Prostate cancer: diagnosis and management (update)

Consultation on draft guideline - Stakeholder comments table
12 December 2018 – 16 January 2019

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Astellas Pharma Limited	Guideline	General	General	Astellas Pharma Ltd is concerned that whilst the final scope for this clinical guideline stipulated that the existing NICE guidance - enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with docetaxel-containing regimen (2014) TA316 would be reviewed for the guideline, the recommendation for its use is not explicitly made. Astellas Pharma Ltd also believe that recommendations for the use of enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377) should also be explicit in the guideline.	Thank you for your comments. We have added links to the TA's on abiraterone and enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with docetaxel. However, TA377 is outside of the scope of this update-
Bayer Plc	Guideline	28	19-21	The allocation of radium 223 to the 'bone targeted therapies' section should be amended so that radium is placed into the 'treatment' section. Radium 223 is a precision medicine that targets the bone, particularly at sites with increased bone turnover such as areas of the skeleton affected by prostate cancer. It is however a cytotoxic agent that undergoes radioactive decay to release an alpha-particle that exerts a direct cytotoxic effect on prostate cancer cells. It is this direct anti-cancer effect that drives the overall survival (OS) benefit of radium 223 as demonstrated in the ALSYMPCA trial with a median OS benefit of 2.6 month verses placebo (median OS radium 14.9 months, Placebo – 11.3 months). Medicines allocated to the bone targeted therapies do not exert a direct anti-cancer effect on prostate cancer, they usually target the bone cells (osteoblasts and osteoclasts) and exert more of an indirect effect on prostate cancer through changing the bone micro-environment with no clinical trials demonstrating a survival benefit due to its effect on the prostate cancer but due their effect on decreasing skeletal related effects. So grouping radium 223 with bone targeted therapies is inaccurate and misleading and it is best placed with other systemic anti-cancer agents in the 'treatment' section.	Thank you. The committee opted to leave the radium-223 recommendation where it is. It is a bone targeted therapy and is only used in people with bone metastases.
Blue Earth Diagnostics Limited	Algorithms	4/9	Biochemical relapse – imaging	The algorithm states that patients should not be imaged prior to salvage radiotherapy. PET/CT with Axumin will identify metastatic disease with greater sensitivity and specificity than MRI, CT or isotope bone scans, and will therefore reduce the number of patients receiving futile salvage radiotherapy.	Thank you. This area of the guideline was not updated and therefore this section of the algorithm has not been changed. We will inform the NICE surveillance team so that this can be considered at the next update.
Blue Earth Diagnostics Limited	Guideline	22/46	8-13	We note with some surprise that NICE does not acknowledge the advances in PET/CT imaging in biochemical relapse since 2008.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
Bradford Teaching Hospitals NHS Foundation Trust	Guideline	6	21	All the evidence has used mpMR targeted Bx (cognitive or machine fused). multiparametric MRI-influenced has no evidence base	Thank you for your comment. The committee feels that the term "MRI-influenced- biopsy" is more descriptive of what they mean - because the information from the mpMRI acquired before prostate gland biopsy is used to determine the optimal biopsy pattern (the needle placement). They felt that 'MRI targeted' might imply an "in bore" technique which is not what they are recommending here. We have added a definition to the 'Terms used in this guideline' section to ensure this is clear.

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Bradford Teaching Hospitals NHS Foundation Trust	Guideline	6	23	You cannot recommend not biopsying PI-RADS/Likerts 1-2 if you are recommending bi-parametric MR. All the papers which say it is safe not to biopsy 1-2 have used 3 sequence mpMR. You could support units not biopsying 1-2 if the unit has proven their personal NPV compared with non-targeted systematic biopsy. There is no evidence to support bi-parametric NPV	Thank you for your comments. We have not made recommendation on bi-parametric MRI. All our new recommendations mention multiparametric MRI, the reviewed studies used mpMRI.
Bradford Teaching Hospitals NHS Foundation Trust	Guideline	31	23	You have described bi-parametric MR, all the major studies of multi-parametric MR have used T2, DWI **AND** DCE	Thank you for your comment. The definition for multiparametric MRI has now been amended and we have aligned it with the ESUR guidance as per the included studies.
