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Disclaimer

Section 2 is based on the best available evidence at the time of development of this publication. Examining the comparative effectiveness of diagnostic or treatment options for prostate cancer was beyond the scope of this project. Section 3, on the benefits and harms of PSA testing, was based on a non-systematic review of the published literature (i.e. did not use systematic and explicit methods to identify and include studies). Therefore, Section 3 should not be used as the basis for formulating Clinical Practice Guideline recommendations.

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List of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AIHW	Australian Institute of Health and Welfare
AUC	Area under curve
BPH	Benign prostatic hyperplasia
CAP	Comparison Arm for ProtecT
CI	Confidence interval
DRE	Digital rectal examination
EAG	Expert Advisory Group
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer
EPIC	Expanded Prostate Cancer Index Composite Short Form
EQ-5D	EuroQol 5-dimension
ERSPC	European Randomised Study of Screening for Prostate Cancer
GnRH	Gonadotrophin-releasing hormone
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
IES	Impact of Events Scale
IIEF	International Index of Erectile Function
LHRH	Luteinising hormone-releasing hormone
LUTS	Lower urinary tract symptoms
MHI-5	5-item Mental Health Inventory
MISCAN	Microsimulation Screening Analysis
MRI	Magnetic resonance imaging
NHMRC	National Health and Medical Research Council
NZGG	New Zealand Guidelines Group
PCPT	Prostate Cancer Prevention Trial
phi	Prostate Health Index
PIVOT	Prostate Cancer Intervention versus Observation Trial
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer screening trial
PROBE	Prostate Biopsy Effects study
ProtecT	Prostate Testing for Cancer and Treatment trial
PSA	Prostate-specific antigen
QALY	Quality-adjusted life year

RCPA	Royal College of Pathologists of Australasia
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SEER	Surveillance, Epidemiology and End Results
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SPCG-4	Scandinavian Prostate Cancer Group Study Number 4
STAI	State-Trait Anxiety Inventory
TNM	Tumour, Nodes, Metastasis staging system
TRUS	Transrectal ultrasound
UCLA-PCI	University of California, Los Angeles Prostate Cancer Index
UK	United Kingdom
USA	United States of America

Executive summary

Prostate cancer is the fifth leading cause of death in Australian men (AIHW, 2012). The cause of prostate cancer is unknown and there is currently no clear prevention strategy to reduce the risk of developing prostate cancer, nor a single, simple test to detect it. The prostate specific antigen (PSA) test is a commonly used blood test to detect possible signs of prostate cancer, but elevated PSA levels do not necessarily mean cancer is present.

Australia does not have an organised PSA screening program for prostate cancer. Instead, PSA testing of asymptomatic men is incorporated opportunistically as part of a medical consultation, often in conjunction with a digital rectal examination (DRE). The decision of whether or not to undertake a PSA test should weigh up the potential benefits of detecting prostate cancer early, against the uncertainties of PSA testing and the risk that detection and treatment may be unnecessary and may adversely affect quality of life.

Given the ongoing debate in Australia about the role of PSA testing and the recent media interest, an objective and unbiased evaluation of the scientific evidence was undertaken, with guidance and oversight from the National Health and Medical Research Council (NHMRC) PSA Testing Expert Advisory Group (EAG). It was agreed that the evaluation would comprise:

- A systematic review of systematic reviews that investigated the effectiveness of using the PSA test in asymptomatic men to reduce mortality and morbidity due to prostate cancer.
- A supplementary non-systematic literature review of additional evidence describing other potential benefits and harms associated with use of the PSA test in asymptomatic men.

The evaluation was restricted to PSA testing in *asymptomatic* men. It was beyond the scope of the evaluation to assess the impact of PSA testing in symptomatic men, the suitability of PSA testing as a population-based screening tool, alternative tests for detecting prostate cancer, comparative effectiveness of treatment options for prostate cancer, or evidence related to the cost effectiveness and resource implications for practice.

Summary of findings

Evidence Statements (based on the systematic review):

In asymptomatic men:

1. The present evidence is inconsistent as to whether there is an effect of PSA testing, with or without DRE, on the risk of ***prostate cancer-specific mortality*** compared with no PSA testing, although the possibilities of no effect or a small protective effect cannot be excluded;

2. PSA testing with or without DRE has no discernible effect on ***all-cause mortality*** compared with no PSA testing;

3. PSA testing with or without DRE reduces the risk of *prostate cancer metastases at diagnosis* compared with no PSA testing; and

4. It is unknown if PSA testing, with or without DRE affects ***quality of life*** due to advanced prostate cancer, compared with no PSA testing.

Other key findings (based on the non-systematic review):

Evidence statements could not be developed for this part of the evaluation, as systematic and explicit methods were not used to identify and select the evidence. The non-systematic review was designed to identify issues but should not be used as the basis for formulating recommendations.

Potential harms of PSA testing

1. **Risk of overdiagnosis**: Patients whose PSA test is positive may be unnecessarily exposed to follow up diagnostic investigations and treatment, as well as suffering potential psychological harm from anxiety. Overdiagnosis is of particular concern because most men with test-detected prostate cancer will have early stage disease and may be offered aggressive treatment with associated harms. Given limitations in the design and reporting of the randomised controlled trials (RCTs) of PSA testing that could affect any conclusions on this issue, there remain important concerns about whether the benefits of testing outweigh the potential harms to quality of life, including the substantial risks for overdiagnosis and treatment complications.

2. **Physical harms associated with the PSA test**: These are generally mild and infrequent.

3. **Effect on quality of life**: The immediate impact of PSA testing is on the psychological domain of quality of life.
    - For men with a false-positive test result, this involves distress up to the point of biopsy, when a negative diagnosis may alleviate their anxiety. However, for some men, particularly those with a family history of prostate cancer, rising PSA may provoke anxiety despite a negative biopsy.
    - Although the psychological impact of a false-positive test result may not be long-lasting, the high rate of false-positive test results makes it an important consideration when deciding whether or not to undertake PSA testing.
    - For men with a true-positive test result, distress increases after the diagnosis is made and may be exacerbated as they face difficult decisions about disease management.
    - The psychological impact of a true-positive test must also be considered in the light of overdiagnosis.

Benefits and harms associated with biopsy

Minor complications of biopsy are frequent and include haematospermia, haematuria, rectal bleeding and voiding problems. Major complications causing significant discomfort, disability, or requiring additional treatment or hospitalisation are less frequent but include pain and infection. Pain is considered a core dimension of quality of life and can be relieved, to some extent, by the use of local anaesthesia or sedoanalgesia. Although some studies have shown high rates of biopsy-related infection, antibiotic prophylaxis was not always administered, and in those studies where it was used, antimicrobial resistance was a growing concern.

Benefits and harms associated with treatment

There are a number of treatment options available to asymptomatic men who have been diagnosed with prostate cancer. This section is based on a non-systematic literature review and does not provide an in depth analysis or compare the effectiveness of treatment options for prostate cancer.

1. **Radical prostatectomy** in men with prostate cancer may decrease the risk of prostate cancer-specific mortality and all-cause mortality compared with watchful waiting. However, this treatment may result in long-term urinary incontinence, erectile dysfunction and peri-operative complications which impact on quality of life.

2. **Radiation therapy** in men with prostate cancer may decrease the risk of prostate cancer-specific mortality and all-cause mortality compared with watchful waiting. However, this treatment may result in urinary incontinence, erectile dysfunction and bowel dysfunction which impacts on quality of life, with adverse effects of androgen deprivation therapy, when given, being additive.

3. **Androgen deprivation therapy** is primarily used for the treatment of patients with advanced prostate cancer. It is associated with an increased risk of erectile dysfunction, impotence and fatigue. The side-effects of androgen deprivation therapy are wide-ranging and include hot flushes, weight gain, emotional and adverse cognitive changes, loss of muscle mass and osteoporosis.

4. **Cryotherapy and high-intensity focused ultrasound** are therapies for localised prostate cancer but few studies have investigated the benefits and harms of these treatments. There are currently no known impacts of cryotherapy and high-intensity focused ultrasound on quality of life.

The negative impact of these treatments on quality of life is widely acknowledged and must be taken into consideration when deciding on the most appropriate management strategy. Treatment related harms should also factor into the decision of whether or not to undergo PSA testing, considering that some early prostate cancers that are detected through PSA testing will not result in future health problems even if left untreated (overdiagnosis). If such cancers are treated (over treatment), any decrement to quality of life caused by treatment (such as urinary incontinence, sexual dysfunction or bowel dysfunction, and any subsequent impacts on role, social and emotional function and global quality of life) may be considered an unnecessary harm (because there may have been no clinical benefit).

1. Introduction

Prostate cancer is the most prevalent cancer affecting men in Australia, with more than 19,000 Australian men newly diagnosed each year (AIHW 2010). Although the five-year survival rate associated with the disease is relatively high (92%; AIHW 2010), prostate cancer remains the second most common cause of cancer-related death in males (after lung cancer), and the fifth leading cause of death in Australian men (AIHW 2012).

Prostate cancers can range from small, slow-growing lesions to very aggressive tumours. They are generally described as being either localised (confined within the prostate), locally advanced (affecting nearby tissues, such as the bladder or rectum) or metastatic (affecting other areas in the body, usually the lymph nodes or bone). Localised prostate cancers are usually asymptomatic but some men may experience changes in urinary or sexual function. Locally advanced and metastatic cancers can have a significant effect on morbidity, mortality and quality of life (Chou et al. 2011).

The PSA test is a common blood test used in the detection and monitoring of prostate diseases. It measures blood levels of PSA, a serine protease produced by epithelial cells in the prostate gland. Elevated PSA levels indicate the likely presence of prostate cancer but can also be caused by conditions such as benign prostatic hyperplasia (BPH) and prostatitis. Although there is some variation in clinical practice, it is commonly recommended that patients consider a prostate biopsy if their blood PSA concentration is greater than 4.0 ng/mL. A prostate biopsy is the only method by which prostate cancer can be definitively diagnosed.

The use of PSA testing as a tool for the early detection of prostate cancer in asymptomatic men is a controversial subject that has been the focus of much debate and media interest. On one hand, more cancers may be detected at a stage where they can be effectively treated. On the other hand, there is a risk that PSA testing in asymptomatic men may lead to overdiagnosis, overtreatment and potential harms.

This Evidence Evaluation Report is intended to provide an objective and unbiased review of the scientific evidence relating to PSA testing in asymptomatic men. It has been prepared by Optum (the evidence reviewer, formerly Health Technology Analysts Pty Ltd), in conjunction with the NHMRC PSA Testing EAG.

The scope, clinical questions, and methodology of the evidence review were discussed by the EAG at a meeting held on 24 August 2012. For pragmatic reasons, it was agreed that the evaluation would comprise:

- A systematic review of systematic reviews that investigated the effectiveness of using the PSA test in asymptomatic men to reduce mortality and morbidity due to prostate cancer.
- A supplementary non-systematic literature review of additional evidence describing other potential benefits and harms associated with use of the PSA test in asymptomatic men.

The Evidence Evaluation Report provides a summary of the findings of the systematic and non-systematic components of the evidence evaluation, evidence statements prepared in conjunction with the EAG, and areas for future research. Full details of the methodology that was used for the assessment and consolidation of the evidence is provided in the Technical Report that accompanies this Evidence Evaluation Report.

1.1 Definitions used within this evidence evaluation

The following definitions were agreed with the EAG and have been used for the purposes of the evidence evaluation:

- *PSA testing* is a tool that can be used for the early detection of prostate cancer. The aim is to reduce disease-specific mortality and morbidity by identifying prostate cancer earlier, thus providing the opportunity for treatment regimens that may be more effective when applied to cancer confined to the prostate gland. The term screening encompasses three methods: mass (i.e. large scale screening of an entire population); selective (i.e. screening high-risk populations); and opportunistic (e.g. incorporated as part of a medical consultation). In Australia, PSA testing is suspected to be largely opportunistic and is often used in conjunction with a DRE.
- *Asymptomatic* is defined as the absence of symptoms suggestive of prostate cancer. For practical purposes, men with stable lower urinary tract symptoms (LUTS), which are very common in ageing men and are not clearly associated with an increased risk for prostate cancer, will be considered to be asymptomatic.
- *Advanced prostate cancer* is defined as prostate cancer that has spread beyond the possibility of local control by surgery or radiation therapy.
- *Quality of life* is a multi-dimensional phenomenon that typically includes symptoms, aspects of functioning, and global assessment of quality of life. Anxiety, depression and other types of psychological distress are considered aspects of emotional functioning, which in turn is considered a key domain of quality of life. PSA testing in asymptomatic men largely impacts on the psychological aspects of quality of life, including anxiety, but it also affects global aspects. Treatment of early prostate cancer can cause urinary incontinence, erectile dysfunction and bowel dysfunction; these are therefore considered key domains of quality of life in the treatment setting. Fatigue and pain are other common symptoms and these can in turn, affect physical, role and social functioning. There are many different quality of life instruments, each covering one or more domains, and some providing direct assessment of global quality of life. Instruments relevant to this review are outlined in Appendix I.
- *Systematic review* is defined as a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies (http://www.cochrane.org/glossary/5). Systematic reviews should aim to identify all studies addressing the question, regardless as to whether or not it has been published. As a minimum, unpublished literature should include trials registered on clinical trial databases.
- *Non-systematic literature review* is defined as a review of the published literature that does not use systematic and explicit methods to identify and include studies. They may be used to 'get a flavour' for an issue but they are vulnerable to bias and should not be used as the basis for formulating recommendations. This part of the review should still include a critical appraisal and evaluation of the methodological rigour of the evidence starting with high level evidence and appraising lower levels of evidence if necessary.

2. Systematic review of Level I evidence

2.1 Overview of the Level I evidence

The systematic review process identified 18 Level I studies that assessed the effect of PSA testing, with or without DRE, on prostate cancer-specific mortality, all-cause mortality and/or morbidity due to advanced prostate cancer in asymptomatic men. Of the 18 Level I studies identified, 11 studies were excluded after full text review and are documented, with their reasons for exclusion, in Appendix A of the Technical Report. Consequently, a total of seven systematic reviews were appraised in this Evidence Evaluation Report with full citation details available in Appendix B of the Technical Report. Sources of funding and declared interests of the authors in each included Level I study are summarised in Appendix C of the Technical Report.

One of the seven eligible Level I studies was a 2010 Cochrane review of PSA screening for prostate cancer (Ilic et al. 2010). As explained in the accompanying Technical Report, this Cochrane review was known by the EAG and NHMRC to be in the process of being updated, with the updated version due for release in late September 2012. At a meeting held on 24 August 2012, the EAG and NHMRC agreed that the update of the Cochrane review was critical to the evidence review of PSA testing in asymptomatic men. Accordingly, a decision was made to incorporate the updated Cochrane review in the systematic review of Level I evidence, considering that the Cochrane literature search was conducted prior to the literature search for the current evidence review. The updated Cochrane review (Ilic et al. 2013) became available to the NHMRC in draft form on 22 November 2012 and was published on 31 January 2013. It supersedes the 2010 version initially identified in the Cochrane Library database.

All of the seven eligible systematic reviews compared PSA testing with no PSA testing in asymptomatic men. A summary of the key features of these reviews is provided in **Table 1**. Studies have been arranged in order of literature search date to demonstrate which of the systematic reviews provided the most up-to-date data.

The quality of each of the included systematic reviews was assessed using NHMRC criteria and is also presented in **Table 1**. The evidence reviewer notes that the systematic review by Lumen et al. (2012) included (and meta-analysed) the Rotterdam-Ireland study which is not a RCT. Therefore, the evidence reviewer notes that Lumen et al. (2012) cannot be considered to be strictly Level I evidence, based on NHMRC's levels of evidence hierarchy (refer to Table 2 of the Technical Report).

Table 1 Characteristics and quality assessment of Level I evidence comparing PSA testing with no PSA testing

Author (year) ***Study quality***	**Date of literature search**	**Population**	**Definition of asymptomatic**	**Intervention**	**Relevant outcomes**	**No. included RCTs/ SRs per outcome**	**Meta-analysis?**
Ilic (2013) [Cochrane review] *Good*	June 2012	All men enrolled in studies of prostate cancer screening	Not specifically defined	PSA (all modalities) and/or DRE and/or TRUS	Prostate cancer-specific mortality All-cause mortality Prostate cancer-specific metastatic disease Quality of life	5 5 3 0	Yes
Basch (2012) *Poor*	March 2012	Asymptomatic men	Not specifically defined	PSA	Prostate cancer-specific mortality All-cause mortality	2 2	No
Lin (2011) [AHRQ] *Good*	July 2011	Asymptomatic men	Without symptoms that are highly suspicious for prostate cancer. Many older men have chronic, stable LUTS (e.g. due to BPH) that are not generally associated with an increased risk for prostate cancer.	PSA (all modalities) with or without DRE and TRUS	Prostate cancer-specific mortality All-cause mortality	5/2 5/2	No
Lumen (2012)[a] *Good*	April 2011	Asymptomatic men	Not specifically defined	PSA with or without DRE	Prostate cancer-specific mortality All-cause mortality	7[a] 4[a]	Yes
Djulbegovic (2010) *Good*	July 2010	Asymptomatic men	Not specifically defined	PSA with or without DRE	Prostate cancer-specific mortality All-cause mortality	5 4	Yes
NZGG (2009) *Good*	April 2009	Asymptomatic men over the age of 45 years	People who have no symptoms of prostate cancer	PSA (all modalities)	Prostate cancer-specific mortality Prostate cancer-specific metastatic disease	6 12[b]	No
Hamashima (2009) *Poor*	September 2006	Asymptomatic men	Not specifically defined	PSA and DRE	Prostate cancer-specific mortality	3	Yes

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; LUTS, lower urinary tract symptoms; NZGG, New Zealand Guidelines Group; PSA, prostate-specific antigen; RCT, randomised controlled trial; TRUS, transrectal ultrasound.

Note: The systematic review shaded in blue is considered the pivotal review.

[a] The authors included the Rotterdam-Ireland trial which it notes was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland). Consequently, the evidence reviewer acknowledged that Lumen (2012) does not fit precisely into NHMRC's classification of a Level I study.

[b] The authors included three RCTs (PLCO, ERSPC and Quebec). The remaining nine studies that were classified as an RCT by the authors were reports of the results from individual centres within the countries that comprised the overall ERSPC trial. These included Belgium, Finland, Rotterdam (two publications), Spain and Sweden (four publications).

There is substantial overlap between many of the systematic reviews. As such, a decision was made to exclude the systematic reviews that were rated as poor quality by the evidence reviewer. Consequently, the findings of Basch et al. (2012) and Hamashima et al. (2009) will not be discussed further in this report. The quality assessment forms for these two systematic reviews, as well as the other five reviews, are provided in Section 1.7.1 of the Technical Report.

A decision was also made to limit the evaluation of the evidence to the most comprehensive and highest quality Level I evidence available. This pivotal review was determined to be Ilic et al. (2013) (hereafter known as the Cochrane review) and is shown in blue shading in **Table 1**. The Cochrane review considered both published and unpublished sources and did not place any language restrictions on studies considered for inclusion. The literature search in the Cochrane review was conducted in June 2012; therefore, an updated literature search of Level II (RCT) evidence was completed by the evidence reviewer to identify any additional studies that were published until September 2012. The results of this search are reported in Section 1.3 of the Technical Report. There were no additional RCTs that were identified in the literature search for recent Level II evidence. However, recent follow-up publications were identified for the RCTs already identified in the systematic reviews.

It is noted by both the Cochrane review and the evidence reviewer, that there are two ongoing RCTs that would be relevant for future consideration; the Prostate Testing for Cancer and Treatment (ProtecT) trial in the United Kingdom (UK) and its extension, the Comparison Arm for ProtecT (CAP) trial. This cluster randomised trial has allocated practices of approximately 460,000 men aged 50–69 years, to either usual care or population-based prostate cancer screening with the PSA test. Participants that were diagnosed with prostate cancer were then randomised to receive radical surgery or conformal radiotherapy or active surveillance. The results of the ProtecT and CAP trials, including prostate cancer-specific mortality, are expected to be published in 2016.

No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature search for the two primary clinical research questions.

2.2 RCTs included in the systematic reviews

Featured across the seven systematic reviews were six RCTs that compared PSA testing with no PSA testing in mass prostate cancer screening trials of men. The RCTs are:

- The Prostate, Lung, Colorectal and Ovarian cancer screening trial (PLCO)
- The European Randomised Study of Screening for Prostate Cancer (ERSPC)
- The Goteborg trial (referred to herein as Goteborg)
- The Norrkoping trial (referred to herein as Norrkoping)
- The Stockholm trial (referred to herein as Stockholm)
- The Quebec trial (referred to herein as Quebec)

The Norrkoping trial was pseudo-randomised in design and is thus classed as Level III–1 evidence (not Level II). Nevertheless, it has been included in this Evidence Evaluation Report for completeness as it is featured in all of the included systematic reviews.

Despite the identification of six RCTs that compared PSA testing with no PSA testing in mass prostate cancer screening trials of asymptomatic men, not all of the RCTs were featured in all of the systematic reviews (**Table 2**). Importantly, there have been variations in the inclusion and reporting of data from the Goteborg and Stockholm trials.

Table 2 Matrix indicating the RCTs that were included in the systematic reviews

		Study ID					
		PLCO [Level II]	**ERSPC** [Level II]	**Goteborg** [a] [Level II]	**Norrkoping** [Level III–1]	**Stockholm** [Level II]	**Quebec** [Level II]
Systematic review	Ilic (2013) [Cochrane review]	✓	✓	✓	✓	✓	✓
	Lumen (2012)	✓	✓[b]	✓	✓	✓	✓
	Djulbegovic (2010)	✓	✓	✓	✓		✓
	Lin (2011) [AHRQ]	✓	✓	✓	✓	✓	✓
	NZGG (2009)	✓	✓[c]		✓		✓
	Basch (2012)	✓	✓	✓	✓	✓	✓
	Hamashima (2009)					✓	✓

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ERSPC, European Randomised Study of Screening for Prostate Cancer; NZGG, New Zealand Guidelines Group; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; RCT, randomised control trial.

Note: The ticked and shaded boxes indicate the studies that were included in a particular systematic review. The unticked boxes indicate the studies that were not included in a particular systematic review.

[a] The Goteborg trial was included in the Cochrane review, but was not reported as a separate RCT because an analysis of all the participants (including those in the Swedish centre) was included in the 2012 ERSPC trial report (Schroder et al. 2012a; Supplementary Appendix Table 7A2); the results for all participants of all ages at recruitment are included in the Supplementary Appendix. In the preceding 2009 ERSPC publication, however, only two of the three cohorts of men within the Goteborg trial were included in the results of the Swedish centre (Schroder et al. 2009). Consequently, Lumen (2012), Djulbegovic (2010), Lin (2011) and Basch (2012) included and reported on the Goteborg trial as a separate RCT.

[b] The authors also included the Rotterdam-Ireland trial which it notes was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland).

[c] The authors also included (and classified as RCTs) publications of results from individual centres within the countries that comprised the overall ERSPC trial. These included Belgium, Finland, Rotterdam (two publications), Spain and Sweden (four publications).

The Goteborg trial was absent from NZGG (2009) as the mortality outcomes were published after the time of the systematic review. The Goteborg trial was included in the Cochrane review but was not reported as a separate RCT because an analysis of all participants (including all those in the Swedish centre) was included in the 2012 ERSPC trial report (Schroder et al. 2012a; Supplementary Appendix Table 7A2). In the preceding 2009 ERSPC publication, however, only two of the three cohorts of men within the Goteborg trial (men born between 1930–1934 and 1935–1939) were included in the results of the Swedish centre (Schroder et al. 2009). Results of the remaining 8057 men in the 1940-1944 cohort were published separately in the Goteborg trial report. Consequently, Lumen et al. (2012), Djulbegovic et al. (2010) and the AHRQ review included the Goteborg trial as a separate RCT. It is noted, though, that Lumen et al. (2012) and the AHRQ review did not exclude the 11,847 men that were reported in both the Goteborg and ERSPC trials. The meta-analysis by Lumen et al. (2012) thus involves double counting of these men. Importantly, the systematic review by Djulbegovic et al. (2010) did account for this discrepancy and excluded the overlapping men from the ERSPC data.

