UK National Screening Committee

Screening for prostate cancer

28 October 2020

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for prostate cancer meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The UK NSC currently does not recommend systematic population screening for prostate cancer. The Committee based this recommendation on the evidence provided by the 2015 review carried out by Dr Karly S Louie.

Evidence Summary

3. The 2020 evidence summary was undertaken by Costello Medical, in accordance with the triennial review process: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process

4. The 2020 evidence summary assesses the quality and volume of evidence published since 2014 on the benefits and harms of prostate-specific antigen (PSA) screening, on risk stratification models to predict clinically important prostate cancer, and on the effectiveness and harms of various treatment strategies.

5. Expert input was sought during the scoping phase of this evidence review update from a variety of bodies and medical experts, which include but are not limited to experts on the UK NSC and reference groups that range from cancer specialists, epidemiologists and public health experts, and we also consulted with prostate cancer specialists and experts in prostate cancer research who gave valuable advice on the key questions that the 2020 review should cover. As per the UK NSC's process, expert advice was also sought before public consultation on the draft evidence summary.

6. The conclusion of the 2020 evidence summary is that the current recommendation, that whole population screening for prostate cancer should not be introduced in the UK, should be retained. This is for the following reasons:

    - the direction of evidence suggests that whilst PSA-based screening is associated with increased incidence of prostate cancer diagnoses, the effect on prostate cancer-specific mortality in comparison with no screening remains unclear. **Criterion 11 not met**

    - in line with the results of the previous review, there was evidence to suggest that PSA-based screening may be associated with overdiagnosis and biopsy-related complications. Also, the effect of PSA-based screening on quality of life remains unclear. Overall, it is not clear whether benefit gained from PSA-based screening programmes outweighs harms. **Criterion 13 not met**

    - no robust conclusions could be made on whether alternative screening tests perform better than PSA alone, and comparison of results between the studies was complicated by the use of varying thresholds for the PSA test comparator. However, magnetic resonance imaging (MRI) (either added to PSA-based screening or alone) and the Stockholm-3 (STHLM3) predictive model represent promising screening methods compared with PSA alone as they may offer greater diagnostic accuracy. Further validation studies are needed to support these findings. **Criteria 4 and 5 not met**

    - of the treatments that are currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of early-stage prostate cancer (those constituting 'usual care'), no single intervention could be identified as conclusively superior. This is because better disease progression offered by radiotherapy or prostatectomy, compared to observation, has to be balanced against increased adverse events, particularly in men who may not go on to develop clinically significant disease. **Criterion 9 not met**

Consultation

7. A three-month consultation was hosted on the UK NSC website. Direct emails were sent to 35 stakeholders. **Annex A**

8. Comments were received from the following stakeholders:

    i. A member of the public
    ii. Royal College of General Practitioners
    iii. Royal College of Radiologists
    iv. Royal College of Nursing
    v. Prostate Cancer UK
    vi. xxxx xxxx, University College London, xxxx xxxx
    vii. Prostate Scotland
    viii. Joint response from CHAPS Charity, TACKLE Prostate Cancer and ORCHID
    ix. Cancer Research UK
    x. British Association of Urological Surgeons (BAUS)
    xi. The National Cancer Research Institute Prostate Research Group

    (See **Annex B** for comments)

9. The public consultation closed on 21 September 2020. The total number of consultation responses received was 11.

10. The consultation comments received are presented below in **Annex B**.

11. Two stakeholders disagreed with the review recommendation. These were:

    - CHAPS Charity, Tackle Prostate Cancer and Orchid, which submitted a joint response
    - A member of the public

12. One stakeholder (Prostate Cancer UK) stated that it was not possible to know whether the conclusion reached by the review was the right one

13. Two stakeholders made no direct comment on the review recommendation. These were:

    - xxxx xxxx, University College London, xxxx xxxx
    - The National Cancer Research Institute Prostate Research Group

14. Six stakeholders broadly supported the conclusion of the evidence summary that a screening programme based on PSA testing alone should not be recommended in the UK. These were:

    - British Association of Urological Surgeons (BAUS)

- Cancer Research UK
- Prostate Scotland
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Radiologists

15. A member of the public shared a very personal account of members of her family being diagnosed with prostate cancer after a raised PSA test

    Response: The personal story submitted by the member of the public is an important statement of the effect that a prostate cancer diagnosis has on individuals and their families. The UK NSC acknowledges this and thanks the member of the public for their contribution to the consultation process.

16. The following themes were reflected across stakeholders' comments:

    - the review "lags behind" NICE guidelines and does not relate to current clinical practice because it should have made more mention of the recent introduction of multiparametric MRI (mpMRI) scanning prior to biopsy

      Response: evidence gaps identified by previous reviews are always the starting point for update reviews commissioned by the UK NSC. The 2015 review noted that the CAP and ProtecT trials were expected to report in 2016 and that these studies would be helpful to try and clarify whether a population-based PSA screening programme is effective to reduce mortality, as well as the comparative effectiveness of active surveillance and radical treatment therapies for screen-detected localised prostate cancers. The 2020 review specifically sets out to address this. During the early scoping stages of this update review, we also consulted with prostate cancer specialists and experts in prostate cancer research to identify the key questions that the review should focus on. The review questions are based on that discussion. Some stakeholders suggest that the review should have made more mention of the recent introduction of mpMRI scanning prior to biopsy in the current diagnostic pathway, as outlined in the NICE guidelines. The current review does indeed suggest that MRI (either added to PSA-based screening or alone) and the STHLM3 predictive model may

offer greater diagnostic accuracy relative to prostate cancer screening with the PSA test only. But the review also pointed out that no two studies evaluated the same index test(s) and comparator(s), and no screening approach was validated by a second, independent study. Therefore, although the evidence is promising, the review concluded that the lack of consistency at the moment precludes drawing robust conclusions on the appropriateness of alternative screening approaches for use in a national screening programme. For more specific information on the lack of evidence relating to the mpMRI treatment pathway, please see the reviewers' response under point 17 i) below

- the UK NSC should consider a more pragmatic approach to reviewing evidence for screening, which includes grey literature

Response: UK NSC evidence summaries are developed using rapid review methodologies. Rapid evidence assessments provide a proportionate approach as stated by the UK Government Social Research Service (https://webarchive.nationalarchives.gov.uk/20140402163101/http://www.civilservice.gov.uk/networks/gsr/resources-and-guidance/rapid-evidence-assessment/how-to-do-a-rea). They provide an evaluation of the 'volume and direction' of the literature on a single question or set of questions on a given screening topic. They are produced in accordance to the UK NSC evidence review process published on the GOV.UK webpage and available to the public: https://www.gov.uk/government/publications/uk-nsc-evidence-review-process

The aim of the process is to ensure that each topic is addressed in a proportionate manner and to provide reassurance to stakeholders that decisions are grounded in, and informed by, up to date evidence.

An analysis of published peer reviewed literature offers some reassurance about the quality of the evidence and is an essential element of the rapid review process. Different levels of evidence are considered for each review, depending on the questions under consideration. The different types of evidence will follow the accepted hierarchy of evidence, that is systematic reviews, meta-analyses, randomised controlled trials, cohort studies, case-control studies, cross-sectional surveys, case reports. The UK NSC aims to ensure that screening does more good than harm at reasonable cost because screening is delivered in large populations of

predominantly healthy people. This approach of evaluating evidence published in peer review journals is in line with the 2014 House of Commons Science and Technology Committee Report on health screening which recommended that the evidential barrier to the introduction of a screening programme should remain high (https://publications.parliament.uk/pa/cm201415/cmselect/cmsctech/244/24402.htm)

- the UK NSC is asked to provide more guidance on the research studies that will address the knowledge gaps outlined in this review, so that these studies can reach the required evidence threshold

  Response: The main function of the UK NSC evidence review process is to provide robust advice on screening to government ministers and the NHS in the four UK countries. The UK NSC is not a research commissioning or funding body, and primary research on screening topics should be undertaken to standards which are current in the UK. Having said that, it is worth noting that uncertainties, limitations of the available evidence and evidence gaps are outlined and discussed in all evidence summaries, including this one on prostate cancer (please see 'evidence uncertainties' section in the executive summary, the 'conclusions and implications for policy' section and the discussion for each individual question). The UK NSC is aware of ongoing modelling exercises which may stimulate discussion on potential screening strategies and the evidence gaps and research questions relating to them. The Committee is happy to be involved in discussions relating to these.

- consideration should be given to alternative approaches, such as a targeted screening programme aimed at selected groups of men who are at increased risk of prostate cancer or for example, a polygenic risk-stratified programme using multiparametric MRI (mpMRI)

  Response: Although screening for prostate cancer does not meet the criteria for a population screening programme, the UK NSC acknowledges that this is a rapidly evolving area and that alternative approaches to population screening for prostate cancer, such as targeted screening aimed at selected group of men at high risk, are gaining increasing attention in the research community. Following the 2019 publication of the Report of the Independent Review of Adult Screening Programmes in England, a clear recommendation was outlined which called for the creation of a

single UK wide advisory body which would look at both population and targeted screening. Work is underway to help define and consider key criteria that will help support decision-making on recommendations for the introduction of targeted screening programmes or risk assessment programmes.