British Association of Urological Nurses	Guideline	14	6	? Benefit of performing a DRE on active surveillance patient in context of Active surveillance programme	Thank you for your comments. The current review did not set out to investigate the role of DRE in active surveillance. In evidence review E, the population is people with a prior negative biopsy but still suspected of prostate cancer. The committee decided to leave DRE as part of the surveillance protocol because they did not see any evidence in this review to challenge its role. In 2014, the committee used evidence from a range of surveillance protocols from across the country that showed that people were using DRE as part of the protocol. In addition the committee noted that the active monitoring in ProtecT also included DRE as part of the protocol. There is currently no evidence on the best follow up – the committee made a research recommendation, to highlight the lack of evidence.
British Association of Urological Surgeons	Guideline	General	General	Presumably it has to state "people " rather than men with prostate cancer? This risks irritating more people than it pacifies. Please take advice as to whether this change is mandated.	Thank you for your comment. An Equality Impact Assessment was carried out and NICE decided to change men to people throughout the guideline,. This is because not everyone who has a prostate will identify as a man, but they will still be at risk of prostate cancer and in need of prostate cancer services. The committee agreed that failing to change this would potentially exclude a group to whom the recommendations may apply.
British Association of Urological Surgeons	Guideline	General	general	There appears to be no guidance for clinicians regarding the threshold PSA value for referral in men 50-69 years of age. This remains controversial in UK urological communities and guidance on this issue would be welcome. Many departments are using the historical age-specific threshold of 4 ug/ml for men 60-69, despite advice from the Prostate Cancer Risk Management Programme (PCRMP) and NHSE to lower the limit to 3 ug/ml.	Thank you for your comments. The current update only focussed on the diagnosis and management of prostate cancer, specifically imaging, follow up and active surveillance, as a result screening was out of scope. We have passed your comment and suggestions for reviews on screening and PSA testing to the NICE surveillance team to help inform their decisions for future updates of this guideline.
British Association of Urological Surgeons	Guideline	General	general	The limitation of feedback to new or newly amended guidelines is problematic. Evidence moves on and guidelines thus change and are worthy of update. For example guideline 1.3.56 specifically advises against concurrent hormones with salvage EBRT for biochemical recurrence after prostatectomy, yet recent evidence from RTOG-96-01 and GETUG-AFU 16 has resulted in amended international guidelines supporting the use of ADT with SRT.	Thank you for your comments. We have passed them to the NICE surveillance team, who will consider any new evidence in this area.
British Association of Urological Surgeons	Guideline	6-7		One of our members commented as follows: "MRI –ve------ To biopsy or not -- The most important information I see from the NICE consultation document is hidden away on Pg 7 of the economic Analysis document https://www.nice.org.uk/guidance/gid-ng10057/documents/economic-report. This is the crux in terms	Thank you for your comment. We have updated table 1.

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				discussing risk of significant cancer in –ve MR with the patient rather than not biopsying all. This graph I feel should be in the **main body and summary** rather than hidden away. I use this in clinic & find it very helpful."	
British Association of Urological Surgeons	Guideline	6	16	Should read 'Do not offer multiparametric MRI….'	Thank you for your comment this has now been amended
British Association of Urological Surgeons	Guideline	6	21	MRI influenced biopsy is a new term in an already crowded field and in our opinion it is not a helpful term – perhaps MRI directed or informed biopsy would be clearer.	Thank you for your comment. The committee feels that the term "MRI-influenced- biopsy" is more descriptive of what they mean - because the information from the mp MRI acquired before prostate gland biopsy is used to determine the optimal biopsy pattern (the needle placement). They felt that 'MRI directed' might imply an "in bore" technique which is not what they are recommending here. We have added a definition to the 'Terms used in this guideline' section to ensure this is clear.
