided governance for the development of the guideline. The members of the steering group are listed below. The GDG project managers were also present at meetings as observers.

Chair

Dr. Jerome Coffey	Interim National Director, NCCP (since Nov 2014)
Dr. Susan O'Reilly	National Director, NCCP (until Nov 2014)

Members

Mr. Justin Geoghegan	Chair Hepatobiliary GI GDG, SVUH
Ms. Noreen Gleeson	Chair Gynaecological GDG, SJH & The Coombe
Prof. Arnold Hill	NCCP Surgical Advisor, NCCP & BH
Dr. Mary Hynes	Deputy Director, NCCP
Dr. Maccon Keane	NCCP Medical Oncology Advisor, NCCP & GUH
Dr. Marcus Kennedy	Chair Lung GDG, CUH
Mr. Brendan Leen	Regional Librarian, HSE South-East
Ms. Debbie McNamara	Chair Lower GI GDG, BH
Dr. Deirdre Murray	Health Intelligence, NCCP
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Dr. Margaret O'Riordan	Medical Director, ICGP (to May 2014) Hospital
Dr. Eve O'Toole	Guideline Methodologist, NCCP
Mr. David Quinlan	Chair Prostate GDG, SVUH
Prof. John Reynolds	Chair Gastrointestinal (GI) GDG, SJH
Dr. Karen Ryan	Consultant Palliative Medicine and Clinical Lead of the National Clinical Programme for Palliative Care, SFH

Appendix 4: Clinical questions in PICO format

The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/

The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
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The section has been updated by the National Cancer Control Programme.

For the updated diagnosis and staging section, please visit:
https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/

Pathology

Clinical question 2.4.1 **What is the optimum handling, processing, and reporting of prostate core biopsies?**	
Population:	Men undergoing prostate core biopsies
Intervention:	Handling, processing, and reporting of prostate core biopsies
Comparison:	-
Outcome:	Optimum treatment options
Clinical question 2.4.2 **What is the best method of determining percentage core involvement or tumour length in prostate biopsies?**	
Population:	Men with prostate cancer undergoing prostate biopsy
Intervention:	Method of determining core length (end-to-end or collapsed)
Comparison:	-
Outcome:	Percentage core involvement
Clinical question 2.4.3 **How should Gleason score be calculated and reported in prostate core?**	
Population:	Men undergoing prostate core biopsies
Intervention:	Optimum calculation and reporting of Gleason Score
Comparison:	-
Outcome:	Treatment options
Clinical question 2.4.4 **Should extent of cancer in a prostate biopsy core be measured in millimetres (mm) or percent?**	
Population:	Men undergoing a prostate biopsy
Intervention:	Extent of cancer in a prostate biopsy core
Comparison:	-
Outcome:	Accurate diagnosis of prostate cancer
Clinical question 2.4.5 **For men who have had a prostate biopsy what are the pathological prognostic factors?**	
Population:	Men with prostate cancer who have had a prostate biopsy
Intervention:	Prognostic factors
Comparison:	-
Outcome:	Decreased morbidity or mortality Urinary, sexual and bowel function Clinical Survival Overall Survival Biochemical Survival

Clinical question 2.4.6 **For men who have had a radical prostatectomy what are the essential reporting items?**	
Population:	Men with prostate cancer who have had a radical prostatectomy
Intervention:	Prognostic factors
Comparison:	-
Outcome:	Decreased morbidity or mortality Urinary, sexual and bowel function Clinical Survival Overall Survival Biochemical Survival
Clinical question 2.4.7 **How do we determine margin status?**	
Population:	Men with prostate cancer who have had a prostate biopsy or a prostatectomy
Intervention:	Method of identification
Comparison:	-
Outcome:	Positive pathological margin
Clinical question 2.4.8 **Should margin positivity be quantified?**	
Population:	Men with prostate cancer who have had a radical prostatectomy
Intervention:	-
Comparison:	-
Outcome:	To quantify margin positivity
Clinical question 2.4.9 **For patients undergoing radical prostatectomy, should location of the positive surgical margin be reported?**	
Population:	Men with prostate cancer who have had a prostatectomy
Intervention:	Reporting location of positive surgical margins
Comparison:	-
Outcome:	Treatment/prognostic
Clinical question 2.4.10 **Should we document, quantify, and specify the location of extra prostatic extension (EPE)?**	
Population:	Men undergoing radical prostatectomy
Intervention:	Quantification of extra prostatic extension
Comparison:	-
Outcome:	Decreased morbidity or mortality Urinary, sexual and bowel function Clinical Survival Overall Survival Biochemical Survival

<u>Clinical question 2.4.11</u> How do we define a dominant tumour nodule in radical prostatectomy specimens?	
Population:	Men undergoing radical prostatectomy
Intervention:	Largest nodule
Comparison:	Nodule with highest Gleason Score
Outcome:	Definition of dominant tumour nodule
<u>Clinical question 2.4.12</u> Is it necessary to give the location of a dominant tumour nodule in radical prostatectomy specimens?	
Population:	Men undergoing radical prostatectomy
Intervention:	Location of dominant tumour nodule
Comparison:	-
Outcome:	Decreased morbidity or mortality Urinary, sexual and bowel function Clinical Survival Overall Survival Biochemical Survival
<u>Clinical question 2.4.13</u> Should reporting of pT2 substage (a, b, and c) be optional?	
Population:	Men who have had a radical prostatectomy
Intervention:	Reporting pT2 substage
Comparison:	-
Outcome:	Prognostic significance
<u>Clinical question 2.4.14</u> For men who have had a radical prostatectomy, should we document prostate cancer volume?	
Population:	Men with prostate cancer who have had a radical prostatectomy
Intervention:	Document tumour volume
Comparison:	-
Outcome:	Treatment options

Active surveillance

Clinical question 2.5.1 **For men with a histological diagnosis of prostate cancer, what are the inclusion criteria for being offered active surveillance?**	
Population:	Men with a histological diagnosis of prostate cancer (low risk cancer)
Intervention:	What are the inclusion criteria?
Comparison:	-
Outcome:	To be offered active surveillance
Clinical question 2.5.2 **What should active surveillance entail?**	
Population:	For men with prostate cancer undergoing active surveillance
Intervention:	Components of active surveillance
Comparison:	-
Outcome:	Decision to commence definitive treatment, remain on active surveillance, or progress to watchful waiting
Clinical question 2.5.3 **Prior to enrolment on active surveillance, should an MRI be performed?**	
Population:	Men being considered for active surveillance for prostate cancer
Intervention:	MRI
Comparison:	No MRI
Outcome:	Inclusion in active surveillance
Clinical question 2.5.4 **For men being considered for active surveillance what is the maximum number of positive cores, and the greatest percentage of any one core that should allow inclusion in active surveillance?**	
Population:	Men being considered for active surveillance for prostate cancer
Intervention:	Maximum number of positive cores Greatest percentage of any one core
Comparison:	-
Outcome:	Inclusion in active surveillance
Clinical question 2.5.5 **After initial biopsy, what type of biopsy should be offered to men before being placed on active surveillance?**	
Population:	Men with prostate cancer being considered for active surveillance
Intervention:	Repeat prostate biopsy; TRUS; saturation prostate biopsy; transperineal prostate biopsy
Comparison:	-
Outcome:	Inclusion in active surveillance
Clinical question 2.5.6 **For men undergoing active surveillance what are the triggers for conversion to radical treatment?**	
Population:	Men with prostate cancer being treated with active surveillance
Intervention:	Indicators of cancer progression
Comparison:	-
Outcome:	Active treatment

Surgery

<u>Clinical question 2.6.1</u> **Is radical prostatectomy a treatment option for men with low-risk prostate cancer (cT1-T2a and Gleason score ≤6 and PSA less than 10µg/L)?**	
Population:	Men with low-risk prostate cancer (cT1-T2a, Gleason score ≤6, PSA less than 10µg/L)
Intervention:	Radical prostatectomy
Comparison:	Active surveillance
Outcome:	Overall survival Recurrence of prostate cancer
<u>Clinical question 2.6.2</u> **Is radical prostatectomy a treatment option for patients with intermediate risk prostate cancer and a life expectancy of greater than 10 years?**	
Population:	Men with intermediate prostate cancer and a life expectancy of greater than 10 years
Intervention:	Radical prostatectomy
Comparison:	-
Outcome:	Overall survival Recurrence of prostate cancer
<u>Clinical question 2.6.3</u> **Is radical prostatectomy a treatment option for patients with high-risk localised and locally advanced prostate cancer?**	
Population:	High-risk localised and locally advanced prostate cancer
Intervention:	Radical prostatectomy
Comparison:	-
Outcome:	Overall survival
<u>Clinical question 2.6.4</u> **During a radical prostatectomy, is an extended lymph node dissection (lymphadenectomy) indicated over a standard (limited) lymph node dissection in all patients?**	
Population:	Men with prostate cancer having a radical prostatectomy
Intervention:	Extended lymph node dissection
Comparison:	-
Outcome:	Overall survival Recurrence of prostate cancer

Medical oncology

Clinical question 2.7.1 **In men with prostate cancer who have biochemical/clinical relapse following definitive treatment, when should you commence hormonal therapy?**	
Population:	Patients who have biochemical/clinical relapse following definitive treatment (surgery, radiotherapy, and rising PSA)
Intervention:	Hormonal therapy (timing)
Comparison:	-
Outcome:	Biochemical progression-free survival Clinical progression-free survival Quality of life
Clinical question 2.7.2 **Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?**	
Population:	Patients with metastatic prostate cancer/biochemical recurrence
Intervention:	Intermittent androgen deprivation therapy
Comparison:	Continuous androgen deprivation therapy
Outcome:	Quality of life Biochemical progression free survival Clinical progression free survival Overall survival
Clinical question 2.7.3 **Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?**	
Population:	Patients with castration resistant prostate cancer
Intervention:	Hormone therapy
Comparison:	No hormone therapy
Outcome:	Biochemical progression-free survival Clinical progression-free survival Overall survival Quality of life
Clinical question 2.7.4 **Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?**	
Population:	Patients with castration resistant prostate cancer
Intervention:	Secondary hormone therapy
Comparison:	No secondary hormone therapy
Outcome:	Biochemical progression-free survival Clinical progression-free survival Overall survival

Clinical question 2.7.5 **Which treatment options are beneficial for patients with castration resistant prostate cancer?**	
Population:	Patients with castration resistant prostate cancer
Intervention:	Treatment options: – Docetaxel – Abiraterone – Cabazitaxel – Enzalutamide – Radium-223
Comparison:	-
Outcome:	Biochemical progression-free survival Clinical progression-free survival Overall survival Quality of life
Clinical question 2.7.6 **Is treatment with bisphosphonates beneficial in patients with castration resistant prostate cancer?**	
Population:	Patients with castration resistant prostate cancer
Intervention:	Bisphosphonates
Comparison:	No bisphosphonates
Outcome:	Benefit to patients

Radiation oncology

Clinical question 2.8.1 **Which subgroup of patients will benefit from adjuvant radiotherapy after radical prostatectomy?**	
Population:	Patients with prostate cancer who have had a radical prostatectomy
Intervention:	Adjuvant Radiotherapy
Comparison:	-
Outcome:	Clinical Survival Overall Survival Biochemical Survival Decreased morbidity or mortality Urinary, sexual and bowel function
Clinical question 2.8.2 **Is external beam radiotherapy (EBRT) and/or brachytherapy a treatment option for the following categories of prostate cancer:** **– Low-risk prostate cancer** **– Intermediate-risk prostate cancer** **– High-risk prostate cancer** **– Very-high-risk prostate cancer**	
Population:	Patients with low-, intermediate-, high- and very-high-risk prostate cancer
Intervention:	Treatment Options: – Brachytherapy – External Beam Radiotherapy – Hormone Therapy
Comparison:	-
Outcome:	Clinical Survival Overall Survival Biochemical Survival Decreased morbidity or mortality Urinary, sexual and bowel function
Clinical question 2.8.3 **For men with prostate cancer, what is defined as a biochemical recurrence after curative treatment?**	
Population:	Patients with prostate cancer following curative treatment
Intervention:	Diagnostic Tests
Comparison:	-
Outcome:	Biochemical recurrence

Clinical question 2.8.4 **For men with prostate cancer with a biochemical recurrence after curative treatment (in the absence of obvious metastatic disease), what additional treatments should be offered?**	
Population:	Prostate cancer patients with a biochemical recurrence following curative treatment
Intervention:	Treatment Options: – Brachytherapy – External Beam Radiotherapy – Hormone Therapy
Comparison:	-
Outcome:	Clinical Survival Overall Survival Biochemical Survival Decreased morbidity or mortality Urinary, sexual and bowel function
Clinical question 2.8.5 **Which patients with prostate cancer will benefit from neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy?**	
Population:	Prostate cancer patients receiving radiotherapy
Intervention:	Neoadjuvant or adjuvant hormone therapy
Comparison:	-
Outcome:	Clinical Survival Overall Survival Biochemical Survival Decreased morbidity or mortality Urinary, sexual and bowel function

Palliative care

Clinical question 2.9.1 **When should palliative care be introduced for patients with cancer?**	
Population:	Patients with metastatic cancer
Intervention:	Timing of palliative care
Comparison:	-
Outcome:	Quality of life

Appendix 5: Systematic literature review protocol

National Cancer Control Programme

HSE Library Services
NCCP Guideline Development

www.hselibrary.ie

SYSTEMATIC LITERATURE REVIEW PROTOCOL

Literature searches to answer clinical questions identified by the relevant tumour group will be conducted using the following procedure. Questions should only be submitted if they have not been adequately answered in the guidelines adopted by the tumour group, or where guidelines need to be updated. Guidelines should be identified in consultation with library services.