The Stockholm trial was not included in Djulbegovic et al. (2010) for unknown reasons. The trial was not classified as an RCT by NZGG (2009), who instead referred to it as a cohort (cross-sectional) study due to the use of a one-time screen for prostate cancer despite the use of a randomisation method.

Longer follow-up data for the PLCO and ERSPC trials were recently published in January and March 2012, respectively. As a result, of the five included systematic reviews, only the Cochrane review reported on the latest follow-up data that is available for all of the RCTs to September 2012 (**Table 3**). It is noted though, that the 13-year follow-up data for the PLCO trial is only complete for 57% of participants, compared with 92% of participants at 10 years of follow-up. Consequently, the Cochrane review used the 10-year follow-up data for all of their analyses of the PLCO trial, with the exception of the analysis regarding tumour stage, which incorporated the 13-year follow-up data.

Table 3 Publications with the longest follow-up for each RCT in the systematic reviews

		Study ID					
		PLCO	**ERSPC**	**Goteborg**	**Norrkoping**	**Stockholm**	**Quebec**
Systematic review	**Ilic (2013)** [Cochrane review]	**Andriole (2012)** ***13 years***	**Schroder (2012a)** ***11 years***	**Included as the Swedish centre in the results of Schroder (2012a)** ***14 years***	**Sandblom (2011)** ***20 years***	**Kjellman (2009)** ***15 years***	**Labrie (2004)** ***11 years***
	Lumen (2012)	Andriole (2009) *7–10 years*	Schroder (2009) *8–9 years*	**Hugosson (2010)** *14 years*	**Sandblom (2011)** ***20 years***	**Kjellman (2009)** ***15 years***	**Labrie (2004)** ***11 years***
	Djulbegovic (2010)	Andriole (2009) *7–10 years*	Schroder (2009) *8–9 years*	**Hugosson (2010)** ***14 years***	Sandblom (2004) *15 years*	Not included	**Labrie (2004)** ***11 years***
	Lin (2011) [AHRQ]	Andriole (2009) *7–10 years*	Schroder (2009) *8–9 years*	**Hugosson (2010)** ***14 years***	**Sandblom (2011)** ***20 years***	**Kjellman (2009)** ***15 years***	**Labrie (2004)** ***11 years***
	NZGG (2009)	Andriole (2009) *7–10 years*	Schroder (2009) *8–9 years*	Not included	Sandblom (2004) *15 years*	Not included	**Labrie (2004)** ***11 years***
Latest data available to September, 2012		**Andriole (2012)** ***13 years***	**Schroder (2012a)** ***11 years***	**Hugosson (2010)** ***14 years***	**Sandblom (2011)** ***20 years***	**Kjellman (2009)** ***15 years***	**Labrie (2004)** ***11 years***

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ERSPC, European Randomised Study of Screening for Prostate Cancer; NZGG, New Zealand Guidelines Group; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial.

Note: The latest follow-up data that is available for all of the RCTs to September 2012 is noted in **bold**.

Quality assessment of the six RCTs as reported within the systematic reviews, and as independently assessed by the evidence reviewer, is summarised in **Table 4**. The Norrkoping, Stockholm and Quebec trials are considered to be poor quality (i.e. high risk of bias). The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

Table 4 Quality assessment of the RCTs that were included in the systematic reviews[a]

Source of quality assessment	PLCO	ERSPC	Goteborg	Norrkoping	Stockholm	Quebec
Evidence reviewer[b]	Good	Fair	Fair	Poor	Poor	Poor
Ilic (2013)[c] [Cochrane review]	Low risk of bias	Low risk of bias	Included as the Swedish centre in the 2012 ERSPC results publication (Schroder et al. 2012a)	High risk of bias	High risk of bias	High risk of bias
Basch (2012)[b]	Fair	Fair	Not considered a separate RCT. Reported to be included in the ERSPC analysis	Poor	Poor	Poor
Lin (2011)[b] [AHRQ]	Fair	Fair	Fair	Poor	Poor	NR
Lumen (2012)[d]	NR	NR	NR	NR	NR	NR
Djulbegovic (2010)[e]	NR	NR	NR	NR	Not included	NR
NZGG (2009)[f]	Good	Poor	Not included	Mixed	Not included: classified as a cohort study and not an RCT	Poor
Hamashima (2009)	NR	NR	Not included	NR	NR	NR

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ERSPC, European Randomised Study of Screening for Prostate Cancer; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NR, not reported; NZGG, New Zealand Guidelines Group; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; RCT, randomised controlled trial.

Note: The systematic review shaded in blue is considered the pivotal review.

[a] The Norrkoping trial was a pseudo-RCT (Level III–1 evidence). All of the other studies represent Level II evidence.

[b] Quality ratings applied to the systematic review are good, fair or poor. See Section 1.7 of the accompanying Technical Report for the quality assessment forms conducted by the evidence reviewer for the purposes of this Evidence Evaluation Report. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3 of the Evidence Evaluation Report.

[c] Quality ratings applied to the systematic review are low, unclear or high risk of bias.

[d] Whilst the quality of the individual studies was not reported, the authors reference the extensive quality assessment of the individual studies with evaluation of the potential sources of bias that were identified by Djulbegovic et al. (2010) and Ilic et al. (2010). Consequently, the authors did not conduct a separate quality assessment.

[e] An overall quality rating for the individual RCTs was not reported. However, the quality rating of the individual components of the GRADE criteria for each RCT was presented. The overall quality of evidence/GRADE result for each outcome that was meta-analysed was also shown.

[f] Quality ratings applied to the systematic review are good, mixed or poor quality.

Each of the six RCTs is described below. **Table 5** summarises the key characteristics of each study. None of the RCT publications provided a formal definition of 'asymptomatic'.

PLCO

The PLCO trial is an RCT that was conducted at 10 study sites across the United States of America (USA) from 1993–2001 to evaluate screening programs for prostate cancer, lung cancer, colorectal cancer and ovarian cancer. Each study site used its own recruitment sources and strategies appropriate to the local situation. The trial consisted of 76,685 men aged 55–74 years who were randomised 1:1 to either the screening or control group. Men with a previous history of prostate, lung or colorectal cancer were excluded from participation, along with those who were currently receiving cancer treatment. In 1995, men who had undertaken more than one PSA test in the previous 3 years were also excluded from participation.

The screening intervention involved an annual PSA test for 6 years, of which four of the years also included an annual DRE. The control group received usual care that could potentially have included opportunistic screening. A PSA value greater than 4.0 ng/mL was considered to be a positive screening result. The overall compliance rate for screening was 85% for PSA testing (i.e. 15% of men randomised to receive PSA testing did not undergo testing) and 86% for DRE. In the control arm, the contamination rate for PSA testing (i.e. men who proceeded with informal self-screening arrangements) increased from 40% at baseline to 52% by the sixth year of the trial. The vital status of 92% of trial participants was known at 10 years of follow-up and of 57% of trial participants at 13 years of follow-up. At the time of the literature search, results of the PLCO trial were reported to 13 years of follow-up.

ERSPC

The ERSPC trial is an ongoing multinational RCT with sites in eight European countries. The trial began in 1991 and originally included nine European countries, however Portugal dropped out of the study in 2000 without contributing data. Of note, data from France has not been included in analyses thus far, as its participation in the trial began in 2001 and thus its length of follow-up is limited. Consequently, current results of the ERSPC are from seven countries (Belgium, Finland, Italy, Netherlands, Spain, Sweden and Switzerland) with a range of reported incidence and mortality rates (Center et al. 2012).

Overall, the ERSPC trial consisted of 182,160 men aged 50-74 years who were randomised 1:1 to either the screening or control group, with the exception of Finland which undertook a 2:3 randomisation process. Men with a previous diagnosis of prostate cancer were excluded. Each country used different recruitment procedures, resulting in variations in the selection of participants with respect to age and length of follow-up. However, all study sites included a predefined core age group of men aged 55–69 years (162,388 men, equating to 89% of the total number of participants in the ERSPC trial). Differences also existed in the screening intervention, PSA cut-off values and screening interval; countries differed in their use of the PSA test, DRE and transrectal ultrasound (TRUS) either as standalone tests or in combination. In general though, most countries conducted screening every 4 years with PSA testing alone, and considered a PSA value greater than 3.0 ng/mL to be a positive screening result. The control group was not offered screening. Compliance rates varied across countries, but overall, 82.2% of men in the screening group received at least one test. Contamination in the control group was reported to be 30.7% (Roobol et al. 2009). At the time of the literature search, results of the ERSPC trial were available to 11 years of follow-up.

Goteborg

The Goteborg trial is an ongoing RCT in Goteborg, Sweden that commenced in 1995. The national population register was used to identify all men aged 50–64 years who resided in Goteborg, of which 20,000 men were randomly sampled and allocated 1:1 to either the screening or control group. Men with a previous diagnosis of prostate cancer were excluded from the trial, as well as those who had emigrated but had not been removed from the population register.

The screening intervention involved an annual PSA test every 2 years until the men had reached the upper age limit (mean age at last invitation to screening was 69 years). The PSA cut-off value which indicated a positive screening result varied over time; 3.4 ng/mL from 1995–1998, 2.9 ng/mL from 1999–2004 and 2.5 ng/mL from 2005 onwards. The overall compliance rate for screening was 76%. The contamination rate in the control group has not been specified and has only been reported as 'low'. At the time of the literature search, results of the Goteborg trial have been reported to 14 years of follow-up.

It should be noted that the men in the Goteborg trial comprise the Swedish arm of the ERSPC trial. The Goteborg trial consisted of three cohorts of men; those that were born 1930–1934 (aged 60–64 years), 1935–1939 (aged 55–59 years), and 1940–1944 (aged 50–54 years). The results of two of the cohorts (1930–1934 and 1935–1939) have been reported in the results of the overall ERSPC trial to 2009, with the results of the remaining 8057 men in the 1940–1944 birth cohort published separately in the Goteborg trial report. However, the 2012 ERSPC trial report (Schroder et al. 2012a; Supplementary Appendix Table 7A2) included results based on all of the men in the Goteborg trial.

Norrkoping

The Norrkoping trial is a pseudo-RCT that took place in Norrkoping, Sweden from 1987. The trial consisted of 9026 men aged 50–69 years who resided in Norrkoping and were identified from the national population register. Men with a previous diagnosis of prostate cancer were excluded from the trial. The trial is classified as a pseudo-RCT because investigators used a list of date of births that was obtained from the national population register, to allocate every sixth eligible man to the screening group (1494 men). The remaining 7532 men served as the control group and were not invited for screening.

The screening intervention utilised a combination of DRE and PSA every 3 years. Importantly, the first and second rounds of screening were by DRE only. The third and fourth rounds of screening included DRE and a PSA test. A PSA value greater than 4.0 ng/mL was considered to be a positive screening result. The overall compliance rate for screening was 70–78% depending on the year of follow-up. The contamination rate in the control arm has not been reported. Results of the Norrkoping trial have been reported up to 20 years of follow-up.

Stockholm

The Stockholm trial is an RCT based in Stockholm, Sweden that commenced in 1988. The Swedish census records were used to identify all men aged 55–70 years with a current address in the catchment area of Stockholm South Hospital. Men with a previous diagnosis of prostate cancer were excluded. The trial thus consisted of 27,204 men, of which 2400 were randomly selected and invited for prostate cancer screening. The remaining 24,804 men served as the control group and received usual care. It should be noted that there is a discrepancy between population sizes because the file that contained the registration numbers of the original cohort could not be retrieved. When the cohort was reconstructed, an additional 602 registration numbers were found compared to the original source population.

The screening intervention involved a one-time screen using a combination of PSA, DRE and TRUS. For this reason, the systematic review by NZGG (2009) classified the Stockholm trial as a cohort (cross-sectional) study and not an RCT. A positive DRE or TRUS was considered a positive screening result. A PSA value greater than 7.0 ng/mL resulted in a repeated TRUS, which, if positive, was considered a positive screening result. Any PSA value greater than 10.0 ng/mL was considered to be a positive screening result. The compliance rate for screening was 74% and the contamination rate in the control group has not been reported. At the time of the literature search, results of the Stockholm trial have been reported to 15 years of follow-up.

Quebec

The Quebec trial is an RCT that took place in Quebec, Canada from 1988. The investigators used the electoral roll to identify all men aged 45–80 years who were registered in the Quebec City metropolitan area. Men with a previous diagnosis of prostate cancer were excluded from the trial. In addition, men who had previously received screening and were referred to the study clinic for consultation were also excluded. This resulted in a total of 46,486 participants in the study who were randomly allocated 2:1 in favour of screening.

Screening was performed annually, with the first round of screening performed with both PSA and DRE. Subsequent rounds of screening involved a PSA test only. A PSA value greater than 3.0 ng/mL was considered to be a positive screening result. Of significance, the overall compliance rate for the Quebec study was low at 23.6% (i.e. 76.4% of men who were randomised to receive PSA testing did not undergo testing). The authors of the study therefore decided to analyse the data according to whether participants actually received screening or not. This deviated from the standard 'as-randomised' intention to screen analysis, however the data to perform an intention to screen analysis was provided. The contamination rate in the control group was reported to be 7.3%. At the time of the literature search, results of the Quebec trial have been published to 11 years of follow-up.

Table 5 Characteristics of the RCTs included in the systematic reviews[a]

Study ID [Level of evidence] *Quality*[b]	**Study population**	**Exclusion criteria**	**Intervention**	**PSA test cut-off**	**Length of follow-up (years)**
PLCO [Level II, RCT] *Good*	• Men aged 55–74 years across 10 study sites in the USA from 1993–2001 • 38,340 men allocated to the screening group – Compliance rate: 85% for PSA and 86% for DRE • 38,345 men allocated to the control group (usual care, which could potentially include screening) – Contamination rate: 40% in the first year to 52% in the sixth year of PSA testing	• History of prostate, lung or colorectal cancer • Previous surgical removal of the entire prostate • Previously participation in another cancer screening or primary prevention study • Use of finasteride in the previous 6 months • From April 1995: more than one PSA blood test in the previous 3 years • From April 1995: any lower gastrointestinal diagnostic procedure in the previous 3 years	• Annual PSA (6 years) and DRE (4 of the 6 years)	• 4.0 ng/mL at all study sites	• Median (range): 11.5 (7.2–14.8)
ERSPC [Level II, RCT] *Fair*	• Men aged 50–74 years across multiple study sites in 7 European countries (Belgium, Finland, Italy, Netherlands, Spain, Sweden and Switzerland) that commenced in 1991[c]. All sites included men in the predefined core age group of 55–69 years • 82,816 men allocated to the screening group, of which 72,891 men were in the core age group (88%) – Compliance rate for the total number of men in the screening group: 82.2% • 99,184 men allocated to the control group (not invited for screening), of which 89,352 men were in the core age group (90%) – Contamination rate for the total number of men in the control group was estimated to be 30.7%[d]	• Earlier diagnosis of prostate cancer	• Variable by centre – Finland, Italy, Spain, Sweden and Switzerland: PSA only – Belgium and Netherlands: PSA + DRE + TRUS (1991–1997); PSA only (1997 onwards) • Most centres performed PSA alone every 4 years except for Sweden (every 2 years)	• Belgium: 10 ng/mL (1991–1994); 4.0 ng/mL (1995–1997) • Finland: 4.0 ng/mL • Italy: 4.0 ng/mL • Netherlands: 4.0 ng/mL (1993–1997); 3.0 ng/mL (1997 onwards) • Spain: 3.0 ng/mL • Sweden: 3.0 ng/mL (1995–1998); 2.5 ng/mL (1999 onwards) • Switzerland: 3.0 ng/mL • Some ancillary testing with lower PSA values	• Overall across 8 countries (includes France) – Median: 9.8 – Mean: 8.6 • Core age group – Median: 11.0 – Mean: 10.5

Table 5 (cont.)

Study ID [Level of evidence] *Quality*[b]	Study population	Exclusion criteria	Intervention	PSA test cut-off	Length of follow-up (years)
Goteborg[e] [Level II, RCT] *Fair*	• Men aged 50–64 years living in Goteborg, Sweden in 1995 • 9952 men invited for screening – Compliance rate: 76% • 9952 allocated to the control group (not invited for screening) – Contamination rate: not reported	• Prior diagnosis of prostate cancer • Men who had died • Men who had emigrated but had not been removed from the population register at the time of randomisation	• PSA test only every 2 years until the participants reached the upper age limit – Mean age at last invitation to screening (range): 69 (67–71)	• 1995–1998: 3.4 ng/mL (WHO corrected value; the nominal value was 3.0 ng/mL) • 1999–2004: 2.9 ng/mL (WHO corrected value; the nominal value was 2.5 ng/mL) • 2005 onwards: 2.5 ng/mL	• Results reported to 14 years of follow-up • Median: not reported
Norrkoping [Level III–1, pseudo-RCT] *Poor*	• Men aged 50–69 years living in Norrkoping, Sweden in 1987 • 1494 men invited for screening – Compliance rate: 70–78% depending on year of follow-up • 7532 men served as controls from the source population (not invited for screening) – Contamination rate: not reported	• Earlier diagnosis of prostate cancer	• 1st and 2nd rounds of screening were performed by DRE only • 3rd and 4th rounds of screening included DRE and PSA • Screening performed every 3 years	• 4.0 ng/mL	• Median: 6.3 • Maximum: 20
Stockholm [Level II, RCT] *Poor*	• Men aged 55–70 years living in the catchment area of Stockholm South Hospital in Sweden in 1988 • 2374 men invited for screening – Compliance rate: 74% • 24,772 men served as controls from the source population (not invited for screening)[f] – Contamination rate: not reported	• Earlier diagnosis of prostate cancer	• Single screening with PSA, DRE and TRUS	• PSA > 7.0 ng/mL led to repeat TRUS • PSA > 10.0 ng/mL led to biopsy	• Mean (range) for screened group: 12.9 (0.2–15.7) • Mean (range) for control group: 13.0 (0.7–15.7)

Table 5 (cont.)

Study ID [Level of evidence] *Quality*[b]	**Study population**	**Exclusion criteria**	**Intervention**	**PSA test cut-off**	**Length of follow-up (years)**
Quebec [Level II, RCT] *Poor*	• Men aged 45–80 years registered in the electoral roll of the Quebec City area, Canada in 1988 • 31,133 men invited for screening – Compliance rate: 23.6% • 15,353 men served as controls from the source population (not invited for screening) – Contamination rate: 7.3%	• Diagnosis of prostate cancer before 15 November 1988 • Previous screening and were referred to the study clinic for consultation	• 1st round of screening was by PSA and DRE • Follow-up screenings were by PSA only • Screening performed annually	• 3.0 ng/mL	• Median: 7.93 • Maximum: 11

Abbreviations: DRE, digital rectal examination; ERSPC, European Randomised Study of Screening for Prostate Cancer; PLCO, Prostate, Lung and Colorectal and Ovarian cancer screening trial; PSA, prostate-specific antigen; RCT, randomised controlled trial; TRUS, transrectal ultrasound.

[a] The Norrkoping trial was a pseudo-RCT (Level III–1). All of the other studies represent Level II evidence.

[b] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[c] The ERSPC trial originally comprised 9 countries. However, Portugal discontinued in 2000 as they were unable to provide the necessary data. France was excluded as they commenced participation in 2001 and thus their duration of follow-up is currently too short (median 4.6 years).

[d] Source of contamination rate in the control group: Roobol et al. (2009).

[e] A proportion of men in the Goteborg trial comprise the Swedish arm of the ERSPC trial. The Goteborg trial consisted of three cohorts of men; those that were born between 1930–1934 (aged 60–64 years), 1935–1939 (aged 55–59 years), and 1940–1944 (aged 50–54 years). The results of two of the cohorts (1930–1934 and 1935–1939) are included in the results of the ERSPC to 2009. The results of the remaining 8057 men in the 1940–1944 cohort were published separately in the Goteborg trial report. However, in the 2012 ERSPC trial report (Schroder et al. 2012a), some results include all of the men in the Goteborg trial.

[f] There was a discrepancy between population sizes because the file containing the registration numbers of the original cohort could not be retrieved. When the cohort was reconstructed, an additional 602 (2%) registration numbers were found compared to the original source population.

2.3 Limitations of the RCTs included in the Level I evidence

All of the six RCTs contained limitations that should be considered in the evaluation of the evidence. Notably, all of the RCTs used fixed PSA test cut offs rather than age-related reference limits which are more consistent with the current standard of practice.

PLCO

The PLCO trial did not exclusively evaluate a screening program for prostate cancer. In the screening arm, men were screened with chest x-ray, flexible sigmoidoscopy, PSA test and DRE, and the screening interval varied for the different screening tests. Men with a history of any of the three cancer types under investigation (lung, colon, or prostate) were excluded from participation. Of concern in the PLCO trial is the high rate of contamination in the control group which was reported to be 40% at baseline, increasing to 52% by the sixth year of the trial (Andriole et al. 2009). The definition of contamination was repeated screenings, at least twice in 7 or 10 years of follow-up. This high contamination rate may potentially introduce a bias towards not finding a benefit of screening. Similarly, in the overall study population, an estimated 45% of men had at least one PSA test and 55% had at least one DRE within the 3 years prior to entering the study (Andriole et al. 2009). Thus, the population in the PLCO trial had already been heavily exposed to screening tests for prostate cancer on an *ad hoc* basis. This is likely to have reduced the number of prevalent tumours (particularly advanced cancers) remaining to be detected, which lowers the power of the trial to detect a mortality difference. Furthermore, the rate of compliance for prostate biopsy following a positive screening result was low at an estimated 30–40% (Andriole et al. 2005).

ERSPC

Ad hoc screening for prostate cancer was not as commonplace in Europe at the commencement of the ERSPC trial as it was in the USA when the PLCO trial commenced. However, the contamination rate in the ERSPC trial was still considerable (estimated to be 30.7% by Roobol et al. 2009), which may introduce a bias towards not finding a benefit of screening. Because there were study centres in different countries, it is possible that the control groups underwent different levels of screening or none at all. It is therefore difficult to assess the level of homogeneity in screening within the control group. The ERSPC trial is further limited by the adoption of different recruitment procedures, screening interventions, PSA cut-off values and screening intervals between each country that comprised the study. The prostate cancer-specific mortality outcome of the ERSPC trial was affected more by Sweden than any other country (Schroder et al. 2012a). There are notable differences between the Swedish arm of the trial and the other study sites which may have affected the outcome (i.e. the inclusion of younger participants, a lower PSA threshold, shorter screening intervals, and a longer follow-up).

Goteborg

Several characteristics of the Goteborg trial may have made it more likely to find a favourable effect of screening on mortality. Importantly, the shorter and more frequent screening interval (every 2 years) and a low PSA cut-off which was reduced over the course of the trial. This would have resulted in more positive screening results and the potential to identify more low-grade prostate cancers.

Norrkoping

The Norrkoping trial was originally designed to assess the feasibility, cost-effectiveness and side-effects of screening. As such, the study was a relatively small pseudo-RCT that was not powered to detect a statistically significant difference in mortality. However, it has since been

argued that the long follow-up of 20 years has rendered the Norrkoping trial a statistical power of the same magnitude as that presented in the first report from the PLCO trial (Andriole et al. 2009; Sandblom et al. 2011). It is also noted that the first and second rounds of screening were by DRE only, and the PSA test was only incorporated in the third and fourth rounds of screening. This may limit the applicability of the Norrkoping trial in assessing the effects of PSA testing on mortality and morbidity in asymptomatic men. Whilst the contamination rate for the trial was not reported, there was a potential for contamination and self-selection bias because trial details were distributed through newspaper, radio and television advertisements.