British Association of Urological Surgeons	Guideline	6	25	Please add In this situation offer systematic prostate biopsy to people who opt for biopsy. [2019]	Thank you. We have changed the recommendation to read "If a person opts to have a biopsy, offer systematic prostate biopsy. [2019]"
British Association of Urological Surgeons	Guideline	7		Why is the word TRUS used before the word Biopsy throughout the document when Trans-perineal approaches are emerging as an alternative and probably superior option. To stay relevant in a rapidly evolving field trans-perineal biopsy warrants a mention early in the diagnostic section. **Table 1** only mentions TRUS biopsy and not Transperineal which is now almost 30% of biopsies. Please add: Consider offering a trans perineal prostate biopsy to men at high risk of sepsis (diabetes, previous UTI, immunosuppression, HIV, steroids) or those with MRIs indicating lesions not easily reached with a TRUS biopsy (apical, anterior). Also there is no mention of SEPSIS which is a huge downside of the TRUS approach and seems to have been ignored throughout. There is a risk of around 0.5% of sepsis which may require admission to ITU and could result in major morbidity. Table 1 is Difficult to read - should adhere to Plain English principles.	Thank you for your comment. The committee was aware that practice is varied across the country with some centres now using transperineal biopsy, however the best available evidence was based on TRUS biopsy, and the PRECISION study also reported that some participants had transperineal biopsies. To address this, the committee used the term prostate biopsy - as a term to encompass both transperineal and trans-rectal biopsy The evidence used in table 1 was derived from a study that used only transrectal biopsy. We are not aware of any studies that have reported similar figures for transperineal biopsy. The table has been updated.
British Association of Urological Surgeons	Guideline	8	1	This should also state consider offering an MRI targeted trans-perineal biopsy. As written the guideline does not represent the direction of travel for the UK with prostate biopsies at present, the guideline reads as if all trans-perineal biopsies are not recommended. However, current HES data and the NICE news article indicates that over 1/3 of all prostate biopsies are actually transperineal but the draft guidance recommends that Transperineal Mapping Biopsy should be a research tool. Several units only perform Trans perineal biopsy now using their own "template" ie protocols. Traditionally a template might have meant saturation or every lumen in the grid. With increasing sepsis	Thank you for your comment. The committee was aware that practice is varied across the country with some centres now using transperineal biopsy, however the best available evidence was based on TRUS biopsy, and the PROMIS study also reported that some participants had transperineal biopsies. To address this, the committee used the term 'prostate biopsy' - as a term to encompass both transperineal and trans-rectal biopsy

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				rates and under sampling of the anterior and apical regions of the prostate there are potential large advantages to the trans-perineal route. Most trans-perineal biopsies currently are not "mapping template biopsies" with 60-90 cores but are instead MRI directed biopsies with a more limited number of cores, often 18-24. Less invasive transperineal biopsy techniques and the use of effective local anaesthetic to facilitate outpatient MRI targeted trans-perineal biopsies will undoubtedly drive an increasing uptake of TP biopsy as a primary diagnostic procedure	
British Association of Urological Surgeons	Guideline	9	1	We appreciate this is an old recommendation on which you are not accepting comments but we feel we must point out that this has changed now to only include the frailest patients as biopsy confirmation is increasingly used to guide secondary treatments. Please alter this statement to men with poor performance status/frailty or significant co-morbidity. With targeted treatments emerging it will become increasingly important.	Thank you for your comment. We are unable to change the wording in parts of the guideline that have not been updated. We will forward your comments to the NICE surveillance team to consider whether this area of the guideline needs to be updated.
British Association of Urological Surgeons	Guideline	9	6	The 2019 guidance also refers to the 2006 guidance on prostate biopsy, which was part of the Prostate Cancer Risk Management Program. This predated MRI and trans perineal biopsies and isn't now relevant advice.	Thank you for your comments, this recommendation has now been deleted.
British Association of Urological Surgeons	Guideline	9	19	There are discrepancies between the recommendations in 1.2 and the recent NHSE publication, 'Implementing a timed prostate cancer diagnostic pathway: a handbook for local health and care systems (April 2018)'. These specifically relate to the recommendations for biopsy in men with Likert 3 lesions on mp-MRI, and also the recommendations for review of negative biopsies in men with mp-MRI visible lesions. In this latter regard, given that PIRADS/Likert 3 lesions have a positive predictive value for cancer of only approx 12-18%, the recommendation in 1.2.11 to discuss all negative biopsies for Likert 3 and above is likely to lead to unnecessary undue pressure on both the MDT and also diagnostic pathways. The recommendation in the aforementioned NHSE document to discuss only PIRADS 4/5 lesions without inflammatory changes seems much more sensible. As written this risks overwhelming MDTs as it is commoner to have a negative biopsy with a Likerts 3 score than not. Perhaps change to consider rediscussion if there is a suspicion of under sampling at biopsy.	Thank you for your comment. The committee made the recommendation because it is important to have this discussion in an MDT as these cases are difficult to deal with. Reviewed scans may fluctuate by 20% between raters and therefore a discussion in an MDT is warranted. The MDT does not necessarily imply the full cancer MDT.but is subject to local arrangement.
