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Cost-effectiveness of prostate cancer screening: a protocol for the systematic review of decision-analytical models

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1.0 Background

There is an ongoing debate about the harms and benefits of implementing a national screening programme for prostate cancer. The screening test (Prostate Specific Antigen, PSA) has poor sensitivity and specificity, meaning it produces a high proportion of false positive and false negative results. The PSA screen is followed by a biopsy which itself has relatively poor sensitivity. The screen test and biopsy are unable to distinguish between aggressive and indolent cancer, which may never cause symptoms within a man's lifetime. The subsequent radical treatments for screen and biopsy detected prostate cancer may impact significantly on quality of life and resources. The potential benefits of screening are for those men who have aggressive prostate cancer that is destined to progress, because the cancer is identified and treated earlier than in clinical practice, potentially improving life expectancy. Other screen detected men are, on the other hand, subjected to unnecessary tests and radical treatments.

Since the mid-1990s, there have been many model-based economic evaluations published assessing the cost-effectiveness of screening for prostate cancer, using a variety of modelling methods that in turn may impact the results from the model. As new data become available and new models are generated to incorporate these, it is important to learn from previous models. Therefore, a systematic review is required to identify the range of modelling methods that have

been employed to carry out an economic evaluation of screening for prostate cancer, the challenges that have been faced and the solutions that have been developed.

1.1 Aim

The aim of this study was to undertake a systematic review of these model-based cost-effectiveness analyses of to summarise the current evidence base and identify which modelling methods are most appropriate for assessing the cost-effectiveness of different screening strategies for prostate cancer.

To achieve this aim, a systematic review will be carried out with the following objectives:

1. Identify the policy question and context of the model-based evaluations
2. Collate evidence on the variability in model types, structures and assumptions used as well as the justification provided
3. Identify the evidence base for the decision model
4. Determine how uncertainty has been quantified in the decision models
5. Synthesise the data to draw out key issues

2.0 Methods

An initial scoping search was carried out in March 2016 to determine whether any systematic reviews have previously been conducted and to identify the most appropriate search terms.

Four relevant reviews were identified; on review was carried out as part of a report for Cancer Research UK (personal comms Wolstenholme) and the other was part of a report to the UK National Screening Committee [1]. The remaining two reviews were published in peer reviewed journals [2,3]. However, the two published reviews did not specifically review the details related to the modelling methods and the findings do not answer the specific review question here. As new model-based economic evaluations in the area have been published since the two reports (2010; 2011) and there is a lack of consistency in the studies identified in all of the reviews, it is necessary to conduct an up-to-date systematic review.

The guidelines by the Centre for Reviews and Dissemination, Cochrane collaboration for reviews and PRISMA for reporting will be followed [4-6]. The review is restricted to evidence

from the last 10 years (January 2006) to reflect current practice both in screening for prostate cancer and economic evaluation modelling methods.

2.1 Search strategy

Search terms

The search terms will include prostate cancer **and** screening **or** testing **and** economic evaluation **or** cost-effectiveness and their variants (See appendix 1 for details)

The search strategy consists of MeSH terms and free text terms. Search terms for economic evaluation and prostate cancer screening are based on previously published reviews [1,7], key words used in the known model-based economic evaluations of prostate cancer and those used by CRD to retrieve economic evaluations.

Databases

In April 2016, four electronic databases, the NICE website, UK National Screening Committee and reference lists from relevant studies will be searched for literature published between January 2006 and April 2016. If required, an update search will be carried out.

Search strategies will be developed for the NHS Economic Evaluation Database (EED) (2006-2014), Medline (2006-2016), EMBASE (2006-2014) and HTA databases (2006-2014).

The NHS EED search was only ran up to 2014 because the database no longer runs searches of other databases to identify economic evaluations, the last search was at the end of 2014.

Reports from NICE and UK National Screening Committee reports are also considered as these studies are important inputs to UK decision-making and can inform practice in other countries.

