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NHMRC Advice for Health Practitioners on Prostate Specific Antigen (PSA) Testing in Asymptomatic Men: Administrative Report

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NHMRC Advice for Health Practitioners on Prostate Specific Antigen (PSA) Testing in Asymptomatic Men: Administrative Report

This administrative report refers to the development of the following three documents:

- *PSA testing in asymptomatic men: Evidence Evaluation Report*[1] (the Evaluation Report)
- *PSA testing in asymptomatic men: Technical Report*[2] (the Technical Report)
- *PSA testing for Prostate Cancer in Asymptomatic Men: Information for Health Practitioners*[3] (the Information Document).

1. Introduction

In June 2012, the Australian Government Department of Health commissioned the National Health and Medical Research Council (NHMRC) to:

a) review the published scientific literature to ascertain the effectiveness of testing for prostate cancer using the PSA test, and the potential benefits and harms of PSA testing in asymptomatic men; and

b) develop an information document to be used by General Practitioners and other health practitioners, which will assist in providing consistent, evidence-based advice about the benefits and harms of PSA testing to asymptomatic men who are considering undergoing a PSA test.

With the assistance of a purposefully appointed Expert Advisory Group (EAG), three reports were prepared from the review of the evidence, the Evidence Evaluation Report and accompanying Technical Report, and the Information Document.

2. Contributors

a) PSA Testing Expert Advisory Group (EAG)

Selection of members

The Office of NHMRC (ONHMRC) selected the Chair and Members of the group with advice from the Department of Health. The intent was to form an EAG that included the perspectives of general practice, medical oncology, urology, pathology, public health, epidemiology, Aboriginal and rural health, evidence-based practice and consumers.

Efforts were made to invite individuals who:

- were able to make the necessary time commitment
- had relevant clinical experience in detecting, diagnosing and/or managing prostate cancer
- had relevant epidemiological experience
- were highly respected in their fields
- collectively gave a geographic spread across the nation.

[1] National Health and Medical Research Council (2013). P*rostate-Specific Antigen (PSA) testing in asymptomatic men: Evidence Evaluation Report*. Canberra: National Health and Medical Research Council.

[2] National Health and Medical Research Council (2013). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report*. Canberra: National Health and Medical Research Council.

[3] National Health and Medical Research Council (2013). *PSA testing for Prostate Cancer in Asymptomatic Men: Information for Health Practitioners*. Canberra: National Health and Medical Research Council.

Consumer representation

A consumer representative and prostate cancer survivor were sought from the Prostate Cancer Foundation of Australia, Australia's peak national body for prostate cancer in Australia. ONHMRC selected a second consumer based on personal experience in developing consumer materials on cancer and their contribution to previous board and committee appointments at both the Commonwealth and state level.

Both consumer representatives attended meetings of the EAG and were involved in the development of the Evidence Evaluation Report and Information Document.

Role of the EAG

The Terms of Reference for the EAG were to:

- advise on the scope, clinical questions and methodology of the evaluation of the evidence
- consider and provide comment on the findings of the evaluation
- advise on the scope, format and key audience for a PSA Testing information document
- assist in drafting this information document
- consider comments received during consultation on the draft information document
- provide input on a report to the Standing Committee on Screening (a subcommittee of the Australian Health Ministers' Advisory Council)

Declaration of conflict of interest process

Members of the EAG were required to declare their interests in writing, prior to appointment, as part of the process of the establishment of any NHMRC committee.

Throughout the project, members were required to inform the Chair of the EAG and ONHMRC of any changes to their interests. Declarations of interests were called for and updates requested as a standing agenda item at the beginning of each EAG meeting. A record of interests was managed by NHMRC and relevant information was made publicly available on the NHMRC website to ensure transparency.

Where EAG members were identified as having a significant real or perceived conflict of interest, the Chair could request that the member leave the room, or remain present but not participate in the discussion or in decision-making on the specific area relating to the conflict. There were no instances in the development process where the Chair required a member to leave the room during the discussion of the evidence because of a significant perceived or real conflict of interest.