British Association of Urological Surgeons	Guideline	11	23	low dose "seed" brachytherapy is an accepted option for low risk disease that isn't mentioned here and should be offered if available.	The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
British Association of Urological Surgeons	Guideline	14	6	Table 4: follow up biopsy has been removed from Active surveillance completely unless other factors change. This guidance should take into account whether the initial MRI was low risk (Likert 1 or 2, or Likert 3) and whether there was low or intermediate risk disease found. All AS without any follow up biopsy seems too radical.	Thank you for your comments. The table states "If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy".
British Association of Urological Surgeons	Guideline	16	25	The recommendations outlined in 1.3.24 for the use of docetaxel in men with non-metastatic prostate cancer conflict with the recently circulated NPOC recommendations (Ref NHS England 1811),	Thank you for your comments. The evidence reviewed for this guideline update showed that clinical progression-free survival improved in those who received docetaxel compared with those who

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				which specifically advise against the use of docetaxel in this setting. Clarification is required.	were on hormone therapy alone. This was from the STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014) trials, As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.
British Nuclear Medicine Society	General	All	All	The BNMS welcome these guidelines and agree with their findings and believe they are the basis for good practice in the management of prostate cancer	Thank you for your comment. We welcome your support for this guideline update.
British Nuclear Medicine Society	Guideline	22	18	In those patients with a rapid doubling time for their PSA if MRI is unhelpful consider PET-CT with F-18 choline or F-18 fluciclovine	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
BXTAccelyon	Guideline	9	6	*"Carry out prostate biopsy following the procedure recommended by the Prostate Cancer Risk Management Programme in Undertaking a transrectal ultrasound guided biopsy of the prostate".* Evidence shows that TRUS biopsy prostate cancer detection rates are recognised to be poor - under 40% with significant cancers missed because of systematic error of the biopsy, particularly the anterior part of the prostate. TRUS biopsy is also associated with complications, the most profound of which is infection and sepsis, a consequence of faecal contamination of the biopsy needle. Overall 3 – 5% of patients are treated or hospitalized because of infection and 1 – 3% may develop life threatening sepsis. The deficiencies of TRUS biopsy are avoided by transperineal prostate biopsies, which sample the prostate through the perineal skin and provide access to all areas of the prostate. TP biopsy reduces the risk of post biopsy urine infection or sepsis with improved cancer detection rates compared to TRUS biopsy. In September 2017 Guy's and St Thomas' Hospital stopped TRUS biopsy and Local naesthetic TP biopsy has become the diagnostic standard of care. The need for general anaesthesia or sedation has reduced by 90%, and 40% of the biopsies are carried out in the outpatients by an Advanced Nurse Practitioner (ANP). Cancer pathway breaches have reduced because TP biopsies have been removed from the GA operating list which causes delays in the pathway. This way of taking prostate biopsies significantly reduces the risk of sepsis and cancer detection rates exceed 85% for primary targeted biopsy and over 63% for systematic biopsy with no need for repeat biopsy. Cost savings from the reduced use of general anaesthetic lists by delivering OP LA TP biopsy have been realised.	Thank you for your comment, this recommendation has now been deleted as in this current guideline the committee referred to prostate biopsy to mean either transperineal or transrectal route. This has been made clear in the guidance.
BXTAccelyon	Guideline	16	20	*"Consider brachytherapy in combination with intermediate and high risk localised prostate cancer."* The ASCENDE RT Trial demonstrated a 50% decrease in biochemical relapse with the use of LDR-B in conjunction with	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.

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				hormones and whole pelvis radiotherapy when compared to using DE-EBRT with the same treatments in patients randomly assigned to the two forms of treatment. Please mention this in the guidelines.	