- a couple of responses drew attention to the Prostate Cancer Risk Management Programme (PCRMP) in different ways:

  i) The Royal College of General Practitioners (GPs) for example was supportive of the current status quo whereby whole population screening for prostate cancer with PSA measurements is not currently recommended, although GPs can, after careful counselling on an individual basis, offer a PSA test to asymptomatic men over the age of 50 upon their request, but they should not proactively encourage PSA testing in asymptomatic men

  ii) The Royal College of Radiologists noted that clear guidance is needed for GPs on what to do when a result demonstrates a raised level (that is, repeat PSA, and if the result is still raised, refer to a urologist and ensure that mpMRI is performed next)

  iii) Cancer Research UK remarked that the PCRMP is fundamentally screening but contradicts the evidence supported by the UK NSC and is not informed by the same robust framework as other national screening programmes. Cancer Research UK recommends that this robust evidence review approach is also applied to the PCRMP, and any other guidance, to explicitly state that PSA tests should not be offered to men without symptoms because of a lack of impact on overall deaths from prostate cancer and the balance of benefit and harms

Response: The UK NSC acknowledges the discussion about the PCRMP and will consider this further as part of any discussion arising from the modelling exercises referred to above. The UK NSC acknowledges that prostate cancer is an important health problem, being the most common cancer in men and the second most common cause of cancer deaths in men in the UK. However, based on the findings of the current review, a national screening programme based solely on PSA testing cannot be recommended. In addition, although alternative approaches such as MRI (with or

without PSA) and STHLM3 appear promising, more validation studies are needed because at present, the lack of consistency among the research studies precludes drawing robust conclusions on the appropriateness of these screening tools for use in a national screening programme.

The PCRMP was established to ensure that men considering a PSA test are given information concerning the benefits, limitations and risks associated with having a test, and to support GPs in giving and discussing that information with men. A pack of materials was produced for primary care to help men make an informed choice about the PSA test, including a leaflet for men.

There is an evidence booklet for GPs, summary sheet for GPs and a leaflet for men. These can be downloaded, and the summary sheet and leaflet are in a print off format. The PCRMP is supported and advised by a multidisciplinary Scientific Reference Group comprising of representatives from the NHS, relevant professional bodies royal colleges, Department of Health and Social Care, patient sector and Prostate Cancer UK. The Group reviewed the evidence packs in 2015 and the revised packs was relaunched in 2016. These can be viewed at: https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview

17. Some technical points were also raised in the consultation comments. These were specifically addressed by the reviewers and are reported below:

- Exclusion of evidence

i) Lack of evidence relating to the mpMRI treatment pathway

Response: The reviewers recognise the important role of mpMRI for triaging prostate cancer risk in current practice in the UK, as detailed in the NICE guideline, NG131.[1] It is noted that the guidance recommends that mpMRI is offered as the first-line investigation for those with **suspected** clinically localised prostate cancer – for example, men who have already been found to have elevated prostate specific antigen (PSA) levels or have a suspicious digital rectal examination (DRE).

However, the remit of the UK NSC is population screening programmes. As such, the evidence considered in the review process was in the context of a general population in a primary care setting who have not previously been identified as at risk or suspicion of

prostate cancer. Therefore, any studies that initially included an unselected population where a group was then identified as being at suspicion of prostate cancer (e.g. by PSA test) followed by mpMRI would have been included in the investigation of question 3. Unfortunately such evidence was limited, however one study that fulfilled these criteria was identified. This was the Göteborg pilot study, which examined PSA ≥3.0 ng/mL alone versus PSA ≥3.0 or ≥1.8 ng/mL followed by mpMRI, and is summarised in the 'Sequential screening' section of the Results for question 3.[2] Similarly, had any studies been identified with general populations that considered the impact of mpMRI on mitigating harms from biopsy or overdiagnosis, these would have been included in the investigation of question 2, but no such studies were identified.

Meanwhile, other studies that did investigate mpMRI, for example the PROMIS study, were not eligible for inclusion in the context of a population-wide screening programme because they only included a preselected population of men who were already known to be at suspicion of prostate cancer, rather than starting with a cohort from the general population. Furthermore, PROMIS compared mpMRI with two biopsy strategies, rather than with PSA-based screening, so does not capture the first step in the pathway in clinical practice of identifying men who are at risk.[3]

As part of the rapid review process, it was only possible to draw conclusions based on the available direct, published, evidence. While it was noted that the evidence on mpMRI was promising in terms of specificity for detecting clinically significant prostate cancer, the Göteborg pilot study identified that this was at the expense of reduced sensitivity whereby clinically significant cases may be missed.[2] As such, it was noted in the conclusions for question 3 that it would be beneficial for more evidence on mpMRI to support these findings.

ii) Exclusion of specific studies

Response: Along with PROMIS, other studies that were identified as having not been included in the review were:

- PRECISION[4]
- STAMPEDE[5]
- ASCENDE-RT[6]

- Kaiser Permanente (Northern California) study[7]

The PRECISION trial was not included for the same reason as the PROMIS trial (please refer to part i). The trial did not include a population that were invited for screening; only men who had already been identified as having elevated risk were included and the comparison was between mpMRI and standard biopsy.

The STAMPEDE trial was not included as this was an interventional study whose eligible patients were those with newly-diagnosed metastatic, node positive or high-risk locally advanced prostate cancer. In order to be included for question 4, studies needed to include a population of men with early-stage prostate cancer to reflect the population that would benefit from treatment having received an early diagnosis following screening.

The ASCENDE-RT trial was included as part of 2 systematic literature reviews (SLRs) that were included for question 4 (NG131 Evidence Review C8 and Chin 20179), therefore the specific publication was not included separately. However, the reviewers have ensured that the result of higher biochemical disease-free survival (bDFS) in the group treated with external beam radiotherapy (EBRT) plus low dose rate brachytherapy (LDR-BT) boost versus EBRT alone is more clearly drawn upon in the results section.

The Kaiser Permanente study was not included as this was a retrospective cohort study that investigated PSA screening. For questions 1 and 2, data from randomised controlled trials (RCTs) was prioritised due to the higher methodological quality of this study design.

- Interpretation of the ProtecT trial

  Response: In this review, the ProtecT trial was included as part of 2 SLRs that were included for question 4 (NG131 Evidence Review G[10] and Ng 2019[11]). ProtecT compared 3 treatment options: active surveillance, radiotherapy (RT) and prostatectomy.

  The reviewers note that the conclusions drawn from ProtecT in this review are similar to those from NG131 Evidence Review G, which informed the committee's recommendations in the latest NICE guidance. Evidence Review G concluded that *"Based on the evidence from the ProtecT trial, the choice of active surveillance,*

prostatectomy or radiotherapy appears to be a trade-off between the benefits offered by prostatectomy and radiotherapy against their potential risk of side effects. Benefits of prostatectomy and radiotherapy over active surveillance included reduced risk of disease progression and metastatic disease. Harms associated with prostatectomy over active surveillance were increased issues with incontinence and issues with erectile dysfunction whilst harms associated with radiotherapy over active surveillance were increased issues with urinary and bowel function" (p. 12). The rapid review performed for the UK NSC similarly concluded that for prostatectomy vs active surveillance: *"The key findings were a lower risk of disease progression/metastases with prostatectomy than either watchful waiting or active surveillance" and "patients undergoing prostatectomy had an increased frequency of adverse events including GI and GU toxicity"* (p. 111). For radiotherapy vs active surveillance: *"disease progression, distant metastases and biochemical failure were decreased in patients treated with RT compared with observation. Prostate cancer-related death was decreased on average when comparing RT with active surveillance in ProtecT, however the upper limit of the wide CIs was also consistent with an increase in prostate cancer-related death. Overall mortality was unchanged"* (p. 112).

Ultimately, the rapid review concluded that "*Overall, of the treatments that are currently recommended by NICE (those constituting 'usual care'), no particular intervention could be identified as conclusively superior. Better disease progression offered with RT or prostatectomy vs observation has to be balanced against increased adverse events"* (p. 114). While it may certainly be a good and safe treatment option for some cases, the evidence unfortunately could not conclusively demonstrate that active surveillance is superior to radical therapy, even for those patients with low/intermediate risk (as in the ProtecT study). This is aligned with the NICE recommendations to offer all three treatments as an option for those with low- to intermediate-risk prostate cancer whereby a preference decision table is included to enable the clinician and patient to make the right choice for them on a case-by-case basis (p. 42).[1]

The notion that the cancer progression seen among the active surveillance cohort in the ProtecT study may be in part the result of the inferior diagnostics used in the trial compared to those in current practice is an interesting consideration. However, it is unfortunately not possible to quantify this based on the available evidence.

Nonetheless, we thank the commenters for raising this point and have expanded on the point surrounding difficulties in predicting significant cases at an early stage to note that in current practice, this may be improved with the addition of mpMRI in the risk triage pathway.

- Other points

Response: Other adjustments that the reviewers have made to the rapid review include rephrasing wording as necessary throughout to improve clarity; clarifying whether evidence was available for specific subgroups including different risk groups of prostate cancer for question 4 (low, intermediate and high) if this was not already discussed; and adding reference to the low rate of overtreatment for prostate cancer in recent years (specifically citing the National Prostate Cancer Audit [NPCA]) in the 'Applicability' section of the summary for question 2.

References cited in the reviewers' responses

1. National Institute for Health and Care Excellence (NG131). Prostate cancer: diagnosis and management. NICE guideline [NG131], 2019.

2. Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Goteborg Randomised Screening Trial. Eur Urol 2016;70:566-573.

3. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-822.

4. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine 2018;378:1767-1777.

5. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. The Lancet 2016;387:1163-1177.

6. Morris WJ, Tyldesley S, Rodda S, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high-and intermediate-risk prostate cancer. International Journal of Radiation Oncology* Biology* Physics 2017;98:275-285.

7. Alpert PF. New evidence for the benefit of prostate-specific antigen screening: data from 400,887 Kaiser permanente patients. Urology 2018;118:119-126.

8. NICE Guideline Updates Team. Prostate cancer: diagnosis and management [C] Evidence review for radical radiotherapy. UK: National Institute for Health and Care Excellence, 2019.

9. Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. J Clin Oncol 2017;35:1737-1743.

10. NICE Guideline Updates Team. Prostate cancer: diagnosis and management - intervention comparisons [G] Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer. UK: National Institute for Health and Care Excellence, 2019.

11. Ng KT, Kwok PE, Teoh WY. Conservative management and radical treatment in localised prostate cancer: A systematic review with meta-analysis and trial sequential analysis. Journal of Clinical Urology 2019;12:228-238.