Stockholm

There are several important limitations that were evident in the Stockholm trial. The randomisation process was unclear and there was not adequate concealment of randomisation so that the study could potentially be classed as quasi-randomised in design. The study also includes the use of a one-time screen for prostate cancer, involving the use of PSA, DRE and TRUS with a high PSA threshold for biopsy at greater than 10 ng/mL. Together, this limits applicability to current practice. The authors also noted that the treatments employed in the trial (radical prostatectomy, external beam radiation with 66 Gy or experimental treatment with extensive transurethral prostate resection followed by Nd-YAG laser therapy) are not likely to be representative of the current standard of practice. In addition, screening subjects had a significantly lower risk for death from causes other than prostate cancer. This suggests imbalances between the screening and control arms of the study and raises the possibility of comorbidity amongst men who did not accept the screening intervention. Furthermore, there was discrepancy between population sizes as the key publication stated that the file that contained the registration numbers of the original cohort could not be retrieved (Kjellman et al. 2009).

Quebec

The Quebec trial is limited by the high cross-over rate between the screening and control groups, whereby 76.4% of men who were randomised to receive PSA testing did not undergo testing. In addition, the results of the study were reported according to whether the participant actually received screening and not by an intention to screen analysis. This breaks randomisation and essentially makes the trial an observational study. The authors did not adjust for potential confounders in their analysis; there is potentially high comorbidity associated with non-participation in screening.

2.4 Effects of PSA testing on mortality

2.4.1 Prostate cancer-specific mortality

The effect of PSA testing on prostate cancer-specific mortality was assessed by meta-analysis in three systematic reviews as summarised in **Table 6**. This outcome was also descriptively discussed in a further two systematic reviews. All six RCTs reported prostate cancer-specific mortality (**Table 7**).

The results of the Quebec study were re-analysed according to an intention to screen analysis by the Cochrane review and Lumen et al. (2012) but not by the other systematic reviews. It should also be noted that in the Goteborg trial, prostate cancer-specific deaths included deaths caused by the disease itself as well as deaths resulting from any diagnostic or treatment-related intervention specific to the disease.

Level I evidence

The Cochrane review meta-analysed the data from the PLCO, ERSPC, Norrkoping, Stockholm, and Quebec trials. As mentioned in Section 2.2, the Cochrane review used 10-year follow-up data from PLCO because the 13-year data was considered less robust (follow-up was available for 57% of participants at 13 years compared with 92% at 10 years). Moderate heterogeneity was evident in the meta-analysis (I^2=46%; P=0.12) and the review concluded that prostate cancer screening did not result in a statistically significant reduction in prostate cancer-specific mortality when all populations in the studies were analysed (RR 1.00; 95% CI 0.86–1.17) (**Figure 1**). This result did not differ when data from the core age group of the ERSPC study were used (RR 1.00; 95% CI 0.83–1.19) except that heterogeneity was greater (I^2=58%; P=0.05). The quality of the evidence was rated as moderate for this outcome, with the ERSPC and PLCO studies assessed as low risk of bias, and the Norrkoping, Stockholm and Quebec trials assessed as high risk of bias. However, sensitivity analysis of the studies according to the risk of bias did not change the overall conclusion; meta-analysis of the two low risk of bias studies produced a risk ratio of 0.96 (95% CI 0.70–1.30). When data from the core age group of the ERSPC study were used, the risk ratio for the two low risk studies was 0.94 (95% CI 0.65–1.35).

Lumen et al. (2012) incorporated data from seven trials in their meta-analysis (PLCO, ERSPC, Goteborg, Norrkoping, Stockholm, Quebec and Rotterdam-Ireland). The evidence reviewer notes that the analysis did not exclude the proportion of men in the Goteborg trial who were also included in the reporting of the ERSPC trial. Thus, 11,847 men were double counted in the meta-analysis. In addition, the Rotterdam-Ireland trial was not a prospective RCT. Nevertheless, the overall results showed that there was not a significant effect of prostate cancer screening on prostate cancer-specific mortality (RR 0.88; 95% CI 0.72–1.06) but heterogeneity was substantial (I^2=65%; P=0.009). However, when the meta-analysis was adjusted to exclude the trials with a short follow-up, high PSA-contamination rate in the non-screened group, and/or those with a low participation rate in the screening group, a significant reduction in prostate cancer-specific mortality of 24% was observed (RR 0.76; 95% CI 0.58–0.98; P=0.04; I^2=66%; P=0.03). This adjusted analysis excluded the PLCO, Stockholm and Quebec trials and only included the results from the ERSPC, Goteborg, Norrkoping and Rotterdam-Ireland studies.

The meta-analysis by Djulbegovic et al. (2010) included the PLCO, ERSPC, Goteborg, Norrkoping and Quebec trials. To prevent double counting, the authors excluded from the ERSPC data, the proportion of men in the Goteborg trial who were also included in the reporting of the ERSPC trial. As event rates were not available in all of the studies, the inverse variance method was used to pool data from individual trials. The authors considered the evidence to be of moderate quality in accordance with the GRADE approach. The results revealed that there was substantial heterogeneity between the RCTs (I^2=55%; P=0.06) and there was no significant effect of screening on prostate cancer-specific mortality (RR 0.88; 95% CI 0.71–1.09) (**Table 6**).

Both the AHRQ and NZGG (2009) descriptively discussed the results of RCTs that reported prostate cancer-specific mortality. Based on a review of the PLCO, ERSPC, Goteborg, Norrkoping and Stockholm trials, as well as consideration of meta-analyses by the Cochrane review and Djulbegovic et al. (2010), the AHRQ concluded that most RCTs have not reported an effect of PSA-based screening on prostate cancer-specific mortality. It found that 'after about 10 years, PSA-based screening results in the detection of more cases of prostate cancer, but small to no reduction in prostate cancer-specific mortality'. The NZGG (2009) examined the data that was available at the time from the PLCO, ERSPC, Norrkoping and Quebec trials, in addition to the results of the Spain and Antwerp centres of the ERSPC. The authors found that the 'evidence from RCTs on prostate cancer-specific mortality is inconsistent and conflicting'. As a result, there is 'currently no evidence to support or refute a decrease in mortality due to PSA screening. The best scenario is that there may be a small benefit in survival to men who have been screened'.

Level II evidence

Prostate cancer-specific mortality was a primary outcome in all six RCTs (**Table 7**). No significant effect of screening on prostate cancer-specific mortality was reported in the PLCO (RR 1.09; 95% CI 0.87–1.36), Norrkoping (RR 1.16; 95% CI 0.78–1.73), Stockholm (RR 1.10; 95% CI 0.83–1.46) and Quebec (RR 1.01; 95% CI 0.82–1.40) trials. On the other hand, the Goteborg trial found that prostate cancer-specific mortality was reduced by almost half over 14 years (RR 0.56; 95% CI 0.39–0.82; P=0.002). The ERSPC trial (which included the Goteborg trial) also reported a statistically significant reduction in prostate cancer-specific mortality as a result of screening in all enrolled men (RR 0.83; 0.72–0.94; P=0.005) as well as the core age group of men (RR 0.79; 95% CI 0.68–0.91; P=0.001). It is worth noting that the Swedish arm of the ERSPC (the Goteborg study) screened men more frequently (every two years) and had a lower PSA threshold (reduced to 2.5 ng/ mL) than other sites.

Subgroup analysis

Age

The evidence reviewer notes that none of the RCTs was sufficiently powered for subgroup analysis by age. Nevertheless, the Cochrane review explored prostate cancer-specific mortality according to the age of participants at the time of the first screening test in the RCTs. It identified no significant difference in prostate cancer-specific mortality regardless of whether the men were screened from age 45 years (RR 1.01; 95% CI 0.76–1.33), 50 years (RR 0.93; 95% CI 0.69–1.27) or 55 years (RR 1.12; 95% CI 0.92–1.37) (**Figure 1**). A second meta-analysis was performed with the difference being that the data from the ERSPC study was represented by the core age group (i.e. men aged 55–69 years) to investigate the impact of screening in men aged above 55 years. Conducting a meta-analysis using this approach also demonstrated no significant difference in prostate cancer-specific mortality in men aged above 55 years (RR 0.98; 95% CI 0.75–1.27) (**Table 6**).

Subgroup analysis of prostate cancer-specific mortality according to age at randomisation was also examined within the PLCO, ERSPC and Goteborg trials. The PLCO trial found that there was no difference in prostate cancer-specific mortality in men who were screened from ages 55–64 years (RR 1.19; 95% CI 0.83–1.72) or 65–74 years (RR 1.02; 95% CI 0.77–1.37). The ERSPC trial also determined there to be no difference in prostate cancer-specific mortality in men who were screened from ages ≤54 years (RR 0.65; 95% CI 0.23–1.83), 55–59 years (RR 0.81; 95% CI 0.62–1.05); 60–64 years (RR 0.92; 95% CI 0.71–1.18) or ≥70 years (RR 1.18; 95% CI 0.81–1.72). However, there was a statistically significant effect of screening on prostate cancer-specific mortality in men aged 65–69 years (RR 0.67; 95% CI 0.53–0.86; P-value not reported). The Goteborg trial reported the number of prostate cancer-specific deaths stratified by age; however, statistical analysis of the data was not performed. The evidence reviewer calculated the relative risk (RR) and determined there to be no statistically significant difference in prostate cancer-specific mortality between the screening and control group in men aged 50–54 years (RR 0.62; 95% CI 0.20–1.88) or 60–64 years (RR 0.78; 95% CI 0.47–1.28). There was, however, a significant effect in favour of screening in men aged 55–59 years in this trial (RR 0.35; 95% CI 0.18–0.67; P-value not reported) (**Table 7**).

Risk factors

None of the Level I or II evidence stratified the population by risk factors in their analysis of prostate cancer-specific mortality.

Comorbidities

Only the PLCO trial reported a subgroup analysis of prostate cancer-specific mortality stratified by comorbidities at baseline. A modified Charlson comorbidity score (0 = no comorbidity, ≥1 = one or more comorbid conditions) was calculated for trial participants based on their baseline questionnaire responses. Because of the scope of the medical history section of the baseline questionnaire, a complete Charlson score could not be determined. Consequently, the modified Charlson score contained the following conditions found in the Charlson score: myocardial infarction, stroke, diabetes, cancer, pulmonary disease (bronchitis and/or emphysema) and liver disease (cirrhosis and/or hepatitis). Not included in the modified score were congestive heart failure, peripheral vascular disease, connective tissue disease, hemiplegia, HIV, renal disease, ulcer disease, and dementia. The subgroup analysis showed that there was no significant difference in prostate cancer-specific mortality between screened and control men with no comorbidities (RR 1.00; 95% CI 0.76–1.31) or with comorbidities (RR 1.11; 95% CI 0.72–1.71) (**Table 7**).

Table 6 Effect of PSA testing on prostate cancer-specific mortality: Summary of Level I evidence

Study ID [Level of evidence] ***Quality***[a]	**No. RCTs (no. patients)**	**Included RCTs**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**	**Heterogeneity**[b]
Ilic (2013) [Cochrane review] [Level I] *Good*	5 (341,342)	• PLCO[c] • ERSPC: **all enrolled men** • Norrkoping • Stockholm • Quebec	698/156,157 (0.45)	1318/185,185 (0.71)	1.00 (0.86–1.17)	• No difference • P=0.99	• Moderate heterogeneity • P=0.12 (I^2=46%)
	5 (321,586)	• PLCO[c] • ERSPC: **core age group of men (55–69 years)** • Norrkoping • Stockholm • Quebec	633/146,232 (0.43)	1258/175,354 (0.72)	1.00 (0.83–1.19)	• No difference • P=0.98	• Substantial heterogeneity • P=0.05 (I^2=58%)
Lumen (2012) [Level I][d] *Good*	7 (486,813)	• PLCO • ERSPC • Goteborg • Norrkoping • Stockholm • Quebec • Rotterdam-Ireland[d]	579/168,182 (0.34)	1786/318,631 (0.56)	0.88 (0.72–1.06)	• No difference • P=0.18	• Substantial heterogeneity • P=0.009 (I^2=65%)
Djulbegovic (2010) [Level I] *Good*	5 (302,500)	• PLCO • ERSPC • Goteborg • Norrkoping • Quebec	Event rate per 1000 with screening (95% CI): 7 (6–9)	Event rate per 1000 with control (95% CI): 8 (NR)	0.88 (0.71–1.09)	• No difference • P=0.25	• Substantial heterogeneity • P=0.06 (I^2=55%)

Table 6 (cont.)

Study ID [Level of evidence] *Quality*[a]	No. RCTs (no. patients)	Included RCTs	Screening n/N (%)	Control n/N (%)	Relative risk estimate (95% CI)	Statistical significance	Heterogeneity[b]
Subgroup analysis: age at randomisation							
Ilic et al. (2013) [Cochrane review]							
Men aged ≥45 years	1 (46,476)	• Quebec	153/31,133 (0.49)	75/15,343 (0.49)	1.01 (0.76–1.33)	• No difference • P=0.97	• Not applicable
Men aged ≥50 years	2 (191,025)	• ERSPC • Norrkoping	394/84,310 (0.47)	652/106,715 (0.61)	0.93 (0.69–1.27)	• No difference • P=0.66	• Substantial heterogeneity • P=0.12 (I^2=59%)
Men aged ≥55 years	2 (103,831)	• PLCO[c] • Stockholm	151/40,714 (0.37)	591/63,117 (0.94)	1.12 (0.92–1.37)	• No difference • P=0.26	• No significant heterogeneity • P=0.79 (I^2=0%)
Subgroup analysis: age at randomisation, analysed using the core group of men aged between 55–69 years from ERSPC							
Ilic et al. (2013) [Cochrane review]							
Men aged ≥45 years	1 (46,476)	• Quebec	153/31,133 (0.49)	75/15,343 (0.49)	1.01 (0.76–1.33)	• No difference • P=0.97	• Not applicable
Men aged ≥50 years	1 (9026)	• Norrkoping	30/1494 (2.01)	130/7532 (1.73)	1.16 (0.79–1.72)	• No difference • P=0.45	• Not applicable
Men aged ≥55 years	3 (266,074)	• PLCO[c] • ERSPC • Stockholm	450/113,605 (0.40)	1053/152,469 (0.69)	0.98 (0.75–1.27)	• No difference • P=0.86	• Substantial heterogeneity • P=0.02 (I^2=73%)

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; NHMRC, National Health and Medical Research Council; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial.

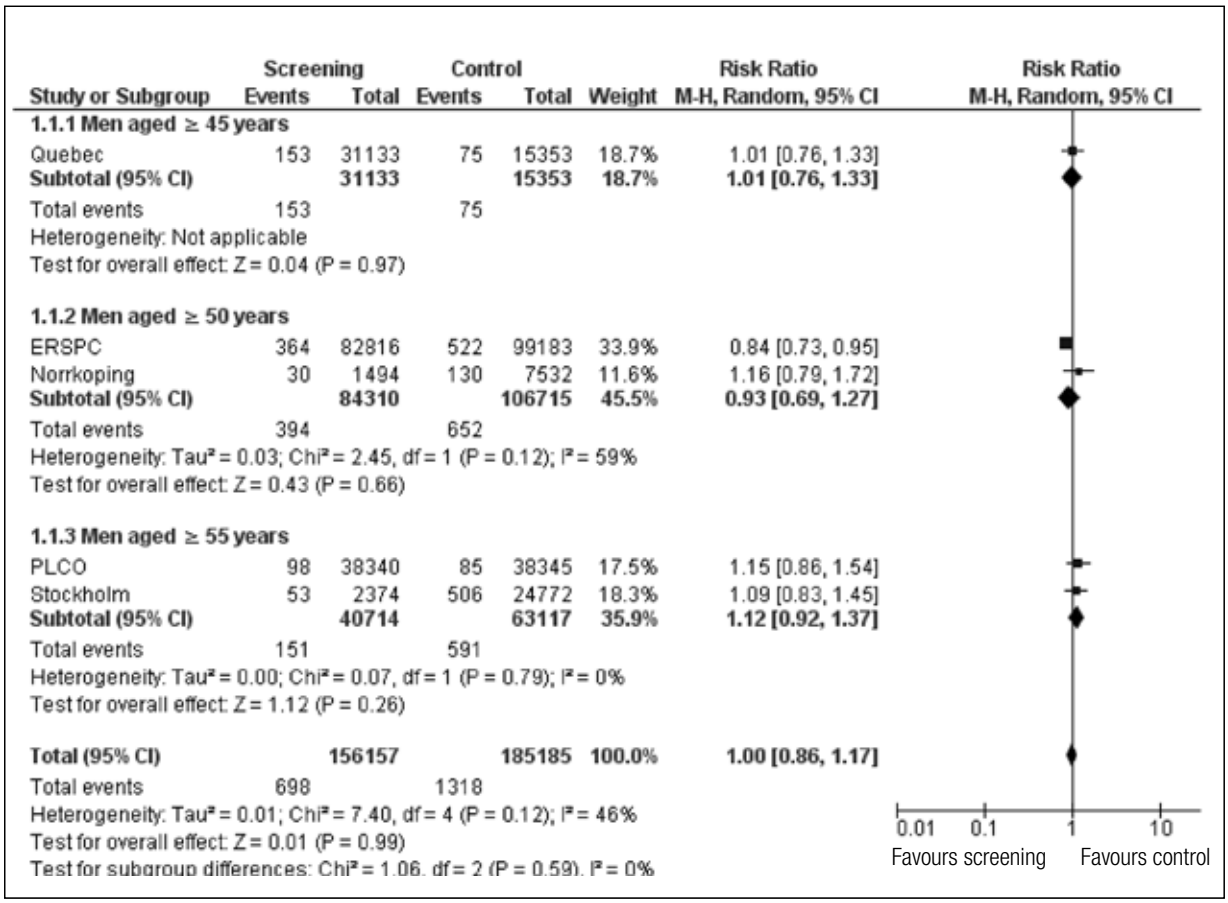
[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

[c] The Cochrane review used 10-year follow-up data from PLCO (Andriole et al. 2009) because the 13-year data (Andriole et al. 2012) was considered less robust (follow-up was available for 57% of participants at 13 years compared with 92% at 10 years).

[d] The authors included the Rotterdam-Ireland trial which it notes was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland). Consequently, the evidence reviewer acknowledged that Lumen (2012) does not fit precisely into NHMRC's classification of a Level I study.

Figure 1 Cochrane review forest plot of the effects of screening for prostate cancer on prostate cancer-specific mortality (subgroup analysis age at randomisation)



Source: Ilic et al. (2013), Figure 2

Table 7 Effect of PSA testing on prostate cancer-specific mortality: Summary of RCT evidence

Study ID [Level of evidence] *Quality*[a]	**Length of follow-up (years)**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**
PLCO [Level II] *Good*	13	158/NR	145/NR	1.09 (0.87–1.36)	• No difference
ERSPC [Level II] *Fair*	11	364/NR	522/NR	0.83 (0.72–0.94)	• Favours screening in **all enrolled men** • P=0.005
	11	299/NR	462/NR	0.79 (0.68–0.91)	• Favours screening in the **core age group of men aged 55–69 years** • P=0.001
Goteborg[b] [Level II] *Fair*	14	44/9952 (0.44)	78/9952 (0.78)	0.56 (0.39–0.82)	• Favours screening • P=0.002
Norrkoping [Level III–1] *Poor*	20	30/1494 (35.3)	130/7532 (44.5)	1.16 (0.78–1.73)	• No difference
Stockholm [Level II] *Poor*	15	53/208 (25.5)	506/1972 (28)	1.10 (0.83–1.46)	• No difference
Quebec [Level II] *Poor*	11	10/7348 (0.14)	74/14,231 (0.52)	1.01 (0.82–1.40)	• No difference
Subgroup analysis: age at randomisation					
PLCO trial					
55–64 years	13	65/NR	54/NR	1.19 (0.83–1.72)	• No difference
65–74 years	13	93/NR	91/NR	1.02 (0.77–1.37)	• No difference

Table 7 (cont.)

Study ID [Level of evidence] *Quality*[a]	**Length of follow-up (years)**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**
ERSPC trial					
≤54 years	11	6/NR	9/NR	0.65 (0.23–1.83)	• No difference
55–59 years	11	94/NR	144/NR	0.81 (0.62–1.05)	• No difference
60–64 years	11	106/NR	136/NR	0.92 (0.71–1.18)	• No difference
65–69 years	11	99/NR	182/NR	0.67 (0.53–0.86)	• Favour screening • P=NR
≥70 years	11	59/NR	51/NR	1.18 (0.81–1.72)	• No difference
Goteborg trial[b]					
50–54 years	14	5/4055 (0.12)	8/4002 (0.20)	0.62 (0.20–1.88)[c]	• No difference
55–59 years	14	12/3123 (0.38)	35/3161 (1.11)	0.35 (0.18–0.67)[c]	• Favours screening • P=NR
60–64 years	14	27/2774 (0.97)	35/2789 (1.25)	0.78 (0.47–1.28)[c]	• No difference
Subgroup analysis: comorbidities					
PLCO trial					
No comorbidities (modified Charlson score of 0)[d]	13	104/NR	100/NR	1.00 (0.76–1.31)	• No difference
With comorbidities (modified Charlson score ≥1)[d]	13	44/NR	39/NR	1.11 (0.72–1.71)	• No difference

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial.

[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[b] Prostate cancer-specific deaths included deaths caused by the disease itself as well as deaths resulting from any diagnostic or treatment-related intervention specific to the disease.

[c] Relative risk and confidence interval as calculated by the evidence reviewer for the purposes of this Evidence Evaluation Report.

[d] A modified Charlson comorbidity score (0 = no comorbidity, ≥1 = one or more comorbid conditions) was calculated for trial participants based on their baseline questionnaire responses. Because of the scope of the medical history section of the baseline questionnaire, a complete Charlson score could not be determined. Consequently, the modified Charlson score contained the following conditions found in the Charlson score: myocardial infarction, stroke, diabetes, cancer, pulmonary disease (bronchitis and/or emphysema) and liver disease (cirrhosis and/or hepatitis). Not included in the modified score were congestive heart failure, peripheral vascular disease, connective tissue disease, hemiplegia, HIV, renal disease, ulcer disease, and dementia.

Evidence statement for prostate cancer-specific mortality

The evidence statement matrix and evidence statement to summarise the evidence on the effect of PSA testing on prostate cancer-specific mortality is shown in **Table 8**. The full Evidence Statement Form is shown in Section 1.9 of the Technical Report.

Table 8 Evidence statement matrix and evidence statement on prostate cancer-specific mortality

Does PSA testing, with or without digital rectal examination, in asymptomatic men reduce prostate cancer-specific mortality?		
Component	**Rating**	**Description**
Evidence base	B[a]	Three Level I studies, comprising a total of five Level II studies (one of good quality, two of fair quality and two of poor quality) and one Level III–1 study of poor quality.
Consistency	C	All of the systematic reviews showed substantial heterogeneity in their meta-analysis of prostate cancer-specific mortality. There is thus some inconsistency, which is likely due to methodological and quality differences between the included studies.
EVIDENCE STATEMENT In asymptomatic men, the present evidence is inconsistent as to whether there is an effect of PSA testing, with or without DRE, on the risk of prostate cancer-specific mortality compared with no PSA testing, although the possibilities of no effect or a small protective effect cannot be excluded.		

Abbreviations: DRE, digital rectal examination; EAG, Expert Advisory Group; PSA, prostate-specific antigen.

[a] When rating this aspect of the evidence, the EAG decided to focus on the quality of the Level II studies, rather than the quality of the Level I studies. Although the quality of each of the Level I studies was good, the quality of the individual studies within them was considered to be variable. The quality rating of the Level II studies should be considered together with the limitations of each RCT as reported in Section 2.3.

2.4.2 All-cause mortality

The effect of PSA testing on all-cause mortality was assessed using meta-analysis in three systematic reviews as summarised in **Table 9**. **Table 10** presents data for all-cause mortality from the most recent publications for each of the individual RCTs.