Tumour Group	1	PICO(T)	Analyse the clinical question using PICO(T) and complete a Clinical Query Request form. See below Annex 1: Clinical Query Request.
Tumour Group/ Library Services	2	Question Category	Assign a question category, if appropriate: Therapy/Intervention ❒ Aetiology/Risk Factors ❒ Diagnosis ❒ Prognosis/Prediction ❒ Frequency/Rate ❒ Phenomena ❒ Other ❒
Library Services	3	Literature Search	Conduct searches of the following bibliographic databases in the order specified below using keywords implicit in the PICO(T) strategy and any identified subject headings:
		Cochrane	3.1 **Cochrane Library** Comprising: the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials (Central); the Database of Abstracts of Reviews of Effects; the Health Technology Assessment Database; the NHS Economic Evaluation Database. Use MeSH and keyword searches to identify systematic reviews and other relevant studies.
		Point-of-Care	3.2 **Point-of-Care Reference Tools** One or more of the following point-of-care reference tools: BMJ Best Practice; DynaMed; UpToDate.
		Medline	3.3 **Medline** Use MeSH and keyword searches. Limit results using the 'Human' search filter. Unless otherwise specified by the tumour group or warranted by the specific clinical question, limit results to studies from the previous five years. Where appropriate, limit intervention questions according to the following priority: Medline clinical queries; Cochrane systematic reviews; other systematic reviews or meta-analyses; RCTs; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources. Where appropriate, limit diagnosis, prognosis or aetiology questions according to the following priority: Medline clinical queries; systematic reviews of cohort or cross-sectional studies; cohort or cross-sectional studies; general Medline or other sources.
		Embase	3.4 **Embase** Repeat the Medline search strategy above using Embase, if available.
		Other Databases	3.5 **Other Bibliographic Databases** Repeat the Medline search strategy above using the Cumulative Index to Nursing and Allied Health Literature and/or PsycINFO, as appropriate.
		Other Sources	3.6 **Other Sources** Use any other sources for background or additional information, as appropriate. Other sources may include: PubMed, particularly for in-process or ahead-of-print citations; quality-assured, subject-specific Internet resources; clinical reference books; patient information materials; etc.

		Trial Registers	**3.7 Trial Registers** When a relevant trial is identified through searching the bibliographic databases, a search of trial registers should be carried out to identify any related trials which have been completed but whose findings have not been published or made available. The tumour group should be alerted to the presence of these unpublished trials. The following sources may be included: **3.7.1 ClinicalTrials.gov**: http://clinicaltrials.gov/ **3.7.2 Cochrane Central Register of Controlled Trials (Central)**: http://www.thecochranelibrary.com/ **3.7.3 EU Clinical Trials Register**: https://www.clinicaltrialsregister.eu/ **3.7.4 International Prospective Register of Systematic Reviews (Prospero)**: http://www.crd.york.ac.uk/prospero/search.asp **3.7.5 WHO International Clinical Trials Registry**: http://apps.who.int/trialsearch/
			3.8 For questions relating to economic evaluations, use the SIGN economic studies filter for Medline as a basis for the search strategy: http://www.sign.ac.uk/methodology/filters.html#econ. The following source may also be consulted, if available: HEED: Health Economic Evaluations Database: http://onlinelibrary.wiley.com/book/10.1002/9780470510933.
Library Services	**4**	**Reference Management**	Retain an electronic record of the search strategy and all search results using the Zotero reference management utility.
Library Services	**5**	**Search Results**	Respond to the tumour group using the Clinical Query Response form to include: ▪ a copy of the search strategy ▪ bibliographic details of all search results identified ▪ optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question See below Annex 2: Clinical Question Response.
Library Services	**6**	**Retracted Publications**	**6.1** Set up an alert to review results lists returned to the tumour group to rapidly capture any articles that are subsequently retracted or withdrawn, and notify the tumour group accordingly.
Tumour Group/ Library Services		**Retracted Publications**	**6.2** Review all articles included in recommendations of the completed guideline to confirm that they have not been subsequently retracted or withdrawn.
Library Services	**7**	**Summary of Search Strategy**	A summary of the search strategy is included as an addendum to the completed guideline. Complete the Clinical Question: Summary of Search Strategy form and return to the tumour group. See below Annex 3: Clinical Question: Summary of Search Strategy.
Library Services	**8**	**[Pre-External Review] Update of Literature Search**	Once internal review of the guideline has been completed, literature searches for all clinical questions should be updated to capture articles published in the interim between the original literature search and the final draft of the guideline. Updated literature searches should be conducted prior to submission of the guideline for external review. Respond to the tumour group as previously using the Clinical Query Response form to include: ▪ a copy of the search strategy ▪ bibliographic details of all search results identified ▪ optionally, a note of studies that seem to the librarian to be of particular relevance to the clinical question See below Annex 2: Clinical Question Response.

ANNEX 1
CLINICAL QUESTION REQUEST TO LIBRARY

Your Contact Details	
Name	
Job Title	
Work Address	
Telephone	
Email	
Employee Number	

Please state your clinical question

… and list any relevant keywords

… or (optional) enter keywords under the following headings (PICO)	
PICO	
Population/Problem	
Intervention/Indicator	
Comparator/Control	
Outcome	

Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male ❒ Female ❒	Infant (0 – 23 months) ❒ Child (2 – 12 years) ❒ Adolescent (13 – 18 years) ❒ Adult (19 – 65 years) ❒ Aged (> 65 years) ❒	Current year only ❒ 0 – 5 years ❒ > 5 years ❒

Question Type
Therapy/Intervention ❒
Aetiology/Risk Factors ❒
Diagnosis ❒
Prognosis/Prediction ❒
Frequency/Rate ❒
Phenomena ❒
Other ❒

Additional Information

ANNEX 2
CLINICAL QUESTION RESPONSE FROM LIBRARY

Dear _____,

Thank you for your email. Please see attached in response to your clinical query and, below, details of the search strategy applied to your question. If you wish to source any of the references contained in these results, or to search further, please do not hesitate to contact us.

Best wishes,

_____.

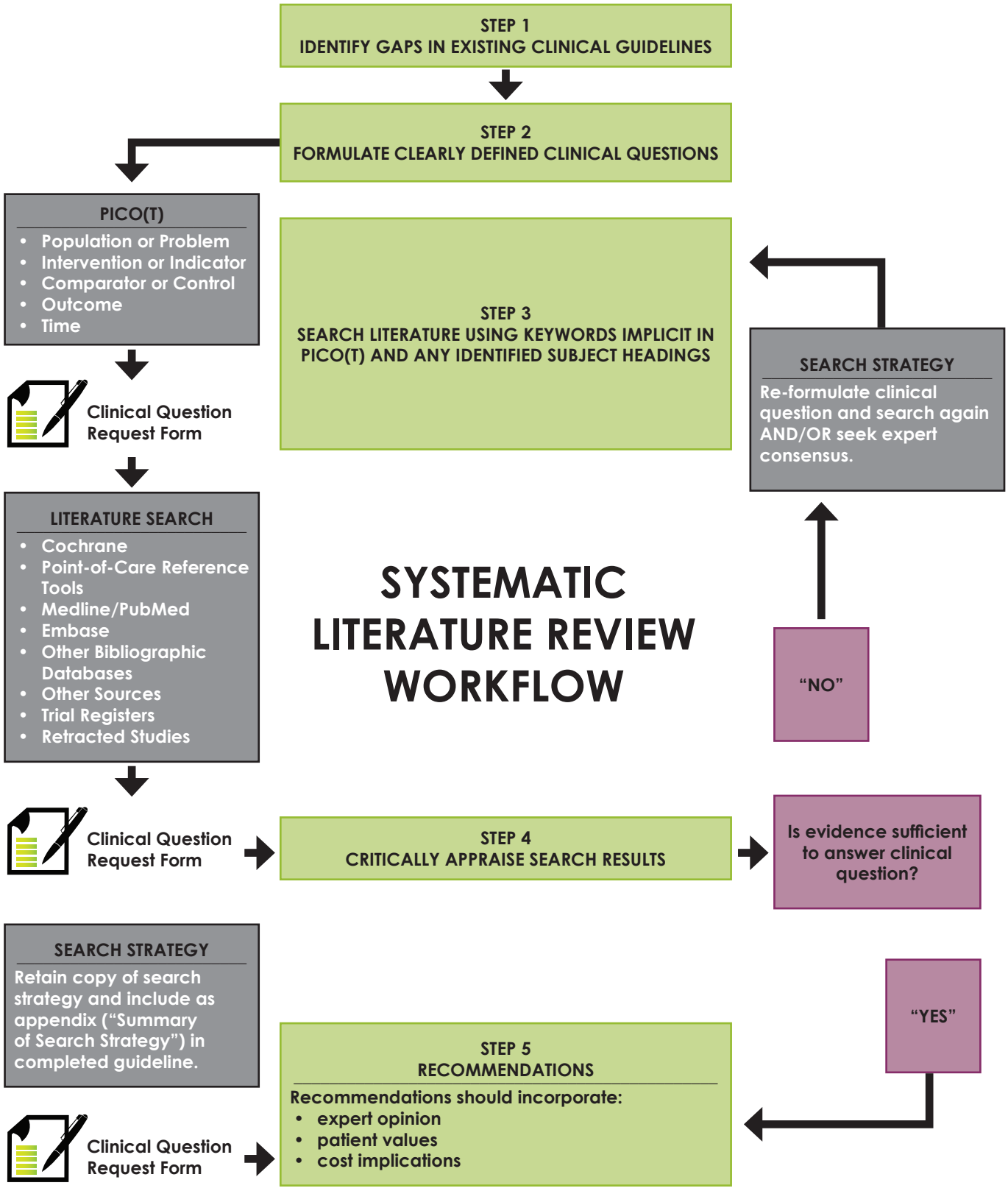
[ATTACH CLINICAL QUESTION REQUEST HERE]

Search Strategy		
Primary Database(s) Searched		
Search Strategy		
Other/Secondary Resources Searched		
Comments		
Contact		
Your Library Staff Contact		
Date		

ANNEX 3
CLINICAL QUESTION: SUMMARY OF SEARCH STRATEGY

Clinical Question		
PICO		
Population/Problem		
Intervention/Indicator		
Comparator/Control		
Outcome		
Is your question specific to any of the categories below?		
GENDER	AGE GROUP	DATE OF PUBLICATION
Male ❒ Female ❒	Infant (0 – 23 months) ❒ Child (2 – 12 years) ❒ Adolescent (13 – 18 years) ❒ Adult (19 – 65 years) ❒ Aged (> 65 years) ❒	Current year only ❒ 0 – 5 years ❒ > 5 years ❒
Question Type		
Therapy/Intervention ❒		
Aetiology/Risk Factors ❒		
Diagnosis ❒		
Prognosis/Prediction ❒		
Frequency/Rate ❒		
Phenomena ❒		
Other ❒		
Search Strategy		
Primary Database(s) Searched		
Search Strategy	[Copy of base Medline and/or PubMed search strategy HERE. Include subject headings and search hits].	
Other/Secondary Resources Searched		
Search Strategy: Other Resources	[Copy of other search strategies HERE. Include subject headings and search hits].	
Comments	[Short paragraph describing search].	
Date		

ANNEX 4
SYSTEMATIC LITERATURE REVIEW WORKFLOW*



* Based in part on "Figure 10: Systematic Literature Review" of SIGN 50: A Guideline Developer's Handbook. – Scottish Intercollegiate Guidelines Network (SIGN). 2011. A Guideline Developer's Handbook. Edinburgh: SIGN; 2011. (SIGN publication no. 50). [cited 01 Nov 2014]. Available: www.sign.ac.uk

Protocol designed by the HSE/hospital librarians in conjunction with the NCCP.