Recommendation

18. The Committee is asked to approve the following recommendation:

A systematic population screening programme for prostate cancer is not recommended.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Test	
4. There should be a simple, safe, precise and validated screening test	**Not Met**
5. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed	**Not Met**
The Intervention	
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered	**Not Met**
The Screening Programme	
11. There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened	**Not Met**
13. The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	**Not Met**

List of organisations and individuals contacted Annex A

1. xxxx xxxx
2. The British Association for Cancer Research
3. British Association of Urological Nurses
4. The British Association of Urological Surgeons
5. Cancer Black Care
6. Cancer Research & Genetics UK
7. Cancer Research UK
8. xxxx xxxx
9. CHAPS
10. Chestnut Appeal
11. Citizens affected by prostate cancer
12. Everyman
13. Faculty of Public Health
14. Macmillan
15. Northern Ireland Cancer Network
16. Orchid
17. PHE adult screening programmes
18. Primary Care Urology Society
19. Primary Care Urology Society
20. Prostate Cancer UK
21. Prostate Scotland
22. Prostate UK
23. Radiology: National Clinical Director for Diagnostics NHSE
24. Royal College of General Practitioners
25. Royal College of Nursing
26. Royal College of Pathologists
27. Royal College of Physicians
28. Royal College of Physicians and Surgeons of Glasgow
29. Royal College of Physicians of Edinburgh
30. Royal College of Radiologists
31. Royal College of Surgeons
32. Royal College of Surgeons of Edinburgh
33. Society and College of Radiographers
34. Tackle Prostate Cancer
35. Tenovus

Annex B

Screening for prostate cancer

Consultation comments

1. xxxx xxxx**, members of the public**

Our men need Prostate Cancer Screening!!!

My husband had no symptoms whatsoever, he went to a PSA testing evening run by the xxxx xxxx March 2017.

We were contacted that he had a score of 12 and to see our GP immediately ,who , retested him he scored 12 again.

Quick referral to a Specialist Urologist who performed a rectal examination and confirmed a large tumour.

Biopsies showed a Gleason score of 9 very aggressive malignant tumour of the prostate.

37 days of radiotherapy followed with hormone treatment running alongside.

This is still on going till August 2020.

My husband would be dead now without this test as he displayed no symptoms whatsoever, and you and I know full well that when men do show symptoms the tumour has usually burst out of the prostate capsule causing secondary tumours. With an inevitable death sentence.

This happened to my brother who survived only 9 months from diagnosis. My husband and brother were diagnosed 5 months apart.

So its very simple, as women have breast screening, our men should have Prostate Cancer Screening .

Our men are being failed and dying unnecessarily.

Regards,

XXXX XXXX

2. Royal College of General Practitioners

Name:	XXXX XXXX XXXX XXXX XXXX XXXX	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Royal College of General Practitioners		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes (organisation name) **No**

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General	General	The RCGP agrees with the UK NSC stance that prostate cancer screening with PSA measurements is not recommended at the current time, but that GPs can, after careful counselling on an individual basis, offer a PSA test to asymptomatic men over the age of 50 upon their request, but should not proactively encourage PSA testing in asymptomatic men.

UK National Screening Committee

3. Royal College of Radiologists

Name:	Paul Alexander	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Royal College of Radiologists (I am submitting on behalf of this organisation)		
Role:	Policy & Academic Research Manager		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
All	General comment	PSA screening on its own is not recommended as it picks up too many men without cancer. PSA screening and multi parametric MRI could be the first part of a dual screening test, backed up by new transperineal biopsy in future, as the latter is far safer than transracial biopsy. When multi parametric MRI is used in the right setting, it is the right test, post PSA and in 5y will be the gold standard. However, reporting multi parametric MRI will provide a significant workforce challenge for radiologists and needs to become part of training with additional courses to teach existing consultants the resource needed to put this in place must be considered.
All	General comment	While screening prostate cancer in this recommendation paper is synonymous with a review of evidence for the benefits vs. the

		risks of PSA testing in asymptomatic men 50 years of age or older: • There is no comment in the summary of using a single PSA test at age 50 as a one-off screen for risk of subsequently developing clinically significant prostate cancer • The focus on a single, previously acknowledged, poorly specific test for screening has potential to significantly limit the benefit of the review • The conclusion that PSA testing is not justified is as correct as it is inevitable - the limitations of PSA alone as a screening test are very well recognised.
Questions 2 and 3	Amalgamation	Question 2 and Question 3 are so inter-linked that a section should be included at looking at the 2 'distilled' summaries together wherein the risks[1] are estimated for PSA/mpMRI screening model.
Question 4	Phrasing ambiguity	Early stage prostate cancer is an ambiguous term and would benefit from greater refinement: • Distinction needs to be made between clinically significant disease[2] and clinically insignificant disease • Distinction needs to be made between organ confined disease and locally advanced disease without nodal/metastatic spread and extra-prostatic disease of stage N1 or worse • These end-points are frequently not established – prostate biopsy is notoriously 'hit and miss', although becoming less so with mpMRI first; histology Gleason grading has large inter-observer variability; many men treated for prostate

[1] (a) over diagnosis, taken to mean the over-detection of clinically insignificant cancer and (b) morbidity and mortality from biopsy

[2] The definition of clinically significant disease, while still debated, will be taken as the definition used in PROMIS definition 1

		cancer 9the majority) do not have definitive surgery and therefore do not have a final pTNM stage; even those undergoing surgery rarely have systematic lymph node resection limiting pTNM stage accuracy; imaging is very poor at identifying lymph node involvement and quite limited in detecting bone spread • mpMRI is not consistently available, is not consistently acquired to a high or even uniform standard, is not consistently reported to a high level with a tendency to over call findings • Biopsy approaches are in a state of flux with more understanding of systematic vs. targeted vs. combined approach as well as a move from trans-rectal to trans-perineal approach with reduced sepsis rates.
Question 2 (page 57)	Conclusion suggestion	These are based on long running RCTS in which PSA alone was used for the majority of assessments, so over-diagnosis (of clinically insignificant disease) would be a given. A two-stage screening model would arguably reduce NND to an acceptably low number.
Question 3 summary	Links	Question 3 summary is consistent with the newly adopted mpMRI first approach that now pertains in UK • Results – sequential screening page 71-79: 'In the Göteborg pilot study, the most clinically useful screening strategy evaluated was PSA ≥1.8 ng/mL followed by MRI (strategy 3), which was superior to both PSA ≥3.0 ng/mL followed by MRI (strategy 2) and PSA testing alone (strategy 1). However, these findings are yet to be validated in the larger Göteborg 2 trial, which is anticipated to involve 40,000 participants and run until 2040.'

		• The Goteborg model is very akin to the UK recommended best practice; the opportunity for men now to have mpMRI in place of TRUS biopsy as a first line test in the event of raised PSA will, despite this recommendation, lead to increasing numbers requesting PSA measurement through primary care
General	Review	It is hoped that this advice will be reviewed in 3 years time when there will likely be more data available to support the use of multiparametric MRI. A section on one-off PSA test at age 50 for exclusion from further follow-up should be included in that review if possible.
General	Guidance	Although GPs may not be incentivised to undertake PSA tests, if they do (often because patients ask for it) it is important that they are clearly guided what to do when a result demonstrates a raised level (repeat PSA, and if still up, refer to a urologist and ensure multi parametric MRI next test).

4. Royal College of Nursing

Name:	xxxx xxxx	**Email address:**	xxxx xxxx
Organisation (if appropriate):	Royal College of Nursing		
Role:	xxxx xxxx		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes **No**

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General	General	This appears to be a suitable approach given the current evidence base. This was an appropriate clinical question and appears to be a robust review of available evidence.
General	General	We recommend that the document makes clear how equality impact analysis would be undertaken when providing screening for people with prostate cancer to ensure that no individual suffers discrimination.

5. **Prostate Cancer UK**

Prostate Cancer UK response to Screening for prostate cancer: External review against programme appraisal criteria for the UK National Screening Committee

1. Recommendations

- A more pragmatic approach to reviewing evidence for screening is needed. This should be one that enables layering of evidence, so that recent changes in diagnostic and low-risk prostate cancer treatment practice can be evaluated, while outcomes from clinically significant prostate cancer diagnoses can be assessed.
- The UK National Screening Committee (UKNSC) must recommend for greater availability of linked NHS data to enable research studies that analyse the dynamics of the prostate cancer pathway and the balance of harms to benefits and vice-versa that these achieve
- The UK National Screening Committee must also be open to review health economics for screening modelling that Prostate Cancer UK has commissioned the *School of Health and Related Research* (ScHARR) to undertake. This work includes current and future diagnostic testing combinations as well as the current treatment pathway and will report in autumn 2020.
- The UK National Screening Committee (UKNSC) must be active participants in designing the research studies that will address the knowledge gaps outlined in this review, so that these studies can reach the required evidence threshold

2. Summary

It's not possible to know whether the conclusion reached *by Screening for prostate cancer: External review against programme appraisal criteria for the UK National Screening Committee* (the Review) is the right one. This is because the route to reaching it is flawed for the following reasons:

- The three screening studies (ERSPC, PLCO and CaP) included in the review (page 8) are now out-dated and their evidence associated with overdiagnosis, complications associated with biopsy, and quality of life (QoL) can no longer be relied upon. This is the result of significant changes to the prostate cancer diagnostic pathway that have increased its accuracy and reduced two of its harms - the potential for both over-diagnosis and fewer patients experiencing immediate unnecessary biopsies, which the PROMIS Study evidenced at 27%.[1]

- The exclusion of two recent studies (PROMIS and PRECISION). This is understandable, given that neither included a population invited for PSA testing nor included long-term follow up. However, the exclusion of this evidence leaves the review lagging NICE Guidelines and entirely unrelated to current sequential testing used in clinical practice. The review discounts these studies because they lack evidence to show they can reduce prostate cancer metastases or mortality. However, PROMIS data suggests that multiparametric MRI-guided biopsy has the potential to double the number of clinically significant cancers detected.[1] Equally, the increased diagnostic accuracy from MRI-influenced biopsy evidenced by PRECISION, enables improved risk stratification of clinically significant prostate cancer, ensuring access to more optimal treatments for each stage of disease.[2]

- Evidence from the ProtecT Study has been misinterpreted and the review has failed to reach the same conclusion:[3]
    - ProtecT results showed that 10-year survival after treatment for localised prostate cancer was equal irrespective of treatment option, enabling active surveillance to be as effective as radical treatment and supporting patients to safely choose a treatment option with considerably less side-effects' associated harm
    - The review by contrast concludes that '*It is .. unclear whether the potential benefits of radical treatments on disease progression in comparison to observation can offset the increased rate of adverse events, particularly for men who may never have clinically important disease'*

  This is because the review has not considered that the cancer progression seen among the active surveillance cohort in the ProtecT study was in part the result of the inferior diagnostics used in the trial compared to those in current practice.[3]

- The misinterpretation of ProtecT evidence is compounded by the exclusion of evidence from the *National Prostate Cancer Audit* (NPCA).[4] This grey literature demonstrates the increased use of active surveillance in patients with low-risk localised prostate cancer in clinical practice. Its omission from the review negates the reduction in over treatment that has occurred in clinical practice over the last 11 years.