It is noted that complete data (including event numbers and rate ratios) on all-cause mortality for the ERSPC trial was first published in March 2012. Otherwise, only the rate ratio for all-cause mortality in the core age group of men had been reported. Consequently, of the included systematic reviews, only the Cochrane review utilised the complete data.

It should also be noted that the PLCO trial did not include deaths from prostate, lung or colorectal cancer in their reporting of causes of death from any cause. However, the Cochrane review obtained this extra data through author contact.

The Norrkoping trial only reported on overall mortality in patients diagnosed with prostate cancer. There were no data available on overall mortality for the whole population. Consequently, it is inappropriate to include the results of the Norrkoping trial in a meta-analysis of all-cause mortality. However, the trial was included in the Cochrane review and Djulbegovic et al. (2010) meta-analyses. In the Cochrane review, the number of randomised men was used in the denominator, which is an incorrect assumption.

Level I evidence

The Cochrane review meta-analysed the results from the PLCO (using 10-year follow-up data), ERSPC, Norrkoping and Stockholm trials and concluded that prostate cancer screening did not result in a statistically significant reduction in all-cause mortality compared with no screening (RR 1.00; 95%

CI 0.96–1.03) (**Figure 2**). This result did not differ when data from the core age group of the ERSPC study were used (RR 0.99; 95% CI 0.96–1.03). The quality of evidence was rated as moderate for this outcome, with the ERSPC and PLCO studies assessed as low risk of bias, and the Norrkoping and Stockholm trials assessed as high risk of bias. The evidence reviewer notes that the Cochrane review included the Norrkoping trial in their meta-analysis, which is inappropriate. However, a sensitivity analysis was also conducted which demonstrated that there was no significant difference in results with the inclusion or exclusion of the Norrkoping and Stockholm trials (RR 0.99; 95% CI 0.96–1.02 for all enrolled men; RR 0.98; 95% CI 0.97–1.00 when data from the core age group of the ERSPC study were used).

Lumen et al. (2012) utilised the results from the PLCO, Stockholm, Goteborg and Rotterdam-Ireland trials and found no significant effect of screening on overall mortality (RR 0.90; 95% CI 0.75–1.08). The evidence reviewer notes though, that the Rotterdam-Ireland trial was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland). Therefore, for this outcome, the systematic review by Lumen et al. (2012) cannot be considered to be strictly Level I evidence, based on NHMRC's levels of evidence hierarchy (refer to Table 2 of the Technical Report).

Lumen et al. (2012) also performed an adjusted meta-analysis of all-cause mortality which excluded studies with a short follow-up of less than 8 years, high PSA-contamination rate of greater than 33.3% in the non-screened group, and/or those with a low participation rate of less than 75% in the screening group. Consequently, the adjusted analysis excluded the PLCO and Stockholm trials and only included the results from the Goteborg and Rotterdam-Ireland trials. The conclusion remained unchanged in that there was no significant effect of screening on all-cause mortality (RR 0.83; 95% CI 0.58–1.20).

Djulbegovic et al. (2010) incorporated the results of the PLCO, ERSPC, Norrkoping and Goteborg trials in their meta-analysis of all-cause mortality. The evidence reviewer notes that the Norrkoping trial was included in the meta-analysis, which is inappropriate. In addition, the authors excluded from the ERSPC data, the proportion of men in the Goteborg trial who were also included in the reporting of the ERSPC trial. Consequently, double counting of these men was prevented. As event rates were not available in all of the studies, the inverse variance method was used by Djulbegovic et al. (2010) to pool data from individual trials. The authors classified the evidence to be of moderate quality and the results revealed that there was no significant effect of screening on overall mortality (RR 0.99; 95% CI 0.97–1.01) (**Table 9**).

Level II evidence

Amongst the four RCTs that reported all-cause mortality for screened compared with unscreened men, the ERSPC (RR 1.00; 95% CI 0.98–1.20) and Stockholm (RR 0.98; 95% CI 0.92–1.05) trials found that there was no significant difference in all-cause mortality between the two groups. Whilst statistical analysis of all-cause mortality was not reported in the Goteborg trial, the evidence reviewer calculated the relative risk to be 1.00 (95% CI 0.95–1.06) and the authors noted that there was no effect of screening on overall mortality. Only the PLCO trial reported a 'borderline statistical significance' in all-cause mortality in favour of screening at 13 years of follow-up (RR 0.96; 95% CI 0.93–1.00; P-value not reported) (**Table 10**).

Subgroup analysis

Age

The evidence reviewer notes that none of the RCTs were sufficiently powered for subgroup analysis by age. Nevertheless, the Cochrane review examined all-cause mortality according to the age of participants at the time of the first screening test in the RCTs. It identified no significant difference in all-cause mortality in men aged 50 years and above (RR 1.14; 95% CI 0.84–1.56) or men aged 55 years and above (RR 0.98; 95% CI 0.95–1.01) (**Figure 2**). A second meta-analysis incorporating the core age group from the ERSPC study (i.e. men aged 55–69 years) demonstrated a significant difference in all-cause mortality only in men aged 50 years and above (RR 1.38; 95% CI 1.06–1.79). This was based on the Norrkoping study alone, which only reported on overall mortality in patients diagnosed with prostate cancer and not for the whole population (**Table 9**).

All of the RCTs varied in the age of participants at the time of the first screening test. Age specific information for this outcome was limited to the Goteborg study, which reported on the number of all-cause deaths stratified by age but did not perform statistical analysis of the data. However, the authors noted that there was no effect of age on overall mortality. The evidence reviewer calculated relative risk and confirmed there to be no effect of screening in men aged 50–54 years (RR 1.05; 95% CI 0.94–1.18), 55–59 years (RR 0.99; 95% CI 0.90–1.09), or 60–64 years (RR 0.99; 95% CI 0.91–1.07) (**Table 10**).

Risk factors and comorbidities

None of the Level I or II evidence stratified the population by risk factors or comorbidities in their analysis of all-cause mortality.

Table 9 Effect of PSA testing on all-cause mortality: Summary of Level I evidence

Study ID [Level of evidence] Quality[a]	**No. RCTs (no. patients)**	**Included RCTs**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**	**Heterogeneity[b]**
Ilic (2013) [Cochrane review] [Level I] *Good*	4 (294,856)	• PLCO • ERSPC: **all enrolled men** • Norrkoping • Stockholm	22,833/125,024 (18.26)	35,790/169,832 (21.07)	1.00 (0.96–1.03)	• No difference • P=0.84	• Substantial heterogeneity • P=0.05 (I^2=62%)
	4 (275,100)	• PLCO • ERSPC: **core age group of men (55–69 years)** • Norrkoping • Stockholm	20,013/115,099 (17.39)	33,020/160,001 (20.64)	0.99 (0.96–1.03)	• No difference • P=0.59	• Substantial heterogeneity • P=0.07 (I^2=58%)
Lumen (2012) [Level I][c] *Good*	4 (269,058)	• PLCO • Goteborg • Stockholm • Rotterdam-Ireland[c]	8596/62,665 (13.7)	43,451/206,393 (21.1)	0.90 (0.75–1.08)	• No difference • P=0.27	• Substantial heterogeneity • P<0.00001 (I^2=98%)
Djulbegovic (2010) [Level I] *Good*	4 (256,019)	• PLCO • ERSPC • Goteborg • Norrkoping	Event rate per 1000 with screening (95% CI): 198 (194–202)	Event rate per 1000 with control (95% CI): 200 (NR)	0.99 (0.97–1.01)	• No difference • P=0.44	• No significant heterogeneity • P=0.60 (I^2=0%)

Table 9 (cont.)

Study ID [Level of evidence] Quality[a]	No. RCTs (no. patients)	Included RCTs	Screening n/N (%)	Control n/N (%)	Relative risk estimate (95% CI)	Statistical significance	Heterogeneity[b]
Subgroup analysis: age at randomisation							
Ilic (2013) [Cochrane review]							
Men aged ≥50 years	2 (191,025)	• ERSPC • Norrkoping	16,806/84,310 (19.93)	20,278/106,715 (19.00)	1.14 (0.84–1.56)	• No difference • P=0.40	• Substantial heterogeneity • P=0.02 (I^2=83%)
Men aged ≥55 years	2 (103,831)	• PLCO • Stockholm	6027/40,714 (14.80)	15,512/63,117 (24.58)	0.98 (0.95–1.01)	No difference P=0.19	No significant heterogeneity P=0.44 (I^2=0%)
Subgroup analysis: age at randomisation, analysed using the core group of men aged between 55–69 years from ERSPC							
Ilic (2013) [Cochrane review]							
Men aged ≥50 years	1 (9026)	• Norrkoping	69/1494 (4.62)	252/7532 (3.35)	1.38 (1.06–1.79)	Favours control P=0.02	Not applicable
Men aged ≥55 years	3 (266,074)	• PLCO • ERSPC • Stockholm	19,944/113,605 (17.56)	32,768/152,469 (21.49)	0.99 (0.97–1.00)	No difference P=0.10	No significant heterogeneity P=0.67 (I^2=0%)

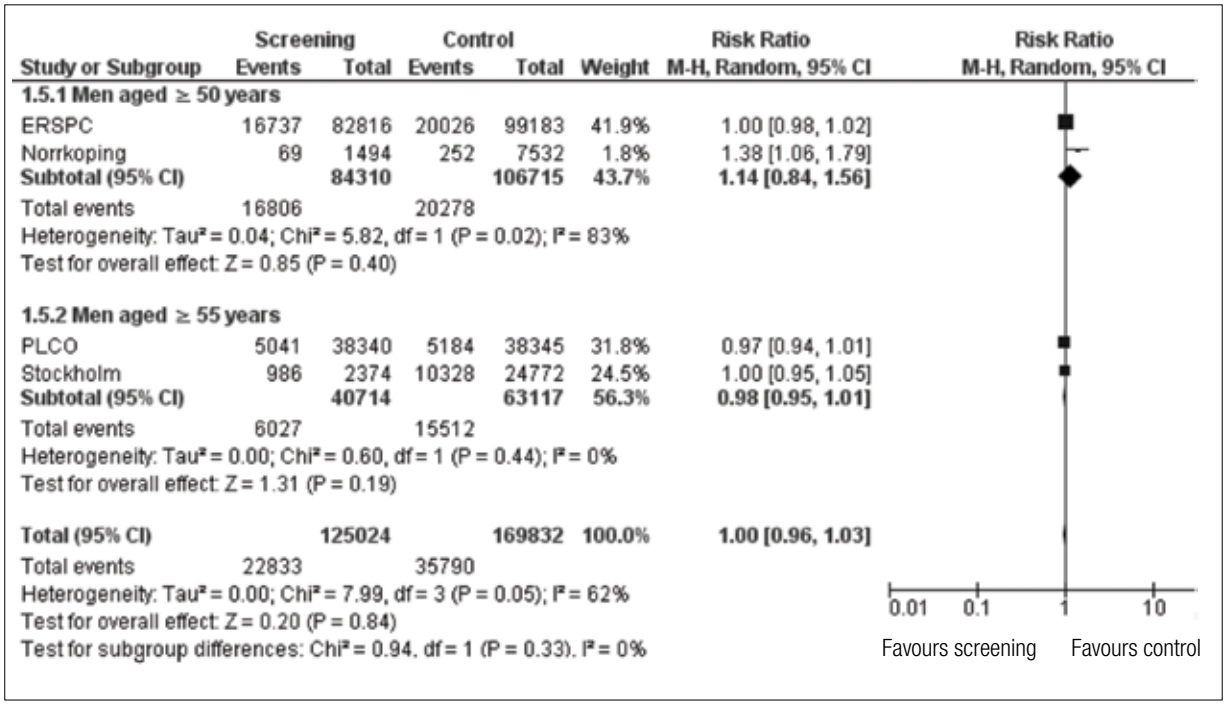
Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial.

[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

[c] The authors included the Rotterdam-Ireland trial which it notes was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland). Consequently, the evidence reviewer acknowledged that Lumen (2012) does not fit precisely into NHMRC's classification of a Level I study.

Figure 2 Cochrane review forest plot of the effects of screening for prostate cancer on all-cause mortality (subgroup analysis age at randomisation)



Source: Ilic et al. (2013), Figure 6.

Table 10 Effect of PSA testing on all-cause mortality: Summary of RCT evidence

Study ID [Level of evidence] *Quality*[a]	**Length of follow-up (years)**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**
PLCO[b] [Level II] *Good*	13	5783/NR	5982/NR	0.96 (0.93–1.00)	• 'Borderline statistical significance' in favour of screening • P=NR
ERSPC [Level II] *Fair*	11	16,737/NR	20,026/NR	1.00 (0.98–1.02)	• No difference in **all enrolled men** • P=0.85
	11	13,971/NR	17,256/NR	0.99 (0.97–1.01)	• No difference in the **core age group of men (55–69 years)** • P=0.50
Goteborg [Level II] *Fair*	14	1981/9952 (19.9)	1982/9952 (19.9)	1.00 (0.95–1.06)[c]	• 'No effect on overall mortality'
Stockholm [Level II] *Poor*	15	986/2374 (41.5)	10,328/24,772 (41.7)	0.98 (0.92–1.05)	• No difference • P=NR
Subgroup analysis: age at randomisation					
Goteborg trial					
50–54 years	14	511/4055 (12.6)	479/4002 (12.0)	1.05 (0.94–1.18)[c]	• 'No effect on overall mortality'
55–59 years	14	634/3123 (20.3)	650/3161 (20.6)	0.99 (0.90–1.09)[c]	• 'No effect on overall mortality'
60–64 years	14	836/2774 (30.1)	853/2789 (30.6)	0.99 (0.91–1.07)[c]	• 'No effect on overall mortality'

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial.

[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[b] Excludes deaths from prostate, lung or colorectal cancer.

[c] Relative risk and confidence interval as calculated by the evidence reviewer for the purposes of this Evidence Evaluation Report.

Evidence statement for all-cause mortality

The evidence statement matrix and evidence statement to summarise the evidence relating to the effect of PSA testing on all-cause mortality is shown in **Table 11**. The full Evidence Statement Form is shown in Section 1.9 of the Technical Report.

Table 11 Evidence statement matrix and evidence statement for all-cause mortality

Does PSA testing, with or without digital rectal examination, reduce all-cause mortality in asymptomatic men?		
Component	**Rating**	**Description**
Evidence base	B[a]	Three Level I studies, comprising four Level II studies (one of good quality, two of fair quality and one of poor quality).
Consistency	B	The findings of all of the systematic reviews were consistent in showing no effect of prostate cancer screening on all-cause mortality. One Level II study of good quality showed borderline statistical significance in favour of screening; all other Level II studies showed no effect.
EVIDENCE STATEMENT In asymptomatic men, PSA testing with or without DRE has no discernible effect on all-cause mortality compared with no PSA testing.		

Abbreviations: DRE, digital rectal examination; EAG, Expert Advisory Group; PSA, prostate-specific antigen.

[a] When rating this aspect of the evidence, the EAG decided to focus on the quality of the Level II studies, rather than the quality of the Level I studies. Although the quality of each of the Level I studies was good, the quality of the individual studies within them was considered to be variable. The quality rating of the Level II studies should be considered together with the limitations of each RCT as reported in Section 2.3.

2.5 Does PSA testing, with or without DRE, in asymptomatic men reduce morbidity due to advanced prostate cancer?

2.5.1 Prostate cancer-specific metastatic disease

Level I evidence

The effect of PSA testing on prostate cancer-specific metastatic disease was assessed by meta-analysis in three systematic reviews and reported in five RCTs as summarised in **Table 12** and **Table 13**, respectively. This outcome was also descriptively discussed in a further two systematic reviews. It should be noted that all of the data are in reference to the incidence of metastatic disease at diagnosis; there were no reports on the risk of metastatic prostate cancer identified after diagnosis and initial management of primary prostate cancer. Only the ERSPC trial collected data on metastatic disease during the entire period of post-diagnosis follow-up. All of the RCTs also used the American Joint Committee on Cancer's Tumour, Nodes, Metastasis (TNM) staging system to classify the stage of prostate cancer. However, the definition of metastatic disease varied between the RCTs and was reported as either an evaluation of the primary tumour ('T'), regional lymph nodes ('N') and/or distant metastasis ('M'), or overall staging (Stage III or IV).

The Cochrane review reported metastatic disease at follow-up as a secondary outcome and noted that 'there were very limited data on metastatic disease'. Nonetheless, meta-analysis of data from the PLCO, ERSPC and Norrkoping trials showed that the proportion of men diagnosed with advanced prostate cancer was significantly lower in the screening group compared to the men in the control group (RR 0.80; 95% CI 0.73–0.87) (**Figure 3**). Incorporating data from the French site of the

ERSPC study resulted in no change in findings (RR 0.77; 95% CI 0.71–0.83). The evidence reviewer notes though, that the Cochrane review included both Stage III and IV prostate cancers from the PLCO trial in their meta-analysis of advanced prostate cancer. However, only Stage IV prostate cancers (and not Stage III) were defined as metastatic in the PLCO trial. In addition, data specific for metastatic disease in the core age group of men in the ERSPC trial was published separately (Schroder et al. 2012c) to the 2012 ERSPC trial report (Schroder et al. 2012a). This separate data was not used in the Cochrane review's meta-analysis of advanced prostate cancer.

Lumen et al. (2012) conducted a meta-analysis using data from six RCTs (PLCO, ERSPC, Goteborg, Norrkoping, French ERSPC and Rotterdam-Ireland). The evidence reviewer notes that preliminary results from the French arm of the ERSPC trial and the Rotterdam-Ireland trial (which was not a prospective RCT) were also included. The results demonstrated that there was no statistically significant effect of prostate cancer screening on the diagnosis of prostate cancer-specific metastatic disease (RR 0.63; 95% CI 0.38–1.05).

Similarly, Djulbegovic et al. (2010) performed a meta-analysis on the results of the PLCO, ERSPC, French ERSPC and Norrkoping trials. This review also found that there was no statistically significant effect of prostate cancer screening on the incidence of metastatic disease (RR 0.94; 95% CI 0.85–1.04) (**Table 12**).

NZGG (2009) descriptively discussed the results of RCTs that reported on prostate cancer-specific metastatic disease. Its review included the results of the PLCO and ERSPC trials, as well as reports from the individual countries that comprised the ERSPC including Belgium, Finland, Rotterdam, Spain and Sweden. It was noted by the authors that the data on metastatic disease was often descriptive and consequently lacked statistical analysis. Only the ERSPC trial and results from the Swedish and Rotterdam sections of the ERSPC presented statistical analysis of metastatic disease in screened compared with control men. All of these studies showed that metastatic disease was significantly reduced by screening, however it is noted that the follow-up period for the RCTs (range from 4.0 to 11.5 years) may not be sufficient to detect the development of metastatic disease. Overall, the authors found that metastatic disease in screened men is relatively low and early detection and early treatment is likely to further reduce the development of metastatic disease.

Level II evidence

The effect of prostate cancer screening on the incidence of metastatic disease at diagnosis was examined in five RCTs, however statistical analysis was not performed in all of the trials; only the ERSPC and Goteborg trials conducted statistical analysis of the metastatic disease data.

The ERSPC evaluation was limited to those countries for which information on metastatic disease was available in both the screening and control arms of the study and was collected during the entire period of post-diagnosis follow-up. Consequently, the data comprised only four of the ERSPC countries (Finland, Netherlands, Sweden and Switzerland). The evaluation was also limited to the core age group of men. The results showed that 0.71% of men in the screening group developed prostate cancer-specific metastatic disease, compared with 1.01% of men in the control group. PSA screening thus significantly reduced the risk of developing prostate cancer-specific metastatic disease (hazard ratio [HR] 0.70; 95% CI 0.60–0.82; P=0.001). The Goteborg trial also found that the incidence of advanced prostate cancer at diagnosis was significantly lower in the screening group compared with the control (0.5% of men in the screening group compared with 0.9% of men in the control group; P=0.0003). The evidence reviewer calculated the relative risk to be 0.53 (95% CI 0.37–0.76).

The PLCO trial reported that 1.36% and 1.70% of cancers diagnosed in the screening and control group, respectively, were Stage III at 13 years of follow-up (RR 0.80; 95% CI 0.56–1.14 as calculated by the evidence reviewer). The number of Stage IV cancers was 2.26% and 2.91% in the screening and control group, respectively (RR 0.78; 95% CI 0.59–1.02 as calculated by the evidence reviewer).

The Norrkoping trial reported that the percentage of men with advanced tumours (T3–4, N1 or MX/M1) at diagnosis was similar in the control group compared with the screening group (2.8% compared with 2.5%; RR 0.88; 95% CI 0.62–1.24) (**Table 13**).

Subgroup analysis

None of the Level I or II evidence stratified the population by age, risk factors or comorbidities in their analysis of prostate cancer-specific metastatic disease.

Table 12 Effects of PSA testing on prostate cancer-specific metastatic disease: Summary of Level I evidence

Study ID [Level of evidence] *Quality*[a]	**No. RCTs (no. patients)**	**Definition of metastatic disease**[b]	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**	**Heterogeneity**[c]
Ilic (2013) [Cochrane review] [Level I] *Good*	• 3 (247,954) • PLCO • ERSPC • Norrkoping	T3–T4, N1, M1	868/112,725 (0.77)	1460/135,229 (1.08)	0.80 (0.73–0.87)	• Favours screening (fewer events) • P<0.00001	• No significant heterogeneity • P=0.51 (I^2=0%)
	• 4 (NR) • PLCO • ERSPC • Norrkoping • French ERSPC[d]	T3–T4, N1, M1	NR	NR	0.77 (0.71–0.83)	• Favours screening (fewer events) • P=NR	NR
Lumen (2012) [Level I][e] *Good*	• 6 (497,945) • PLCO • ERSPC • Goteborg • Norrkoping • French ERSPC[d] • Rotterdam-Ireland[e]	Stage IV or any T, any N, M+	281/177,259 (0.16)	1360/320,686 (0.42)	0.63 (0.38–1.05)	• No difference • P=0.079	• Substantial heterogeneity • P<0.00001 (I^2=88%)
Djulbegovic (2010) [Level I] *Good*	• 4 (332,743) • PLCO • ERSPC • French ERSPC[d] • Norrkoping	Stage III and IV	701/155,317 (0.45)	975/177,426 (0.55)	0.94 (0.85–1.04)	• No difference • P=0.22	• No significant heterogeneity • P=0.75 (I^2=0%)

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial; TNM, Tumour, Nodes, Metastasis staging system.

[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

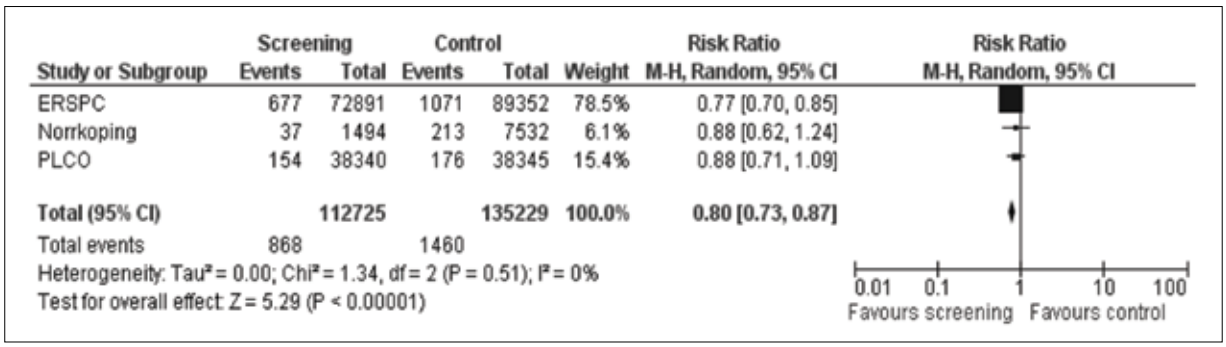
[b] All of the studies utilised the American Joint Committee on Cancer's TNM staging system to classify the stage of prostate cancer.

[c] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25–50%; substantial heterogeneity I^2 >50%.