The process to manage conflicts of interest and consensus for decision making was in accordance with the NHMRC *Guideline Development and Conflicts of Interest: Identifying and Managing Conflicts of Interest of Prospective Members and Members of NHMRC Committees and Working Groups Developing Guidelines*[4], which applies to all members of the Council of the NHMRC, Principal Committees and Working Committees (in accordance with the requirements of the *National Health and Medical Research Council Act 1992*).

EAG Membership

Professor Adele Green (Chair)—Senior Scientist, Queensland Institute of Medical Research

Professor Bruce Armstrong—School of Public Health, University of Sydney

Professor Dallas English—Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne

Professor Ian Olver—Chief Executive Officer, Cancer Council Australia

Professor Judith Clements—Institute of Health and Biomedical Innovation, Queensland University of Technology

Emeritus Professor Villis Marshall—General Manager, Royal Adelaide Hospital

Professor Robert Gardiner—UQ Centre for Clinical Research, Royal Brisbane and Women's Hospital

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[4] National Health and Medical Research Council (2012). *Guideline Development and Conflicts of Interest: Identifying and Managing Conflicts of Interest of Prospective Members and Members of NHMRC Committees and Working Groups Developing Guidelines*. Canberra: National Health and Medical Research Council.

Professor Jon Emery—School of Primary, Aboriginal and Rural Health Care, University of Western Australia

Dr Helen Zorbas—Chief Executive Officer, Cancer Australia

Professor Paul Glasziou—Centre for Research in Evidence-Based Practice, Bond University

Professor James Kench—Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital

Mr David Sandoe—Prostate Cancer Foundation of Australia

Mr John Stubbs—Chief Executive Officer, Canspeak, Sydney

Professor Madeline King—School of Psychology, the University of Sydney

b) NHMRC Project Team:

Ms Cathy Connor

Ms Melissa Lawrance

Ms Emma Breen

c) Department of Health Project Team:

Ms Toni Smith

Mr Chris Milton

Ms Kim Dobbie

Dr Tracey Bessell

3. Evidence Evaluation

The evaluation of the evidence was contracted by ONHMRC through a competitive process using the NHMRC Health Evidence Panel. The successful provider, Health Technology Analysts (trading as Optum), prepared a research protocol that outlined the scope, clinical questions, and methodology of the evidence review. Feedback on and approval of the protocol was sought from the EAG at their 24 August 2012 meeting before the review began.

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 drew on the procedures and requirements in *How to use the evidence: assessment and application of scientific evidence*[5] and *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines*.[6] This allowed each relevant article to be critically appraised and assigned a level of evidence based on a hierarchy according to the type of research question. Using standardised NHMRC processes, data was extracted from included studies and assessed for strength of evidence, size of effect and relevance of evidence. The evidence reviewer then translated the evidence into body of evidence statements.

Full details of the methodology used for the assessment and consolidation of the evidence are provided in the Technical Report that accompanies the Evidence Evaluation Report. This includes research question development, PICO (population, intervention, comparator, outcomes) criteria, search strategy, study eligibility, data extraction, and assessment of the body of evidence.

Internal methodological support was provided as needed by Professor Davina Ghersi, Senior Principal Research Scientist, particularly in wording of the evidence statements.

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5 National Health and Medical Research Council (2000). How to use the evidence: assessment and application of scientific evidence. Canberra: National Health and Medical Research Council.

6 National Health and Medical Research Council (2009). NHMRC additional levels of evidence and grades for recommendations for developers of guidelines Canberra: National Health and Medical Research Council.

Independent methodological review

The draft Evidence Evaluation Report and Technical Report (the draft Reports) were appraised by an independent reviewer, Professor Jenny Doust, Centre for Research in Evidence-Based Practice, Bond University. This review was used to assess the methodology and ensure the review activities articulated in the draft Reports were undertaken in a transparent, accurate and unbiased manner. The independent reviewer was required to declare any interests as per NHMRC standard processes described above.

The review highlighted some areas where clarity was needed to describe the methodology or outcomes of studies, ensure a clear distinction of issues or appropriate prioritisation of issues. If within scope, text was amended in response to the comments received.

Governance and stakeholder involvement

The project funder, the Department of Health, was consulted at various stages throughout the evidence review, with feedback provided on the research protocol and draft reports.