- The review contains nothing about the improved outcomes among men with higher-risk localised and locally advanced stages of the disease that have resulted from changes in treatment practice. These offer benefits that should be measured against the harms associated with PSA testing in asymptomatic men at risk of prostate cancer and cannot be drawn from screening studies that pre-date these advancements.

The current prostate cancer diagnostic pathway and the treatment pathway for low-risk prostate cancer have the potential to reduce both the over diagnosis and over treatment harms associated with PSA testing in asymptomatic men at risk of prostate cancer. In time, and with the widespread uptake of these pathways, they offer the potential for clinical practice to mainly diagnose and radically treat clinically

significant disease. By using data to establish the length and quality of survival across this better risk stratified prostate cancer population, it can be possible to know the extent of benefit provided.
The closest the review came to assessing current clinical practice was its inclusion of the Grenabo-Bergdahl 2016 (Göteborg pilot study). However, this study will not be validated for a further 20 years, by which time genetic biomarkers and polygenic risk-based science will likely make it irrelevant.
Prostate Cancer UK recommends that:

- A more pragmatic approach to reviewing evidence for screening is needed. This should be one that enables layering of evidence, so that recent changes in diagnostic and low-risk prostate cancer treatment practice can be evaluated, while outcomes from clinically significant prostate cancer diagnoses can be assessed.
- The UKNSC must recommend for greater availability of linked NHS data to enable research studies that analyse the dynamics of the prostate cancer pathway and the balance of harms to benefits and vice-versa that these achieve
- The UKNSC must also be open to review health economics for screening modelling that Prostate Cancer UK has commissioned the *School of Health and Related Research* (ScHARR) to undertake. This work includes current and future diagnostic testing combinations as well as the current treatment pathway and will report in autumn 2020.
- The UKNSC must be active participants in designing the research studies that will address the knowledge gaps outlined in this review, so that these studies can reach the required evidence threshold

3. Detailed response

Recent outcomes from increased PSA testing

Prostate Cancer UK has analysed 2018 stage at diagnosis data from the Office of National Statistics to understand the outcomes of the 19% surge in suspected prostate cancer diagnoses caused by the '*Fry and Turnbull*' effect.
The results showed that compared to 2017, there was a 2% decrease in the number of men diagnosed with stage IV, and a 31% increase in stage III diagnoses. However, this was accompanied by a paralleled increase of 31% in stage I diagnoses. The number of men diagnosed with stage II cancers also increased by 6%.[5]
It is important however to put these results into context.
In 2018, only 60% of Trusts had implemented the new diagnostic pathway. By 2019, this had increased by 15% to 75%, with 91% off men getting access across trusts offering mpMRI[6]
It is not possible yet to know the grade of disease among the stage I population or to understand the treatment pathway these patients chose. This means we cannot yet know how many of these men were diagnosed with clinically significant stage I prostate cancer. We also cannot know how many were treated with active surveillance and whether over-treatment was reduced. This data is not available from Public Health England and the National Prostate Cancer Audit until 2020/1.

Both these currently unknown factors prevent an effective assessment of the increase in PSA testing in asymptomatic men referred to the new diagnostic pathway. It will also not be possible to know the extent to which the increase in stage III diagnosis enabled any reduction in stage IV diagnoses. There is however evidence of prostate cancer specific survival outcomes in men diagnosed with stage III disease. Data from Public Health England across 2013-2017 shows 95.6% of these men survived more than 5 years, compared with 49.0% of men diagnosed with stage IV cancer, showing a benefit from being diagnosed at this earlier stage of disease.[7]
The impacts of COVID-19 will make it challenging to replicate and assess this effect alongside the more widespread availability of the new diagnostic pathway. This means that further research is needed.
The UKNSC must recommend for greater availability of linked NHS data to enable research studies that analyse the dynamics of the prostate cancer pathway and the balance of harms to benefits and vice-versa that these achieve.

Lagging current practice

In 2019, *NICE Guidelines for the diagnosis and management of prostate cancer* (NG131) recommended that clinical practice update to:[8]

- Offer multiparametric MRI as the first-line investigation for people with suspected clinically localised prostate cancer. Report the results using a 5-point Likert scale. [2019]
- Offer multiparametric MRI-influenced prostate biopsy to people whose Likert score is 3 or more. [2019]
- Consider omitting a prostate biopsy for people whose multiparametric MRI Likert score is 1 or 2, but only after discussing the risks and benefits with the person and reaching a shared decision (see table 1). If a person opts to have a biopsy, offer systematic prostate biopsy. [2019]
- Offer a choice between active surveillance, radical prostatectomy or radical radiotherapy to people with low-risk localised prostate cancer for whom radical treatment is suitable. Use table 3 to discuss the benefits and harms with them**. [2019]**
- Consider brachytherapy in combination with external beam radiotherapy for people with intermediate- and high-risk localised prostate cancer**. [2019]**
- Discuss the option of docetaxel chemotherapy with people who have newly diagnosed non-metastatic prostate cancer. [2019]

These recommendations were the result of a detailed analysis of evidence from several recent clinical studies that include PROMIS, PRECISION, ProtecT and STAMPEDE.[1-3,9-10]
Combined, they deliver a more accurate diagnostic pathway, with reduced biopsy harms, that either avoids detection of low-risk disease or enables its more accurate stratification. This provides the opportunity for an active surveillance regimen, introduced by NICE, that does not require repeat biopsy and enables the side-effects associated with radical treatments to be delayed or avoided. Additionally, where clinically significant disease is diagnosed, higher-risk cancers can be treated with new technologies that provide improved outcomes.
The uptake of several of these recommendations is widespread with the NPCA reporting in 2019 that from April 2017 to March 2018, “multiparametric MRI is available at 98% of the diagnostic Trusts in England and Wales. Its use is increasing, with a concomitant increase in its use prior to biopsy” and “The potential “over-treatment” of men with low-risk disease has remained low at 4%”.[4]

By excluding three of the four studies that underpinned this significant shift in prostate cancer diagnostic and treatment practice and ignoring evidence of its widespread application, the review has reached a conclusion that is out of step with the potential that real-world practice has to a) reduce the harms associated with PSA testing and b) reduce metastases or time to metastases and potentially prolong overall survival.

This leads the review to draw potentially inaccurate conclusions that include: "*existing risk stratification tools are relatively inaccurate at differentiating clinically significant and insignificant prostate cancer. Consequences of this may include the unnecessary treatment of patients with clinically insignificant cancer or conversely, the delayed initiation of necessary treatment for significant disease*". This completely discounts PROMIS trial evidence showing multiparametric MRI as an effective triage[1]. Equally, the review has missed evidence demonstrating delayed clinical progression in newly diagnosed high-risk, non-metastatic cancer.

Instead, the review has assessed evidence in isolation and drawn its main conclusion from screening studies associated with overdiagnosis and complications associated with biopsy, that this real-world clinical practice has rendered out of date. It has also narrowly focused on evidence for treating localised disease started so long ago that its cohorts will be more likely to have received an inaccurate diagnosis.

As these screening and long-term treatment studies can no longer be relied upon to effectively determine the balance of harms and benefits associated with a population-wide screening programme using the PSA test, **the review should have taken a more pragmatic approach that considered the grey literature and that enabled newer evidence to be layered. This could have ensured that recent changes in diagnostic pathway and low-risk prostate cancer treatment practice was evaluated, while survival from clinically significant prostate cancer diagnoses was assessed**. Without this, it is not possible to know whether the conclusion it has reached is the right one.

Misinterpreting evidence

In 2019, NICE reviewed a breadth of evidence associated with the treatment of low and intermediate risk prostate cancer.[8] This included the ProtecT study.[3] As a result, it was concluded that:

'*The available good body of evidence for the treatment of localised prostate cancer and … trade-off seen in the evidence between the clinical benefits of radical treatments and potential side effects in people with low-risk prostate cancer … enabled active surveillance to become an equal choice alongside prostatectomy and radiotherapy*'. In addition, it concluded that '*active surveillance was a safe option for people with low-risk localised prostate cancer because most people live with low-risk cancer for many years with no disease progression. The lasting negative effects of radiotherapy or prostatectomy*' it went on to recommend, '*mean that many people may prefer active surveillance'. It also agreed that active surveillance might be a safe option for some people with intermediate-risk localised prostate cancer, although for this group there was more risk that the cancer would have an impact on their lives and they are more likely to need radical treatment*.'

This does not tally with the conclusions reached by the review, after appraising similar evidence. The review by contrast concludes that '*there is still a lack of evidence comparing outcomes in clinically significant and insignificant disease, likely largely due to difficulties in predicting which cases will be significant at an early stage'* (page 111).