BXTAccelyon	Guideline	32	20	"For the purposes of this guideline, this included 12 core biopsy by transrectal or transperineal biopsy". The PRECISION study has shown that a 12 core TRUS biopsy picked up less cancers than an MRI targeted biopsy. We would therefore recommend performing a 18-24 core systematic sector biopsy, to ensure a targeted and systematic biopsy that provides a reliable and accurate pickup of any significant cancer.	Thank you for your comments. You have quoted the definition of prostate biopsy - The transperineal biopsy referred to here is the 12 core biopsy LA transperineal route biopsy and not the mapping biopsy. We agree with your understanding of the PRECISION study, as this is part of the evidence that led to the recommendations in this guidance. The committee are recommending multiparametric MRI as the first-line of investigation. As evidenced by the PRECISION study, if positive lesions the committee recommends MRI-influenced prostate biopsy and consider omission of biopsy in those with MRI Likert score of 1 or 2. The committee made a recommendation to not offer template mapping biopsy as this is resource intensive and may lead to a high proportion of clinically insignificant cancer diagnosis.
BXTAccelyon	Guideline	36	25	New evidence ***is*** available from The ASCENDE - RT RCT, specifically the recommendation of a combination of EBRT and LDR Brachytherapy Boost for intermediate and high risk patients.	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
BXTAccelyon	Guideline	38	26	*"For brachytherapy, the committee agreed that only a small number of people 27 (typically those with high-risk prostate cancer) would currently have brachytherapy, 28 so the changes to the recommendations are unlikely to have a significant impact on 29 current practice."* Here (and in other sections of the guidelines), there has not been a definition between the two types of Brachytherapy available to patients. Please specify when referring to LDR Brachyherapy, as this is a different technique to HDR brachytherapy.	Thank you for your comment. Brachytherapy refers to either HDR or LDR, the committee explains that most centres only offer one type and since there are only two types they felt that the recommendation was clear so that centres will choose either based on what is available. We have now added this to the rationale section to make this decision clear
Department of Health and Social Care	General	General	General	Thank you for the opportunity to comment on the draft for the above guideline. I wish to confirm that the Department of Health and Social Care has no substantive comments to make, regarding this consultation.	Thank you for your comment.
Greenvits	General	General	General	*There is very strong evidence that boosting the level of Vitamin D can help to reverse early stage prostate cancer.* Test and adjust dose of Vitamin D3 so that 25(OH)D is between 100-150 nmol/L Overview at: www.vitamindwiki.com/Cancer+-+Prostate https://grassrootshealth.net/?s=prostate Trials have been done that showed improvement in Gleason Score when 100micrograms/day (4,000IU) of oral Vitamin D were given to men with early-stage Prostate cancer where the recommendation was "Wait & Watch"	Thank you for your comment. None of the questions in the current scope looked at reversing prostate cancer, so this was beyond the scope of the update. We have forwarded this information to the NICE surveillance team for consideration in any future guideline updates

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				More at: B.W. Hollis, et al., Vitamin D3 supplementation, low-risk Prostate cancer, and health disparities, J. Steroid Biochem. Mol. Biol. (2012), http://dx.doi.org/10.1016/j.jsbmb.2012.11.012 Trials have been done with different oral doses of Vitamin D to evaluate vitamin D metabolite levels and Ki67 labelling in surgical prostate tissue. Safety measures, PTH, and prostate-specific antigen (PSA) were also assessed More at: https://academic.oup.com/jcem/article/98/4/1498/2536841	
Greenvits	General	General	General	*There is good evidence that improving the **Omega-6/3 Ratio** can help to reverse early stage prostate cancer.* Test and supplement with high strength Fish Oil so that: • Omega-3 Index: >8% • Omega-6/3 Ratio: <2:1 More at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232341/ http://www.expertomega3.com/omega-3-studies https://www.greenvits.eu/collections/omega-3/products/fatty-acid-test-kit	Thank you for your comment. The current update focussed on the diagnosis and management of prostate cancer - in specific areas of imaging, follow up and active surveillance, as a result supplement use was out of scope. We have forwarded this information to the NICE surveillance team for consideration in the next guideline update