Appendix 6: Levels of evidence and grading systems

Table 9 Levels of Evidence for diagnostic studies (Oxford CEBM, 2009)

1a	Systematic review (with homogeneity*) of Level 1 diagnostic studies; clinical decision rule (CDR") with 1b studies from different clinical centres.
1b	Validating** cohort study with good reference standards" " "; or CDR tested within one clinical centre.
1c	Absolute SpPins (specificity) and SnNouts (sensitivity)" ".
2a	Systematic review (with homogeneity*) of Level >2 diagnostic studies.
2b	Exploratory** cohort study with good reference standards; CDR after deviation, or validated only on split-samples§§§ or databases.
3a	Systematic review (with homogeneity*) of 3b and better studies.
3b	Non-consecutive study; or without consistently applied reference standards.
4	Case-control study, poor or non-independent reference standard.
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

" Clinical Decision Rule (these are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category).

** Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.

" " " Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

" " An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a negative result rules-out the diagnosis.

§§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Table 10 Grades of recommendations for diagnostic studies (Oxford CEBM, 2009)

A	Consistent level 1 studies.
B	Consistent level 2 or 3 studies; or Extrapolations from level 1 studies.
C	Level 4 studies; or Extrapolations from level 2 or 3 studies.
D	Level 5 evidence; or Troublingly inconsistent or inconclusive studies of any level.

Extrapolations are where data is used in a situation that has potentially clinically important differences than the original study situation.

Table 11 Levels of evidence for interventional studies (SIGN grading system 1999-2012)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

Table 12 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Good practice point

Recommended best practice based on the clinical experience of the GDG.

Appendix 7: National stakeholder and international expert reviewers

Clinical leaders and healthcare managers	HSE Clinical Programme in Surgery HSE Clinical Programme in Radiology HSE Clinical Programme in Palliative Care HSE Clinical Programme in Medicines Management CEOs of the designated Cancer Centres HSE Clinical Programme in Primary Care
National groups, organisations, faculties and committees	National Clinical Leads group Hospital Pharmacists Association of Ireland Oncology Pharmacists Special Interest Group Faculty of Surgery, RCSI Faculty of Radiology, RCSI Irish Society for Medical Oncologists (ISMO) Irish Association for Nurses in Oncology (IANO) Irish College of General Practitioners (ICGP) Irish Association of Directors of Nursing and Midwifery Irish Association of Emergency Medicine Irish Society of Clinical Microbiologists Infection Prevention Society Surveillance Scientists Association Irish Antimicrobial Pharmacists Group (IAPG) Irish Association of Urology Nurses (IAUN) Irish Society of Urology (ISO)
Patient support and advocacy groups	HSE Patient Forum Irish Cancer Society Cancer Care West Marie Keating Foundation Gary Kelly Cancer Support Centre Bray Cancer Support Centre All Ireland Institute of Hospice and Palliative Care The Irish Hospice Foundation The Irish Association for Palliative Care
External review	European Association Urology (EAU) American Urology Association (AUA)

The following organisations and individuals responded to the stakeholder review and submissions were discussed with the members of the GDG in July 2014:

- Mr. Garrett Durkan (Consultant Urologist)
- Mr. Donal Buggy (Head of Services, Irish Cancer Society)
- Mr. Fintan Wallis (Consultant Radiologist)
- Dr. Nemer Osman (Consultant Medical Oncologist).

The GDG is also very grateful to Mr. Thomas Lam, Mr. Philip Cornford, Dr. R.C.N. van de Gerg (EAU), and Dr. Deborah Lightner (AUA) for sharing their expertise. We appreciate the time commitment that was involved in reviewing this guideline.

Appendix 8: Implementation plan

The guideline implementation plan is based on the COM-B model of behaviour change (Michie et al., 2011). Changing clinical behaviour with clinical guidelines is more likely if the behaviour is specified in the implementation plan (Michie et al., 2004). The Behaviour Change Wheel (Michie et al. 2011) was developed in 2011 as a tool for designing and evaluating behaviour change interventions. This model is based around the three conditions which influence behaviour: capability, opportunity and motivation. Each component can be mapped onto one of nine different intervention functions (education, training, enablement, persuasion, incentivisation, coercion, modelling, restrictions and environmental restructuring). This model has been used to assess barriers and facilitators to guideline development and implementation and is outlined in detail in the NCCP Guideline Methodology Manual. Identification of barriers and facilitators is carried out during recommendations meetings with consultants and is recorded in the 'considered judgement forms'. The table below outlines the possible intervention functions for each recommendation in the guideline. Where the recommendation is already current practice, intervention functions are not required.

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.2.1 What are the definitions for the following categories of prostate cancer: - Low-risk prostate cancer - Intermediate-risk prostate cancer - High-risk prostate cancer - Very-high-risk prostate cancer	It is recommended that the risk categories stated are used when interpreting and placing patients into risk groups: - **Low-risk**: cT1-T2a and Gleason score ≤and PSA <10µg/L - **Intermediate-risk**: cT2b-T2c or Gleason score = 7 or PSA 10-20µg/L - **High-risk**: cT3a, Gleason score 8-10 or PSA >20µg/L - **Very-high-risk**: cT3b-T4 or any T, N1	Risk categories influences treatment options and outcomes. All European-based guidelines are applicable to Ireland.	Current practice	-	-

***Capability** Psychological or physical ability to enact the behaviour.
Opportunity Physical and social environment that enables behaviour.
Motivation Reflective and automatic mechanisms that activate or inhibit behaviour.

Radiology and diagnosis

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.3.1 What is the clinical importance of an abnormal prostate on digital rectal examination (DRE)?	A suspect DRE is usually an indication for prostate biopsy which commonly involves needle biopsy in conjunction with transrectal ultrasound, regardless of PSA level.	None	Current practice	-	-
Q.2.3.2 Is magnetic resonance imaging (MRI) recommended for diagnosing prostate cancer in men with an elevated PSA and repeated negative transrectal ultrasound (TRUS) biopsies?	In patients with persistent clinical concern for prostate cancer following at least one negative prior prostate biopsy, consider multiparametric MRI with a view to targeted biopsy if appropriate.	Implementable in the Irish context. Evidence and guidelines to date do not state Tesla strength of MRI or routine use of endorectal coil. Images may be optimised with use of endorectal coil and 3T magnet strength but there will be cost implication of routine use.	Images may be optimised with use of endorectal coil and 3T magnet strength but there will be cost implication of routine use.	Capability (physical) Opportunity (physical)	Training, Enablement, Environmental restructuring
Q.2.3.3 Which patients with prostate cancer should have an MRI for staging?	Consider multiparametric MRI if knowledge of the T or N stage could affect management.	A considerable no. of clinically significant occult prostate cancers may be detected. Some indirectness. Limitations in the applicability is due to the use of MR guided Prostate biopsy which may not be generally available. There may be a limitation in the availability of expertise required to do both MR and targeted biopsy. Potential increase in number of MRI and MR targeted biopsies. Time – more labour intensive work; pathology time; radiology time.	There may be a limitation in the availability of expertise required to do both MR and targeted biopsy. Potential increase in no. of MRI and MR targeted biopsies. Time – more labour intensive work; pathology time; radiology time	Capability (physical) Opportunity (physical)	Training, Enablement, Environmental restructuring
Q.2.3.4 What is the role of computed tomography (CT) scan for diagnosis and staging of prostate cancer?	CT may be considered for the staging of men with high-risk prostate cancer when the PSA is >20µg/L or when locally advanced or when the Gleason score is ≥ 8.		Current Practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.3.5 Which men with prostate cancer should have an isotope bone scan?	An isotope bone scan is recommended for patients with prostate cancer with a Gleason score ≥ 8, PSA > 20µg/L or stage ≥ T3, regardless of serum PSA.		Current Practice	-	-
Q.2.3.6 What is the role of the conventional isotope bone scan versus single-photon emission computed tomography (SPECT-CT) in diagnosing bone metastases?	All patients with prostate cancer with an abnormality identified on planar scintigraphic imaging in the lumbosacral spine, pelvis or upper femora should have a SPECT scan, where available.	Current practice regarding SPECT. A majority of cancer centres have SPECT capability. SPECT-CT not yet widely available Only if decision made to purchase SPECT-CT for every department	Resources may be required	Opportunity (physical)	Enablement
Q.2.3.7 What is the role of ^{18}F-Fluorocholine / ^{11}C-Choline imaging in the diagnosis of prostate cancer?	There is no reliable evidence to support the routine use of ^{18}F-Fluorocholine / ^{11}C-Choline imaging in patients with prostate cancer at present.	For assessing the treated prostate cancer patient As evidence emerges, it is likely this is the area for which it is most applicable. Substantial investment required to upgrade the only cyclotron (Blackrock clinic) in the country. Possible collaboration with Belfast, if upgrade occurs to Belfast cyclotron.	Resources required	Opportunity (physical)	Enablement
Q.2.3.8 What is the optimum number of cores that should be taken in prostate biopsies for the diagnosis and staging of prostate cancer?	A prostate biopsy of 10-12 cores is recommended.	Minor increase in pathology workload in centres which are not already performing extended TRUS biopsy.	Resources required	Opportunity (physical)	Enablement

Pathology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.4.1 What is the optimum handling, processing, and reporting of prostate core biopsies?	A report should be generated for each designated site of biopsy. A maximum of three cores should be submitted per cassette. To optimise the detection of small lesions, blocks should be cut and examined at three levels.	Potential for nerve sparing surgery. There are implications for correlation with clinical and imaging studies and effective treatment planning (Amin et al., 2005; Touma et al., 2006). In addition, there is a correlation between the presence and amount of cancer in different regions with risk of higher pathologic stage and margin positivity (Zhou and Epstein, 2003). Directly applicable.	Implications re: transperineal biopsies due to increase in core numbers.	Opportunity (Physical)	Environmental Restructuring Enablement
Q.2.4.2 What is the best method of determining percentage core involvement or tumour length in prostate biopsies?	For determining tumour extent in prostate core biopsies, when there are multiple foci of prostate cancer in a single core separated by benign intervening stroma, it is suggested that the collapsing method is used (i.e. where intervening benign tissue is excluded from the measurement).	This will impact on eligibility criteria for inclusion in active surveillance. Slight prognostic significance. Both methods can and are being done here (in Ireland) – these methods do not need any specific equipment. Currently more pathologists use the collapsing method in Ireland. There are no resource implications.	Current practice	-	-
Q.2.4.3 How should Gleason score be calculated and reported in prostate core?	For each biopsy site the presence of biopsies positive for carcinoma and the ISUP 2005 Gleason score should be reported. The pathologists should assign a separate Gleason score to each sample core (or site) rather than an overall score for the entire biopsy session. Depending on clinical practice, it may be useful to provide an overall Gleason score to the case, in addition to site specific Gleason scores.	This has the potential to affect the option for nerve sparing surgery. However in some hospitals cores are not currently submitted in individual cassettes or by individual site per cassette.	May not be current practice in all hospitals	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.4.4 Should extent of cancer in a prostate biopsy core be measured in millimetres (mm) or percent?	The extent of cancer involvement in a core biopsy should be reported. This may be done in millimetres (mm) or percentage involvement.	There is a potential clinical impact of reporting the percentage involved of prostate core biopsy, because of the size criteria (>50% or >5mm might trigger treatment vs. active surveillance).	Current Practice	-	-
Q.2.4.5 For men who have had a prostate biopsy what are the pathological prognostic factors?	All prostate core biopsies should be reported with the pathological prognostic factors as outlined in Table 2.	Current practice – no significant change.	Current Practice	_	_
Q.2.4.6 For men who have had a radical prostatectomy what are the essential reporting items?	All radical prostatectomy specimens should be reported with the minimum dataset items as outlined in Table 3.	No change.	Current Practice	_	_
Q.2.4.7 How do we determine margin status?	Positive surgical margins are defined by microscopic tumour in touch with ink. A margin status is negative if tumour is very close to the inked surface of the margin or when they are at the surface of the tissue lacking any ink.	Prognostic and treatment implications	Current Practice	-	-
Q.2.4.8 Should margin positivity be quantified?	It is optional, according to local practice, to report extent of margin positivity. This can be done either as mm of involvement or by documenting focal versus extensive involvement.	No clinical impact. Query: may have potential for treatment (radiotherapy)	May be done, and is current practice in some centres	-	-
Q.2.4.9 For patients undergoing radical prostatectomy, should location of the positive surgical margin be reported?	The location of positive margins should be reported. Locations may be noted as follows: left or right and posterior, posterolateral, lateral, or anterior at either the apex, mid, or base (or bladder neck).		Current Practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.4.10 Should we document, quantify, and specify the location of extraprostatic extension (EPE)?	Extraprostatic extension should be documented. Extraprostatic extension should be quantified. The method of quantification should be according to local practice.	It may dictate treatment (adjuvant radiotherapy).	Current Practice	-	-
Q.2.4.11 How do we define a dominant tumour nodule in radical prostatectomy specimens?	Good practice point A dominant tumour nodule, where identifiable, may be defined according to local practice e.g. largest nodule or nodule with the highest Gleason Score.		There is not sufficient evidence on how to define a dominant nodule.		
Q.2.4.12 Is it necessary to give the location of a dominant tumour nodule in radical prostatectomy specimens?	If it is possible to identify a dominant tumour nodule in an anterior location then this should be documented. There is less definitive evidence at this time to specify peripheral versus transitional location.	Prognostic factor.	Current Practice	-	-
Q.2.4.13 Should reporting of pT2 substage (a, b, and c) be optional?	The reporting of pT2 substage (a, b, and c) is optional as it has not been proven to be of prognostic significance.	Not of prognostic significance.		Opportunity (Physical)	Modelling
Q.2.4.14 For men who have had a radical prostatectomy, should we document prostate cancer volume?	There is insufficient evidence regarding the additional prognostic value of tumour volume to recommend mandatory reporting of prostate cancer volume. It may be recommended to assess the greatest dimension of the dominant tumour nodule, if identified, or to provide a rough estimate of the percentage of cancer tissue in the prostate.	If done properly would have impact on pathology services without proven benefit, therefore not cost effective. This would have significant resource implications for pathology.	Insufficient evidence to make this recommend-ation. If it was endorsed it would have significant resources implications for pathology.	Opportunity (Physical)	Environmental Restructuring Enablement