The review also states that '*It is .. unclear whether the potential benefits of radical treatments on disease progression in comparison to observation can offset the increased rate of adverse events, particularly for men who may never have clinically important disease'*. This however misses the fact that ProtecT study results made it possible, for the first time, for active surveillance to be a beneficial treatment for localised prostate cancer because of its equal 10-year survival outcomes to radical treatment and its reduced side-effect profile.[3]
It is also fair to suggest that the cancer progression seen among the active surveillance cohort in the ProtecT study was in part the result of the inferior diagnostics used in the trial compared to those in current practice.[3]
By misinterpreting this evidence, the review has ignored the reduction in harms made possible for men diagnosed with low-risk prostate cancers.

Improved outcomes for clinically significant disease

In 2016, the ASCENDE-RT trial published results of its study comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. It found that men randomized to the LDR-PB boost were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years.[9]
Also in 2016, the STAMPEDE trial released evidence showing that offering docetaxel to men with high-risk locally advanced prostate cancer who are receiving long-term hormone treatment with or without radiotherapy lived for 3.7 years before their disease got worse. This was 9.4 months longer than the current standard of care.[10]
The inclusion of these treatments in a prostate cancer pathway that is more likely to have accurately diagnosed them, significantly reduces time to metastases for men with higher-risk disease. They deliver a benefit that cannot be disregarded, even if it does not result in a curative outcome. When combined with the potential for a less harmful treatment option for low-risk localised disease it must surely create a shift in the harm to benefit ratio critical to assessing the potential for population-wide screening. Without this, it is not possible to know whether the conclusion the review has reached is the right one.

END

1. Ahmed, H.U. et al. (2017) Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet*. 389(10071): 815-822
2. Kasivisvanathan, V. et al (2018) MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *The New England Journal of Medicine*. 378: 1767-1777
3. Lane, J.A. et al. (2014) Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. *The Lancet Oncology*. 15(10): 1109-1118
4. The Royal College of Surgeons of England (2019) National Prostate Cancer Audit. [accessed 17.09.2020] available at: https://www.npca.org.uk/reports/npca-annual-report-2019/

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6. Prostate Cancer UK (2019) Freedom of Information request
7. Office for National Statistics (2019) Cancer survival in England - adults diagnosed. [accessed 17.09.2020] available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed
8. National Institute for Health and Care Excellence (2019) Prostate cancer: diagnosis and management NICE guideline [NG131] [accessed on 17.09.2020] available at: https://www.nice.org.uk/guidance/NG131
9. Morris W.J. (2017) Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate CancerAscendre-RT. *International Journal of Radiation Oncology*. 98(2): 275-285
10. James, N.D. et al (2016) Addition of docetaxel, zoledronic acid, or both to first-line long- term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *The Lancet*. 387: 1163-1177

6. University College London

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No

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Thank you for the opportunity to respond to this consultation.		
Page 20-21	Novel biomarkers, diagnostic and risk stratification tools	Since your review, there has been further evidence of the potential for polygenic risk-stratification to improve the benefit/harm profile of PSA screening. Compared with age-based PSA screening, risk-stratified screening using age and polygenic profile was shown in a modelling analysis to be more cost-effective, prevent comparable numbers of deaths from prostate cancer and reduce overdiagnosis. https://journals.plos.org/plosmedicine/article?id=10.1371%2Fjournal.pmed.1002998
Page 20-21	Novel biomarkers, diagnostic and risk stratification tools	Furthermore, modelling analyses (submitted for publication) have shown the potential benefits of mp-MRI as a triage test prior to biopsy in a screening programme. By comparison with an age-based programme without mp-MRI, an age-based PSA screening programme incorporating mp-MRI could prevent an additional 1% prostate cancer-specific deaths whilst reducing overdiagnosis by 15% and biopsies by 34%.

		The benefits of using mp-MRI in a screening programme are compounded when combined with risk-stratified screening, where risk is determined by age and polygenic profile. A polygenic risk-stratified programme using mp-MRI further improves the benefit/harm profile and cost-effectiveness of screening by comparison with an age-based screening programme using mp-MRI.

7. Prostate Scotland

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Yes **No**

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Executive Summary P10. and Review summary P. 118	Overall Conclusion We note that the Draft Evidence Review concludes that 'based on the overall synthesis of evidence against UK NSC screening of men for prostate cancer should still not be recommended'. The reviewers concluded that 'screening for prostate cancer in unselected men is associated with increased incidence of prostate cancer diagnoses and the impact of PSA-based screening on prostate cancer- specific mortality remains unclear. Supporting findings of the previous review, overdiagnosis associated with PSA-based screening is still a concern as a harm of screening, although the effects of this and biopsy-related complications on QoL remain unclear'	We have considered the review study and its' results and conclusions and we have doubts that a population based screening programme based on PSA Testing, given its limitations, would fully meet the criteria that we believe need to be met for an effective and appropriate screening system that could lead to positive health improvements for men with prostate cancer through early and earlier diagnosis and potential reductions in prostate cancer related death ratios and increased survival; stage shifts in cancers diagnosed, as well as ensuring that benefits of increased detection, treatment and improved survival ratios justified any impact of any overtreatment. Whilst we wish to see greater early detection and improved survival, and these are likely to result from PSA testing we have concerns that a full population PSA based screening scheme for men over the age of 50 could also result in levels of

		overtreatment that could reduce the benefits of screening, and that PSA testing can lead to some false negatives and positives. However, we believe that the format of the review study by having a narrow focus on recent PSA testing on full population screening (ie unselected), based only on recent developments, has led to/ precluded/ missed consideration of several important wider prostate cancer related screening considerations - such as the whether there is a need for considering any targeted screening systems for groups of selected men such as for men most at risk of prostate cancer. We feel therefore that it would be helpful if the Committee when reviewing the draft review report on population based screening could in addition consider the wider issue of prostate cancer screening - such as whether there are any sub groups of the population where there could be benefits of targeted screening or other actions that might overcome some of the drawbacks of the absence of an effective and screening population based system for prostate cancer. We were encouraged that, following the previous Review in 2015 by the decision of the Committee to helpfully pro- mote and set out availability for men over 50 via their GP for a test to measure their PSA levels, if they have been counselled on the benefits and drawbacks of such a test. We ask the Committee on this occasion to also take a similar forward looking step and consider what further ways of screening could be considered that could further help reduce the number of men presenting with meta- static prostate

		cancer. We believe that one such way could be to look at a targeted screening system for those men most at a risk of prostate cancer such as those with a family history of prostate cancer, where there is a much increased risk of them developing prostate cancer. A second such step might be to commission a study to look at what would need to be done to enable an effective prostate cancer screening system to be developed (and overcome the drawbacks of a PSA based population based system).
Summary Page 10 and Review summary Page 118	We note that the evidence on prostate cancer screening since the previous review in 2015 has moved forward, but, that the review has concluded that there is not enough evidence at present to show that there are better tests than PSA and that it also concludes that 'No robust conclusions can be made about tests superior to PSA , though it appears that adding MRI to PSA may improve test performance'	Whilst as set out above we have concerns that a PSA screening system has its drawbacks and could lead to overtreatment we were surprised that the Review study made little mention of the recent introduction of multiparametric MRI scanning prior to biopsy – see NICE guideline NG 131 May 2019 . This is likely to have reduced the number of men going forward for biopsy, and therefore the number of men facing potential for any complications associated with biopsy.
Page 14 -15	Prostate Cancer risk	We note that the study/review sets out the key groups of men most at risk of prostate cancer including Black men, men with a family history of prostate cancer, those with the BRCA 1 and 2 genes. This is significant and important in relation to consideration of screening. We were therefore disappointed and surprised that there was not further discussion and consideration of this evidence and whether this issue merited further consideration such as targeted screening for men who may fall into these groups. At present a key determining factor as to whether men who may fall into these groups receive or are offered PSA tests is reliant on the Prostate Cancer Risk Management Programme

		(PCRMP) and its effective application, awareness by doctors and awareness from men themselves. Whilst the PCRMP has an important role and it is to be welcomed, its effectiveness depends on awareness of it by primary health. Unfortunately, we continue to come across and receive reports of men who fall into one of the higher risk group categories, who are not aware of their increased risk. In addition, we also receive reports from some men who fall into these categories who have been turned down for PSA tests by their GPs. Whilst we have produced specific information in Scotland for men in these categories about risk factors (and also about the benefits and drawbacks of the PSA test) – there remains a significant and important task to increase awareness amongst men and especially men most risk of prostate cancer. We believe that there urgently needs to be a proactive approach to reaching out to men with information who fall into the highest risk categories. The absence of discussion in the draft review of how to reach these important groups and whether and what role screening could play in assisting early diagnosis needs remedying
Page 10 and pages 52 and 116	Question1 'Overall, the direction of evidence would suggest that whilst PSA-based screening increases the incidence of prostate cancer, the effect on prostate cancer specific mortality in comparison with no screening or usual care is unclear'.	We understand that there was congruence on the question of whether screening increased incidence of prostate cancer but that there was more conflicting evidence be- tween the various trials on the issue of prostate specific mortality, and that the findings were in alignment with the 2015 UK Committee's Study. (UKNSC Screening for Prostate Cancer Review 2014 update Dr Karly Louie February 2015) We were puzzled though that there was not more discussion in the draft review about comparisons on diagnosis and overtreatment, under the various screening trials. This issue becomes relevant as the main trial which did show a benefit in terms of reduction in prostate cancer specific mortality from