[d] The French arm of the ERSPC has not been included in the results of the overall ERSPC trial due to a short length of follow-up.

[e] The authors included the Rotterdam-Ireland trial which it notes was not a prospective RCT. Rather, it was a comparison between a screened population (part of the Rotterdam section of the ERSPC trial) and a population where screening is not routinely carried out (Ireland). Consequently, the evidence reviewer acknowledged that Lumen (2012) does not fit precisely into NHMRC's classification of a Level I study.

Figure 3 Cochrane review forest plot of the effects of screening for prostate cancer on prostate cancer-specific metastatic disease (advanced T3–T4, N1, M1)



Source: Ilic et al. (2013), Figure 13.

Table 13 Effects of PSA testing on prostate cancer-specific metastatic disease: Summary of RCT evidence

Study ID [Level of evidence] *Quality*[a]	**Length of follow-up (years)**	**Metastatic disease**	**Screening n/N (%)**	**Control n/N (%)**	**Relative risk estimate (95% CI)**	**Statistical significance**
PLCO [Level II] *Good*	13	Stage III	58/4250 (1.36)	65/3815 (1.70)	0.80 (0.56–1.14)[c]	• No difference
	13	Stage IV	96/4250 (2.26)	111/3815 (2.91)	0.78 (0.59–1.02)[c]	• No difference
ERSPC[b] [Level II] *Fair*	12	M1 and/or PSA value >100 ng/mL	256/36,270 (0.71)	410/40,543 (1.01)	Hazard ratio: 0.70 (0.60–0.82)	• Favours screening • P=0.001
Goteborg [Level II] *Fair*	14	N1 or M1, or PSA value ≥100 ng/mL	46/9952 (0.5)	87/9952 (0.9)	0.53 (0.37–0.76)[c]	• Significantly lower advanced prostate cancer in the screening group compared with the control • P=0.0003
Norrkoping [Level III–1] *Good*	20	T3–4. N1 or MX/M1	37/1494 (2.5)	213/7532 (2.8)	0.88 (0.62–1.24)[c]	• No difference

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; NR, not reported; PLCO, Prostate, Lung and Colorectal and Ovarian; RCT, randomised controlled trial; TNM, Tumour, Nodes, Metastasis staging system.

[a] Level of evidence and study quality assessed by the evidence reviewer. The quality ratings should be considered together with the limitations of each RCT as reported in Section 2.3.

[b] The current evaluation is limited to the core age group of men (55–69 years) in those countries for which information on metastatic status is available in both the screening and control arms of the study and was collected during the entire period of post-diagnosis follow-up. Consequently, the data comprises four of the seven ERSPC countries: Finland, Netherlands, Sweden and Switzerland. **Source:** Schroder et al. (2012c).

[c] Relative risk and confidence interval as calculated by the evidence reviewer for the purposes of this Evidence Evaluation Report.

Evidence statement for prostate cancer-specific metastatic disease

The evidence statement matrix and evidence statement to summarise the evidence on the effect of PSA testing on prostate cancer-specific metastatic disease is shown in **Table 14**. The full Evidence Statement Form is shown in Section 1.9 of the Technical Report.

Table 14 Evidence statement matrix and evidence statement on prostate cancer-specific metastatic disease

Does PSA testing, with or without digital rectal examination, in asymptomatic men reduce prostate cancer-specific metastatic disease due to advanced prostate cancer?		
Component	**Rating**	**Description**
Evidence base	B[a]	Three Level I studies, comprising a total of three Level II studies (one of good quality and two of fair quality) and one Level III–1 study of poor quality.
Consistency	B	Most studies consistent and inconsistency can be explained.
EVIDENCE STATEMENT In asymptomatic men, PSA testing with or without DRE reduces the risk of prostate cancer metastases at diagnosis compared with no PSA testing.		

Abbreviations: DRE, digital rectal examination; EAG, Expert Advisory Group; PSA, prostate-specific antigen.

[a] When rating this aspect of the evidence, the EAG decided to focus on the quality of the Level II studies, rather than the quality of the Level I studies. Although the quality of each of the Level I studies was good, the quality of the individual studies within them was considered to be variable. The quality rating of the Level II studies should be considered together with the limitations of each RCT as reported in Section 2.3.

2.5.2 Skeletal-related events

At a meeting of the EAG and NHMRC held on 22 January 2013, a decision was made to subsume the skeletal-related events outcome within the prostate cancer-specific metastatic disease outcome presented in Section 2.5.1. The basis for this decision is that skeletal-related events are largely associated with bone metastasis, a common form of metastatic disease among patients diagnosed with advanced prostate cancer (Jin et al. 2011; Lee et al. 2011), but also includes effects from androgen deprivation therapy. Accordingly, a separate evidence statement for skeletal-related events was not formulated.

2.5.3 Quality of life

Although there is a large volume of literature describing the negative effects on quality of life of treatments for advanced prostate cancer, there is currently no Level I or II evidence that specifically addresses the effect of PSA testing in asymptomatic men on quality of life due to advanced prostate cancer.

The evidence reviewer notes though, that quality of life was an outcome in three of the identified systematic reviews and two of the included RCTs. The Cochrane review, Djulbegovic et al. (2010) review, and the AHRQ review all commented that no RCTs of PSA-based screening had yet provided sufficiently long follow up to report data on quality of life due to advanced prostate cancer subsequent to PSA testing. However, the ERSPC trial noted that quality of life were currently being reviewed and would form the basis of future publications. Similarly, the effect of screening on quality of life is the subject of an ongoing substudy of the PLCO trial.

Evidence statement for quality of life

The evidence statement matrix and evidence statement to summarise the evidence for the effect of PSA testing in asymptomatic men on quality of life due to advanced prostate cancer is shown in Table 15.

Table 15 Evidence statement matrix and evidence statement on quality of life due to advanced prostate cancer

Does PSA testing, with or without digital rectal examination, in asymptomatic men affect quality of life due to advanced prostate cancer?		
Component	**Rating**	**Description**
Evidence base	NA	No Level I or Level II studies of PSA-based screening in asymptomatic men were identified that reported data on quality of life due to advanced prostate cancer.
Consistency	NA	Not applicable.
EVIDENCE STATEMENT It is unknown if PSA testing, with or without DRE, in asymptomatic men affects quality of life due to advanced prostate cancer, compared with no PSA testing.		

Abbreviations: DRE, digital rectal examination; NA, not applicable; PSA, prostate-specific antigen.

3. Supplementary non-systematic review

The non-systematic literature review component of this Evidence Evaluation Report is intended to supplement the information from the systematic review with additional evidence describing the potential harms and other benefits associated with PSA testing in asymptomatic men. It is structured as follows:

- **Section 3.1** reviews other (non-RCT) evidence on the benefits of PSA testing in asymptomatic men.
- **Section 3.2** reviews the potential harms of PSA testing. It includes a review of PSA test performance characteristics and discussion around the risk of overdiagnosis, physical harms, and the effect of PSA testing on quality of life in asymptomatic men.
- **Section 3.3** reviews the potential benefits and harms of follow up investigative procedures, such as prostate biopsy.
- **Section 3.4** reviews the potential benefits and harms of treatments for prostate cancer, including active surveillance, radical prostatectomy, radiotherapy, androgen deprivation hormone therapy, cryotherapy, and high-intensity focused ultrasound.

3.1 Other benefits of PSA testing

3.1.1 Evidence from observational studies

In addition to the RCTs discussed in the systematic review of Level I evidence, several cohort and case-control studies have investigated the effects of PSA testing in asymptomatic men. Such studies are considered to be Level III–2 evidence according to the NHMRC Levels of Evidence hierarchy (NHMRC 2009).

The NZGG included evidence from cohort and case-control studies in its 2009 systematic review of PSA testing in asymptomatic men, but noted that such evidence was unreliable and subject to bias (NZGG 2009). With the exception of two cohort studies that investigated the effect of intensive PSA- based screening on prostate cancer-specific mortality (Vutuc et al. 2005; Lu-Yao et al. 2008), most of the identified observational evidence reviewed came from small case-control studies or analyses of subgroups within the ERSPC or PLCO trials. Overall, there was no evidence from observational studies to suggest that PSA testing in asymptomatic men reduces prostate cancer-specific mortality, and low-quality evidence to suggest that PSA testing in asymptomatic men reduces prostate cancer-related metastatic disease (NZGG 2009).

The results of several cohort and case-control studies have suggested that a low PSA reading can provide the benefit of reassurance to men, by indicating that they are unlikely to have prostate cancer. A longitudinal cohort study found that men aged 75–80 years with a PSA <3.0 ng/mL were unlikely to die of, or experience aggressive prostate cancer, during their remaining life (Schaeffer et al. 2009). A case-control study found that men aged 60 years with a PSA <1.0 ng/mL may harbour prostate cancer but the cancer would unlikely become life threatening (Vickers et al. 2010).

3.2 Potential harms of PSA testing

3.2.1 Review of PSA test performance characteristics

The utility of the PSA test for early detection of prostate cancer is controversial. PSA is elevated in a number of benign conditions and there are also transient causes of PSA elevation that may affect the ability of the PSA test to detect prostate cancer. Determining the accuracy of the PSA test is problematic for several reasons. Biopsy is not a perfect gold standard; the diagnostic performance of PSA ideally needs to be calibrated against 'clinically significant' cancers and there is currently no consensus on defining such cancers. The detection of non-lethal cancers leads to overestimation of test performance. Furthermore, sensitivity is overestimated and specificity underestimated because most men with normal PSA values will not undergo biopsy unless their DRE is abnormal.

While there is no clear threshold at which prostate cancer can be conclusively ruled out, the traditional cut-off for an abnormal PSA level in the major screening studies has ranged from 3.0-4.0 ng/mL. In current clinical practice a fixed cut-off is not considered appropriate because other factors, particularly age, impact on the diagnostic performance of the test. The Royal College of Pathologists of Australasia (RCPA) has advocated that PSA results should be interpreted with reference to the relevant age-related median and age-related 95% upper limit cut offs (McKenzie et al. 2011). Any choice of PSA cut-off involves an inevitable trade-off between test sensitivity and specificity; while lowering the PSA cut-off improves sensitivity, it also reduces specificity, leading to more false-positive tests and unnecessary biopsies. Additionally, many of the cancers detected at these lower levels may never have become clinically evident, thereby leading to overdiagnosis and overtreatment (see Section 3.2.2).

Elevated PSA levels can be caused by several conditions other than prostate cancer, including urinary tract infections, BPH, prostatitis, recent ejaculation, DRE, and possibly, vigorous exercise (Sikaris, 2012). While the chance of having prostate cancer increases with increasing PSA levels, there is no clear threshold at which prostate cancer can be conclusively diagnosed or ruled out.

The diagnostic accuracy of the PSA test in asymptomatic men directly affects the risk of prostate cancer overdiagnosis and overtreatment. The better the sensitivity, specificity and positive predictive value of the PSA test, the less likely it is that men without prostate cancer will be exposed to unnecessary follow up investigations or treatment-related harms. Evaluating the diagnostic accuracy of PSA testing is challenging as prostate biopsy is not a perfect reference standard. Depending on the protocol and number of samples collected, initial biopsies may fail to detect 10–30% of prostate cancers (Eichler et al. 2005). Additionally, most men will not undergo a prostate biopsy unless their PSA or DRE results are abnormal. This verification bias tends to overestimate sensitivity and underestimate specificity of the PSA test in asymptomatic men (Punglia et al. 2003; Thompson and Ankerst, 2009).

The Prostate Cancer Prevention Trial (PCPT) is the only large-scale prospective trial conducted to date, that required all participants to undergo a prostate biopsy at the end of the study, regardless of PSA or DRE status. This permitted analysis of the prevalence of prostate cancer in asymptomatic men across the full spectrum of PSA levels and minimised the risk of verification bias influencing the sensitivity of the PSA test (Thompson et al. 2006). The PCPT was primarily a Phase 3 RCT of finasteride versus placebo for the prevention of prostate cancer. It was conducted from 1993 to 2003 in 221 centres in the USA and enrolled a total of 18,882 healthy men, aged 55 years or older, that had a normal DRE result and a baseline PSA level less than or equal to 3.0 ng/mL. Participants underwent annual assessments

and were referred for a prostate biopsy if their PSA level increased to greater than 4.0 ng/mL, or if DRE results were abnormal. All participants without a diagnosis of prostate cancer underwent a prostate biopsy at the end of the 7-year follow-up period. In total, prostate cancer was detected in 21.9% of all subjects in the placebo arm of the trial (Thompson et al. 2006).

Sensitivity and specificity values observed in the PCPT study for PSA test-based detection of prostate cancer and high-grade (Gleason grade ≥8) prostate cancer are shown in **Table 16.** With the commonly used 4.0 ng/mL PSA cut-off, the PSA test had a sensitivity of 20.5% for detection of prostate cancer, and 50.8% for the detection of high-grade prostate cancer (Thompson et al. 2005). The diagnostic accuracy of PSA testing was better in men aged younger than 70 years (n = 2956; AUC value of 0.699), compared with men aged 70 years and older (n = 2631; AUC value of 0.663). An important finding of the PCPT was that prostate cancer is prevalent in men with very low PSA levels. Even if the threshold for a positive PSA test was lowered to 1.1 ng/mL, 16.6% of all prostate cancers, and 5.3% of high-grade cancers would be missed. The generalisability of estimates from the PCPT trial, however, could be affected by the selection of a healthy population with generally low initial PSA values. Furthermore, because of repeated screening, cases in this series were likely to be diagnosed at an early stage of disease progression (Thompson et al. 2005).

Table 16 Sensitivity and specificity of the PSA test for detection of prostate cancer and high-grade (Gleason grade ≥8) prostate cancer as observed in the Prostate Cancer Prevention Trial

Threshold for a positive PSA test (ng/mL)	Prostate cancer[a]		High-grade prostate cancer[b] (Gleason grade ≥8)	
	Sensitivity[c]	Specificity[d]	Sensitivity[c]	Specificity[d]
1.1	83.4	38.9	94.7	35.9
1.6	67.0	58.7	89.5	53.5
2.1	52.6	72.5	86.0	65.9
2.6	40.5	81.1	78.9	75.1
3.1	32.2	86.7	68.4	81.0
4.1	20.5	93.8	50.9	89.1
6.1	4.6	98.5	26.3	97.5
8.1	1.7	99.4	10.5	99.0
10.1	0.9	99.7	5.3	99.5

Source: Thompson et al. (2005), page 69

[a] Any cancer (n = 1225) versus no cancer (n = 4362)

[b] High-grade prostate cancer, Gleason grade ≥8 (n = 57) versus no cancer (n=5518)

[c] Sensitivity: (# true-positive tests) / (# true-positive tests + # false-negative tests) x 100

[d] Specificity: (# true-negative tests) / (# true-negative tests + # false-positive tests) x 100

False-positive PSA test results were common in both the ERSPC and PLCO studies. During the first 9 years of follow-up in the ERSPC trial (Schroder et al. 2009), men in the predefined core age group (55 to 69 years) received an average of 2.1 PSA tests per subject (n = 72,952). In total, 16.2% of all PSA tests performed were positive (range of 11.1–22.3% across centres). The average rate of compliance with biopsy recommendations was 85.8% (range 65.4–90.3%). No prostate cancer was detected in 75.9% of men who underwent biopsy for an elevated PSA level (n = 13,308). Kilpelainen et al. (2011) analysed the rate of false-positive PSA test results based on data from ERSPC centres in Belgium, Finland, Italy, the Netherlands and Sweden (n = 61,604). A false-positive result was defined as a positive PSA test result with no prostate cancer diagnosis within 1 year of the test being performed. This definition is subject to bias as it assumes that biopsy is a perfect reference standard and does not account for the risk that a clinically significant cancer may have been missed. Overall, 17.8% of men

screened for prostate cancer received at least one false-positive result over four rounds of PSA testing (n = 10,972). The analysis excluded men who had a positive PSA test result but did not undergo biopsy within 1 year.

Croswell et al. (2009) analysed the cumulative risks of receiving false-positive cancer screening results based on data from subjects who underwent at least one screening test and were followed for more than 3 years in the PLCO study (n = 68,436). A false-positive was defined as a positive PSA test with no prostate cancer diagnosis within 3 years of follow-up. In total, 10.4% of men that received the PSA test received at least one false-positive PSA test result. After four rounds of PSA testing, the cumulative risk of receiving at least one false-positive was 12.9%. This was lower than the cumulative false-positive risks associated with flexible sigmoidoscopy for the detection of colorectal cancer (41.8% after two rounds of screening) and chest x-rays for the detection of lung cancer (21.5% after four rounds of screening), observed in the PLCO trial.

Several reviews have assessed the diagnostic accuracy of the PSA test from different perspectives. The most recent of these was a systematic review performed by the American Cancer Society as part of its guideline for early prostate cancer detection (Wolf et al. 2010). The review included nine prospective studies of PSA screening, including the PCPT, ERSPC and PLCO trials. Each study included in the systematic review used prostate biopsy as the reference standard and a PSA cut-off value of either 3.0 ng/mL or 4.0 ng/mL. Pooled estimates for PSA test positivity, cancer detection rates, sensitivity, specificity and positive predictive values were similar to those observed in the PCPT study and are shown in **Table 17.** These estimates are subject to verification bias and specificity was calculated based on an assumption that there were no false-negative PSA test results, which is not supported from other studies. The authors of the American Cancer Society review noted that PSA test characteristics using either 3.0 ng/mL or 4.0 ng/mL thresholds compare reasonably with the characteristics of other commonly used screening tests (e.g. the faecal occult blood test for colorectal cancer; Wolf et al. 2010).

Table 17 Pooled analysis by the American Cancer Society of PSA test performance characteristics in asymptomatic men

	Threshold for a positive PSA test	
Test characteristics	**Normal PSA <4.0 ng/mL[a]**	**Normal PSA <3.0 ng/mL[b]**
Test positivity (%)[c]	12	18
Cancer detection rate (%)[d]	3	4
Sensitivity (%)[e]		
• Prostate cancer	21	32
• High-grade prostate cancer (Gleason grade ≥8)	51	68
Specificity (%)[f]	91	85
Positive predictive value (%)[g]	30	28

Source: Wolf et al. (2010), page 88

[a] Pooled analysis of PSA test performance as reported in the following studies: Andriole et al. 2005; Hugosson et al. 2003; Kwiatkowski et al. 2003; Maattanen et al. 2007; McLernon et al. 2006; Schroder et al. 2005; Shim et al. 2007; Roobol et al. 2003; Thompson et al. 2006.

[b] Pooled analysis PSA test performance as reported in the following studies: Hugosson et al. 2003; Kwiatkowski et al. 2003; Schroder et al. 2005; Roobol et al. 2003

[c] Test positivity: (# positive / # tested) x 100

[d] Cancer detection rate: (# prostate cancer / # tested) x 100

[e] Sensitivity: (true-positive tests) / (true-positive tests + false-negative tests) x 100

[f] Specificity: (true-negative tests) / (true-negative tests + false-positive tests) x 100, estimated from: (# tested – # positive) / (# tested – # cancer) x 100, assuming that negative tests are true-negatives

[g] Positive predictive value: (# prostate cancer / # biopsied) x 100

The NZGG assessed the sensitivity and specificity of total PSA testing, PSA velocity and free to total PSA ratios for prostate cancer in its 2009 evidence report on PSA testing in asymptomatic men (NZGG 2009). Total PSA testing measures the total concentration of PSA in a blood or serum sample, and is the PSA test modality most commonly used in clinical practice. PSA velocity refers to the rate of increase in blood PSA levels over time, with increases of greater than 0.75 ng/mL/year considered to be unusual. Free to total PSA ratios assist with discrimination between prostate cancer and benign prostate conditions, with ratios of less than 10–31% considered to be abnormally low (Sikaris, 2012; NZGG 2009; Wolf et al. 2010). The review identified 23 publications that reported information relating to the accuracy of total PSA testing as a prognostic indicator for prostate cancer, 13 publications that reported PSA velocity, and 15 publications that reported free to total PSA ratios (NZGG 2009). Estimates for sensitivity and specificity of the total PSA test varied widely according to the threshold used for a positive PSA test, study quality, the likelihood of bias and the age of study participants. The NZGG did not meta-analyse total PSA test performance characteristics, however the findings of NZGG were generally consistent with the systematic review conducted by the American Cancer Society (Wolf et al. 2010). The prognostic value of PSA velocity, and free to total PSA ratios for the detection of prostate cancer was uncertain due to verification bias and significant heterogeneity between the populations and prostate biopsy methods used in the included studies. The NZGG concluded that neither PSA velocity nor free to total PSA ratios should be used as the sole prognostic indicator for prostate cancer, however they may be useful when used alongside other PSA isoforms (NZGG 2009).

The most recent adaptation of PSA is the prostate health index (*phi)* which combines serum PSA, a truncated form of the PSA molecule (pro-PSA) and percentage free PSA (Catalona et al. 2011). Although initial results suggest a possible diagnostic advantage for phi compared with PSA alone, these claims remain to be verified through large, multicentre, prospective trials with detailed health economic analyses to determine clinical applicability (Hori et al. 2012). Another proposed test utilises the non-coding RNA, PCA3, which has been shown to be highly expressed in, and specific for, prostatic tissue, and is detectable in urine immediately following firm DRE or prostatic massage (Clarke et al. 2010). Although the PCA3 urine test has been reported to improve identification of serious disease compared with serum PSA in a pre-screened population (Roobol et al. 2010), its role in the initial assessment of patients suspected of having prostate cancer has yet to be established (Nyberg et al. 2010; Roobol 2011).

Mistry and Cable (2003) performed a systematic review of PSA test characteristics based on a search of the OVID database from 1966 to November 1999. This review included 13 studies of the diagnostic accuracy of DRE and PSA testing in asymptomatic men, with prostate biopsy as the reference standard. A pooled analysis of the studies showed that 10.1% of the men tested had a PSA level greater than 4.0 ng/mL (n = 47,791). Overall, the PSA test had a positive predictive value of 25.1%, sensitivity of 72.1% and specificity of 93.2% (**Table 18**). It was concluded that the PSA test had greater overall sensitivity, specificity and positive predictive value, when used as a screening tool to detect prostate cancer in asymptomatic men, compared with DRE alone.

Table 18 Pooled analysis of test characteristics for PSA testing and digital rectal examination in asymptomatic men

Test characteristics	PSA test[a, b]	Digital rectal examination[c]
Population with abnormal test results (%)	10.1	5.0
Sensitivity for prostate cancer (%)[d]	72.1	53.2
Specificity (%)[e]	93.2	83.6
Positive predictive value (%)[f]	25.1	17.8

Source: Mistry and Cable (2003), page 97–98

[a] Pooled analysis of PSA test performance as reported in the following studies: Bangma et al. 1995; Brett 1998; Bretton 1994; Gustafsson et al. 1998; Higashihara et al. 1996; Horniger et al. 1999; Imai et al. 1994; Imai et al. 1995; Jubelirer et al. 1994; Maattanen et al. 1999; Reissigl et al. 1997; Stenman et al. 1994; Tsukamoto et al. 1995.

[b] Abnormal PSA test results were defined as a PSA level > 4 ng/mL.

[c] Pooled analysis of digital rectal examination test performance as reported in the following studies: Bangma et al. 1995; Brett 1998; Bretton 1994; Gustafsson et al. 1998; Higashihara et al. 1996; Imai et al. 1994; Imai et al. 1995; Jubelirer et al. 1994; Reissigl et al. 1997; Tsukamoto et al. 1995.

[d] Sensitivity: (# true-positive tests) / (# true-positive tests + # false-negative tests) x 100.

[e] Specificity: (# true-negative tests) / (# true-negative tests + # false-positive tests) x 100, assuming that negative tests are true-negatives.

[f] Positive predictive value: (% of positive biopsies) /(# true-positive tests + # false-positive tests).