Study selection and inclusion criteria

Studies will be included if they meet the following criteria:

- Model-based economic evaluation of PSA screening strategies for prostate cancer
- Comparator of no screen or any screening interval

- Cost-effectiveness, cost-utility analysis, cost-consequence analysis, cost-benefit analysis
- Model-based economic evaluation using primary or secondary data
- Any PSA threshold for determining a positive result
- Any subsequent treatments following the PSA screen
- Any country and context
- An outcome of QALYs or life years gained/saved
- Natural history models of prostate cancer that did not include an economic evaluation, but were used to inform the model structure

The study selection will be carried out in two stages:

Firstly, the titles and abstracts of the identified studies will be assessed against the inclusion criteria to identify potentially relevant papers. 10% of the titles and abstracts will be reviewed by a second reviewer (SM). Where it is unclear if a study should be included it will be carried forward to the next stage and if an abstract is not provided the full text of the paper will be retrieved.

Secondly, the full text of the papers that may be relevant will be screened. Those studies that are deemed to be relevant following review of the full text will then be carried forward to the data extraction process. All of the full text papers will be reviewed by a second reviewer (SM).

Disagreements about study eligibility will be discussed and if they are not resolved a third reviewer will be consulted and a decision made by consensus.

Data extraction

Data extraction forms will be developed and pilot-tested on a random sample (5%) of included studies, and refined accordingly. Data extraction will be performed independently by two reviewers (SS, SM). Disagreement will be resolved by discussion between the two review authors.

Information will be extracted from each included study on:

1) The policy question and context (including the comparators and country)

2) Characteristics of the screening strategy (including frequency of screening, starting age and PSA threshold for a positive result)
3) Type of treatments and biopsies
4) Type of outcome measure (including cost per QALY gained and life-year gained)
5) Cost-effectiveness result
6) Characteristics of the model (including model type, structure, handling of disease natural history)
7) Sensitivity analysis (including the extent to which uncertainty in the cost-effectiveness result had been quantified.
8) Evidence base for quality of life, resource use and adverse effects
9) Reporting of overdiagnosis and overtreatment
10) Other key areas included quantification of overdiagnosis and overtreatment, the clinical basis for the model (stage or grade progression), and the method for incorporating quality of life and resource use.

Quality assessment

As the purpose of the review was to report the methodological approaches used in model-based economic evaluations, a formal quality checklist was not used to select studies, but relevant sections of an existing economic evaluation checklist along with recommendations from NICE were used to evaluate studies [8,9]. In addition, key clinical issues that are known to be a concern in prostate cancer were included, such as reporting and capturing of overdiagnosis. The methodological components that will be assessed include appropriateness of: (1) screening strategies and treatments considered, (2) reporting of overdiagnosis and overtreatment (3) appropriateness of model inputs, (4) consistency of model structure with disease pathway theory, (5) model type and justification, (6) time horizon of analysis, (7) cycle length and justification, (8) model inputs and data modelling (including baseline data, cost and quality of life), and (9) assessment of uncertainty.

Data synthesis

A narrative synthesis of data will be taken and therefore a discussion reflecting on the modelling methods used and the impact on the cost-effectiveness will be provided. As the

purpose of the review is to identify key issues in modelling screening for prostate cancer and the types of modelling methods used, the quality of the studies is not assessed in relation to deciding whether they are included in the review. Rather, analysis of quality issues will form part of the synthesis.

3.0 Dissemination

The review findings will be disseminated at conferences, including the 2016 symposium on 'Methods for Evaluating Biomarkers and Tests' and published in a peer reviewed journal such as Medical Decision Making, Value in Health or a high profile prostate cancer journal.

4.0 References

[1] Chilcott J, Hummel S, Mildred M. Option Appraisal: Screening for Prostate Cancer. School of Health and Related Research: University of Sheffield 2010.

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[7] Ramsay CR, Adewuyi TE, Gray J, Hislop J, Shirley MD, Jayakody S, et al. Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Health Technol Assess. 2015;19:1-490.

[8]NICE. Guide to the methods of technology appraisal. London: National Institute for Health and Care Research; 2013.

[9] Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8:iii-iv, ix-xi, 1-158.

Appendix

Appendix 1: Search terms

Search terms on prostate cancer were adapted from the 2015 HTA report by Ramsay et al [7] on Ablative therapy for people with localised prostate cancer: a systematic review and economic evaluation. Screening terms were adapted from the Chilcott et al [1] report. Economic search terms were based on the search terms used by analysts to retrieve evidence for the NHS EED.

Ovid - Medline

1. exp prostatic neoplasms/

2. (cancer adj3 (prostate or prostatic)).tw.