		screening (the European Randomised Study of Screening for Prostate Cancer Trial ERSPC) is showing an increased benefit over time. In the ESPRPC trial the number of men needed to be diagnosed with prostate cancer to save one life had fallen considerably since the UK Committee's 2015 Study and has now reported that after 16 years duration that the number of men needed to be diagnosed with prostate cancer to save one life was 18 men, by comparison with the position after 13 years where the ratio had been 27 men needing to be diagnosed to save one life, and after 9 years of study 48 men to be diagnosed to save one life. See Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up– the Lancet – Schroder F., Hugosson et al https://doi.org/10.1016/S0140-6736(14)60525-0) and Screening and Prostate-Cancer Mortality in a Randomized European Study in NEJM Schroder F. DOI: 10.1056/NEJMoa0810084 It might also be useful to gain a better understanding of context and relevance if there had been comparisons on the numbers to be diagnosed to save one life with other tumour types where there is and isn't screening e.g. breast cancer where one study has shown the ratio appears to be 28 cases need to be diagnosed to save 2.5 lives). See Duffy et al J Med Screen. 2010 Mar; 17(1): 25–30. Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England
Page 10 and pages 111 to 113, and117	Question 4 What are the harms and benefits of currently available treatment approaches for	A key criterion for screening is that 'there should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symp- tomatic phase leads

	early stage prostate cancer to reduce morbidity and mortality? The review summarises that 'There was a lack of evidence distinguishing the effects of treatment for low, intermediate and high risk disease. It is unclear whether the potential benefits of radical treatments on disease progression in comparison to observation can offset the increased rate of adverse events, particularly for men who may never have clinically important disease' . The review goes on to say that: 'It is thus unclear whether early identification of men with prostate cancer would them with a therapeutic advantage'.	to better outcomes for the screened individual compared with usual care'. To this end the study looked at issue of harms and benefits which is an important consideration. Whilst we do not doubt the evi- dence that the study has brought together – we think the analysis of it needs to be put in the context of current treatment pathways. The study appears to look at the comparison between observation and radical treatment as direct opposites and insufficiently as part of the treatment pathway/and options/usual care. Current practice and NICE guidelines (see NICE NG131)- set out for early low risk disease the options of active surveillance, radical prostatectomy or radical radiotherapy (with active surveillance moving from being a 'non-preferred treatment' to 'an equal choice alongside prostatectomy and radiotherapy'). NICE agreed that active surveillance was 'a safe option for people with low-risk localised prostate cancer because most people live with low-risk cancer for many years with no disease progression'. The introduction in recent years of active surveillance has in practice led to many men opting for it, and then going on to radical treatment if disease progression warrants it (NICE indicates 21% of men on active surveillance showed signs of disease progression). It should also be noted as the ProtecT trial showed, (and as the UK Screening review study itself recognises), that both prostatectomy and radiotherapy reduce disease progression compared with active monitoring and the rate of development of distant metastases compared with active monitoring. (Note that the definition of active monitoring in the study is slightly less in scope to that of active surveillance as set out by NICE). See Hamdy F. et al. 10 year Outcomes after monitoring, surgery or radiotherapy for localised prostate cancer https://www.nejm.org/doi/full/10.1056/NEJMoa1606220).

		(Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial Lane JA & Donavan J et all,DOI:https://doi.org/10.1016/S1470-2045(14)70361-4 In this regard the introduction of this revised treatment pathway, with active surveillance included as a standard option for men with low risk disease changes the terms of the debate on the question that the study asks of 'whether the potential benefits of radical treatments on disease progression in comparison to observation can offset the increased rate of adverse events, particularly for men who may never have clinically important disease'. (This is without even considering the question that Dr. D'Amico has asked in the wake of the ProtecT trial as to whether future comparisons between Active Surveillance versus treatment for prostate cancer the end point should be a comparison between metastases rather than death as the end point – given quality of life considerations in relation to treatment for metastatic disease). See D'Amico A. Journal of Clinical Oncology https://ascopubs.org/doi/full/10.1200/jco.2016.70.9527
Page 38	Screening interval	We note that the studies of trials listed in the Review varied in frequency of screening, from the CAP trial having a single screen, the PLCO being annual and ERSPC between 2, 4 and 7 years. It would be interesting if there were analysis as to whether and what impact of the screening of single, versus multiple screenings may have on outcomes. In addition we suggest that it might be worthwhile also looking at the findings from the studies by Vickers et al and Lijla et al from the Malmo Preventative Project which showed that a

		single PSA test measured at age 44- 50 could predict advanced prostate cancer up to 20 years earlier. The authors of the studies suggest 'that an early PSA value could be used to individualise later screening for prostate cancer' and that this information be used, based on a single screen, to significantly reduce the numbers of men needing to be called for later screening enabling screening to focus on men with higher concentrations of PSA. The authors advocate 'a change in the paradigm for prostate cancer screening and propose that screening frequency be determined by individual risk from an early PSA test. Early PSA testing could also serve as the foundation for a more comprehensive risk assessment that also includes genetic markers, family history, race and risk factors defined in the future'. We feel that the review for the UKNSC could potentially benefit from considering this evidence as it has the potential for adding to/changing the nature of the discussion about screening. Hans Lilja, Angel Cronin and Andrew J Vickers Predictions of signifi- cant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50 - Cancer 2011 Mar 15: 117(6): 1210-1219 also Lilja H, Ulmert D, Bjork T et al Long-term prediction of prostate cancer up to 25 years before diag- nosis using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol2007;25:431-6. Vickers AJ. Cronin Bjork et al PSA concentration at age 60 and death or metastasis from prostate cancer : case control study BMJ 2010; 341:4521 and also Andrew J Vickers, Monique Roobol, and Hans Lilja Annual Rev Med 2012; 63: 161-170 Screening for Prostate can- cer: Early Detection or Over Detection

Page 6	Percentage of men diagnosed with metastatic prostate cancer	The study references the percentage of men being diagnosed in England and Wales with metastatic prostate cancer - as being 16% (in 2015-16) It does not give figures for Scotland. It should be noted that in Scotland the figure for the years 2012-14 was higher with 26% of men being diagnosed with Stage IV prostate cancer – See Public Health Scotland 2016 Prostate survival data

8. Chris Booth, on behalf of CHAPS Charity; TACKLE Prostate Cancer; ORCHID

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Organisation (if appropriate):	CHAPS Charity; TACKLE Prostate Cancer; ORCHID		
Role:	**Clinical Director, CHAPS; Clinical Advisory Board, TACKLE**		

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Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
As attached in separate documents		

Appendices embedded below:

Appendix 1: "NSC Report Critique – It is recommended that this Appendix is read in conjunction with the full text of the NSC Draft"

8. 12966 CHAPS NSC Response APPENDIX

Appendix 2: "Organisations supporting this response and/or conducting PSA testing events"

8. 12966 CHAPS NSC
Response APPENDIX 2

Joint response copied below:

SCREENING FOR PROSTATE CANCER

A Joint Response to the UK National Screening Committee's (NSC) Draft 5

SEPTEMBER 2020

Executive Summary

Prostate Cancer (PCa) screening with the simple Prostate Specific Antigen (PSA) blood test aims to detect PCa at an early, curable stage. Although fully entitled, most UK men do not avail themselves of the test and GPs are not encouraged to provide the test on the grounds that the "harms" of screening outweigh the benefits of cure for a small number of men with aggressive PCa. However, over 12,000 UK men die from PCa every year, our mortality rate languishes below most of our western neighbours and the UK has not experienced the fall in PCa mortality seen in countries extensively using PSA; indeed our death rate is rising.

That the "harms" of screening outweighed the benefits was arguably true during the first 20 years of PSA use due to PSA not being a specific marker for PCa and unable to differentiate between aggressive, lethal PCa and non-aggressive, insignificant PCa. Neither was there an accurate, non-invasive second line test to provide the answers. As a result, thousands of men diagnosed with cancers we would now consider harmless, underwent radical "overtreatment" with its significant risk of serious complications – impotence, incontinence and bowel damage. Consequently, in 2015 the NSC recommended against a national PCa screening policy and this has been endorsed by the latest NSC report.

A detailed appraisal of the 2020 NSC draft is attached in the Appendix 1, but in summary this latest NSC report draws principally on 3 randomised, controlled trials (RCTs) of PSA-based screening to draw its conclusion. Unfortunately 2 of these trials – "PLCO" and "CAP" – are entirely inadequate to draw this conclusion. Regarding the third trial – " ERSPC" - the report has emphasized its flaws but failed to

acknowledge an overall reduction of PCa mortality of 30% or highlight individual trial centres within ERSPC reporting 50% reductions in PCa mortality.

Medicine does not advance on the basis of RCTs alone and the report's biggest omission is its failure to connect with actual clinical practice in western Europe and specifically the UK.

During the last 10 years good research evidence and clinical practice in the UK have entirely changed the diagnosis and management of early PCa. The key advances have been:

- The risk factors for PCa have been clearly identified.
- International screening guidelines have achieved a high degree of consensus, and there is comprehensive UK guidance available for the optimum use of PSA.
- mp-MRI has been confirmed as an accurate, non-invasive second line test capable of differentiating between aggressive and non-aggressive PCa.
- Over-treatment of non-aggressive PCa in the UK has been virtually eliminated with active surveillance proven as a safe "treatment" option.
- Screening studies running up to 20 years are demonstrating up to 50% falls in PCa mortality.
- Screening and early intervention is a superior clinical option providing better quality of life and at less cost than lengthy treatment and eventual death from advanced PCa.

In summary, this clinical evidence supports an urgent, clinically driven, re-appraisal of the options now open for PSA- based screening in the UK. We recommend a fundamental change in approach moving to a risk-based, case-finding 'Smart Screening' strategy. Anything less would be highly discriminatory

Introduction

The objective of screening is to identify cancer at an early, curable stage to prevent death from late stage cancer. Prostate Cancer (PCa) is the UK's commonest male cancer and second commonest male cancer killer causing over 48,000 new cases and over 12,000 deaths every year, figures that continue to rise, with deaths now exceeding deaths from breast cancer[1]. Half of UK men still present with late stage PCa with no sign that this ratio is decreasing[2].