Greenvits	General	General	General	Refer patient to Dietitian or Nutritional Therapist to review diet and lifestyle (www.bda.org.uk or www.bant.org.uk) More at: http://www.ncbi.nlm.nih.gov/pubmed/16425098 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3631124/pdf/10552_2013_Article_179.pdf https://www.lifeextension.com/Protocols/Cancer/Prostate-Cancer-Treatment/Page-01	Thank you for your comment. The current update focussed on the diagnosis and management of prostate cancer - in specific areas of imaging, follow up and active surveillance, as a result dietary or nutritional support was out of scope. We have forwarded this information to the NICE surveillance team for consideration in the next guideline update
Greenvits	General	General	General	Provide advice about diet and physical activity More at: http://prostatecanceruk.org/media/11576/diet_physical_activity_and_prostate_cancer_final.pdf	Thank you for your comment. The current update focussed on the diagnosis and management of prostate cancer - in specific areas of imaging, follow up and active surveillance, as a result diet or physical activity was out of scope. We have forwarded this information to the NICE surveillance team for consideration in the next guideline update
Greenvits	General	General	General	Ensure that the patient has 8-10 hours of sleep a night Offer natural sleeping aids such as Natrasleep or prescribe equivalents to Melatonin such as Circadin Adjust dose by trial so that sleep is adequate without the patient being drowsy the next day More at: https://www.cancer.gov/about-cancer/treatment/side-effects/sleep-disorders-hp-pdq	Thank you for your comment. The current update focussed on the diagnosis and management of prostate cancer - in specific areas of imaging, follow up and active surveillance, as a result lifestyle factors such as sleeping patterns was out of scope. We have forwarded this information to the NICE surveillance team for consideration in the next guideline update

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Guy's and St Thomas' NHS Foundation Trust	Guideline	General		There appears to be no guidance for clinicians regarding the threshold PSA value for referral in men 50-69 years of age. This remains controversial in UK urological communities and guidance on this issue would be welcome. Many departments are using the historical age-specific threshold of 4 ug/ml for men 60-69, despite advice from the Prostate Cancer Risk Management Programme (PCRMP) and NHSE to lower the limit to 3 ug/ml. This risks overwhelming an already pressurised system and needs to be evidence based.	Thank you for your comments. The current update only focussed on the diagnosis and management of prostate cancer, specifically imaging, follow up and active surveillance, as a result screening was out of scope. We have passed your comment and suggestions for reviews on screening and PSA testing to the NICE surveillance team to help inform their decisions for future updates of this guideline.
Guy's and St Thomas' NHS Foundation Trust	Guideline	General		MRI –ve------ To biopsy or not -- The most important information I see from the NICE consultation document is hidden away on Pg 7 of the economic Analysis document https://www.nice.org.uk/guidance/gid-ng10057/documents/economic-report. This is the crux in terms discussing risk of significant cancer in –ve MR with the pt rather than not biopsying all . This graph I feel should be in the main body and summary rather than hidden away. I use this in clinic & find it very helpful.	Thank you for your comment. NICE guidelines do not contain graphs or charts as these can be difficult to interpret. We have updated table 1 and believe it provides similar information in a more accessible way.
Guy's and St Thomas' NHS Foundation Trust	Guideline	General		88% of all diagnostic prostate biopsy in England and 96% in Wales were transrectal biopsy as per NPCA 2017. I doubt this will change significantly in the 2018 report. Therefore TRUS is currently standard of care in the UK (we like it or not). I am guessing this is likely to have influenced cost effectiveness analysis of TP biopsy in NICE workup….	Thank you for your comment. We could not identify evidence to compare the clinical and cost effectiveness of transperineal (TP) vs transrectal prostate biopsy. It is an important area that is recommended for future research.