Active surveillance

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.5.1 For men with a histological diagnosis of prostate cancer, what are the inclusion criteria for being offered active surveillance?	Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable. **Definition of lowest risk for prostate cancer progression:** cT1c, PSA < 10µg/L, biopsy Gleason score ≤ 6 (at least 12 cores), ≤ 2 positive cores, minimal biopsy core involvement (< 50% cancer per biopsy).	Delay or avoid treatment and its impact on QoL (up to c.5%). AS will result in prolonged follow-up in specialist clinic, potential for repeat prostate biopsy, and additional MRI scanning. Body of evidence is generated outside Ireland, except in the Beaumont study. AS will result in prolonged follow-up in specialist clinic, potential for repeat prostate biopsy, and additional MRI scanning. The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that an increasing number of men would have active surveillance as a result of these recommendations. However, they agreed that any additional costs were likely to be offset by savings from a corresponding decrease in the number of men having radical treatment.	AS will result in prolonged follow-up in specialist clinic, potential for repeat prostate biopsy, and additional MRI scanning.	Motivation (Reflective Motivation) Opportunity (Social opportunity)	Education, Persuasion, Restrictions, Environmental Restructuring, Enablement

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.5.2 What should active surveillance entail?	The protocol in Figure 2 is recommended for men who have chosen active surveillance.	Resource impact – increased no. of biopsies; increased out-patient time; MRI studies; theatre space/time	Resource impact – increased no. of biopsies; increased out-patient time; MRI studies; theatre space/ time	Opportunity (physical)	Environmental Restructuring and Enablement
Q.2.5.3 Prior to enrolment on active surveillance, should an MRI be performed?	Prior to enrolment in an active surveillance programme, a multiparametric MRI scan should be performed.	Potential impact of increasing number of men with low risk prostate cancer with the advent of rapid access clinics, who are eligible for active surveillance with an increase in demand for MRI. It is implementable but may cause delay in the decision making process due to access to public MRIs.	Additional access to MRI will be required.	Opportunity (physical)	Enablement
Q.2.5.4 For men being considered for active surveillance what is the maximum number of positive cores, and the greatest percentage of any one core that should allow inclusion in active surveillance?	Given the evidence available from large centre trials, ≤ 2 cores and a maximum of 50% involvement of one core is recommended.		Current practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.5.5 After initial biopsy, what type of biopsy should be offered to men before being placed on active surveillance?	A repeat prostate biopsy is mandatory for all patients considering active surveillance and this can be done by either the transrectal or transperineal approach. There is emerging evidence that transperineal biopsies identify more clinically important prostate cancer.	20% of newly diagnosed prostate cancer patients would be candidates for transperineal biopsy (approx. 600 patients) with the associated impacts described above. This could lead to increasing number of patients being offered radical treatment at an earlier stage in their disease trajectory. Due to limited resources, there will be many challenges to implementing transperineal biopsy as the standard repeat biopsy for active surveillance these include theatre access and resources, GA, increased pathology workload, necessary equipment and staff training.	Resources required	Opportunity (physical)	Enablement
Q.2.5.6 For men undergoing active surveillance what are the triggers for conversion to radical treatment?	Criteria for conversion to active treatment include: • Change in PSA • Change in DRE findings • Upgrade of disease (including increase in core volume, increase in number of positive cores and increase in Gleason grade) • MRI findings suggestive of disease progression • Patient preference for radical treatment	The more stringent the criteria the greater number of men who convert to treatment.	Resources required	Opportunity (physical)	Environmental Restructuring and Enablement

Surgery

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.6.1 Is radical prostatectomy a treatment option for men with low-risk prostate cancer (cT1-T2a and Gleason score ≤6 and PSA less than 10µg/L)?	Radical treatment may be an option for men with low-risk prostate cancer and life expectancy of ≥10 years. If radical treatment is being provided then radical prostatectomy is a treatment option for men with low-risk prostate cancer.	Treatment options – offering potential surgery or repeated biopsies.	If surgery is offered to and taken up by all patients, there are major implications to resources. Longer consultation process with patients.	Opportunity (Physical)	Enablement
Q.2.6.2 Is radical prostatectomy a treatment option for patients with intermediate-risk prostate cancer and a life expectancy of greater than 10 years?	Radical treatment is recommended for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years. Radical prostatectomy is a treatment option for men with intermediate-risk prostate cancer with a life expectancy of ≥10 years.	Benefit to patient – curing prostate cancer.	Current practice	-	-
Q.2.6.3 Is radical prostatectomy a treatment option for patients with high-risk localised and locally advanced prostate cancer?	Radical prostatectomy may be considered as a treatment option in high-risk disease, either alone or in combination with other therapies.	Applies to 30% of patients with prostate cancer. Potential curable therapy.	Increased surgical demand.	Opportunity (Physical)	Enablement
Q.2.6.4 During a radical prostatectomy, is an extended lymph node dissection (lymphadenectomy) indicated over a standard (limited) lymph node dissection in all patients?	A lymph node dissection is not necessary in low-risk, localised prostate cancer, because the risk for positive lymph nodes does not exceed 5%. Extended lymph node dissection should be performed in intermediate-risk, localised prostate cancer if the estimated risk for positive lymph nodes exceeds 5%, using an available nomogram. Extended lymph node dissection should be performed in high-risk cases. In these circumstances, the estimated risk for positive lymph nodes is 15-40%.	Potential curative treatment in patients with micro-metastases, but also allows patients access to clinical trials or additional treatments by its ability to provide more accurate staging.	It may save surgeons 30 minutes during surgery Pathologist will require extra time to process specimens	Opportunity (Physical)	Enablement

Medical oncology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.7.1 In men with prostate cancer who have biochemical / clinical relapse following definitive treatment, when should you commence hormonal therapy?	The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life.	None	Current practice	-	-
Q.2.7.2 Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?	For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option. Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients.	Intermittent approach would be cheaper. Both are currently utilised.	Current practice	-	-
Q.2.7.3 Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?	Androgen deprivation therapy should be continued indefinitely in these patients.	Potential resource implications for MDT.	Current practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.7.4 Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?	For men with castration resistant prostate cancer, second line hormone therapy should be considered. For men with castration resistant prostate cancer in whom chemotherapy is not yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide. For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) and enzalutamide.	HSE Reimbursement approval (Enzalutamide currently not reimbursed for this indication.)	Current and emerging practice	Opportunity (Physical)	Enablement
Q.2.7.5 Which treatment options are beneficial for patients with castration resistant prostate cancer?	Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy. Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have not received docetaxel. Patients with mCRPC who have predominantly bone metastases may benefit from radium-223.	HSE Reimbursement approval (Enzalutamide currently not reimbursed for this indication.)	Current and emerging practice	Opportunity (Physical)	Enablement

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.7.6 Is treatment with bisphosphonates beneficial in patients with castration resistant prostate cancer?	For men with castration resistant prostate cancer and bone metastases, treatment with zoledronic acid should be considered. Consider denosumab for men in whom zoledronic acid is contraindicated or not tolerated.	None	Current practice	-	-

Radiation oncology

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.8.1 Which subgroup of patients will benefit from adjuvant radiotherapy after radical prostatectomy?	**Patients with undetectable PSA post-operatively** Patients who are classified as margin positive or with seminal vesicle involvement after radical prostatectomy, should be considered for adjuvant radiotherapy. Patients who are classified as margin negative and who have no other adverse prognostic features should be monitored, pending the results of ongoing clinical trials (e.g. RADICALS, RAVES, GETUG), with early salvage radiotherapy when PSA becomes detectable using ultra-sensitive PSA assay. **Patients with detectable PSA post-operatively** Salvage radiotherapy is recommended for patients who develop a detectable PSA, in the absence of metastatic disease.	None	Current practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.8.2 Is external beam radiotherapy (EBRT) and/or brachytherapy a treatment option for the following categories of prostate cancer: - Low-risk prostate cancer - Intermediate-risk prostate cancer - High-risk prostate cancer - Very-high-risk prostate cancer	**Low-Risk** All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with low-risk prostate cancer. **Intermediate-Risk** All radiotherapy treatment options are appropriate (EBRT and/or brachytherapy) to be considered for patients with intermediate-risk prostate cancer. Hormonal Therapy should be considered in addition to EBRT. **High-Risk** Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy. **Very-High-Risk** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	**Low-Risk** Current Practice **Intermediate-Risk** Current Practice **High-Risk** Current Practice **Very-High-Risk** Current Practice	Current practice	-	-
Q.2.8.3 For men with prostate cancer what is defined as a biochemical recurrence after curative treatment?	Following radical prostatectomy, a recurrence of prostate cancer can be defined as at least two PSA readings ≥ 0.2µg/L. Following radiotherapy, a recurrence of prostate cancer can be defined as a PSA value of 2µg/L above the nadir after treatment.	None	Current practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.8.4 For men with prostate cancer with a biochemical recurrence after curative treatment (in the absence of obvious metastatic disease), what additional treatments should be offered?	Standard of care. **Good practice points** Salvage therapies should be considered when PSA rise is evident. Offer men with biochemical relapse after radical prostatectomy, with no known metastases, radical radiotherapy to the prostatic bed. Salvage brachytherapy should be considered for selected patients with biopsy proven local recurrence. Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have symptomatic local disease progression, or any proven metastases, or a PSA doubling time of less than three months.	None	Current practice	-	-

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.8.5 Which patients with prostate cancer will benefit from neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy?	**Low-Risk** There is a lack of evidence to suggest that the addition of androgen deprivation therapy to radical radiotherapy is of benefit in patients with low-risk disease. **Intermediate-Risk** Androgen deprivation therapy for four to six months should be considered in conjunction with EBRT. A pooled analysis suggests that a duration of six months is optimal. **High-Risk** The options for this group include: A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy. EBRT plus brachytherapy with or without androgen deprivation therapy. **Very-High-Risk** A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients.	None Current clinical practice.	Current practice	-	-

Palliative care

Clinical questions	Recommendation	Facilitators/barriers to implementation	Target behaviour (B)	COM*	Possible intervention functions
Q.2.9.1 When should palliative care be introduced for cancer patients?	For patients with cancer, early provision of palliative care can improve patient outcomes. Assessment of palliative care needs should be an ongoing process throughout the course of a patient's cancer illness and services provided on the basis of identified need.	Resource limitations. There is a five year implementation framework	Early provision of palliative care	Opportunity (Physical)	Enablement

***Capability** Psychological or physical ability to enact the behaviour.
Opportunity Physical and social environment that enables behaviour.
Motivation Reflective and automatic mechanisms that activate or inhibit behaviour.