However, statistics for England alone in 2018 show a remarkable rise to 49,029 new cases, an increase of 7,828 on 2017 attributed to the "Turnbull/Fry effect"[3].

UK Background

In 2015 the UK NSC recommended against the introduction of a PSA-based national screening programme because PSA was not specific for PCa and could not discriminate between aggressive and non-aggressive PCa[4]. The former results in "false positives" leading to unnecessary invasive prostate biopsies whilst the latter leads to detection of non-aggressive PCa for which many men received unnecessary radical "over-treatment". The resultant harms of "over-diagnosis" and "over-treatment" thus outweighed the benefit of cure for a minority of men detected with early, aggressive PCa.

Although the UK has no national screening programme, the Prostate Cancer Risk Management Programme (PCRMP)[5] permits men over age 50 to have a PSA test, once counselled by a professional.

Alongside this somewhat paradoxical position, UK clinical practice has made substantial advances. The 6th National Prostate Cancer Audit (NPCA) for the latest clinical year, 2017/2018, shows that mp-MRI scanning is replacing prostatic biopsy as the optimum second line test for men with a persistently raised PSA[2] and NICE guidance now recommends mp-MRI before biopsy[6]. The likelihood of an underlying aggressive PCa existing when an MRI is normal is extremely low[7] leading to biopsy rates falling by 30%[8]. If an MRI is abnormal, more accurate, targeted biopsies can take place with the trans-perineal route being increasingly used to lessen the infection rate associated with the trans-rectal route[2].

The 6th NPCA shows that the UK over-treatment rate has now dropped to only 4%[2] with Active Surveillance proven as a safe treatment option for men diagnosed with non-aggressive PCa[9].

Unfortunately, UK men still remain largely unaware of the potential risk of PCa and UK PSA test rates have till now remained low[10]. GPs are advised not to "pro-actively raise the question of PSA testing"[11]. Two surveys have shown that insufficient GPs are familiar with PCRMP or have sufficient knowledge to offer balanced counselling[12,13]. Substantial anecdotal evidence

confirms that numerous men, even men at high risk, are refused a PSA test or told to report back only "when symptoms arise"; PCa that has grown sufficient to cause symptoms is usually advanced and incurable.

The overall consequence is that the UK death rate from PCa continues to rise and our mortality rate continues to languish below most of our western neighbours.

International Background

In all countries extensively using PSA for screening after its introduction in the 1990s, the PCa mortality rate fell, but at the cost of substantial over-treatment. Whilst urologists then sought to bring order and consensus into PCa screening[14], some early screening trials failed to show that screening reduced PCa mortality[15]. Thus in 2012 the influential United States Preventive Services Task Force (USPSTF)counselled unequivocally against screening[16]. Since then the percentage of US men presenting with metastatic disease has risen[17] and the death rate has started to rise for the first time[18] forcing a change in the USPSTF's recommendation to one of individual, informed decision making for PSA tests[19].

During the last decade well conducted screening studies running up to 20 years are reporting reductions in mortality reaching 50%[20] or more[21].

Consequently, nearly all current major national and international urological guidelines recommend PSA-based screening for appropriately selected, counselled men who can then make an informed decision[14,22,23]. In summary, the majority of international, expert panels recommend men should:

- Screen from age 45 for men with a family history of an immediate male relative with PCa and for black or mixed race men of African or African Caribbean descent (risk 1 in 4).
- Screening from age 45 with a family history of breast or ovarian cancer on the maternal side[24].
- Obtain a baseline PSA in a man's 40s to predict future risk:

- For men aged 40-60 a "normal" initial PSA of 1-2ng/ml carries a 26% risk of later PCa; an initial PSA of 2-3ng/ml carries a 40% risk of later PCa[25].

- Do not screen men below 40 or with less than 10 years' life expectancy.
- Link PSA to a "risk calculator" to assess need and frequency of future PSA testing.

Summary of Research, Trial & Practice-based Evidence

- There are **no** new markers available to replace PSA as the initial screening test for PCa.
- There are comprehensive UK consensus guidelines available on the optimum use of PSA[26].
- Men confirm PSA is an acceptable test[27].
- PSA is a useful marker for identifying BPH[28].
- Risk prediction models can double the sensitivity of PSA for PCa detection.
- Men in PSA screening programmes running for up to 20 years are benefiting from c.50% reductions in PCa mortality with numbers needed to screen and to diagnose falling to 139 and 13 respectively to prevent 1 PCa death – numbers lower than current colon and breast cancer screening[29].
- A persistently raised PSA must be followed by second line tests **before** a prostate biopsy. In the UK mp-MRI is the NICE recommended test[6], but numerous blood and urine tests are competing for recognition.
- A normal mp-MRI indicates that a significant, aggressive PCa is unlikely to be present.
- mp-MRI has reduced the number of biopsies by approximately one-third and greatly reduced over-diagnosis.
- The UK treatment options are determined by multidisciplinary teams and together with informed choice have reduced the over-treatment rate over the last 4 years from 12% to 4%[2].
- NICE approved, individual prognostic models are available to assist men make appropriate choices in the treatment of non-metastatic PCa[30].

- Active surveillance is a safe treatment option for non-aggressive PCa[9].
- Minimally invasive treatments for localised PCa report reduced side effects and good cancer control.
- There is an economic case for increased PSA screening. PCa develops slowly in its early stages when detectable and curable but when diagnosed at a late state, treatment is rarely successful and very costly. A robotic radical prostatectomy costs £15,000 compared with a typical cost of £300,000 for late stage palliation[31].

A risk-based screening model based on age, race and polygenic risk assessment can reduce over-diagnosis, provide a cost-effective screening programme for large populations[32] and improve upon current unregulated screening in the UK (Appendix 2)

Conclusion

The UK's current annual death rate of over 12,00 men – that's one death every 45 minutes – is unacceptable and the NSC report's claim that the harms of screening still outweigh the benefits is no longer valid.

The low rate of PSA testing in the UK has resulted in little opportunity to use the tools we already have for early detection, discrimination between aggressive and non-aggressive cancer and the cheaper option of early, curative treatment compared with late, expensive, palliation of advanced PCa. Adoption of proven, best practice use of PSA on a national scale could halve the UK death rate.

The NSC report lacks clinical insight, is retrospective, based on flawed data and totally divorced from current clinical practice. Its adoption will continue to discourage and delay the early diagnosis and cure of men with aggressive PCa. In 2020 we cannot repeat the mistake of the USPSTF report of 2012.

The status quo discriminates against men, especially those known to be at high risk. It is financially unsound and medically unsustainable. We therefore recommend a clinically driven, fundamental change in the delivery of PSA screening commencing with men at high risk as the first steps in establishing a systematic, case-finding 'Smart Screening' approach to reducing the UK's unacceptable death rate from this most pernicious cancer.

xxxx xxxx

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Clinical Advisory Board, National Federation of Prostate Cancer Support Groups

This submission is dedicated to Roger Wotton (1949-2019), Chairman, National Federation of Prostate Cancer Support Groups

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9. Cancer Research UK

September 2020

Cancer Research UK response to the UK National Screening Committee consultation on Prostate Cancer Screening

Each year in the UK there are around 48,500 cases of prostate cancer and over 11,000 men lose their lives to the disease every year[i]. Some of these cancers grow extremely slowly and will never cause a person harm during their lifetime, while others can be aggressive and require treatment. It is therefore crucial that we find accurate ways to detect and treat lethal cancers as well as sparing men with harmless cancers an unnecessary but life altering diagnosis.

The PSA test is a blood test that detects the level of a protein called prostate specific antigen (PSA) in the blood. PSA is a protein produced by both normal and cancerous prostate cells and it's normal for all men to have some PSA in their blood.

A raised PSA level may be a sign of prostate cancer, but it can also be caused by several other health conditions including an enlarged prostate, urinary or other infections, or inflammation of the prostate gland. There are also many other factors that can affect PSA levels such as vigorous exercise, recent ejaculation, anal sex that stimulates the prostate and certain medications.

Prostate cancer incidence rates have increased by 41% since the early 1990s[ii], following the introduction of PSA testing. In the same time period, prostate cancer mortality has decreased by 26%[ii], whilst survival increased[ii]. This points to the overdiagnosis of prostate cancer from PSA testing and survival statistics being inflated by latent slow-growing tumours.

Prostate cancer remains a significant problem in the UK as demonstrated by the number of cases, the high burden of late stage disease and lives lost to the disease, but the PSA test is not reliable enough as a screening tool to help us tackle that problem.

Summary

Cancer Research UK supports the UK National Screening Committee's recommendation to not introduce a national screening programme based on PSA for prostate cancer. Overall, the evidence shows that giving asymptomatic men the PSA test has no mortality benefit i.e. it does not save lives.

The Prostate Cancer Risk Management Programme (PCRMP) allows men aged 50 and over without symptoms to ask their GP for a PSA test but urges consideration of pros and cons before any decision is made. Men should be offered mpMRI triage after an abnormal result from a PSA test but before biopsy. While mpMRI does result in fewer men having unnecessary biopsies it doesn't improve the PCRMP in terms of the mortality benefit of giving asymptomatic men a PSA test. As well as not completely removing the physical harms of overdiagnosis, it does not address the psychological harms of being told you potentially have prostate cancer following a PSA test.

The PCRMP is fundamentally screening but contradicts the evidence supported by the UK NSC and is

not informed by the same robust framework as other national screening programmes. We strongly recommend that this evidence review is applied to the PCRMP, and any other guidance, to explicitly state that PSA tests shouldn't be offered to men without symptoms because of a lack of impact on overall deaths from prostate cancer and the balance of benefit and harm.

Too many men are dying from prostate cancer every year so further research is needed to a find a way to stop men with aggressive prostate cancer dying from their disease by developing better tests and more effective treatments. Cancer Research UK is continuing to fund research to address this.