The draft Evidence Evaluation Report and Technical Report were discussed at a meeting of the EAG held on 22 January 2013, with the content further refined and the evidence statements finalised using a consensus approach. The revised draft Reports were circulated to EAG members on 6 February 2013 for further feedback.

After minor modifications, these versions were provided for comment to NHMRC's Health Care Committee (HCC) and Prevention and Community Health Committee (PCHC) on 26 February 2013 and 28 February 2013 respectively. The resultant draft Reports were discussed again by the EAG at a meeting held on 9 April 2013, and their approval of these draft Reports achieved on 29 April 2013.

The draft Reports were again provided to PCHC and HCC on the 9 May 2013 and 14 May 2013 respectively, who were satisfied with the content and the process undertaken to develop these.

The final Evidence Evaluation Report and the Technical Report were considered by the Council of NHMRC on 21 June 2013 for recommendation to the CEO for issuing. The CEO was pleased to accept the Council's advice and agreed to issue the reports under Section 7(1a) of the *National Health and Medical Research Council Act 1992*.

4. Information Document

Technical writing of the Information Document was contracted by ONHMRC through a competitive process using the NHMRC Health Evidence Panel. The successful provider, Health Technology Analysts (trading as Optum), prepared the draft Information Document.

The content of the Information Document was primarily drawn from the evidence statements and background text in the Evidence Evaluation Report, and informed by discussion of the EAG, and other authoritative reports.

Early in the development process, the EAG decided that the Information Document should extend beyond the evidence reviewed in the Evidence Evaluation Report only to include quantitative data and answers to questions frequently asked by patients and their families. Exclusion of this material would have greatly reduced the usefulness of the Information Document for health practitioners. The EAG therefore decided to source and cite additional authoritative references regarding Australian data on age-specific risks of diagnosis and death from prostate cancer, and risk estimates of potential harms and benefits of PSA testing. The EAG's discussion of public consultation submissions informed the refinement of the narrative as discussed below.

Governance and stakeholder involvement pre public consultation

The project funder, the Department of Health, was consulted at various stages throughout the development of the Information Document.

The scope, format and content of the Information Document were discussed at a meeting of the EAG held on 22 January 2013. Advice on the proposed plan was sought from NHMRC's HCC, PCHC and the Council of NHMRC on 26 and 28 February 2013, and 14 March 2013 respectively.

The structure of the Information Document was confirmed via a teleconference of the EAG on 9 April 2013. After the meeting, a draft Information Document was prepared by the Technical Writer and circulated to the EAG for comments. A teleconference of the EAG was held on 15 May 2013 to finalise the draft document for public consultation.

A pre public consultation draft was emailed to HCC and PCHC in early June 2013 for out of session comments, and discussed by the Council of NHMRC on 21 June 2013. Comments received were considered by the NHMRC Project Team, internal methodologist Professor Davina Ghersi, Senior Principal Research Scientist and the Chair of the EAG. Any modifications were confirmed with the Technical Writers to ensure language and wording was consistent and reflected the evidence identified in the Evidence Evaluation Report.

Public Consultation

The draft Information Document was released for a 30 day public consultation period, as required in the *National Health and Medical Research Council Act 1992*, from Monday 22 July 2013 to Tuesday 20 August 2013. The public consultation was advertised in major Australian newspapers and on the NHMRC website. Invitations were also sent to a number of key stakeholders.

A total of 17 formal submissions were received from seven individuals and 10 organisations, including health departments and non-government organisations. During this time, the draft Information Document was available on the NHMRC website, in addition to the evidence underpinning the Information Document[7], which was provided for background purposes only.

The EAG met on 17 September 2013 to consider all submissions, suggest a response, and where necessary, advise on revisions to the Information Document ensuring alignment with the evidence base. The revisions were made by the Technical Writer, and confirmed with the EAG.