Appendix 9: Summary of tools to assist in the implementation of the National Clinical Guideline

National Clinical Guidelines for Cancer – Methodology Manual.
National Cancer Control Programme, 2014.

Health Professional and Patient Information

NCCP GP Referral Guidelines

NCCP Chemotherapy Protocols

NCCP Patient Booklet: Having your Prostate Checked: What you should know.
www.hse.ie/eng/services/list/5/cancer/profinfo/Prostate_Booklet_new.pdf

NCCP Patient Booklet: Having your Prostate TRUS Biopsy: What you should know.
www.hse.ie/eng/services/list/5/cancer/patient/leaflets/

National Policy on the Prevention and Management of Infection Post Trans Rectal Ultrasound (TRUS) Guided Prostate Biopsy 2014.
www.hse.ie/eng/services/list/5/cancer/pubs/guidelines/guidelines.html

Health Information and Quality Authority (HIQA). National Standards for Safer Better Healthcare

Centre for Evidence Based Medicine

Improving Health: Changing Behaviour - NHS Health Trainer Handbook

UCL Centre for Behaviour Change

Michie, S., Atkins, L., West, R. 2014. The Behaviour Change Wheel: A Guide to Designing Interventions. (1st ed.). Silverback Publishing: London.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*; 337.

Medical Research Council. (2008). Developing and evaluating complex interventions: new guidance. www.mrc.ac.uk/complexinterventionsguidance.

Appendix 10: Audit criteria

It is important that both the implementation of the guideline and patient outcomes are audited to ensure that this guideline positively impacts on patient care.

The following audit criteria will be monitored:

Access
Referrals to the rapid access prostate clinic shall be offered an appointment within 20 working days of the date of receipt of a letter of referral in the cancer centre.

Time to Treatment
For all patients diagnosed with a primary prostate cancer, the interval between the date of decision to treat and date of first surgical intervention, where surgery is the first treatment, shall be less than or equal to 30 working days.

Multidisciplinary Working
All patients who are diagnosed with prostate cancer shall be discussed at Multidisciplinary Team (MDT) meeting.

Diagnosis
The histology report following a prostate biopsy should be available within 10 working days of the procedure being carried out in 80% of cases.

Radiotherapy
New patients with a primary prostate cancer undergoing radical therapy will be treated within 15 working days of being deemed ready to treat.

Surgery
• For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT2, the positive margin status should not exceed 15%. • For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT2, post-operative PSA at three months will be below detection levels in 90% of cases. • For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT3, the positive margin status should not exceed 40%. • For patients who have a radical prostatectomy for prostate cancer and the specimen is classified as a pathological stage pT3, post-operative PSA at three months will be below detection levels in 70% of cases.

Appendix 11 Budget impact assessment

Key message
This review of the literature on the economic evaluation of the diagnosis, staging and treatment of prostate cancer and the budget impact analysis highlights potential economic consequences of the clinical guideline recommendations.

The report was compiled by:
Ms. Eileen Nolan, NCCP Project Manager, Prostate Tumour Group;
Mr. Gary Killeen, NCCP Research Officer;
In collaboration with:
Ms. Michelle O'Neill, Senior Health Economist, Health Technology Assessment Directorate, Health Information and Quality Authority (HIQA);
Dr. Conor Teljeur, Senior Statistician, HIQA;
Ms. Marie Carrigan, Librarian, St Luke's Radiation Oncology Network;
Ms. Gethin White, Librarian, HSE.

Economic literature review results
A literature search for evidence of clinical and cost effectiveness, cost and resource impact, including primary (research studies) and secondary (reviews) sources was performed. The literature sources searched are specified in the literature search strategy and include relevant resources, such as trial/guideline registries and relevant citation databases. The economic literature review was undertaken using the same search terms as derived from the clinical literature review (available as a separate document) but with an economic filter applied.

Budget impact of National Clinical Guideline
For recommendations which affect resource requirements, the budget impact was calculated. Additional resources where required will be sought through the HSE service planning process.

The burden of cancer is growing, and the disease is becoming a major economic expenditure for all developed countries. In 2008, the worldwide cost of cancer due to premature death and disability (not including direct medical costs) was estimated to be US$895 billion. This is not simply due to an increase in absolute numbers, but also the rate of increase of expenditure on cancer. Several drivers of cost, such as over-use, rapid expansion, and shortening life cycles of cancer technologies (such as medicines and imaging modalities), and the lack of suitable clinical research and integrated health economic studies, have converged with more defensive medical practice, a less informed regulatory system and a lack of evidence-based socio-political debate (Sullivan et al., 2011).

"The cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost." (Sullivan et al., 2011)

Sullivan et al., (2011) believe that value and affordable cancer care can be introduced into the cancer policy lexicon without detracting from quality, and that the management tools, evidence, and methods are available to affect this transformation across all developed countries.

A recent population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer was estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). In Ireland, inpatient care costs were estimated to account for €417 million of cancer-related healthcare

costs out of a total of €619 million. Drug expenditure accounted for a further €127 million, while primary, outpatient and emergency care were estimated at €32 million, €30 million and €13 million, respectively. Across the EU, healthcare costs per person were estimated to cost between €1 and €21 for prostate cancer (€11 per person in Ireland) (Luengo-Fernandez et al., 2013). With cancer incidence expected to increase by 99% by 2040 (NCRI, 2014b), there could be a significant increase seen in healthcare costs per person in Ireland, in cancers with costs that can accrue over several years (e.g. prostate cancer). The cost of prostate cancer related informal care and productivity losses were estimated at €1.88 billion and €0.73 billion, respectively (Luengo-Fernandez et al., 2013).

Methods

The search strategy for economic literature is based on the search used in the clinical literature review, with the addition of a SIGN economic studies filter for Medline (Table 1) including the Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database (EED), Health Technology Assessment Database, the Cochrane Library, and Google Scholar.

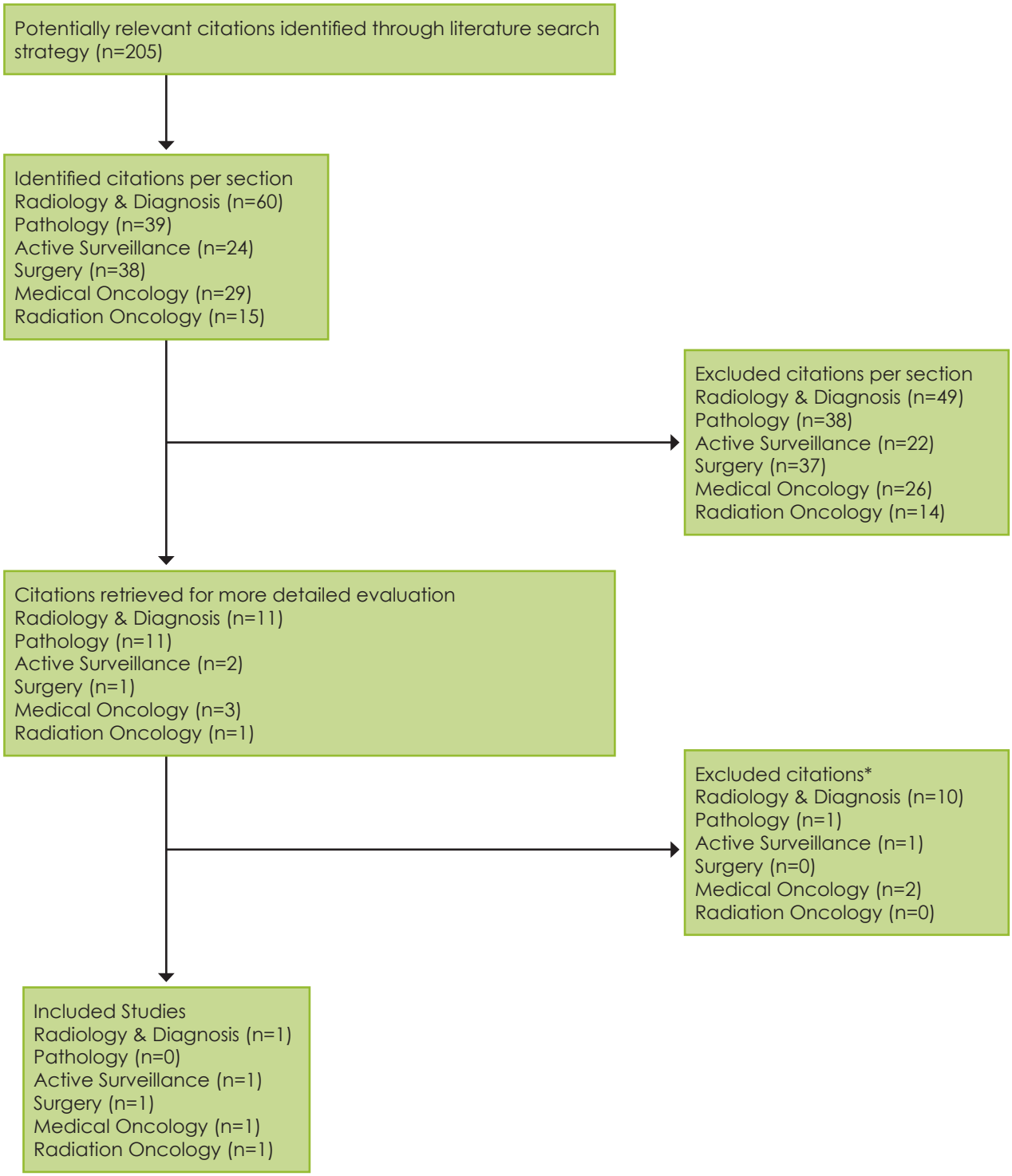
The estimated costs per quality adjusted life year (QALY) or life years gained (LYG) given in the following summaries are those reported by NICE and have been adjusted to reflect UK levels. These costs-effectiveness ratios have been complemented in brackets by euro estimates to correct for the exchange rate and purchasing power parity (PPP) between countries and health inflation to 2013 costs as per the Health Information and Quality Authority's Economic Evaluation Guidelines (HIQA, 2014).

In Ireland, a threshold of €45,000 per QALY has been applied to pharmaceuticals. This is equivalent to a threshold of GBP £28,535 per QALY. Hence an intervention that is considered cost-effective at £30,000 per QALY may be cost-effective in the Irish setting, presuming that treatment pathways, patient demographics and epidemiology are similar to Ireland. The threshold is subject to change.

It is important to note that the thresholds of cost-effectiveness in other countries differ from that in Ireland and that statements of cost-effectiveness made in another context therefore may not be applicable to Ireland. While Ireland has no explicit cost-effectiveness threshold for non-drug interventions, cost-effectiveness ratios falling within the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland.

Despite the conversion of the reported costs to PPP-adjusted 2013 euro values it is also important to remember that there may still be a number of other factors which mean that cost-effectiveness ratios from other countries are not necessarily directly applicable to the Irish setting. For example, Ireland's discount rate is higher than that applied in the UK, so many interventions assessed in the UK may have less favourable ratios if the Irish discount rate was applied. Similarly, some analyses are conducted from the societal perspective and may account for more benefits than are considered in Irish cost-effectiveness analyses (CEAs), which only account for costs to the health sector. Accordingly, the euro-adjusted ratios reported here should be only be considered broadly indicative of the level of cost-effectiveness rather than precisely adjusted estimates for the Irish health system.

Economic literature review results



***Inclusion criteria**
Costly utility model
Applicable to the Irish healthcare system
Applicable to patient population
English Language
Clinically relevant outcomes
Relevant to guideline recommendations

***Exclusion criteria**
Not a cost effectiveness study
Not in English language
Methodological or quality issues
Not applicable to Irish healthcare system
Applicable to patient population
Not relevant to guideline recommendations

Figure 8 Economic literature review results

Table 13 Economic literature review protocol (SIGN)

ID	Search
1	Economics/
2	"costs and cost analysis"/
3	Cost allocation
4	Cost-benefit analysis/
5	Cost control/
6	Cost savings/
7	Cost of illness/
8	Cost sharing/
9	"deductibles and coinsurance"/
10	Medical savings accounts/
11	Healthcare costs/
12	Direct service costs/
13	Drug costs/
14	Employer health costs/
15	Hospital costs/
16	Health expenditures/
17	Capital expenditures/
18	Value of life/
19	Exp economics, hospital/
20	Exp economics, medical/
21	Economics, nursing/
22	Economics, pharmaceutical/
23	Exp "fees and changes"/
24	Exp budgets/
25	(low adj cost).mp.
26	(high adj cost).mp.
27	(health?care adj cost$).mp.
28	(fiscal or funding or financial or finance).tw.
29	(cost adj estimate$).mp.
30	(cost adj variable).mp.
31	(unit adj cost$).mp.
32	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
33	Or/1-32

Section I Economic literature appraisals

The recent publication of a high quality guideline on the diagnosis and treatment of prostate cancer, with an extensive economics component (NICE, 2014) and the paucity of evidence identified through the literature search process has led to the NCCP utilising the economic evidence presented by NICE in determining the cost-effectiveness of diagnostic and treatment options. There was no economic evidence identified for pathology.