Evidence against PSA-based screening

The CAP trial was the largest study to date looking at whether one-off PSA screening can reduce the number of men dying from prostate cancer. In 2018 the CAP trial[iii] added further weight to the growing evidence that giving a one-off PSA test to men without symptoms didn't save lives from prostate cancer and risked diagnosing more men with a cancer that would never have caused them any harm. After an average of 10 years, the researchers found that the one-off PSA test led to many more prostate cancers being found. But crucially, the men who had the test were no less likely to die of prostate cancer than the men that hadn't had it.

As Cancer Research UK funded the CAP trial, we are very pleased that of the three randomised control trials examined as part of this review, CAP was found to be at lowest risk of bias. As the largest, most recent and only UK based trial in this review, the CAP trial is the best evidence available on PSA based screening. We have funded a further 5 years of follow-up of participants from the CAP trial.

Although this review didn't conduct a meta-analysis of the available evidence to understand the reduction in prostate cancer-specific and overall mortality, the 2013 Cochrane review[iv] did. The CAP trial specifically looked at a one-off test, whereas the Cochrane also considered studies offering multiple PSA tests. The review of the five studies of the largest and most rigorous trials, available at the time, for prostate cancer screening using the PSA test found that giving asymptomatic men the PSA test, either one-off or multiple times, would do more harm than good. PSA screening did not significantly decrease prostate cancer-specific and overall mortality but usually resulted in overdiagnosis.

The combination of the CAP trial and the 2013 Cochrane review provide strong evidence that offering PSA screening would not reduce deaths from prostate cancer.

Prostate Cancer Risk Management Programme

Although there is no national prostate cancer screening programme in the UK recommended by the UK National Screening Committee, men without symptoms over the age of 50 can currently make an informed choice to have a PSA test as per the Prostate Cancer Risk Management Programme (PCRMP)[v].

This programme was developed by the Department of Health in 2002, with the third edition of guidance published in 2015 based on combined evidence from the UK NSC and recommendations of the National Institute for Health and Care Excellence (NICE) in the prostate cancer: diagnosis and treatment guidelines. Therefore, it is concerning that this programme still exists irrespective of the

continual growing body of evidence that demonstrates that giving PSA screening to asymptomatic men does more harm than good.

After the results of the PROMIS trial[vi], NICE approved the introduction of mpMRI triage for men after an abnormal result from a PSA test but before biopsy. The PROMIS trial showed that in a best-case scenario, using mpMRI to triage men might allow 27% fewer primary biopsies and diagnosis of 5% fewer clinically insignificant cancers. While mpMRI does result in fewer men having unnecessary biopsies it doesn't improve the PCRMP in terms of the mortality benefit of giving asymptomatic men a PSA test. As well as not completely removing the physical harms of overdiagnosis, it also does not address the psychological harms[vii] of being told you potentially have prostate cancer or prevent men from opting for a biopsy[viii].

If a man is diagnosed with prostate cancer after having a PSA test through the PCRMP, active surveillance is recommended for low and intermediate risk localised prostate cancer. At this point, men have been diagnosed and are living with prostate cancer, and the psychological harms and anxiety that can accompany a cancer diagnosis. It also does not prevent overtreatment, because men will still undergo multiple biopsies as part of monitoring.

Treatment for early stage disease will be associated with significant harm, as it's likely a substantial proportion of these cancers will be a result of overdiagnosis and would not have gone on to cause death, and therefore no treatment was necessary. Furthermore, research indicates many men will opt for more radical treatments during their surveillance[ix], even if the clinical evidence suggests their cancer is not progressing.

Cancer Research UK has in the past worked with Public Health England and Prostate Cancer UK on the information provided to men and GPs as part of the Prostate Cancer Risk Management Programme, to try and ensure it communicates up-to-date evidence and promotes informed choice.

However, it is clear that the Prostate Cancer Risk Management Programme is prostate cancer screening. This has been created against the recommendation of the UK NSC, the body responsible for advising ministers and the NHS about all aspects of population screening; therefore, the programme hasn't been informed by evidence-based policy, including the balance of benefits and harms, nor is it subject to national oversight and assurance including the collection of robust data. Since the conclusion from the UK NSC is to not introduce prostate screening, we strongly recommend that this evidence is applied to the PCRMP and any other guidance, to explicitly state that PSA tests shouldn't be offered to men without symptoms.

Ongoing research to improve prostate cancer outcomes

To improve prostate cancers outcomes in the UK it is crucial that we find accurate methods to detect aggressive cancers at the earliest stage when successful treatment is more likely. Cancer Research UK is continuing to fund research to address this from understanding the biology of the disease to improving treatments combinations for advanced prostate cancer.

In 2019/20, Cancer Research UK funded £12 million into prostate cancer research. Research which may help provide evidence for a future screening programme includes the ReIMAGINE trial which is trying to determine whether MRI scans can be used as a population-based screening tool to detect

prostate cancer, rather than the PSA blood test. Although given the time required to determine whether a screening intervention provides mortality benefit, it will be some time before we understand the possibility of MRI screening. We are also funding research into the genetics of prostate cancers looking for faulty genes which make some people more likely to develop prostate cancer, and whether it could be used in the future to monitor men who have a greater chance of developing prostate cancer or used for a targeted screening programme.

Although the UK NSC is only considering population level PSA testing in this review, with the forthcoming Screening Advisory Body which is to consider and advise on population and targeted screening programmes, it should be noted that how to identify and manage high risk groups for prostate cancer is still an issue that requires more research. There is no clear evidence as to whether screening could be more helpful or more harmful than for average-risk men. Without that evidence, we cannot make an assumption in either direction. Evidence shows that whilst black men have a higher incidence of prostate cancer than white men, the proportion of patients diagnosed with prostate cancer who die from the disease seems to be similar in black patients and white patients[x]. People who carry BRCA mutations are also thought to be at a higher risk of prostate cancer, however these mutations are only found in a very small number of prostate cancer cases. CRUK is currently funding the IMPACT trial[xi] which focuses on men who carry genetic mutations.

We agree with the UK National Screening Committee that both the STHLM3[xii] and MRI represent the most promising screening methods compared with PSA testing alone. However, both methods require more evidence on their impact on prostate cancer mortality before they could be recommended as a screening tool for a national programme.

About us

Cancer Research UK (CRUK) is the world's largest cancer charity dedicated to saving lives through research. We support research into over 200 types of cancer, and our vision is to bring forward the day when all cancers are cured. In 2019/20, we committed £468 million to cancer research in institutes, hospitals and universities. Our long-term investment in state-of-the-art facilities has helped to create a thriving network of research at 90 laboratories and institutions in more than 40 towns and cities across the UK supporting the work of over 4,000 scientists, doctors and nurses. Our retail network of 600 shops is staffed by over 1,800 people.
From more information, please contact XXXX XXXX XXXX XXXX XXXX XXXX

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10. British Association of Urological Surgeons (BAUS)

Name:	Section of Oncology	**Email address:**	XXXX XXXX
Organisation (if appropriate):	British Association of Urological Surgeons (BAUS)		
Role:			

Do you consent to your name being published on the UK NSC website alongside your response?

Yes

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
General comment		BAUS agrees with the review and supports the conclusion that a systematic population screening programme is not recommended. BAUS believes more work needs to be done to support access to PSA testing for at risk groups; men with a family history, African and Caribbean men and those with LUTS.

11. The National Cancer Research Institute Prostate Research Group

Name:	Professor Hashim Ahmed, Imperial College London	**Email address:**	xxxx xxxx
Organisation (if appropriate):	NCRI Prostate Research Group		
Role:	**Chair**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes **No**

Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Review question 3 (various points in document)	Various points through document	UK NSC should have given greater thought to inclusion of MRI pre-biopsy studies and the recent Cochrane SLR demonstrating the impact in secondary care of conducting a MRI before biopsy in terms of reductions in biopsy rates (reduced biopsy related harms), reductions in diagnosis of low risk disease (reductions in harm of over-diagnosis) and increases in detection of significant cancer (improved efficiency of diagnostic process). Whilst page 20 mentions and discusses MR imaging studies, the inclusion criteria within the searches and the review's overall assessment of this change in secondary care should have been given greater weight. Whilst conducting an MRI scan as a screening test is something that is being pursued within studies, the use of pre-biopsy MRI in hospitals as a triage test has significant implications for the entirety of the pathway of screening.
Review question 4	In various places in document	The NSC should give due weight to evidence from the NPCA that rates of active surveillance in those suitable for it being in excess of 90%. Indeed, the NPCA 2019 report states, "*The*

		potential "over-treatment" of men with low-risk disease has remained low at 4%." https://www.npca.org.uk/content/uploads/2020/01/NPCA-Annual-Report-2019_090120.pdf This fact adds to the weight of evidence that secondary care pathways have significantly changed for the better with over-treatment significantly reduced and treatment on the whole concentrated on those men with clinically important cancer.
Page 11 and 12	Research needs	We feel that there should be a separate and specific section outlining the research gaps that require strategic investments. First, we welcome the call for further research in this field. We recommend highlighting that there is engagement with primary care cancer researchers in future in order to address how best to encourage those most at risk to attend studies of screening interventions, GP advice and endorsement for patients invited, delivery of community based steps to screening, identification and eligibility of screenees and impact of screening on primary care provision. Second, it is important that level 1 evidence using largescale multi-arm or paired cohort study designs evaluating cross-sectional validity of novel fluidic or imaging biomarkers are delivered. The NSC should give clear guidance on whether longitudinal studies of mortality assessment are required for a significant shift in recommendations, if cross-sectional studies of novel screening strategies can demonstrate reduced harms (biopsy rates, over-diagnosis) and improved efficiency (similar or higher rates of significant cancer diagnosis) compared to PSA; this is considering that the highest quality PSA screening RCT ERSPC has already shown a mortality benefit and therefore, novel screening strategies need only demonstrate detection of clinically significant disease is as good or better with reductions in the harms of PSA alone screening. This is especially important given the already described improvements in secondary care as above.