3. (carcinoma adj3 (prostate or prostatic)).tw.

4. (neoplas$ adj3 (prostate or prostatic)).tw.

5. (malignan$ adj3 (prostate or prostatic)).tw

6. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw

7. 1 or 2 or 3 or 4 or 5 or 6

8. Prostate-Specific Antigen/

9 (prostate specific antigen or prostate-specific antigen or psa) tw

10. Mass screening/

11. (Screen$ or test$) tw

12. 8 or 9 or 10 or 11

13. exp “costs and cost analysis”/

14. (model adj3 (economic or cost)).tw.

15. (cost adj3 (effect$ or util$)).tw.

16. (economic adj3 (anal$ or eval$)).tw.

17. (natural history model) tw

18. (screen$ model$) tw

19. (disease progression model$) tw

20. 13 or14 or 15 or 16 or 17 or 18 or 19

21. 7 and 12 and 20

22. limit 12 to yr=”2006-Current”

Ovid - EMBASE

1. prostatic neoplasms [not a MESH term]

2. exp prostate tumor/ [broader than cancer]

3. (cancer adj3 (prostate or prostatic)).tw.

4. (carcinoma adj3 (prostate or prostatic)).tw.

5. (neoplas$ adj3 (prostate or prostatic)).tw.

6. (malignan$ adj3 (prostate or prostatic)).tw

7. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. Prostate-Specific Antigen/

10 (prostate specific antigen or prostate-specific antigen or psa) tw

11. Mass screening/

12. (Screen* or test*) tw

13. 9 or 10 or 11 or 12

14. exp Economic evaluation/

15. (model adj3 (economic or cost)

16. (cost adj3 (effect$ or util$))

17. (economic adj3 (anal$ or eval$)

18. (natural history model) tw

19. (screen$ model$) tw

20. (disease progression model$) tw

21. 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 8 and 13 and 21

23. limit 12 to yr="2006-Current"

Cochrane – NHS EED

#1 MeSH descriptor: [Prostatic Neoplasms]

#2 (prostat* NEAR/3 (neoplasm* or cancer or carcinoma or tumor* or tumour* or malignan*)):

#3 screen* or test*

#4 MeSH descriptor: [Mass screening]

#5 (prostate specific antigen or prostate-specific antigen or psa) tw

#6 Prostate-Specific Antigen/

#7 #1 or #2

#8 #3 or #4 or #5 or #6

#9 #7 and #8

#10 limit publication year from 2006 to 2016, in Economic Evaluations

Cochrane - HTA

#1 MeSH descriptor: [Prostatic Neoplasms]

#2 (prostat* NEAR/3 (neoplasm* or cancer or carcinoma or tumor* or tumour* or malignan*)):

#3 screen* or test*

#4 MeSH descriptor: [Mass screening]

#5 (prostate specific antigen or prostate-specific antigen or psa) tw

#6 Prostate-Specific Antigen/

#7 #1 or #2

#8 #3 or #4 or #5 or #6

#9 #7 and #8

#10 limit publication year from 2006 to 2016, in Technology Assessments

Appendix 2: Data extraction forms

Data extraction form for systematic review of model-based economic evaluation methods in prostate cancer screening.

Reviewer	Date
Author	Year of study
Title	Publication type
Study objective	
Study characteristics	
Screening strategy	Comparator
Setting	Geographical location
Population -Participant age/ethnicity	Treatments considered
PSA threshold	Biopsy type
Economic evaluation type	Outcome measure
Economic evaluation	
Perspective	Direct costs & source
Measure of benefit used/valuation method/ population elicited & year	Indirect costs & source
Evidence source for quality of life	Currency
Decision model	
Model type & justification	Time horizon & justification
Model structure & justification	Time cycle & justification
Model pathway & justification	Software used
Natural history model/ comparator	
Characterisation of disease(stage and grade)	Evidence source for pathway
Data sources	
Sensitivity analysis	Cost-effectiveness result
Subgroup analysis	

Methods for uncertainty analysis (probabilistic sensitivity analysis/ Deterministic sensitivity analysis)	
Other	
Method for incorporating sensitivity and specificity	
Methods for handling conditional dependence between screen and biopsy	
How is overdiagnosis assessed and reported?	
How is overtreatment assessed and reported?	