Radiology and diagnosis

Multiparametric/functional MRI before TRUS biopsy in men with suspected prostate cancer
NICE performed an economic evaluation aimed at assessing the cost-effectiveness of multiparametric MRI before TRUS guided prostate biopsy in men with suspected prostate cancer. The analysis considered the perspective of the NHS.

A systematic literature review was performed to assess the current economic literature in this area. The review identified 827 possibly relevant economic papers relating to prostate cancer. Of these, 824 papers were excluded based on the titles and abstracts and thus three full papers relating to the topic at hand were obtained for appraisal. Two of these papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore only one paper, Stadlbauer et al. (2011), was included in the review of published economic evidence for this topic. It should be noted that the paper was written in a non-English language (German) and as such would not typically be included in the evidence review. However, given the paucity of other evidence available in this area, an exception was made. (NICE, 2014)

Since the current economic literature did not adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness. This evaluation was based on an existing discrete event simulation (DES) model developed by the London School of Hygiene and Tropical Medicine (LSHTM). The LSHTM designed the model as a way of assessing the feasibility of using full treatment pathway models in guideline development. As such, the model fully covers the period that is relevant to the decision problem. It starts with men entering secondary care with an elevated PSA and follows them through the various diagnostic, treatment and management strategies that they may need until they die. The underlying disease progression rate in the model was informed by the watchful waiting arm of a study of 695 men with localised prostate cancer (Bill-Axelson et al. 2011). Patients receiving radical treatment are assumed to have a reduced rate of progression and follow the local progression rates observed in the radical prostatectomy arm of Bill-Axelson et al. (2011). The model was adapted to allow for different diagnostic interventions to be applied to the patients entering with elevated PSA (i.e. patients with and without prostate cancer), with the results of the clinical evidence review used to inform the diagnostic accuracy rates in the model. (NICE, 2014)

The overall costs and benefits for each treatment are then estimated based on the total length of time individuals spend in each health state over the modelled time horizon. Costs and benefits were discounted at 3.5% per year as recommended by NICE. (NICE, 2014)

The effectiveness and cost-effectiveness of using multiparametric MRI before a systematic biopsy depends upon the targeting system that is used. The cognitive targeting approach was found to be less effective than systematic TRUS biopsy (8.79 vs. 8.81 QALYs) and less costly (£10,064 (€15,864) vs. £9,897 (€15,607)). This results in an estimated incremental cost-effectiveness ratio (ICER) of £7,425 (€11,708) per QALY. Given that both the incremental costs and benefits are negative; this value needs to be interpreted with caution. It implies that, for every QALY lost by using the cognitive targeting strategy, £7,425 (€10,007) is saved. For the strategy to be considered cost-effective, this saving needs to exceed the WTP threshold. Thus, at the commonly accepted willingness to pay (WTP) threshold of £20,000 (€31,540) per QALY, this strategy would not be considered cost-effective. (NICE, 2014)*

Note that the cognitive targeting strategy was found to be less effective overall than the systematic TRUS biopsy despite having better sensitivity. This is a result of the assumptions regarding patients that are negative after their first biopsy. The NICE GDG felt that it was likely that 50% of patients that underwent a systematic biopsy would receive a scheduled re-biopsy, whereas this would not be necessary in patients that have had a MRI and a biopsy. Thus, patients in the systematic biopsy arms would get re-biopsies more quickly and this ultimately leads to the systematic biopsy arm being more effective. The results for the fusion targeting approach were very different as it was found to be more effective (0.009 QALYs) and more costly (£326 (€514)) than the systematic TRUS biopsy strategy. This results in an estimated ICER of £35,341 (€55,729) per QALY i.e. a systematic + fusion multiparametric MRI biopsy strategy provides one additional QALY at a cost of £35,341 (€55,729), in comparison to systematic TRUS biopsy. Therefore, at a WTP of £20,000 (€31,540) per QALY, this strategy would not be considered cost-effective. (NICE, 2014)*

In conclusion, the economic analysis suggests that the cost-effectiveness of biopsying additional cores identified using multiparametric MRI is dependent upon the targeting strategy that is employed. Cognitive targeting was not found to be cost-effective in any of the modelled analyses whilst the cost-effectiveness of fusion targeting was substantially better. However, the ICER associated with fusion targeting was above £20,000 (€31,540) per QALY and so would not be considered cost-effective at the WTP thresholds commonly accepted by NICE*. However, it should be acknowledged that the analysis does suggest that there could be substantial benefits associated with the use of MRI before diagnosis. This is particularly true in the analysis where it was assumed that biopsies would not be performed in patients with a negative multiparametric MRI. In this strategy costly and detrimental (in QoL terms) potentially unnecessary biopsies could be avoided. However, further evidence will be required to convince clinicians that multiparametric MRI does not miss a substantial amount of significant cancers. (NICE, 2014)

*While Ireland has no explicit cost-effectiveness threshold for non-drug interventions, cost-effectiveness ratios falling within the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland. Given the similarities of the epidemiology, patient demography and treatment pathways, it is assumed that the results of UK studies will be broadly applicable to the Irish setting.

Prognostic factors that determine the need for further investigation following a negative biopsy

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. No further economic modelling was undertaken because identifying prognostic factors that determine the need for further investigation was a clinical issue and therefore not appropriate for modelling. (NICE, 2014)

Next investigation(s) in men with suspected prostate cancer whose initial TRUS biopsy is negative

NICE performed a literature review of published economic evidence identified one relevant paper; a comprehensive report conducted as part of the National Institute for Health Research (NIHR) health technology assessment (HTA) programme by Mowatt et al., (2013). Despite the high economic importance of this topic, no further health economic analysis was undertaken. This is because the economic analysis conducted in this study was deemed to be of sufficiently high equality to be used by the GDG when making their recommendations. (NICE, 2014)

Mowatt et al., (2013) was deemed to be directly applicable to the decision problem that NICE were evaluating since it considers a UK population and does not have any other applicability issues. No serious limitations were identified with Mowatt et al., (2013), however there were some issues identified with the clinical evidence base upon which the analysis was based. This was particularly true of the analysis where DW-MRI was modelled, where assumed values were used for sensitivity and specificity. (NICE, 2014)

The base case results from Mowatt et al., (2013) suggest that the use of T2-MRI to determine and direct biopsies is cost-effective in comparison with systematic TRUS-guided extended

cores biopsy (ICER = £10,626 (€16,756) per QALY). This results from its modest additional cost and slightly improved sensitivity over systematic biopsies. The more sensitive, enhanced MRI/MRS techniques were not found to be cost-effective in the base case analysis (ICER > £30,000 (€47,310) per QALY). However, these techniques were found to be cost-effective in some of the sensitivity analysis, such as the analysis in a high prevalence cohort (prevalence = 50%) or a scenario where MRS was adjusted to only miss low risk cancer. Owing to a lack of data on its effectiveness, DW-MRI was not included in the base case analysis. However, an illustrative analysis on the use of DW-MRI was conducted where it was assumed that DW-MRI had the same sensitivity as MRS (92%) and the same specificity as T2-MRI (55%). Under these assumptions, DW-MRI was found to have an ICER value of £31,061 (€48,982) per QALY or £24,221(€38,195) per QALY when comparing it against a common baseline (systematic TRUS).

The results of the probabilistic sensitivity analysis showed that none of the diagnostic strategies have a high probability of being preferred on the grounds of cost-effectiveness. At a willingness to pay threshold of £20,000 (€31,540) per QALY, T2-MRI had a 33% probability of being cost-effective. (NICE, 2014)

While Ireland has no explicit cost-effectiveness threshold for non-drug interventions, cost-effectiveness ratios falling within the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland. Given the similarities of the epidemiology, patient demography and treatment pathways, it is assumed that the results of UK studies will be broadly applicable to the Irish setting, and therefore it is also likely to be cost-effective in the Irish setting.

Staging with MRI in men with prostate cancer

NICE performed a literature review of published economic evidence which identified one relevant paper by Stadlbauer et al., (2012). Stadlbauer et al., (2012) considered a German and Austrian healthcare setting and is written in German. Typically, non-English language studies are excluded from evidence reviews but, given the paucity of economic evidence in this area, an exception was made. The study included a cost-effectiveness analysis where effectiveness was measured using QALYs i.e. a cost-utility analysis. No further health economic analysis was undertaken for this topic because other topics were deemed to be of greater economic importance and were thus given greater priority. (NICE, 2014)

Stadlbauer et al. (2012) was considered to be only partially applicable to the NICE 2014 guideline because it was not set in the UK (study considered a German and Austrian healthcare setting). In addition, it is unclear whether discounting has been considered in the analysis as it has not been reported. Likewise, the modelled time horizon was not reported, although it is presumed to cover the patient's expected lifetime. Potentially serious limitations were also identified with the study. Further sensitivity analysis could have been conducted (particularly probabilistic sensitivity analysis). Furthermore, it was difficult to verify that the data inputs were drawn from the best available evidence because of insufficient detail provided in the report (a problem that was exacerbated by the report being written in a non-English language). (NICE, 2014)

The results from Stadlbauer et al. (2012) show staging with MRI to be cost-effective in all modelled scenarios. Furthermore, in the majority of scenarios, MRI was found to be dominant i.e. more effective and less costly than standard clinical staging.

However, the study setting and potential methodological problems limit the applicability of these otherwise strong results. Thus, it is difficult to draw any firm conclusions about the decision problem under consideration by using the results of this analysis and the cost-effectiveness of MRI staging remains, to a large degree, uncertain. (NICE, 2014)

In which patients with prostate cancer will MRI staging alter treatment?
NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. No further economic modelling was undertaken because identifying those patients with prostate cancer in whom MRI staging will alter management was a clinical issue and therefore not appropriate for modelling. (NICE, 2014)

Relevance to the guideline recommendations
The effectiveness and cost-effectiveness of using multiparametric MRI before a systematic biopsy is dependant upon the choice of targeting system used. The cognitive targeting approach was found to be less effective than systematic TRUS biopsy (8.79 vs. 8.81 QALYs) and less costly (£10,064 (€15,864) vs. £9,897 (€15,607)).

None of the diagnostic strategies have a high probability of being preferred on the grounds of cost-effectiveness in the Irish setting.

Staging with MRI was shown to be cost-effective in all modelled scenarios in the Irish setting.

However, the study setting and potential methodological problems limit the applicability of these otherwise strong results. Thus, it is difficult to draw any firm conclusions about the decision problem under consideration by using the results of this analysis.

Active surveillance

Inclusion criteria for active surveillance
NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. No further economic analysis was undertaken partly because the selection of patients who are offered active surveillance is more of a clinical issue than an economic one. Furthermore, even if the topic was considered a high priority for economic analysis, development of an economic model would have been hindered by the clinical evidence available. In particular, equivalent risk groups were not applied across clinical trials making it difficult to pool the clinical data by risk groups. (NICE, 2014)

Active surveillance protocols

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. Despite this being an area of high economic importance, further economic analysis was not undertaken primarily because of concerns about the feasibility of building a model in this area. The lack of clinical evidence available coupled with inconsistency amongst the active surveillance protocols used in studies makes it very difficult to pool and compare strategies. (NICE, 2014)

Relevance to the guideline recommendations
Due to a lack of clinical evidence and the variation in both inclusion criteria and protocols, it is not possible to give any economic insight at present.

Surgery

Radical prostatectomy

NICE performed a literature review of published economic evidence which identified two relevant papers; Hohwu et al., (2011) and Ramsay et al., (2012). Ramsay et al., (2012) was a comprehensive report conducted as part of the National Institute for Health Research (NIHR) HTA programme. Both papers were cost-utility analyses that quantified health effects in terms of QALYs. Despite the high economic importance of this topic, no further health economic analysis was undertaken. This is because the economic analysis conducted in this study was deemed to be of sufficiently high equality to be used by the NICE GDG when making their recommendations. (NICE, 2014)

NICE deemed Hohwu et al., (2011) only partially applicable to the guideline, primarily because it considered a country other than the UK (Denmark). Ramsay et al., (2012) was deemed to be directly applicable because it considered a UK setting and there were no other applicability issues. Potentially serious limitations were identified in the study by Hohwu et al., (2011). The one year time horizon was possibly too short to capture all the relevant costs and benefits (as a comparison, Ramsay et al., (2012) considered a ten year time horizon). Also, while numerous one-way sensitivity analyses were conducted, additional analyses could have been conducted in other important areas. No serious limitations were identified with Ramsay et al., (2012). However, there were a few minor limitations with some important information not being reported (e.g. price year) and an important (and uncertain) parameter left out of the probabilistic sensitivity analysis.