Guy's and St Thomas' NHS Foundation Trust	Guideline	6	21	Guy's has abandoned TRUS biopsy for the last 18 months and have taught over 20 other centres the technique of local anaesthetic Trans perineal biopsy. TRUS will diminish significantly over the next few years and to keep these guidelines relevant we urge more focus on Trans PERINEAL biopsy. Specifically **1.2.3 Offer multiparametric MRI-influenced prostate biopsy to people whose** **Likert score is 3 or more. [2019]** MRI influenced biopsy is a new term in an already crowded field and I don't think is a helpful term – perhaps MRI directed or informed biopsy would be clearer. I don't understand why TRUS is used before the word Biopsy throughout the document when Trans-perineal approaches are emerging as an alternative and probably superior option. To stay relevant in a rapidly evolving field trans-perineal biopsy warrants a mention early in the diagnostic section.	Thank you for your comment. The committee was aware that practice is varied across the country with some centres now using transperineal biopsy, however the best available evidence was based on TRUS biopsy, and the PRECISION study also reported that some participants had transperineal biopsies. To address this, the committee used the term prostate biopsy - as a term to encompass both transperineal and trans-rectal biopsy As explained above we have used the term prostate biopsy and not TRUS. TRUS was mentioned only in the table as that evidence could not be extrapolated to transperineal biopsy. We have modified the table to make this clearer

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Guy's and St Thomas' NHS Foundation Trust	Guideline	6	23	Please add In this situation offer systematic prostate biopsy to people who opt for biopsy. [2019] **Table 1** only mentions TRUS biopsy and not Transperineal which is now almost 30% of biopsies. Please add: Consider offering a trans perineal prostate biopsy to men at high risk of sepsis (diabetes, previous UTI, immunosuppression, HIV, steroids) or those with MRIs indicating lesions not easily reached with a TRUS biopsy (apical, anterior). Also There is no mention of SEPSIS which is a huge downside of the TRUS approach and seems to have been ignored throughout. There is a risk of around 0.5% of sepsis which may require admission to ITU and could result in major morbidity.	Thank you. We have changed the recommendation to read "If a person opts to have a biopsy, offer systematic prostate biopsy. [2019]" Table 1 is populated by data from a trial that used TRUS biopsy. There is limited equivalent information about TP biopsy. We have amended the table and hope it is clearer now.
Guy's and St Thomas' NHS Foundation Trust	Guideline	8	1	This should also state consider offering an MRI targeted trans-perineal biopsy. At present this is does not represent the direction of travel for the UK with prostate biopsies at present as it seems as if all trans-perineal biopsies are not recommended. However, current HES data and the NICE news article indicates that over 1/3 of all prostate biopsies are actually transperineal but the draft guidance recommends that Transperineal Mapping Biopsy should be a research tool. Several units only perform Trans perineal biopsy now using their own "template" ie protocols. Traditionally a template might have meant saturation or every lumen in the grid. With increasing sepsis rates and under sampling of the anterior and apical regions of the prostate there are potential large advantages to the trans-perineal route. Most trans-perineal biopsies currently are not "mapping template biopsies" with 60-90 cores but are instead MRI directed biopsies with a more limited number of cores, often 18-24. Less invasive transperineal biopsy techniques and the use of effective local anaesthetic to facilitate outpatient MRI targeted trans-perineal biopsies will undoubtedly drive an increasing uptake of TP biopsy as a primary diagnostic procedure	Thank you for your comment. The committee was aware that practice is varied across the country with some centres now using transperineal biopsy, however the best available evidence was based on TRUS biopsy, and the PRECISION study also reported that some participants had transperineal biopsies. To address this, the committee used the term prostate biopsy - as a term to encompass both transperineal and trans-rectal biopsy
Guy's and St Thomas' NHS Foundation Trust	Guideline	9	1	This has changed now to only include the frailest patients as biopsy confirmation is increasingly used to guide secondary treatments. Please alter this statement to men with poor performance status/frailty or significant co-morbidity. With targeted treatments emerging it will become increasingly important.	Thank you for your comment. We are unable to change the wording in parts of the guideline that have not been updated. We will forward your comments to the NICE surveillance team to consider whether this area of the guideline needs to be updated.
Guy's and St Thomas' NHS Foundation Trust	Guideline	9	6	The 2019 guidance also refers to the 2006 guidance on prostate biopsy, which was part of the Prostate Cancer Risk Management Program. The predated MRI and trans perineal biopsies and isn't now relevant advice.	Thank you for your comment, this recommendation has now been deleted as in this current guideline the committee referred to prostate biopsy to mean either transperineal or transrectal route. This has been made clear in the guidance.
Guy's and St Thomas' NHS Foundation Trust	Guideline	9	19	This risks overwhelming MDTs as it is commoner to have a negative biopsy with a Likerts 3 score than not. Perhaps change to consider rediscussion if there is a suspicion of under sampling at biopsy.	Thank you for your comment. The committee made the recommendation because it is important to have this discussion in an MDT as these cases are difficult to deal with. They explained reviewed scans may fluctuate by 20% therefore a discussion in an MDT is warranted. The MDT does not necessarily imply the full cancer MDT.but is subject to local arrangement.