Harvey et al. (2009) conducted a systematic review of PSA test performance based on a search of the Medline and EMBASE databases from January 1998 to January 2008. The review included 10 studies that assessed PSA test performance characteristics in men participating in BPH or prostate cancer studies in Europe. Many of the included studies investigated PSA levels in men previously diagnosed with prostate disease, those with abnormal PSA levels or DREs, and those that were already indicated for biopsy. Although the results of the systematic review by Harvey et al. (2009) may be applicable to symptomatic men in the primary and secondary healthcare setting, they should not be generalised to asymptomatic men.

3.2.2 Risk of overdiagnosis

In the context of this review, overdiagnosis refers to the detection by PSA testing of prostate cancer that would not result in future health problems even if left untreated. Patients whose PSA test is positive may be unnecessarily exposed to follow up diagnostic investigations and treatment, as well as suffering potential psychological harm from anxiety. Overdiagnosis is of particular concern because most men with test-detected prostate cancer will have early stage disease and may be offered aggressive treatment with associated harms. Given limitations in the design and reporting of the RCTs of PSA testing, there remain important concerns about whether the benefits of testing outweigh the potential harms to quality of life, including the substantial risks for overdiagnosis and treatment complications.

The most important risks associated with PSA testing in asymptomatic men are overdiagnosis and consequential overtreatment of clinically insignificant cancers that would not otherwise be detected over a patient's lifetime (Wolf et al. 2010). A review of evidence from autopsy studies by Welch and Black (2010) estimated that men aged over 60 years have a 30–70% lifetime risk of dying with prostate cancer but only a 4% lifetime risk of prostate cancer-related death or metastatic disease. In Australia, the prevalence of undiagnosed invasive prostate cancer in men aged 50 years or over that have died from other causes is estimated to be 25.7% (Orde et al. 2009). The significance of

overdiagnosis is also reflected in the high proportion of patients eligible for, and who undertake active surveillance, and low rates of aggressive disease detected with follow-up biopsies and in those electing to undergo radical prostatectomy (Eggener et al. 2013).

Evidence for overdiagnosis is available from the two largest RCTs of PSA testing in asymptomatic men. In the ERSPC trial, the rate of overdiagnosis in the screening group was estimated to be up to 55% (Draisma et al. 2003; Schroder et al. 2012c). According to Schroder et al. (2012a), to prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected. The rate of overdiagnosis in the PLCO trial has been estimated at 17% to 30% (Miller, 2012). It should be noted that estimation of overdiagnosis is affected by less than 100% participation in screening in the screened population and occurrence of screening in the unscreened population (Biesheuvel et al. 2007).

Several studies have sought to quantify the frequency of prostate cancer overdiagnosis by comparing incidence trends in the presence of PSA testing with those in the absence of PSA testing. The measurement of overdiagnosis in such studies is dependent on lead time (i.e. the time by which the availability of the test advances prostate cancer diagnosis) and the background incidence of disease (Wolf et al. 2010).

Etzioni et al. (2002) and Telesca et al. (2008) developed simulation models of PSA testing in men in the USA based on data from the Surveillance, Epidemiology and End Results (SEER) registry of the National Cancer Institute. The models were similar in structure but considered men of different age ranges and used different methods for estimating lead time. Etzioni et al. (2002) included men aged 65 years and older and estimated lead times of 5 years for white men and 7 years for black men. It was estimated that, between 1988 and 1998, 28.8% of white men and 43.8% of black men diagnosed with prostate cancer following a PSA test were overdiagnosed (Etzioni et al. 2002). Telesca et al. (2008) updated the inputs used by Etzioni et al. (2002) and estimated lead times of 4.50 years for white men and 6.43 years for black men. The overdiagnosis rate associated with PSA testing in men aged between 50 and 64 years was estimated to be 22.7% for white men and 34.4% in black men.

Three studies have used the Microsimulation Screening Analysis (MISCAN) model to estimate lead times and overdetection rates associated with PSA screening (Draisma et al. 2003; Draisma et al. 2009; Heijnsdijk et al. 2009). This model combines data from the Rotterdam section of the ERSPC trial with epidemiological data from the SEER database. Unlike the studies described above by Etzioni et al. (2002) and Telesca et al. (2008), the MISCAN model distinguishes between prostate cancers that would have been clinically diagnosed within a person's lifetime, and those that would not have been diagnosed in the absence of screening. Estimates from the MISCAN model indicate that 23–42% of prostate cancers are overdetected in situations where men of all ages are screened for prostate cancer every 1–4 years (Draisma et al. 2009; Heijnsdijk et al. 2009). The overdetection rate associated with a single PSA test is age-dependent, ranging from 27% in men aged 55 years to 56% for men aged 75 years (Draisma et al. 2003).

3.2.3 Physical harms associated with the PSA test

Physical harms associated with the PSA test are generally mild and infrequent.

In the screening arm of the PLCO trial, the PSA test led to complications at a rate of 26.2 per 10,000 screenings (primarily dizziness, bruising and haematoma), including three episodes of fainting per 10,000 screenings (Andriole et al. 2009).

3.2.4 Effects of the PSA test on quality of life

The immediate impact of PSA testing is on the psychological domain of quality of life. For men with a false-positive test result, this involves distress up to the point of biopsy, when a negative diagnosis may alleviate their anxiety. However, for some men, particularly those with a family history of prostate cancer, rising PSA may provoke anxiety despite a negative biopsy. For men with a true-positive test result, distress increases after the diagnosis is made and may be exacerbated as they face difficult decisions about disease management. Although the psychological impact of a false-positive test result may not be long-lasting, the high rate of false-positive test results makes it an important consideration when deciding whether or not to undertake PSA testing. Furthermore, the psychological impact of a true-positive test must be considered in the light of overdiagnosis.

There is a large body of literature from non-randomised trials concerning the psychological impact of clinically based cancer screening, primarily focused on false-positive results from cervical or colorectal cancer screening or mammography. Findings regarding the psychological impact of false-positive results have varied depending on the length of follow-up. Whilst cross-sectional studies of cancer screening programmes have reported a negative psychological impact of false-positive test results, a number of longitudinal studies have reported that false-positives have no lasting effects (Taylor et al. 2004). Considering that a large proportion of men undergoing PSA testing will never develop cancer but are exposed to the potential risk of false-positive test results, the main impact on health-related quality of life (HRQoL) of PSA testing is likely to be related to the psychological domains of quality of life and is therefore relevant to the decision of whether or not to test.

It is also important to acknowledge that men who undergo PSA testing and are true positives (i.e. subsequently receive a diagnosis of prostate cancer) will also experience a negative impact on quality of life due to psychological distress (Linden et al. 2012), which will be longer lasting than a false-positive result. This is particularly important when weighing up the overall benefits and harms of screening given that PSA testing increases the risk of detecting clinically insignificant cancers (see Section 3.2.2). In men who proceed with treatment, there will be further quality of life decrements as described in Section 3.4.

Evidence from randomised studies

As discussed in Section 2.5.3, both the PLCO and ERSPC trials are collecting data on the quality of life effects of PSA testing. Only interim results have been published to date. Johnson (2006) used the generic 36-item Short Form Health Survey (SF-36) to assess physical and mental components of quality of life in participants enrolled in the screening and control arms of the PLCO-Hawaii study site. Interpretation of the findings in the context of PSA testing is limited because the Johnson study does not report quality of life results specifically for patients screened for prostate cancer. Male subjects in the PLCO trial were screened for prostate, lung and colon cancer, while female subjects were screened for ovarian, lung and colon cancer. The questionnaire was mailed to all newly randomised PLCO-Hawaii participants at baseline (N=899). A follow-up questionnaire was mailed to respondents after they had been informed of the initial screening results (at which stage screen positive results had not been verified), and a second follow-up was sent approximately 3.5 years later. Results were provided for the 522 participants (58%) who completed all three questionnaires. The authors hypothesised that cases with more abnormal screens would have a lower self-perceived physical and mental health than those with fewer abnormal screens or those with no abnormal screens at each follow-up. Of the 282 screened participants who completed all three questionnaires, 31.6%

had one or more abnormal screening results. On the basis of physical and mental component summary scores (subscales were not reported), there was no significant difference between the genders and study groups (screened versus control), and no difference over time. The authors concluded that the number of abnormal screenings (at both the first and second follow-up) is not a significant determinant of self-perceived physical or mental health status. They acknowledged that the number of cancer diagnoses verified during the study (five PLCO diagnosed cancers plus seven others) was insufficient to show a significant effect of cancer diagnoses on SF-36 summary scores.

Taylor et al. (2004) reported the HRQoL of participants enrolled in the screening and control arms of the PLCO-Georgetown University study site (N = 483). As above, the study did not specifically assess the impact on HRQoL of screening for prostate cancer. Physical and mental components of quality of life were assessed using the 12-item Short Form Health Survey (SF-12). The Intrusion Subscale of the Impact of Events Scale (IES) was used to measure cancer-specific distress; however, only four of the standard seven items were selected to reduce respondent burden.[1] Participants in both study arms received two assessments; one via telephone at baseline (before screening) and another mailed at 1 year post-baseline (9 months post-results in the screening arm). Additionally, screening arm participants received a telephone assessment before the diagnostic work-up, an average of 17.9 days after screening results were sent via mail. Participants diagnosed with cancer were excluded from the 1 year assessment so that the results reflected the impact of screening rather than a diagnosis of cancer. Of the 215 screening arm participants who completed the baseline assessment, 77.2% were eligible for short-term outcomes and 69.3% completed all three assessments. Of those who were eligible for analysis, 63.3% had at least one abnormal screening result after the initial screen and 61.1% had at least one abnormal screening result after the second screen. Of note, the majority of the abnormal results were due to abnormal flexible sigmoidoscopy results. In the control arm, of 217 participants who completed the baseline assessment, 93.5% were eligible for short-term outcomes and 82.5% completed all three assessments. Controlling for baseline IES and potential confounding variables, Taylor et al. (2004) found that shortly after notification of cancer screening results, participants with abnormal results experienced a higher level of intrusive thoughts about cancer than those with all normal results (odds ratio [OR] 2.9; 95% CI 1.3–6.3; P=0.008). This difference was not maintained at the 9 month follow-up visit (where abnormal screen results were known to be false-positive; OR 1.9; 95% CI 0.89–4.2; P=0.096). The authors reported that screening result status was not significantly associated with the physical or mental component summary score outcomes in the logistic regression model (results from SF-12 subscales were not reported).

An early analysis of the Rotterdam section of the ERSPC investigated the short-term effects of PSA testing in a sample of men who underwent PSA testing, DRE and TRUS screening for prostate cancer (N = 626; Essink-Bot et al. 1998). Participants were asked to complete a health status questionnaire at baseline, immediately prior to screening, and at various times during follow-up. The health status questionnaire consisted of two generic self-assessed quality of life measures (SF- 36 and the EuroQol 5-dimension [EQ-5D] utility instrument); a specific measure for anxiety (the State-Trait Anxiety Inventory [STAI]); and a supplementary questionnaire about specific physical and functional consequences related to PSA testing and prostate biopsy.[2] To enable comparison with the general population, SF-36, EQ-5D and STAI scores were also assessed in a sample of asymptomatic men that had declined to participate in the ERSPC (N = 235). Men who received an unsuspicious screening result (N = 381) had significantly improved SF-36 bodily pain and mental

1 The four items were: i) 'I thought about cancer when I did not mean to', ii) 'I had waves of strong feelings about cancer', iii) 'Other things kept making me think about cancer', and iv) 'Any reminder brought up feelings about cancer'.

2 Subjects were retrospectively asked to grade pain and discomfort experienced during venous blood sampling for PSA testing, DRE, transrectal ultrasound, and, if relevant, prostate biopsy. Biopsy-specific items related to symptoms experienced one week after the biopsy. Participants were asked to grade limitations on daily activities, social activities and sex life that occurred as a result of prostate biopsy, on a five point Likert scale with the end points 'no limitations' and 'extremely limited'.

health scores, and SF-36 physical summary scores, compared with baseline. Anxiety levels, measured 1 week after being notified of an unsuspicious screen result on the STAI state anxiety and trait anxiety subscales, were significantly lower than anxiety levels measured immediately prior to screening. No significant differences were observed before and after notification of an unsuspicious screen result measured using the other SF-36 scores[3], SF-36 mental summary scores and EQ-5D scores. Men who received a false-positive screen result (N = 116) had significantly improved SF-36 bodily pain and general health perception scores, and SF-36 physical summary scores after a negative biopsy, compared with baseline. Anxiety levels increased in men that were waiting for biopsy results but returned to baseline values after a negative biopsy result was confirmed. Although a large proportion of subjects reported experiencing physical discomfort following investigative procedures (37% for DRE, 29% for TRUS, and 55% for prostate biopsy), most men reported that investigative procedures caused little to no interference with daily, social and sexual activities. Essink-Bot et al. (1998) noted that the STAI may have been too general for measuring anxiety in a screening context, but concluded that PSA testing did not affect the general health status of subjects in the short-term, and suggested that the HRQoL-related harms of PSA testing mainly occur in the treatment phase.

Taylor et al. (2002) investigated the impact of screening on prostate cancer-related distress through telephone interviews with a sample of men registered to undergo free prostate cancer screening at two hospitals in the United States. Baseline and post-screening interviews were completed by 136 of the 268 men (50.7%) invited to participate. Participants with normal screen results were asked to rate the importance of factors influencing their decision to undergo screening, cancer-related distress (measured by the full IES[4]), general psychological distress (measured by the 5-item Mental Health Inventory [MHI-5]), and knowledge about risk factors for prostate cancer[5] and the pros and cons of screening[6]. The most important reason for undergoing screening was 'seeking peace of mind about prostate cancer'. The number of men who endorsed prostate cancer-related intrusive thoughts decreased significantly from 49.6% at baseline to 34.5% after notification of a normal screen result ($P<0.01$). No change was observed in the number of men who endorsed avoidant thoughts or exhibited general psychological distress. Although awareness of the benefits of screening was high, few participants reported knowledge of limitations of screening. Controversy about the utility of prostate cancer screening was noted as a limitation by 11.2% of participants; pain, discomfort or embarrassment were noted by 8.2%; and the possibility of receiving a false-positive or false-negative screen result was recognised by 3.7%.

Korfage et al. (2006) analysed the impact of prostate cancer diagnosis on mental health and self-rated overall health in 52 patients with screen-detected cancer in the Rotterdam section of the ERSPC. HRQoL was measured before screening and after diagnosis, using the SF-36 mental health summary score, the SF-36 vitality summary score and the 'EQ-5D valuation of Own Health' visual analogue scale. One month after diagnosis with prostate cancer, participants had significantly lower SF-36 mental health summary scores and EQ-5D scores, compared with baseline (mean [standard deviation] SF-36 mental health summary score, 75.8 [17] versus 83.2 [12], P=0.001; mean EQ-5D, 74.5 [15] versus 80.2 [12], P=0.01). Seven months after diagnosis (after the initiation of active treatments), mental

3 No change was observed in SF-36 physical functioning, role-physical, general health perceptions, vitality, social functioning and role-emotional scores for men that received an unsuspicious screen result.

4 The full IES is a 15-item measure that rates the occurrence of intrusive and avoidant thoughts on a 4-point weighted scale (0, 1, 3 or 5), from 'not at all' to 'often', with a higher score indicating more distress. The intrusion subscale includes 7 items (e.g. 'I thought about it when I didn't mean to ' and 'I had waves of strong feelings about it'), and the avoidance subscale includes 8 items (e.g. 'I tried not to think about it' and 'I stayed away from reminders of it'). Due to the non-normal distribution of scores, Taylor et al. (2002) dichotomised subscale scores (one or more items endorsed versus none endorsed) for use in analyses.

5 Knowledge of risk factors was measured by asking participants to rate the degree to which 11 risk factors (including age, African American descent, family history and smoking) were related to developing prostate cancer on a 4-point scale (1 = not at all related to 4 = highly related).

6 Knowledge of the benefits and limitations of prostate cancer screening was measured by asking participants to answer an open-ended question: 'What is your understanding about the pros and cons of undergoing screening for prostate cancer?'

and self-rated overall health scores no longer differed significantly from baseline scores. Korfage et al (2006) suggested, however, that the observed impact of prostate cancer diagnosis on mental and self-rated health may have been underestimated, given that questionnaire respondents were participants in the ERSPC screening trial. Participants would have been more aware that there was a chance that they could be diagnosed with prostate cancer, compared with men who received a PSA test as part of a routine health check-up.

Evidence from non-randomised studies

Evidence for the effect of PSA testing on psychological aspects of quality of life is also available from non-randomised studies. Two prospective cohort studies (Level III–2 evidence) have compared psychological distress in men who receive false-positive and negative PSA test results. Both studies (McNaughton-Collins et al. 2004; Fowler et al. 2006) were based on a questionnaire that asked participants to provide information about their general health status, prostate biopsy experience and prostate cancer knowledge. The questionnaire included specific items on how many times the patient had a biopsy; reason for the biopsy (abnormal PSA test result, DRE, or both); whether results showed 'atypical cells but no cancer'; and how painful the biopsy was (rated on a scale of 0–10, with 0 being 'no pain at all' and 10 being 'pain as bad as you can imagine'). Men were asked how often during the past month they had thought or worried about prostate cancer, and whether or not they felt reassured following receipt of their biopsy or PSA results. McNaughton-Collins et al. (2004) compared the short-term impact of receiving a normal PSA test result (defined by PSA value <2.5 ng/mL; N = 233), with the impact of receiving a false-positive PSA test result, indicated by a benign prostate biopsy result (N = 167). Six weeks after notification of PSA test or biopsy results, 49% of men that received a false-positive PSA test result reported having thought about prostate cancer 'a lot' or 'some of the time', compared with 18% of men with a normal PSA test result. Men that had received a false-positive PSA test result worried more frequently about developing prostate cancer; reported a perception that life had changed for the better after receiving their biopsy result; and reported a perception of elevated prostate cancer risk (McNaughton-Collins et al. 2004).

Fowler et al. (2006) followed participants in the study by McNaughton-Collins et al. (2004) for an additional 12 months and reported that the observed differences in the proportion of men who thought or worried about prostate cancer were maintained. Overall, 26% (32/121) of men who received a false-positive PSA test result reported having worried 'a lot' or 'some of the time' that they may develop prostate cancer, compared with 6% (10/164) of men who received a normal PSA test result (P<0.0001). A larger proportion of men who received a false-positive PSA test result reported thinking about prostate cancer 'a lot' or 'some of the time', compared with men who received a normal PSA test result (33% versus 18%; P=0.0049); and a larger proportion reported thinking that their chance of developing prostate cancer was 'much more' or 'a little more' than average (45% versus 13%; P<0.0001). Medical record reviews showed that men who received a negative prostate biopsy result (N = 121) were more likely than those who received a negative PSA test result (N = 164) to have had at least one follow-up PSA test within 1 year (73% versus 42%, P<0.001); more likely to have had another biopsy (15% versus 1%, P<0.001); and more likely to have visited a urologist (71% versus 13%, P<0.001).

The studies by McNaughton-Collins et al. (2004) and Fowler et al. (2006) suggest that receiving false-positive PSA test results may have long-lasting psychological and socio-behavioural consequences but have several limitations. The absence of pre-screening data precluded determination of whether men in each group had similar psychological profiles at baseline. Men who had a previous biopsy were excluded from the group of men with a normal PSA test result but not from the group of men who underwent prostate biopsy. Additionally, a higher proportion of men who underwent prostate

biopsy had histories of prostatitis and BPH. These limitations are likely to bias the findings of McNaughton-Collins et al. (2004) and Fowler et al. (2006), overestimating the detrimental psychological effects of receiving a false-positive PSA test result.

Predicted net impact of PSA testing on quality of life

Heijnsdijk et al. (2012) used the MISCAN model described in Section 3.2.2 to predict the number of prostate cancers, treatments, deaths and quality-adjusted life years (QALYs) gained after the introduction of PSA screening. The model followed a hypothetical cohort of men aged 55–69 years over for the duration of their lifetime. Utility weights applied to screening attendance, biopsy, cancer diagnosis and post-treatment recovery health states were based on assumptions and observations from breast cancer screening studies. Utility weights applied to treatment health states were derived from published studies of treatment-related quality of life in men with prostate cancer. Such studies did not report specific utility weights for screen-detected cancers. It is unclear whether the utility weight estimates were measured in symptomatic or asymptomatic men. It was estimated that for every 1000 men screened annually for prostate cancer, there would be nine fewer prostate cancer-deaths (28% reduction), 14 fewer men receiving palliative therapy (35% reduction), 73 life years gained (8.4 years per prostate cancer-death avoided), and 56 QALYs gained (23% reduction from the number of life years gained). Model predictions indicated that the benefit of PSA screening was diminished by loss of QALYs resulting from the long-term effects of overdiagnosis and overtreatment. This relates to the specific quality of life impacts of treatment outlined in Section 3.4. Heijnsdijk et al. (2012) noted that longer term follow-up data from the ERSPC and other quality of life studies are essential before conclusive recommendations about quality of life effects of PSA screening can be made.

3.3 Benefits and harms associated with biopsy and other possible follow-up investigations

Follow-up investigative procedures for asymptomatic men who have an elevated PSA test include TRUS-guided biopsy, or less commonly transperineal biopsy, magnetic resonance imaging (MRI) and multi-parametric MRI (which is an emerging technology). Prostate biopsy is not a perfect diagnostic test, but sensitivity increases with the number of cores collected. Thus, the evidence for the diagnostic accuracy of biopsy varies according to the technique used.

Minor complications of biopsy are frequent and include haematospermia, haematuria, rectal bleeding and voiding problems. Major complications causing significant discomfort, disability, or requiring additional treatment or hospitalisation are less frequent but include pain and infection. Pain is considered a core dimension of quality of life and can be relieved, to some extent, by the use of local anaesthesia or sedoanalgesia. Although some studies have shown high rates of biopsy-related infection, antibiotic prophylaxis was not always administered, and in those studies where it was used, antimicrobial resistance was a growing concern.

Prostate biopsy is the most commonly performed follow-up investigative procedure for asymptomatic men with elevated PSA levels. In most instances, it is performed as a TRUS-guided biopsy or a transperineal biopsy. Both procedures involve use of a biopsy gun to collect tissue samples from regions of the prostate where clinically significant cancers commonly occur (Wolf et al. 2010). The diagnosis and grading of prostate cancer is based on histopathological examination of biopsy

samples. In general, the sensitivity of prostate biopsy increases with the number of biopsy cores collected. The diagnostic accuracy of different prostate biopsy methods has been reviewed in detail by Eichler et al. (2005).

Prostate biopsy is generally considered a safe procedure, with few severe but frequent minor complications. The main benefit of undergoing a prostate biopsy for asymptomatic men with elevated PSA levels is that it can confirm the presence of prostate cancer. If cancer is detected, a prostate biopsy can provide information about the extent of tumour differentiation, the location of the cancer within the prostate and note features that indicate whether the cancer remains localised (Eichler et al. 2005). Prostate biopsy can lead to the detection of high-risk pre-cancerous conditions that require monitoring such as high-grade prostatic intraepithelial neoplasia (Merrimen et al. 2009). Additionally, confirmation of a negative biopsy result can potentially relieve prostate cancer-related anxiety in men that have received a positive PSA test (Section 3.2.4).

The two primary risks associated with prostate biopsy are bleeding and infection. In most instances, bleeding resolves without additional treatment, however biopsy-related complications as a result of infection may be severe enough to require hospitalisation or cause death (Wolf et al. 2010). In the PLCO trial, diagnostic follow-up procedures (including prostate biopsy) for men with elevated PSA levels were decided on an individual basis by study participants and their primary physicians. Staff members at the PLCO study centres obtained medical records and medical record abstractors recorded information on relevant diagnostic follow-up results. Medical complications from diagnostic procedures occurred in 68 of 10,000 evaluations. These complications were primarily infection, bleeding, clot formation and urinary difficulties (Andriole et al. 2009).