The conclusions of in the two studies were markedly different. Hohwu et al., (2011) found Robotic-Assisted Laparoscopic Prostatectomy (RALP) to be dominated by radical retropubic prostatectomy (RRP) i.e. RRP was both more effective and less costly. Conversely, Ramsay et al., (2012) found robot assisted prostatectomy to be cost-effective in at least some scenarios when compared to laparoscopic prostatectomy. Given the better applicability and fewer limitations associated with Ramsay et al., (2012), more weight is attached their results. The results of the sensitivity analysis in Ramsay et al., (2012) suggest that the cost-effectiveness of robot assisted prostatectomy is highly dependent upon the number of procedures conducted per year (thereby affecting the cost per procedure) and the positive margin rates.

Relevance to the guideline recommendations
The cost-effectiveness of robot assisted prostatectomy is highly dependent upon the number of procedures conducted per year (thereby affecting the cost per procedure) and the positive margin rates.

Medical oncology

Neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy in patients with prostate cancer

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. No further economic analysis was undertaken partly because finding a group of patients that could benefit from hormones in combination with EBRT is primarily a clinical problem rather than an economic one. In addition, even if the topic was considered a high priority for economic analysis, the development of a model would have most likely been hindered by limitations in the clinical evidence base. In particular, the papers did not stratify patients into useful and consistent subgroups.

Optimal duration of hormone therapy when combined with external beam radiotherapy

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. Despite being a topic that is quite well suited to economic modelling, no further economic analysis was undertaken. This was primarily because other topics were considered to be of higher economic importance and were thus assigned to a higher priority for analysis. In addition, it was relatively straightforward to estimate the likely economic impact of the recommendation without undertaking economic modelling. (NICE, 2014)

Intermittent hormone therapy versus continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. No further economic modelling was undertaken for this topic as it was not thought to be necessary because estimating the likely economic effects of the recommendation seemed relatively straightforward. Thus, other topics with more complex cost and benefit trade offs were prioritised for economic modelling. (NICE, 2014)

Adverse cardiovascular effects of long-term androgen deprivation

NICE performed a literature review of published cost-effectiveness analyses which did not identify any relevant papers. The limited clinical evidence base for this question made it unfeasible to undertake further economic modelling. (NICE, 2014)

Effective interventions for osteoporosis as a result of long term androgen deprivation for prostate cancer

NICE performed a literature review of published economic evidence and identified one relevant paper (Ito, 2010). The paper was a cost-effectiveness analysis, which quantified health effects in terms of quality adjusted life years (QALYs) and thus can be considered a cost-utility analysis.

No further health economic analysis was undertaken for this topic because other topics were deemed to be of greater economic importance and were thus given greater priority. (NICE, 2014)

Relevance to the guideline recommendations
The limited economic evidence base and straightforward nature of estimating the likely economic impact for some of these scenarios made it both unfeasible and unnecessary to undertake further economic modelling.

Radiation oncology

Brachytherapy and/or external beam radiotherapy in patients with localised or locally advanced non-metastatic prostate cancer

NICE performed an economic evaluation aimed at assessing the cost-effectiveness of LDR or HDR brachytherapy in combination with external beam radiotherapy. The analysis considered the perspective of the NHS.

A systematic literature review did not identify any existing evidence that sufficiently addressed the current decision problem. However, a report (Lord et al., 2013) on the use of full pathway models in guideline development included an analysis that does address the decision problem. (NICE, 2014)

Since the economic analysis in its original form did not adequately address the decision problem, the model was adapted and an updated analysis was performed. The primary changes were made to the clinical evidence used to inform the effectiveness of the interventions and to the costs used in the analysis, which were updated to reflect a more recent price year (2011/12). The results of the clinical evidence review were used to inform the efficacy of the interventions in the model. Since no high quality evidence was identified on the use of LDR brachytherapy in combination with EBRT, this intervention was not modelled. Instead, the analysis was focused on the areas where RCT evidence was available. Thus, only a comparison of HDR brachytherapy in combination with EBRT versus EBRT alone was modelled using the results of two RCTs (Sathya et al., 2005, Hoskin et al., 2012). However, it should be noted that, although these RCTs provide the best evidence currently available, they do lack some applicability to current practice. Both studies used lower doses in their EBRT-only arms (66 Gy and 50 Gy respectively) (Sathya et al., 2005, Hoskin et al., 2012) than the minimum of 74 Gy recommended in the 2008 NICE prostate cancer guideline. (NICE, 2014)

The effectiveness data (biochemical free survival) from these studies were modelled individually as two separate scenarios using pre-loaded effectiveness data in the LSHTM model (Scenario 1: Sathya et al. 2005; Scenario 2: Hoskin et al. 2007).

The results show that the model is fairly insensitive to most of the changes made. However, there is one noticeable exception and that is the influence of a higher brachytherapy cost. This scenario was based on the use of inpatient costs from NHS reference costs for interstitial planning and delivery (whereas day case costs were used in the base case). However, it should be noted that in all modelled scenarios the ICER remained below a WTP threshold of £20,000 (€31,540) per QALY. Thus, the addition of HDR brachytherapy to EBRT would still be considered cost-effective in all modelled scenarios. Probabilistic sensitivity analysis showed that, at a threshold of £20,000 (€31,540) per QALY, HDR brachytherapy in addition to radiotherapy was likely to be the preferred strategy with a 100% probability of being considered cost-effective. (NICE, 2014)

While Ireland has no explicit cost-effectiveness threshold for non-drug interventions, cost-effectiveness ratios falling within the range of €20,000-€45,000/QALY are conventionally considered cost-effective in Ireland. Given the similarities of the epidemiology, patient demography and treatment pathways, it is assumed that the results of UK studies will be broadly applicable to the Irish setting, and therefore it is also likely to be cost-effective in the Irish setting.

In conclusion, the economic analysis suggests that HDR brachytherapy in combination with EBRT is a cost-effective use of resources. However, there are concerns about the applicability of the evidence upon which this conclusion is based because of doses used in the RCTs. (NICE, 2014)

Relevance to the guideline recommendations
Further research is required that investigates the cost-effectiveness of the strategies when using doses that would be typical of clinical practice and considers equivalent overall doses in both arms.

Table 14 Economic literature evidence table

All monetary values given in the table below are those which are detailed in the original paper, adjusted euro equivalents of these can be found in the main text above.

Study	Intervention	Analysis details	Clinical and QALY outcomes	Costs	Results
The section has been updated by the National Cancer Control Programme. For the updated diagnosis and staging section, please visit: https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/					
Hohwu et al., 2011	Comparing robot-assisted laparoscopic and open retropubic radical prostatectomy.	**Country:** Denmark **Discount rate:** None **Perspective:** Societal **Time Horizon:** 1 year **Model Type:** One-way sensitivity analysis.	The difference in effectiveness between RALP and RRP procedures was 7% in favour of RALP. In the present study no QALY was gained 1 year after RALP, however this result is uncertain due to a high degree of missing data.	The ICER per extra successful treatment was €64,343 using RALP. For indirect costs, the ICER per extra successful treatment was €13,514 using RALP.	RALP was more effective and more costly. A way to improve the cost effectiveness may be to perform RALP at fewer high volume urology centres and utilise the full potential of each robot.
Ramsay et al., 2012	Laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer	**Country:** United Kingdom **Discount rate: 3.5%** **Perspective:** N/A **Time Horizon:** 10 Years **Model Type:** D**iscrete-event simulation model**	The results of this study demonstrated that the outcomes were generally better for robotic than for laparoscopic surgery for major adverse events such as blood transfusion and organ injury rates and for rate of failure to remove the cancer	When the difference in positive margins is equivalent to the estimates in the meta-analysis of all included studies, robotic radical prostatectomy was on average associated with an incremental cost per QALY that is less than threshold values typically adopted by the NHS and becomes further reduced when the surgical capacity is high.	This study demonstrated that robotic prostatectomy had lower perioperative morbidity and a reduced risk of a positive surgical margin compared with laparoscopic prostatectomy although there was considerable uncertainty. Robotic prostatectomy will always be more costly to the NHS because of the fixed capital and maintenance charges for the robotic system. There is a need for further research to establish how positive margin rates impact on long-term outcomes.

Study	Intervention	Analysis details	Clinical and QALY outcomes	Costs	Results
Ito, 2010	No BMD test or alendronate therapy, a BMD test followed by selective alendronate therapy for patients with osteoporosis, or universal alendronate therapy without a BMD test.	**Country:** USA **Discount rate: N/A** **Perspective:** Societal **Time Horizon:** Lifetime **Model Type:** Markov state-transition model	**RESULTS OF BASE-CASE ANALYSIS:** The ICERs were $66,800 per QALY gained and $178,700 per QALY gained, respectively. **RESULTS OF SENSITIVITY ANALYSES:** The ICER decreased to $100,000 per QALY gained, assuming older age, a history of fractures, lower mean BMD before ADT, or a lower cost of alendronate.	–	In patients starting adjuvant ADT for locally advanced or high-risk localized prostate cancer, a BMD test followed by selective alendronate for those with osteoporosis is a cost-effective use of resources. Routine use of alendronate without a BMD test is justifiable in patients at higher risk for hip fractures.
Lord et al., 2013	This project aimed to test the feasibility of building full guideline models for NICE guidelines and to assess if, and how, such models can be used as a basis for cost-effectiveness analysis.	Not a cost effectiveness study, results used in conjunction with Sathya et al. (2005) and Hoskin et al. (2012) for cost utility analysis	–	–	Discrete event simulation can be used to model full guideline pathways for CEA, although this requires a substantial investment of clinical and analytic time and expertise. Further work is needed to extend the analysis of the case study models to estimate population-level budget and health impacts.
Sathya et al., 2005	Iridium implant plus external-beam radiation therapy compared with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate	Not a cost effectiveness study, results used in conjunction with Lord et al. (2013) for cost utility analysis	In the IM plus EBRT arm, 17 patients (29%) experienced BCF compared with 33 patients (61%) in the EBRT arm. Eighty-seven patients (84%) had a post-radiation biopsy; 10 (24%) of 42 in the IM plus EBRT arm had biopsy positivity compared with 23 (51%) of 45 in the EBRT arm. Overall survival was 94% in the IM plus EBRT arm versus 92% in the EBRT arm.	–	The combination of IM plus EBRT was superior to EBRT alone for BCF and post-radiation biopsy. This trial provides evidence that higher doses of radiation delivered in a shorter duration result in better local as well as biochemical control in locally advanced prostate cancer.
Hoskin et al., 2012	External beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer.	Not a cost effectiveness study, results used in conjunction with Lord et al. (2013) for cost utility analysis	EBRT+HDR-BTb resulted in a significant improvement in RFS compared to EBRT alone with a 31% reduction in the risk of recurrence (p=0.01) and similar incidence of severe late urinary and rectal morbidity.	–	RFS was significantly higher in patients treated with EBRT+HDR-BTb (log rank p=0.04). In multivariate analysis treatment arm, risk category and ADT were significant covariates for risk of relapse. Differences in OS were not significant. Incidence of severe late urinary and bowel morbidity was similar.

Section II Budget impact of the guidelines for the staging, diagnosis and treatment of prostate cancer

Scope of the budget-impact analysis

Since 1994, a significant upward trend in the number of patients diagnosed with prostate cancer has been observed. Information on the expected future trends in prostate cancer can be found in the epidemiology section of the guideline (appendix 1).

It is estimated that there is a 50:50 split between patients with prostate cancer being treated in the public and private setting. Costings have been calculated on the assumption that all patents diagnosed annually with prostate cancer will attend publicly. This budget impact assessment focused on those recommendations considered to affect resource requirements, as determined by the guideline development group at the recommendation meetings held for each clinical question.

Please note all costs provided are average and are calculated on one year's activity. Capital costs have been included in figures provided by St. James's Hospital (SJH), Finance Department.