Major considerations and how these were addressed by the EAG are outlined below:

- *The evidence evaluation was limited to Level I and II evidence, but lower levels of evidence should also be considered.* No changes were made as the EAG agreed that lower level evidence was outside the scope of the Information Document.
- *There was a lack of a formal recommendation on the use of PSA testing in asymptomatic men, and thus the need to acknowledge that the Information Document should not be used as the basis for formulating recommendations for clinical practice guidelines.* The Information Document was revised to clarify that it is not a substitute for relevant clinical practice guidelines and a reference provided to relevant clinical practice guidelines.
- *The need to specify the age-related reference limits for a PSA test result.* The EAG agreed the inclusion of age specific reference ranges may be useful for health practitioners but advised to refrain from including these ranges due to variations between pathology laboratories. The text was amended to acknowledge that an age-specific reference range is commonly used in interpreting the test results.
- *The distinction between prostate cancer diagnosis and treatment for prostate cancer needs to be clearer because treatment should not be assumed with diagnosis.* The EAG agreed that the text should be clearer in separating detection and treatment and surveillance option is now covered more explicitly.
- *The quantitative risk data presented were for low-risk men aged 60 years. A number of submissions requested the inclusion of quantitative risk data for other age groups of men.* The EAG agreed that their rationale for reporting estimates in the 60 year old age group remained current. This reflects the core age group reported in the studies identified in the Evidence Evaluation Report. The inclusion in this section of figures for ages <50 years is likely to be misleading, as PSA testing at this age is often used in the clinical setting to gain a baseline reading against which to compare results at later ages.
- *Disagreement over the evidence statement on the effect of PSA testing on prostate cancer-specific mortality, given the variability in the results of the individual randomised controlled trials.* The EAG agreed that the current wording is consistent with the evidence statement in the Evidence Evaluation Report. An amendment was made to clarify the findings of the two largest and most recent trials.
- *Confusion over the evidence statement on the effect of PSA testing on quality of life.* The EAG agreed that the wording is consistent with the research question and evidence statement in the Evidence Evaluation Report. The text was clarified to reflect the focus on quality of life in the long term and contain a cross reference to other quality of life effects discussed elsewhere in the document.
- *Confusion over the treatment options available after a man receives a diagnosis of prostate cancer. In particular, the need to distinguish between watchful waiting and active surveillance.* Surveillance is now covered more explicitly as a treatment option, and a definition of watchful waiting has been included.

Full submissions are available on the NHMRC Public Consultations website.

[7] The two documents were 1. National Health and Medical Research Council (2013). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Evidence Evaluation Report.* Canberra: National Health and Medical Research Council and 2. National Health and Medical Research Council (2013). *Prostate-Specific Antigen (PSA) testing in asymptomatic men: Technical Report.* Canberra: National Health and Medical Research Council. Both are available at http://www.nhmrc.gov.au/guidelines/publications/men4

Independent Expert Review

The post public consultation draft of the Information Document was reviewed by four independent expert reviewers. In particular, reviewers were asked whether the information paper served the purpose it was intended for and whether the evidence identified in the Evidence Evaluation Report and accompanying Technical Report had been appropriately translated into the Information Document. Expert reviewers were required to declare any interests as per NHMRC standard processes described above.

Expert review participants included:

- Dr Evan Ackerman—General Practitioner, Condamine Medical Centre, Queensland
- Professor Anthony Costello—Director of Urology, The Royal Melbourne Hospital
- Dr Addie Wooten—Clinical Psychologist and Director of Clinical and Allied Health Research Australian Prostate Cancer Research Centre, Epworth
- Professor James Bishop—Victorian Comprehensive Cancer Centre, Royal Melbourne Hospital (former Chief Health Officer)

Comments provided were discussed by the Chair of the EAG, the Evidence Reviewer/Technical Writer and ONHMRC Project Team, and the Information Document changed where appropriate.

Governance and stakeholder involvement post public consultation

Following public consultation and the incorporation of comments from expert review, a final draft Information Document was provided to PCHC and HCC on 25 and 28 October 2013 respectively, who were satisfied with the content and the process undertaken to develop the document.

The final Information Document was noted by the Council of NHMRC on 28 November 2013. The CEO subsequently agreed to release the Information Document to the Department of Health on 5 December 2013. The CEO agreed to issue the Information Document on 4 March 2014 under Section 7(1a) of the *National Health and Medical Research Council Act 1992*.