Numerous publications have reported on biopsy-related complications observed at specific ERSPC study centres (Rietbergen et al. 1997; Djavan et al. 2001; Raaijmakers et al. 2002; Makinen et al. 2002; Carlsson et al. 2010; Loeb et al. 2012). The first large analysis by Raaijmakers et al. (2002), measured the frequency of complications associated with TRUS-guided biopsy in 5802 men that had been screened for prostate cancer within the Rotterdam section of the ERSPC between June 1994 and August 2001. Questionnaires on the occurrence of minor and major complications (including fever greater than 38.5°C, haematuria for longer than 3 days, haematospermia, pain after biopsy, medication use and hospital admission) were completed by staff urologists following 5676 of the 5802 biopsies (97.8% response rate). Minor complications were defined as expected side-effects of the biopsy procedure causing minimal or no discomfort and requiring no additional treatment. The most frequent minor complication was haematospermia (present in 50.4% of participants), followed by haematuria lasting longer than 3 days (22.6%), rectal bleeding (1.3%) and voiding problems (0.8%). Major complications, defined as adverse effects causing significant discomfort, disability, or requiring additional treatment, were far less frequent. Pain after biopsy was present in 7.5% of participants. Other major complications included fever (3.5%), hospitalisation (0.5%), and urinary retention (0.4%). Twenty-five men were admitted to hospital due to prostatitis and/or urosepsis (0.4%). One of these men was admitted to intensive care because of signs of septic shock.

Makinen et al. (2002) compared the acceptability and complications of TRUS-guided prostate biopsy in 100 asymptomatic men enrolled in the screening arm of the Finnish section of the ERSPC and 100 hospital-referred symptomatic men seen at the Tampere University Hospital in Finland during the period 1997 to 2000. Participants were asked to complete a self-administered questionnaire about their biopsy experience within 2 weeks of the biopsy before a definitive diagnosis. This questionnaire included specific questions on the psychological aspects of biopsy, acceptability of biopsy, and possible late complications (for example haematuria, rectal bleeding, haematospermia).[7] It was

7 Psychological aspects of biopsy included discomfort at biopsy, pain at biopsy and willingness to undergo repeat biopsy. Acceptability of biopsy and perception of adverse effects were assessed using a verbal rating scale with the options no or minor, moderate, and severe. Information on adverse effects and their duration and possible treatment were collected using structured questions. The amount of bleeding from the urethra and rectum or blood in the semen was subjectively evaluated using a similar three-point scale.

returned by 97% of screened men and 84% hospital-referred men. No major complications were seen immediately after biopsy but men in both groups experienced minor rectal haemorrhage and urethral bleeding. Although a large proportion of men in both groups considered biopsy to be moderately or very unpleasant, most men would be willing to undergo a repeat biopsy if needed. Persistent rectal bleeding and hematuria were common but less than one fourth of participants considered this disturbing. No differences were observed in the frequency of late complications between screened men and those that were hospital-referred.

Loeb et al. (2012) examined the risk of infectious complications and hospitalisations following prostate biopsy based on updated results from the Rotterdam section of the ERSPC. Between 1993 and 2011, 10,174 lateralised sextant prostate biopsies were performed in subjects with abnormal prostate cancer screen results. Antibiotic prophylaxis was administered to reduce the risk of biopsy-related infection. In most instances, this consisted of trimethoprim-sulfamethoxazole or a ciprofloxacin regimen administered prior to the prostate biopsy. Information on biopsy-related complications was collected by urologists 2 weeks after biopsy using a standard questionnaire that included specific questions regarding any fever or hospital admission.[8] Further information on hospital admissions, bacterial cultures and drug-resistance patterns was obtained from medical records if required. Fever was reported on 392 of 9241 questionnaires (4.2%) and was primarily managed on an outpatient basis. Hospital admission was reported in 78 of 9198 questionnaires (0.8%); only two patients required admission to the intensive care unit and no biopsy-related deaths were observed. Infection was the leading cause of hospitalisation, accounting for 81% of admissions in the 2 weeks following biopsy. Although culture data were only available for a limited subset of patients (n=60 for urine and n=56 for blood), the predominant pathogen detected in blood and urine cultures was Escherichia coli, followed by Pseudomonas aeruginosa and Klebsiella oxytoca. Of positive urine and blood cultures, 78.9% and 94.1% were resistant to at least one of the eight most common antimicrobial agents tested. The authors commented that because the key trials on antimicrobial prophylaxis for prostate biopsy were conducted more than a decade ago and antimicrobial resistance patterns have changed, additional studies are warranted to re-evaluate the optimal regimen in the contemporary era.

Carlsson et al. (2010) explored the possibility of excess mortality due to biopsy-related complications among men in the screening arm of the ERSPC trial. Participants from ERSPC centres in Finland, Netherlands and Sweden were identified for inclusion in the analysis if they had at least one eligible screening result (N = 50,194). Participants were prospectively followed for 365 days after their screening test with overall mortality (other than prostate cancer-specific mortality) as the major outcome. In total, 12,959 men had a positive screen and were indicated for TRUS-guided prostate biopsy, while 37,235 men had negative screening results. The compliance rate with biopsy recommendations for men with a positive screening result was 90.4%. Cumulative mortality rates were calculated by the Kaplan-Meier method at 120 days and 365 days after the screening test. To reduce the risk of selection bias (as men who undergo biopsy do not have contraindications, and may therefore have reduced risk of biopsy-related complications), mortality rates were compared between the full population of screening-positive men (i.e. including men that did not undergo biopsy, N=12,959), and screening-negative men (N=37,235). No statistically significant differences in the 120-day and 365-day cumulative mortality rates were observed between these groups[9] and none of the screening-positive men who died within 120 days of the screening test died of an obvious biopsy-related complication. Based on this large prospective study, Carlsson et al. (2010) concluded that prostate biopsy is not associated with excess mortality and that severe and fatal biopsy-related complications are rare.

8 Specific details of this questionnaire were not reported by Loeb et al.

9 At 120 days after the screening test, the cumulative mortality rate for screening-positive men was 0.24% (95% CI, 0.17% to 0.34%) versus 0.24% (95% CI, 0.20% to 0.30%) for screening-negative men (P=0.96). At 365 days after the screening test, the cumulative mortality rate for screening-positive men was 0.89% versus 0.84% for screening-negative men (95% CI not reported, P=0.96).

Rosario et al. (2012) reported on the rates of biopsy-related complications in men enrolled in a prospective cohort study, called the Prostate Biopsy Effects (PROBE) study, which was conducted within the ongoing ProtecT trial in the UK. Between 1999 and 2008, the ProtecT trial invited 222,700 community-dwelling men aged 50–69 years to attend nurse-led clinics in the community for counseling about PSA testing. Men who attended a clinic were informed about the implications and uncertainties associated with PSA testing (n = 111,148), and those who elected to undertake the test were offered a prostate biopsy if their PSA level was between 3.0–19.9 ng/mL (n = 10,297). Between February 2006 and May 2008, 1753 men enrolled in the ProtecT trial received a TRUS-guided prostate biopsy and 1147 of these participants also consented to participate in the PROBE study (65% participation rate). The PROBE study response rate 35 days after prostate biopsy was high at 89%.

Participants in the PROBE study completed a purpose-designed questionnaire on the adverse effects of prostate biopsy at baseline, 7 days after biopsy, and 35 days after biopsy. This questionnaire measured several outcomes including self-reported pain and discomfort[10]; biopsy-related symptoms[11], attitudes towards having a repeat biopsy[12]; and healthcare resource use. Prostate biopsy was well-tolerated in most men, with 85% of participants describing no pain or mild pain associated with the biopsy procedure itself. Adverse effects reported in the immediate period within 7 days of prostate biopsy were generally mild: 3% of men felt lightheaded or dizzy after biopsy; 7% passed blood in their urine; and 3% passed 'clots' in their urine. Adverse effects reported in the delayed period within 35 days of prostate biopsy, however, occurred more frequently and more men described their biopsy-related symptoms as moderate or severe problems. A summary of the prevalence of biopsy-related symptoms reported by Rosario et al. (2012) is presented in **Table 19**.

Within 35 days of prostate biopsy, 15 of the 1147 men included in the PROBE study required admission to a hospital (1.3%, mainly admitted for sepsis), and 119 (10.4%) had initiated a biopsy-related consultation with their general practitioner, a urology department nurse, or other source of medical advice (such as NHS Direct). The predominant reasons for seeking post-biopsy healthcare advice were infective symptoms (n=38) and urinary symptoms including haematuria (n=34), followed by the possibility of antibiotic-related adverse events (n=14), and discomfort or bleeding on defecation (n=10). In summary, findings from the PROBE study suggest that the risk of complications associated with follow-up procedures for asymptomatic men with elevated PSA levels may be greater than originally reported in publications from the PLCO and ERSPC studies. These findings are consistent with other analyses of biopsy-related hospital trends in Canada and the USA (Nam et al. 2010; Loeb et al. 2012).

10 Self-reported pain and discomfort were rated on a four-point Likert scale as none, mild, moderate or severe.

11 Questions on biopsy-related symptoms included the validated International Continence Society–male; International Consultation on Incontinence Modular Questionnaire–urinary incontinence; and UCLA-PCI Questionnaires. Participants were asked to rate the presence of specific biopsy-related complications (e.g. fever, flu-like shivers, pain, haematuria, haematochezia and haemoejaculate) as being none, minor, moderate or major. This information was used to derive a binary outcome for each symptom as present with moderate/severe problem versus not present/minor problem.

12 Men were asked to record their attitudes towards repeat biopsy by answering the question 'how much of a problem would you find having another biopsy in the future?' on a four point Likert scale (no problem, minor, moderate, major problem).

Table 19 Prevalence of biopsy-related symptoms in asymptomatic men with PSA levels greater than 3.0 ng/mL, aged 50 to 69 years, as observed in the Prostate Biopsy Effects prospective cohort study

Symptom	Presence of symptom		Presence of symptom causing a moderate or serious problem[a]	
	Reporting/ Respondents	% (95% CI)	Reporting/ Respondents	% (95% CI)
Experienced within 7 days:				
• Pain	425/1089	39.0 (36.2–42.2)	62/1085	5.7 (4.4–7.3)
• Fever	128/1090	11.7 (10.0–13.8)	44/1088	4.0 (3.0–5.4)
• Shivers	135/1089	12.4 (10.6–14.5)	35/1086	3.2 (2.3–4.5)
• Haematuria	693/1085	63.9 (61.0–66.7)	52/1074	4.8 (3.6–6.3)
• Haematochezia	354/1076	32.9 (30.0–35.8)	18/1061	1.7 (1.0–2.7)
• Haemoejaculate[b]	645/747	86.3 (83.7–88.6)	148/740	20.0 (17.2–23.1)
• Any infective/haemorrhagic symptom[c]	936/1047	89.4 (87.4–91.1)	196/1013	19.3 (17.0–21.9)
Experienced within 35 days[d]:				
• Pain	429/984	43.6 (40.5–46.7)	71/977	7.3 (5.7–9.1)
• Fever	172/985	17.5 (15.2–20.0)	54/981	5.5 (4.2–7.1)
• Shivers	185/985	18.8 (16.5–21.3)	49/979	5.0 (3.7–6.6)
• Haematuria	642/976	65.8 (62.7–68.7)	59/958	6.2 (4.7–7.9)
• Haematochezia	356/967	36.8 (33.8–39.9)	24/951	2.5 (1.6–3.7)
• Haemoejaculate[b]	605/653	92.6 (90.4–94.4)	172/646	26.6 (23.3–30.2)
• Any infective/haemorrhagic symptom[c]	881/937	94.0 (92.3–95.4)	240/887	27.1 (24.2–30.1)

Source: Adapted from Rosario et al. (2012), page 12, Table 2

[a] As part of the study questionnaire, participants were asked to rate the presence of specific biopsy-related complications as being none, minor, moderate or major. This information was used to derive a binary outcome for each symptom as present with moderate/severe problem versus not present/minor problem.

[b] Excludes 339 men reporting no sexual activity at either the 7-day or 35-day assessment.

[c] One or more of fever, shivers, haematuria, haematochezia and haemoejaculate, including men reporting no sexual activity at either 7-day or 35-day assessment.

[d] Includes only men with evaluable data for both 7-day and 35-day assessments.

3.4 Benefits and harms associated with treatment

There are a number of treatment options available to asymptomatic men who have been diagnosed with prostate cancer. These include radical prostatectomy, radiation therapy, androgen deprivation therapy, cryotherapy, and high-intensity focused ultrasound. The negative impact of these treatments on quality of life is widely acknowledged and must be taken into consideration when deciding on the most appropriate management strategy. Treatment-related harms should also factor into the decision of whether or not to undergo PSA testing, considering that some early prostate cancers that are detected through PSA testing will not result in future health problems even if left untreated (overdiagnosis). If such cancers are treated (over treatment), any decrement to quality of life caused by treatment (such as urinary incontinence, sexual dysfunction or bowel dysfunction, and any subsequent impacts on role, social and emotional function and global quality of life) may be considered an unnecessary harm (because there may have been no clinical benefit).

Current treatment options for asymptomatic men who have been diagnosed with prostate cancer include active surveillance, radical prostatectomy, radiation therapy (with and without androgen deprivation therapy), androgen deprivation therapy without radiation therapy, cryotherapy and high-intensity focused ultrasound (**Table 20**). Treatment choices are dependent on the stage and

histologic grade of cancer at the time of diagnosis, patient preferences for therapy, and factors such as age and comorbidities that affect a patient's overall health (Chou et al. 2011). Given that prostate cancer often progresses slowly and is generally diagnosed in older men with lower life expectancy, many patients do not require immediate therapy. The treatment goals for asymptomatic men with prostate cancer are therefore to reduce cancer-related death and disability while minimising intervention-related harms.

In men that do require treatment for prostate cancer, however, the active treatment options are associated with profound impacts on quality of life. These include urinary dysfunction, bowel dysfunction, sexual dysfunction, and fatigue (**Table 20**).

Table 20 Treatment options for prostate cancer

Treatment option	Treatment description and impact on quality of life
Active treatments	
Radical prostatectomy	Complete surgical removal of prostate gland with seminal vesicles, ampulla of vas, and sometimes pelvic lymph nodes (generally retropubic or, uncommonly, perineal approach). Risk of peri-operative complications and long-term effects on urinary and sexual function. Sometimes performed laparoscopically or with robotic assistance.
Radiation therapy	Delivered as external beam radiation therapy, in which multiple doses of radiation from an external source are applied over several weeks to destroy tumour cells; or brachytherapy, in which radioactive implants placed under anaesthesia using radiologic guidance. Risk of acute toxicities (lower urinary tract symptoms, loose bowel movements or diarrhoea, increased bowel dysfunction), long-term erectile dysfunction and a risk of bleeding from irradiation-induced telangiectatic vessels involving the rectum and bladder. Newer techniques, such as conformal radiotherapy, image-guided radiotherapy and proton radiation therapy, may enable more targeted delivery of radiation therapy and have a lower risk of treatment-related adverse events. Patients stratified as having high-risk disease, and many with intermediate risk disease (determined on the basis of Gleason score, serum PSA and clinical stage), are routinely administered androgen deprivation therapy neo-adjunctively, with continuation of this treatment for considerable periods following completion of the radiation treatment.
Androgen deprivation therapy (hormone therapy)	Oral or injection medications, or surgical removal of testicles to lower or block circulating androgens. Wide range of side-effects, including weight gain, sexual problems, emotional changes, loss of muscle mass, osteoporosis, adverse cognitive changes and fatigue. Primarily used for patients with advanced disease.
Cryotherapy	Destruction of tumour cells through rapid freezing and thawing using transrectal guided placement of probes and injection of freezing/thawing gasses. Risk of bladder outlet obstruction, tissue sloughing and impotence. No known impact on quality of life.
High-intensity focused Ultrasound	Tissue ablation achieved by intense heat focused on the identified cancerous area. Primarily used for patients with localised prostate cancer not suitable for radical prostatectomy. No known impact on quality of life.
Observational management strategies	
Active surveillance	Active plan to postpone intervention, in which patients are closely monitored for signs of disease progression. The decision to proceed with treatment with curative intent is based on factors such as rate of rise of PSA level and results of repeat biopsies.
Watchful waiting	Active plan to postpone intervention until patients exhibit symptoms of disease progression.

Source: Descriptions adapted from Chou et al. (2012); Wolf et al. (2010); Wilt et al. (2008).

Taylor et al. (2012) assessed the long-term effects of treatment for prostate cancer in a sample of prostate cancer survivors (N = 529) and non-cancer controls (N = 514) from the PLCO trial. The group of prostate cancer survivors included 269 men from the screening arm of the PLCO (mean [SD] years since diagnosis 7.52 [1.35]) and 260 men from the control arm (mean [SD] years since diagnosis 7.30 [1.30]). Disease-specific functioning was measured using items from the Expanded Prostate Cancer Index Composite Short Form (EPIC) scale on the level of bother associated with urinary, bowel, sexual and hormonal function (higher scores indicate better

functioning and less bother; range 0 to 100). Prostate cancer survivors in the control arm of the PLCO trial were older, less likely to have had a radical prostatectomy, and more likely to have advanced disease than prostate cancer survivors in the screening arm. Disease-specific functioning measured on the EPIC scale, however, did not differ between prostate cancer survivors in each arm of the trial. Among screened men, prostate cancer survivors had significantly worse sexual and urinary function than non-cancer controls (P<0.01). Screened men who received treatment with radiation therapy had significantly better sexual and urinary function, but worse bowel bother, compared with those who received radical prostatectomy or a combination of treatments including androgen deprivation therapy[13] (P<0.05 for all outcomes). Taylor et al. (2012) noted several study limitations (including the lack of pre-treatment data on disease-specific functioning and sampling bias) that may have accounted for the lack of difference in disease-specific functioning between screened and unscreened men.

Carlsson et al. (2011) compared the frequency of urinary incontinence and erectile dysfunction, before and 18 months after radical prostatectomy, in a subset of men with prostate cancer in the screening (N = 205) and control (N = 89) arms of the Goteborg trial. Urinary incontinence was measured using a questionnaire regarding the sporadic or regular use of pads or diapers where answers were measured on a five point scale ranging from 0 to 4, with scores greater than 2 indicating urinary incontinence. Before prostatectomy, 0.5% of men in the screening arm of the Goteborg study and 2.3% of men in the control arm reported urinary incontinence. After prostatectomy, urinary incontinence was reported by 14.3% of screened men and 20.5% of controls. Erectile function was assessed using the International Index of Erectile Function (IIEF)-5 questionnaire, which rates five items on a scale of 1 to 5, yielding a total score ranging from 1 to 25, where a higher score indicates a better sexual health. The version of the IIEF-5 used by Carlsson et al. (2011) included the answer 'no sexual activity' or 'did not attempt intercourse'. No total IIEF-5 score was calculated for men who reported this answer. Of men who reported being potent at baseline, 79.1% in the screening arm and 90.7% in the control arm reported impotence or sexual inactivity 18 months after radical prostatectomy. Carlsson et al. (2011) did not present any statistical comparisons between the rates of urinary incontinence and erectile dysfunction observed for men in the screening and control arms of the Goteborg study but suggested that the excess burden of permanent side-effects after population-based screening was relatively low.

Most other studies of the benefits and harms of treatments for prostate cancer have compared active treatments with observational management strategies, most commonly active surveillance or watchful waiting. Active surveillance is generally used to manage younger men with low-risk cancer who are otherwise healthy and involves regular monitoring of disease activity through PSA testing, DRE and prostate biopsy. The aim of active surveillance is to delay curative treatment for prostate cancer for as long as possible if and when it is warranted on the basis of biochemical, histologic or anatomical signs of disease progression. This deferral of treatment helps to minimise the impact of long-term treatment-related complications, such as impotence and urinary difficulty, in otherwise asymptomatic men (Dahabreh et al. 2012). Watchful waiting is a more passive strategy, where treatment is deferred until cancer-related symptoms develop. It is generally used to manage older men with localised prostate cancer and patients with comorbid conditions who are unlikely to benefit from aggressive treatment (Wolf et al. 2010). There is not yet a consensus among clinicians or researchers as to the definitions of active surveillance or watchful waiting, the standard protocols for the interventions, or how to optimally manage patients whose cancers show signs of progression. It should be noted that both active surveillance and watchful waiting can, in themselves, be associated with an increased risk of biopsy-related complications and an increased risk of prostate cancer-related obstructive urinary symptoms (Wolf et al. 2010).

13 The treatment combination group included all men who received hormone therapy, and men who received any combination of radical prostatectomy/radiation therapy/hormone therapy.

The AHRQ systematically reviewed the benefits and harms associated with treatments for screen-detected prostate cancer in 2011 (Chou et al. 2011). Given that many studies do not report on how prostate cancer was initially detected, the review also included studies of treatments for localised (Stages T1 and T2) prostate cancer, which accounts for the majority of cancers diagnosed in asymptomatic men. In total, the AHRQ review identified two RCTs and nine cohort studies on the benefits of prostate cancer treatment; and two RCTs, 14 cohort studies and 11 case series of treatment-related harms. It was noted that there was heterogeneity and potential bias in the way that different studies defined treatment-related harms.

One of the studies identified in the AHRQ review was a population-based prospective cohort study of HRQoL in Australian men with localised prostate cancer (Level III–2 evidence; Smith et al. 2009). This study included 2031 men aged less than 70 years who resided in New South Wales; were diagnosed with histopathologically confirmed localised prostate cancer (Stage T1a to T2c with no evidence of lymph node or distant metastases) between October 2000 and October 2002; and were notified to the New South Wales central cancer registry by May 2003 or no more than 12 months after their diagnosis (63.6% of cases identified from the central cancer registry and 76.4% of those invited to participate). Control subjects were randomly selected from the New South Wales electoral roll and were matched to cases by age and postcode (N=495; 62.8% of men contacted and eligible). Self-reported HRQoL was measured using the long-form University of California, Los Angeles Prostate Cancer Index (UCLA-PCI), which includes all items of the SF-12; 20 items that measure the domains of urinary, bowel and sexual function; and a single item measure of 'bother' for each urinary, bowel and sexual function domain. Study results were stratified by type of treatment (active surveillance; radical prostatectomy [nerve sparing and non-nerve sparing]; external beam radiation therapy; androgen deprivation therapy; combined external beam radiation therapy and androgen deprivation therapy; and brachytherapy [high-dose and low-dose]). It was unclear whether participants had received their prostate cancer diagnosis following an initial PSA test.

In addition to follow-up being short for survival considerations in the PSA screening studies mentioned above, the duration of monitoring required to clearly indicate any benefits that may result from local control from treating early disease is even longer. LUTS in the form of unrelenting frequency, incontinence and bleeding causes an undignified and unpleasant demise for a number of patients and are most commonly encountered at a very late phase in the natural history of prostate cancer. The significance of the problem, which constitutes a considerable workload in urology practice, is not addressed in any of the randomised studies or reflected in the paucity of publications on the topic.

The following sections of the non-systematic review summarise the findings of the AHRQ review of the benefits and harms of treatments for screen-detected or localised prostate cancer, with particular consideration of the results of the Australian cohort study (Smith et al. 2009). Additional evidence on the benefits and harms of radical prostatectomy has been included from recent publications on the Prostate Cancer Intervention versus Observation Trial (PIVOT; Wilt et al. 2012). The risk of confounding must be taken into consideration when interpreting the results of comparisons made in observational studies; in particular, the potential for bias due to differences in baseline morbidities between the two groups.

3.4.1 Radical prostatectomy

Radical prostatectomy in men with prostate cancer may decrease the risk of prostate cancer-specific mortality and all-cause mortality compared with watchful waiting. However, this treatment may result in long-term urinary incontinence, erectile dysfunction and peri-operative complications which impact on quality of life.