Radiology and diagnosis

Clinical questions	Recommendation	Additional resources required	Budget impact
The section has been updated by the National Cancer Control Programme. For the updated diagnosis and staging section, please visit: https://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/			

Pathology

Clinical questions	Recommendation	Additional resources required	Budget impact
Q.2.4.1 What is the optimum handling, processing, and reporting of prostate core biopsies?	A report should be generated for each designated site of biopsy. A maximum of three cores should be submitted per cassette. To optimise the detection of small lesions, blocks should be cut and examined at three levels.	Transperineal biopsies due to increase in core numbers.	Cost of Transperineal Prostate biopsies. €236.06 (Ref. St. James's Finance Team) Transperineal Prostate Biopsies are a new and emerging procedure. Based on current activity of 10 cases per month on one NCCP prostate cancer surgery centre, we have estimated 120 cases per year X €236.06 = €28,327.20. If this was rolled out across all six surgical prostate cancer centres this would be a total of €88,327.20, including half hour theatre time per biopsy at a cost of €500. The total annual cost is estimated to be €529,963.20.

Active surveillance

Clinical questions	Recommendation	Additional resources required	Budget impact
Q.2.5.1 For men with a histological diagnosis of prostate cancer, what are the inclusion criteria for being offered active surveillance?	Active surveillance is an option for men with the lowest risk of prostate cancer progression for whom radical treatment is suitable.	The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. It was the opinion of the GDG that an increasing number of men would have active surveillance as a result of these	Costs of MRI: €274.35 (Ref SJH Finance Dept). Cost of PSA Test: €7.20 (Ref. NCRI) Cost of OPD Appointment: €130 (Ref. HIPE). We are assuming that the DRE will be performed as part of the OPD visit. PSA blood test:€7.20 (Ref NCRI) Cost savings in reduced active treatments of surgery and radiotherapy According to NCRI 24% of men with prostate cancer receive no treatment, and we have made the assumption that they are placed on active surveillance. Please see figure 2 for active surveillance protocol.
Q.2.5.2 What should active surveillance entail?	The guideline development group recommends the protocol in figure 3 for men who have chosen active surveillance.		The following figures represent the five year costs for a cohort of men in receipt of active surveillance. It should be noted that some may discontinue active surveillance for a variety of reasons (e.g., death, progression to treatment). In any given year, the group of patients in active surveillance will comprise a mix of those in years 1 to 5. The full budget impact is unlikely to be realised as some portion on active surveillance at present are receiving care in line with this recommendation. **Prior to enrolment and Year 1** Please note MRI is not included as a cost as the initial diagnosing/ staging MRI is used for this purpose in year 1. Biopsy(€236.06)X1=€236.06 PSA(€7.20) X 4=€28.80 Cost of OPD Appointment: €130 (Ref. HIPE) **Total Year 1 Costs=€394.86** **Year 2** Biopsy(€236.06)X1=€236.06 PSA(€7.20) X 2=€14.40 Cost of OPD Appointment: €130 (Ref. HIPE) **Total Year 2 Costs=€380.46** **Year 3** PSA(€7.20) X 2=€14.40 Cost of OPD Appointment: €130 (Ref. HIPE) **Total Year 3 Costs=€144.40**

Clinical questions	Recommendation	Additional resources required	Budget impact
			Year 4 PSA(€7.20) X 1=€7.20 Cost of OPD Appointment: €130 (Ref. HIPE) **Total Year 4 Costs=€137.20** **Year 5** Biopsy(€236.06)X1=€236.06 PSA(€7.20) X 1=€7.20 Cost of OPD Appointment: €130 (Ref. HIPE) **Total Year 5 Costs=€373.2**6 Total Five Year Cost: €1430.18 x 812 prostate cancers diagnosed annually =€1,161,306.10
Q.2.5.3 For men being considered for active surveillance does having an MRI influence the decision to proceed with active surveillance?	Prior to enrolment to an active surveillance programme, a multiparametric MRI scan should be performed.	Additional access to MRI will be required X 812	Please note all men with prostate cancer have a MRI for diagnosis. This MRI will be used for enrolment on active surveillance and will therefore not have a budget impact as it is current practice.

Medical oncology

The current guideline does not contain economic information on the drugs proposed under the guideline as the funding of these drugs is already the subject of a robust HSE procedure which involves the National Centre for Pharmacoeconomics (NCPE) and in the case of medicines used in the treatment of cancer, input from NCCP. The HSE decision considers the budget impacts as outlines in the NCPE information in light of the health service demands and authorises the drugs for reimbursement or not. The NCPE data on populations and expected budget impact is not available in the public domain.

Some background on the process:

The HSE has a robust assessment process in place for new medicines, including those used in the treatment of cancer. The intention of this process is to ensure that the HSE can provide access to as many new and existing medicines as possible, at sustainable prices and from within the resources which government and taxpayers have provided. This process includes a requirement for pharmaceutical companies to justify the pricing which they propose for new medicines, as well as the production of high quality technical assessments, by the National Centre for Pharmacoeconomics (NCPE), in relation to each new medicine with significant budget impact potential. These technical assessments are used by the HSE and the National Cancer Control Programme to assist in decision making around new cancer medicines and during formal price negotiations with pharmaceutical companies. The National Cancer Control Programme has also put a multidisciplinary Therapeutic Review Committee in place, specifically for the assessment of new, and on occasion existing, cancer medicines with regard to their benefits, costs and budget impact implications. This Committee makes recommendations directly to the Director of the NCCP.

The Department of Health agreed a pricing and reimbursement framework agreement with the Pharmaceutical industry, the 2012 IPHA agreement. That has been further enhanced by the enactment and commencement of the Health and the HSE (Pricing and Supply of Medical Goods) Act 2013. In the 2012 agreement, the Department of Health and the HSE agreed processes with the pharmaceutical industry with clearly documented procedures and timelines for the assessment of new medicines in as timely a fashion as possible. The Health Act places statutory responsibilities on the HSE in relation to pricing and reimbursement of medicines.

The HSE, in any considerations around pricing and reimbursement is required to follow the procedures outlined in the agreement and the Act. The HSE considers information from the National Centre for Pharmacoeconomic Evaluation, the priorities of the NCCP and the company submissions prior to making a decision on funding.

Appendix 12: Glossary of terms and abbreviations

Definitions within the context of this document

Case Control Study	The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and non-diseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (Oxford CEBM)
Case Series	A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (NCI Dictionary)
Clinician	A healthcare professional such as a doctor involved in clinical practice.
Cohort study	A research study that compares a particular outcome (such as lung cancer) in groups of individuals who are alike in many ways but differ by a certain characteristic (for example, female nurses who smoke compared with those who do not smoke). (NCI dictionary)
External validity	The extent to which we can generalise the results of a study to the population of interest.
Internal validity	The extent to which a study properly measures what it is meant to measure.
Isotope Bone Scan	Bone scans use radionuclides to detect areas of the bone which are growing or being repaired. An isotope is a chemical which emits a type of radioactivity called gamma rays. A tiny amount of radionuclide is put into the body, usually by an injection into a vein. Cells which are most 'active' in the target tissue or organ will take up more of the isotope. So, active parts of the tissue will emit more gamma rays than less active or inactive parts.
Meta-analysis	A process that analyses data from different studies done about the same subject. The results of a meta-analysis are usually stronger than the results of any study by itself. (NCI dictionary)
Radical Retropubic Prostatectomy	Surgery to remove all of the prostate and nearby lymph nodes through an incision in the wall of the abdomen. (NCI dictionary)
Radical Transperineal Prostatectomy	Surgery to remove all of the prostate through an incision between the scrotum and the anus. Nearby lymph nodes are sometimes removed through a separate incision in the wall of the abdomen. (NCI dictionary)

Randomised trial	An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, manoeuvre, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (Oxford CEBM)
Systematic review	The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardized methods for selecting and assessing articles. A systematic review differs from a meta-analysis in not including a quantitative summary of the results. (Oxford CEBM)

Abbreviations

^{18}F-FCH	^{18}F-Fluorocholine
^{99m}Tc-HDP	^{99m}Tc-oxidronate
ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
AGREE II	Appraisal of Guidelines for Research and Evaluation II
ART	Adjuvant Radiotherapy
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
BCCA	British Columbia Cancer Agency
BH	Beaumont Hospital
CAP	College of American Pathologists
CAPRA	Cancer of the Prostate Risk Assessment
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CINAHL	Cumulative Index to Nursing and Allied Health Literature database
COM-B	Capability, Opportunity and Motivation Behaviour Model
CRPC	Castration Resistant Prostate cancer
CSO	Central Statistics Office
CT	Computed Tomography
CUH	Cork University Hospital
DES	Diethylstilbestrol
DOH	Department of Health
DOHC	Department of Health and Children (now DOH)
DRE	Digital Rectal Examination
DW-MRI	Diffusion Weighted Magnetic Resonance Imaging
EAU	European Association of Urology
EBP	Evidence-Based Practice
EBRT	External Beam Radiotherapy
EED	Economic Evaluations Database
eLND	Extended Lymph Node Dissection
EORTC	European Organisation for Research and Treatment of Cancer
EPE	Extra Prostatic Extension
ESUR	European Society of Urogenital Radiology
EU	European Union
FOV	Field of View
GA	General Anaesthetic
GDG	Guideline Development Group
GETUG	Groupe d'Etude des Tumeurs Uro-Génitales
GG	Gleason Grade
GP	General Practitioner
GS	Gleason Score
GUH	Galway University Hospital
Gy	Gray (unit of radiation)
HDR	High-Dose Rate
HEED	Health Economic Evaluations Database
HIFU	High-Intensity Focused Ultrasound
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	Health Technology Assessment
IANO	Irish Association for Nurses in Oncology
IAUN	Irish Association of Urology Nurses
ICER	Incremental Cost-Effectiveness Ratio
ICGP	Irish College of General Practitioners

IPHA	Irish Pharmaceutical Healthcare Association
ISMO	Irish Society for Medical Oncologists
ISUP	International Society of Urological Pathology
KPI	Key Performance Indicator
LDR	Low-Dose Rate
LHRH	Luteinising Hormone Releasing Hormone
LND	Limited Lymph Node Dissection
LSHTM	London School of Hygiene and Tropical Medicine
LYG	Life Years Gained
mCRPC	Metastatic Castration Resistant Prostate Cancer
MDT	Multi Disciplinary Team
MH	Mercy Hospital
mm	Millimetre
MMUH	Mater Misericordiae University Hospital
MPH	Mater Private Hospital
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Screening
Multi-FOV	Multi Field of View
NALA	National Adult Literacy Agency
NB	Needle Biopsy
NICE	National Institute for Health and Care Excellence
NCPE	National Centre for Pharmacoeconomics
NCCP	National Cancer Control Programme
NCCN®	National Comprehensive Cancer Network®
NCRI	National Cancer Registry Ireland
NHS	National Health Service
NIHR	National Institute for Health Research
NNT	Number Needed to Treat
OLH	Our Lady's Hospice
PCRMP	Prostate Cancer Risk Management Programme
PET	Positron Emission Tomography
PET–CT	Positron Emission Tomography–Computed Tomography
PFS	Progression Free Survival
PICO(T)	Population; Intervention; Comparison/Control; Outcome;(Time)
PPP	Purchasing Power Parity
PPV	Positive Predictive Value
iPSA	Initial (pretreatment) Prostate Specific Antigen
PSA	Prostate Specific Antigen
PSADT	Prostate Specific Antigen Doubling Time
PSMA	Prostate-Specific Membrane Antigen
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
QUB	Queen's University Belfast
RADICALS	Radiotherapy and Androgen Deprivation In Combination After Local Surgery
RALP	Robotic-Assisted Laparoscopic Prostatectomy
RAVES	Radiotherapy Adjuvant Versus Early Salvage
RCPath	Royal College of Pathologists
RCSI	Royal College of Surgeons in Ireland
RCT	Randomised Controlled Trial
ROI	Republic of Ireland
RRP	Radical Retropubic Prostatectomy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SFH	St. Francis Hospice

SIGN	Scottish Intercollegiate Guidelines Network
SLH	St. Luke's Hospital
SJH	St. James's Hospital
SLRON	St. Luke's Radiation Oncology Network
SPECT	Single Photon Emission Computed Tomography
SPECT – CT	Single Photon Emission Computed Tomography- Computed Tomography
SRT	Salvage Radiotherapy
SVUH	St. Vincent's University Hospital
SWOG	Southwest Oncology Group
TH	Tallaght Hospital
TROG	Trans-Tasman Oncology Group
TRUS	Transrectal Ultrasound
TTMB	Transperineal Template-Guided Mapping Biopsy
UK	United Kingdom
WBS	Whole Bone Scintigraphy
WRH	Waterford Regional Hospital
WTP	Willingness to Pay
µg/L	Micrograms per litre

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(Background section)

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(Recommendations section)

Radiology and diagnosis

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