The AHRQ review of treatments for localised prostate cancer identified one good quality RCT, the Scandinavian Prostate Cancer Group Study Number Four (SPCG-4), that reported on the benefits and harms of radical prostatectomy (Level II evidence). After approximately 13 years of follow-up, prostatectomy in men with localised (primarily Stage T2) prostate cancer was associated with a 6.1% decrease in prostate cancer-specific mortality (RR 0.62; 95% CI 0.44–0.87) and a 6.6% decrease in all-cause mortality (RR 0.75; 95% CI 0.61–0.92), compared with watchful waiting (Bill-Axelson et al. 2011). Subgroup analyses suggested that these benefits were limited to men younger than 65 years of age. The applicability of the SPCG-4 to asymptomatic men undergoing PSA testing is unclear as randomisation occurred between 1989 and 1999, before the use of PSA testing became widespread. The relevance of this study to current practice in Australia is questionable since only 12% of patients had impalpable disease at diagnosis which was made by core biopsy or needle aspiration cytology. Furthermore, those recruited were required to have well-differentiated or moderately differentiated histology.

Observational studies identified in the AHRQ review found prostatectomy to be associated with decreased risk of prostate cancer-specific mortality (6 cohort studies; median adjusted HR 0.46; range 0.32–0.67) and all-cause mortality (5 cohort studies; median adjusted HR 0.32; range 0.25–0.50), compared with watchful waiting after 4–13 years of follow-up. These findings are consistent with the 2010 Cochrane review of radical prostatectomy versus watchful waiting for localised prostate cancer (Hegarty et al. 2010).

The PIVOT study is a recently published well-conducted RCT designed to compare the effectiveness of radical prostatectomy versus observation in 731 asymptomatic men diagnosed with localised prostate cancer after PSA testing (Level II evidence; Wilt et al. 2012). Participants in the PIVOT study were randomised to either radical prostatectomy (N=364), or observation with palliative therapy or chemotherapy offered on signs of symptomatic or metastatic progression (N=367). During the median follow-up of 10.0 years, no statistically significant difference in all-cause or prostate cancer-specific mortality was observed between men in the intervention and control groups. By the end of the study, 171 (47.8%) men in the intervention group had died, with 21 (5.8%) deaths attributed to prostate cancer or treatment. In comparison, there were 183 (49.9%) deaths in the control group, with 31 (8.4%) deaths attributed to prostate cancer or treatment. The hazard ratio for all-cause mortality was 0.88 (95% CI 0.71–1.08; P=0.22), while the hazard ratio for prostate cancer-specific mortality was 0.63 (95% CI 0.36–1.09; P=0.09). Wilt et al. (2012) concluded that radical prostatectomy did not significantly reduce all-cause or prostate cancer-specific mortality in men with localised prostate cancer detected by PSA testing, compared with observation. Bone metastases, however, were significantly less frequent in the intervention group (HR 0.40; 95% CI 0.22–0.70; P<0.0001).

Adverse effects associated with radical prostatectomy include peri-operative complications, urinary incontinence and long-term erectile dysfunction. Limited evidence on the frequency of peri-operative prostatectomy complications was identified in the AHRQ review of treatments for localised prostate cancer, however based on large database studies and case series investigations (Level IV evidence), the risk of peri-operative (30-day) mortality was estimated to be around 0.5%, and the risk of peri- operative cardiovascular events was estimated to be 0.6% to 3% (Chou et al. 2011). In the PIVOT

study, peri-operative complications occurred in 21.4% of men during the first 30 days after radical prostatectomy. The most common complications associated with radical prostatectomy were wound infection (4.3%), followed by urinary tract infection (2.5%), surgical repair (2.5%), bleeding requiring transfusion (2.1%) and urinary catheterisation more than 30 days after surgery (2.1%; Wilt et al. 2012).

Prostatectomy was associated with an increased risk of urinary incontinence compared with watchful waiting in the SPCG-4 (RR 2.3; 95% CI 1.6–3.2) and four cohort studies (median RR 4.0; range 2.0–11; Chou et al. 2011). In the Australian cohort study (Smith et al. 2009), 12.3% of men who underwent radical prostatectomy reported urinary incontinence (defined as needing to wear one or more pad per day to control urinary leakage) 3 years after diagnosis, compared with 1.1% at baseline (N = 81). The frequency of self-reported urinary incontinence was lower in men who underwent nerve sparing prostatectomy (43 of 494 cases, 9.4%), than those who underwent non-nerve sparing prostatectomy (66 of 476 cases, 15.1%). Compared with controls, men treated surgically reported significantly worse urinary function at one year (adjusted OR 0.17; 95% CI 0.13– 0.22). In the PIVOT study, 17.1% of men who underwent radical prostatectomy reported urinary incontinence[14] two years after prostatectomy, compared with 6.3% of those who underwent watchful waiting (P<0.001; Wilt et al. 2012).

Prostatectomy was also associated with an increased risk of erectile dysfunction in the SPCG-4 (RR 1.8; 95% CI 1.5–2.2) and five cohort studies (median 1.5, range 1.3–2.1; Chou et al. 2011). In the Australian cohort study (Smith et al. 2009), 77.4% of men who underwent radical prostatectomy reported impotence (defined as being unable to obtain an erection sufficient for sexual intercourse), 3 years after prostatectomy, compared with 21.5% at baseline. As with urinary incontinence, the frequency of self-reported impotence was lower in men who underwent nerve sparing prostatectomy (307 of 494 cases, 67.9%), than those who underwent non-nerve sparing prostatectomy (379 of 476 cases, 86.7%). Compared with control, cases who had nerve sparing radical prostatectomy had a better sexual functioning at three years (adjusted OR 0.10; 95% CI 0.08–0.13) than those who had non-nerve sparing surgery (adjusted OR 0.05; 95% CI 0.04-0.07; p<0.001). In the PIVOT study, 81.1% of men who underwent radical prostatectomy reported erectile dysfunction[15] two years after prostatectomy, compared with 44.1% of those who underwent watchful waiting (P<0.001; Wilt et al. 2012).

There was no evidence of a difference in bowel function between patients that underwent prostatectomy and watchful waiting, however the AHRQ review noted that side-effects including constipation, diarrhoea, haemochetzia and faecal leakage were sometimes reported (Chou et al. 2011). In the Australian cohort study, 3.5% of men who underwent radical prostatectomy reported moderate or severe bowel problems 3 years after diagnosis, compared with 4.4% at baseline (Smith et al. 2009).

The AHRQ review identified nine observational studies that reported HRQoL outcomes for men undergoing radical prostatectomy. Overall, prostatectomy was not associated with lower SF-36 physical and mental component subscores compared with watchful waiting. It was, however, associated with improvements on physical function and emotional function subscale scores (Chou et al. 2011). The AHRQ review noted that no difference in the risk of treatment-related anxiety was observed between those who underwent watchful waiting in the SCPG-4 study after 4 years of follow-up (Steineck et al. 2002). Subsequently published HRQoL results from this study, however, showed that more men who underwent radical prostatectomy reported moderate or great distress from erectile dysfunction (48% versus 36%), urinary leakage during the daytime (28% versus 15%) and urinary leakage at night (18% versus 9%), compared with those who underwent watchful waiting after a median follow-up of 12.2 years. Fewer men who underwent radical prostatectomy reported distress from voiding problems (27% versus 32%; Johansson et al. 2011[16]).

14 Defined as by patient reports 'have a lot of problems with urinary dribbling', 'lose larger amounts of urine than dribbling but not all day,' 'have no control over urine,' or 'have an indwelling catheter'.

15 Defined as the inability to have an erection or an erection sufficient for vaginal penetration.

16 Participants were asked to rate psychological symptoms (anxiety, depressed mood), sense of wellbeing, and HRQoL on a 7-point visual digital scale: one and two on this scale were assessed as low intensity, three to five as moderate, and six and seven as high intensity. Distress associated with physical symptoms (erectile dysfunction, weak urinary stream, urinary leakage, and nocturia) were assessed according to a verbal scale.

3.4.2 Radiation therapy

Radiation therapy in men with prostate cancer may decrease the risk of prostate cancer-specific mortality and all-cause mortality compared with watchful waiting. However, this treatment may result in urinary incontinence, erectile dysfunction and bowel dysfunction which impacts on quality of life, with adverse effects of androgen deprivation therapy, when given, being additive.

The AHRQ review of treatments for localised prostate cancer did not identify any RCTs comparing radiation therapy with observational management. Five cohort studies found that compared with watchful waiting, radiation therapy (delivered as external beam radiation therapy or unspecified modality) was associated with decreased risk of prostate cancer-specific mortality (median adjusted HR 0.66; range 0.63–0.70) and all-cause mortality (median adjusted HR 0.68; range 0.62–0.81), in men with localised prostate cancer after 4–13 years of follow-up (Chou et al. 2011). One population-based retrospective cohort study stratified mortality results by treatment modality (Zhou et al. 2009). This study analysed United States Medicare data on 10,179 men aged 65 years or older, diagnosed with incident prostate cancer in Ohio, between 1999 and 2001. All-cause mortality and prostate cancer-specific mortality results for men with localised prostate cancer (defined as local or regional disease; N = 8255) after 7 years of follow-up are shown in **Table 21**.

Table 21 All-cause mortality and prostate cancer-specific mortality for men with localised prostate cancer treated with radiation therapy versus watchful waiting, after 7 years of follow-up

Radiation treatment modality	Retrospective cohort of men with localised prostate cancer (N=8255)[a]	
	All-cause mortality Hazard ratio (95% CI)	Prostate cancer-specific mortality Hazard ratio (95% CI)
External beam radiation therapy	0.63 (0.53–0.75)	0.66 (0.41–1.0)
Brachytherapy	0.40 (0.32–0.52)	0.45 (0.23–0.87)
External beam radiation therapy with androgen deprivation therapy	0.57 (0.49–0.66)	0.97 (0.70–1.33)
Brachytherapy with external beam radiation therapy or androgen deprivation therapy	0.32 (0.26–0.41)	0.46 (0.27–0.8)

Abbreviations: CI, confidence interval

Source: Results from Zhou et al. (2009), as reported in Chou et al. (2011), page 41, Table 6.

[a] Localised prostate cancer was defined as local or regional disease.

The main harms associated with radiotherapy for treatment of localised prostate cancer are urinary incontinence, erectile dysfunction and bowel dysfunction. The AHRQ review identified one small RCT that reported an increased risk of urinary incontinence associated with radiation therapy compared with watchful waiting, however noted uncertainty around the estimate for risk of urinary incontinence due to small numbers of events reported in the trial (RR 8.3; 95% CI 1.1–63; Fransson et al. 2001). No increase in the risk of urinary incontinence was found in four cohort studies comparing radiation therapy to watchful waiting (median RR 1.1; range 0.71–2.0; Chou et al. 2011). The frequency of self- reported urinary incontinence did not increase in men that underwent external beam radiation therapy (with or without androgen deprivation therapy) in the Australian cohort study, and slightly increased in men who underwent brachytherapy (three cases reported in the low-dose brachytherapy group, N = 58; and three cases in the high-dose brachytherapy group, N = 47; Smith et al. 2009).

Radiation therapy was associated with an increased risk of erectile dysfunction, compared with watchful waiting, in six cohort studies, with similar estimates across studies (median RR 1.3; range 1.1–1.5; Chou et al. 2011). The frequency of self-reported impotence reported in the Australian cohort study was higher 3 years after diagnosis for all modalities of radiation therapy, compared with baseline (67.9% versus 30.2% for external beam radiation therapy, N = 123; 82.3% versus 39.1% for combined external beam radiation therapy and androgen deprivation therapy, N = 166; 36.4% versus 19.0% for low-dose brachytherapy, N = 58; and 72.1% for high-dose brachytherapy, N = 47; Smith et al. 2009).

Several cohort studies found radiation therapy to be associated with an increased risk of bowel dysfunction. In studies that evaluated bowel function over a period of time, bowel complications occurred frequently during the first few months after radiation therapy and lessened with follow-up. In the Australian cohort study (Smith et al. 2009), men who had external beam radiotherapy, both with and without androgen deprivation therapy, had worse bowel function than controls at one year (OR 0.51; 95% CI 0.34–0.74) and at three years (OR 0.58; 95% CI 0.39–0.86) after diagnosis. Compared with controls, bowel bother was worse in men who received external beam radiotherapy either alone at one year (OR 0.24; 95% CI 0.15–0.36) and three years (OR 0.22; 95% CI 0.14–0.34) or in combination with androgen deprivation therapy at one year (OR 0.24; 95% CI 0.16–0.35) and three years (OR 0.19; 95% CI 0.13–0.28). No cases of self-reported moderate or severe bowel problems were reported within the group that underwent low-dose brachytherapy (N = 58; Smith et al, 2009).

Despite the association between radiation therapy and urinary incontinence, erectile dysfunction and bowel dysfunction, no differences were observed in the HRQoL of men who received radiation therapy and those that underwent watchful waiting in one RCT and nine observational studies as measured by the SF-36 (physical and mental component summary scores) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer (EORTC QLQ-30; Chou et al. 2011).

3.4.3 Androgen deprivation therapy

> Androgen deprivation therapy is primarily used for the treatment of patients with advanced prostate cancer. It is associated with an increased risk of erectile dysfunction, impotence and fatigue. The side-effects of androgen deprivation therapy are wide-ranging and include hot flushes, weight gain, emotional and adverse cognitive changes, loss of muscle mass and osteoporosis.

Androgen deprivation therapy is primarily used for the treatment of advanced prostate cancers, which are not common in asymptomatic men diagnosed with prostate cancer after receiving a positive PSA test result (see Section 3.4). Approaches to androgen deprivation therapy include surgical castration (orchidectomy/orchiectomy) and treatment with luteinising hormone-releasing hormone (LHRH) agonists, anti-androgens, or gonadotrophin-releasing hormone (GnRH) antagonists. Androgen deprivation therapy can be administered as a monotherapy or as a neo-adjuvant and adjuvant to radiation therapy. It is associated with a wide range of common adverse effects including: weight gain, obesity, diabetes, cardiovascular disease, breast enlargement/tenderness, sexual problems, emotional changes, osteoporosis loss of muscle mass, anaemia and cognitive changes (Wolf et al. 2010; Schroder et al. 2012b).

Few studies have reported the benefits and harms of androgen deprivation therapy for men with screen-detected or localised prostate cancer. The AHRQ review identified two retrospective cohort

studies that compared the risk of all-cause mortality and prostate cancer-specific mortality between men who received androgen deprivation therapy for localised prostate cancer and those that underwent watchful waiting (Chou et al. 2011). The first retrospective cohort study was based on the SEER database and linked United States Medicare data of 19,271 men with localised prostate cancer aged 66 years or older (Lu-Yao et al 2008). Participants who had received androgen deprivation therapy as their primary treatment in the first 180 days following diagnosis (N = 7867) were compared with participants who received conservative management (excluding prostatectomy and radiation therapy; N = 11,404). The median age of the study cohort was 77 years and the median follow-up for overall survival was 81 months. Androgen deprivation therapy was associated with an increased risk of all-cause mortality (adjusted HR 1.2; 95% CI 1.1–1.2) and prostate cancer-specific mortality (adjusted HR 1.8; 95% CI 1.6–2.0). The second was conducted as part of a larger study of the effects of radiation therapy in men with localised prostate cancer. Zhou et al. (2009) reported that androgen deprivation therapy was associated with increased risk of prostate cancer-specific mortality (adjusted HR 1.3; 95% CI 1.0–1.7), but slightly decreased risk of all-cause mortality (HR 0.89; 95% CI 0.80–0.98) after 7 years of follow-up.

Androgen deprivation therapy was associated with an increased risk of erectile dysfunction in three cohort studies in men with localised prostate cancer (pooled RR 2.3; 95% CI 1.5–3.6), but was not associated with an increased risk of urinary incontinence or bowel dysfunction (Chou et al. 2011). In the Australian cohort study (Smith et al. 2009), androgen deprivation therapy was the treatment with greatest adverse impact on sexual function compared with control (OR 0.02; 95% CI 0.01–0.07). Of men who received androgen deprivation therapy, 97.8% (N = 61) reported impotence 3 years after diagnosis compared with 42.1% at baseline. No details were provided about specific androgen deprivation therapy regimens. A larger proportion of men who received combination androgen deprivation therapy and external beam radiation therapy reported impotence 3 years after diagnosis (82.3%; N = 166), compared with those who received external beam radiation therapy alone (67.9%; N = 123).

The AHRQ review noted that few studies reported on other harms associated with androgen deprivation therapy in men with localised prostate cancer. In one cohort study, breast swelling (20.0% versus 4.2%) and hot flushes (58.0% versus 10.6%) were more frequent in men who received androgen deprivation therapy during their first year of treatment (N = 245), compared with those who underwent watchful waiting (N = 416; Potosky et al. 2002). The AHRQ review excluded several studies on important harms (such as coronary heart disease, myocardial infarction, diabetes, or fractures) associated with androgen deprivation therapy for prostate cancer as they were not conducted in men with localised disease (Chou et al. 2011).

The AHRQ review of treatments for localised prostate cancer identified four cohort studies that compared the HRQoL of men who received androgen deprivation therapy and those that underwent watchful waiting. Each of the four cohort studies identified measured health status using the SF-36. Androgen deprivation therapy was associated with lower SF-36 physical component summary scores (mean differences of –3 to –8 points) and lower scores on most SF-36 subscales, in particular, vitality (fatigue). However, the AHRQ considered that there were too few studies to draw strong conclusions (Chou et al. 2011).

3.4.4 Cryotherapy and high-intensity focused ultrasound

Cryotherapy and high-intensity focused ultrasound are therapies for localised prostate cancer but few studies have investigated the benefits and harms of these treatments. There are currently no known impacts of cryotherapy and high-intensity focused ultrasound on quality of life.

Cryotherapy and high-intensity focused ultrasound are therapies for localised prostate cancer. Both therapies have been developed with the aim of reducing morbidity associated with radical prostatectomy and radiation therapy and both work by inducing cell death at tumour sites on the prostate gland (Heidenreich et al. 2012).

Cryotherapy uses freezing techniques to induce cell death by several mechanisms including dehydration resulting in protein denaturation, direct rupture of cellular membranes by ice crystals, vascular stasis, and apoptosis (Heidenreich et al. 2012). The AHRQ review of treatments for localised prostate cancer did not identify any studies that reported on the benefits of cryotherapy (Chou et al. 2011). One cohort study in men with screen-detected localised prostate cancer followed a small (N = 21) group of participants who received cryotherapy for a mean duration of 46 months (Smith et al. 2000). Among men older than 70 years of age, 25% of those who received cryotherapy reported total urinary control and 75% reported occasional urinary dribbling, compared with 55% and 39% among men who underwent watchful waiting. Among men younger than 70 years of age, 81% of those who received cryotherapy had total urinary control and 19% had occasional dribbling compared with 74% and 21% in those who underwent watchful waiting. A smaller proportion of men who underwent cryotherapy reported erections firm enough for intercourse for both age groups (0% versus 47% for men aged older than 70 years; 20% versus 81% for men aged younger than 70 years). The 2007 Cochrane review of cryotherapy for localised prostate cancer did not identify any relevant RCTs, however in case series studies (Level IV evidence), rates of erectile dysfunction following cryotherapy ranged from 47–100%, and rates of urinary incontinence ranged from 1–19% (Shelley et al. 2007).

High-intensity focused ultrasound is still considered to be an experimental treatment and uses focused ultrasound waves emitted from a transducer to induce tissue damage by mechanical and thermal effects (Heidenreich et al. 2012). The AHRQ review of treatments for localised prostate cancer did not identify any studies that reported on the benefits of high-intensity focused ultrasound (Chou et al. 2011). Five uncontrolled observational studies were identified, however the studies were relatively small (sample sizes ranged from 63–402; median N = 142), and all studies were limited by methodological shortcomings (e.g. incomplete information regarding method of patient selection). Rates of urinary incontinence following high-intensity focused ultrasound ranged from 2–11%, and rates of erectile dysfunction ranged from 45–53%.

4. Identified areas for further research

Evidence gaps:

- HRQoL effects (in particular, psychological impacts) of PSA testing.
- HRQoL effects (in particular, self-reported symptoms and aspects of functioning) of active surveillance or watchful waiting in screened men compared with unscreened men.
- Extent of overdiagnosis and overtreatment in Australia and worldwide.
- Long-term (>10 years) HRQoL effects of treatment of PSA-detected prostate cancer.
- Differences in harms and benefits between standard and nerve sparing radical prostatectomy and newer surgical techniques (e.g. robotic-assisted laparoscopic surgery) and older and newer radiation therapy regimens.

Areas that require further research and investigation include:

- The identification of age and risk related PSA cut-off values for 'negative' and 'positive' tests to maximise the probability that men who choose PSA testing are referred for further investigations when warranted and avoid invasive investigations and possible treatment when not warranted.
- Whilst the PSA test may be prostate-specific, it is not specific to prostate cancer. Therefore, continued research into alternative prostate cancer-specific markers and markers that differentiate between indolent and aggressive prostate cancers is required.

The evidence base will need to be updated after the following are published:

- HRQoL data from the ERSPC and PLCO studies.
- Extended follow-up results from the PLCO and ERSPC studies (**http://prevention.cancer.gov/plco/follow-up** and **http://www.erspc-media.org/**).
- Results from the ongoing ProtecT, CAP and PIVOT trials.

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Appendix I

There are many different quality of life instruments that have been used to assess the impact of PSA testing. The table below summarises the quality of life instruments reported in this Evidence Evaluation Report, together with the domains that they are designed to assess.

Name	Type	Domains	HRQoL issues/ symptoms
Generic instruments			
EQ-5D	HRQoL (also known as 'utility')	Mobility; self care; usual activities; pain/discomfort; anxiety/depression	Pain/discomfort; Self care; Emotional wellbeing
SF-36	HRQoL (sometimes considered 'health status')	Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health	Fatigue; Pain/discomfort; Emotional wellbeing; Occupation (employment/housework); Physical/activities of daily living; Social/family
SF-12	HRQoL (sometimes considered 'health status')	Physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health	Fatigue; Pain/ discomfort; Emotional wellbeing; Occupation (employment/housework); Social/ family; Physical/ activities of daily living
IES	Psychological morbidity (post-traumatic stress disorder)	Intrusion, avoidance, hyper-arousal	
MHI-5	Psychological morbidity (general distress)	Distress	
STAI	Psychological morbidity (anxiety only)	Trait anxiety and state anxiety	
Cancer-specific instruments			
EORTC QLQ-30	HRQoL	Global health status/QOL Functional scales: physical; role; emotional; cognitive; social Symptom scales/items: fatigue; nausea and vomiting; pain; dyspnoea; insomnia; appetite loss; constipation; diarrhoea. Financial difficulties	Physical/ activities of daily living; Constipation; Emotional wellbeing; Appetite; Pain/discomfort; Fatigue; Diarrhoea; Breathing; Sleeping; Nausea/vomiting; Social/ family; Financial; Cognitive (e.g. memory); Occupation (employment/housework); Recreation/leisure; Self care
Prostate-specific instruments			
EPIC	HRQoL	Urinary, sexual and hormonal function, bowel habits and overall satisfaction	Urinary; Incontinence (faecal); Fever/chills/ sweats/flushes; Hair loss; Incontinence (urinary); Sexual; Genital (male); Diarrhoea; Fatigue; Weight; Medical care; Pain/discomfort
UCLA-PCI	HRQoL	Urinary function, bowel function, sexual function, urinary bother, bowel bother, sexual bother	Urinary; Incontinence (urinary); Diarrhoea; Stomach (bloating/discomfort/ gas); Sexual; Genital (male)
IIEF-5	Erectile dysfunction	Erectile function	Erectile dysfunction, satisfaction with intercourse

Abbreviations: EORTC QLQ-30, 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer; EQ-5D, EuroQoL 5-dimension; IES, Impact of Events Scale; EPIC, Expanded Prostate Cancer Index Composite; HRQoL, health-related quality of life; IIEF-5, International Index of Erectile Function; MHI-5, Mental Health Inventory-5; SF-12, 12-item Short Form Health Survey; SF-36, 36-item Short Form Health Survey; STAI, State-Trait Anxiety Inventory; UCLA-PCI, University of California, Los Angeles, Prostate Cancer Index

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