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Guy's and St Thomas' NHS Foundation Trust	Guideline	10	3	Suggest the secondary biopsy could be via a trans-perineal approach as it could miss cancer in the same way the first biopsy could have.	Thank you for your comment. We preferred not to be specific when referring to prostate biopsy in the majority of this guideline updates, due to the lack in evidence on the accuracy data of transperineal biopsies. The way the recommendation is worded should allow clinicians some discretion.
Guy's and St Thomas' NHS Foundation Trust	Guideline	11	23	Low dose "seed" brachytherapy is an accepted option for low risk disease that isn't mentioned here and should be offered if available.	The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
Guy's and St Thomas' NHS Foundation Trust	Guideline	14	6	Follow up biopsy has been removed from Active surveillance completely unless other factors change. This guidance should take into account whether the initial MRI was low risk (Likert 1 or 2, or Likert 3) and whether there was low or intermediate risk disease found. All AS without any follow up biopsy seems too radical CT-PET for staging in metastatic prostate cancer: There is no mention of Choline or PSMA PET scanning which is now widely used. Prostatectomy Definition: As >80% of radical prostatectomies in the UK are robotically assisted perhaps this should be mentioned first now and open and lap afterwards. Also worried about the impact of saying it should only be offered in trials. It doesn't seem to distinguish mapping biopsies from targeted (which could also be TP).	Thank you for your comments. The table states "If there is concern about clinical or PSA changes at any time during active surveillance, reassess with multiparametric MRI and/or re-biopsy". CT-PET was out of scope for this guideline update. We have passed your concerns to the NICE surveillance team for consideration in future updates. We have now made the definitions of biopsies clearer in the Terms used in this guideline section.
Guy's and St Thomas' NHS Foundation Trust	Guideline	16	25	The recommendations for the use of docetaxel in men with non-metastatic prostate cancer conflict with the recently circulated NPOC recommendations (Ref NHS England 1811), which specifically advise against the use of docetaxel in this setting. Clarification is required.	Thank you for your comments. The evidence reviewed for this guideline update showed that clinical progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. This was from the STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014) trials, As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.
Guy's and St Thomas' NHS Foundation Trust	Table 1	7	1	1. We have concern that the figures in Table 1 don't seem to tally with data from the PROMIS trial. The supplementary data for PROMIS is shown below. The definition of clinically significant disease that was chosen wasn't in line with most UK urologists. The secondary definition most closely approximates to most clinician's definition of clinically significant prostate cancer. This gives a value for clinically significant prostate cancer in mp-MRI missed cases of 13.3%, not 28% as indicated in Table 1.	Thank you for your comment. Using the secondary definition of clinically significant cancer, the figures in Table 1 correspond to PROMIS data: 44 out of 158 cases (27.8%) with MRI Likert score 1 or 2 were found to be having significant prostate cancer. We have updated Table 1.

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				Table S7 - Histological characteristics on TPM-biopsy of cases missed by MP-MRI and TRUS-biopsy using the 3 definitions of clinically significant prostate cancer **Definition of significant** / **MP-MRI missed cases** / **TRUS-Biopsy missed cases** Primary n=230 / Total = 17 1 x 3+3 with core length 8mm 16 x 3+4 with core lengths 6-12mm / Total = 119 7 x 3+3 with core lengths 6-11mm 99 x 3+4 with core lengths 6-14mm 13 x 4+3 with core lengths 3-16mm Secondary n=331 / Total = 44 6 x 3+3 with core lengths 4-8mm 38 x 3+4 with core lengths 1-12mm / Total = 132 18 x 3+3 with core lengths 4-11mm 104 x 3+4 with core lengths 1-14mm 10 x 4+3 with core lengths 3-16mm Gleason >/=7 n=308 / Total = 38 38 x 3+4 with core lengths 1-12mm / Total = 159 146 x 3+4 with core lengths 1-14mm 13 x 4+3 with core lengths 3-16mm	
Intuitive Surgical	Evidence review G	103	No line number given	Intuitive believes it may be unjustified to exclude non-European studies - especially for other countries with socialized medicine, such as Canada (Sanyal et al, 2016), which found: "For all risk groups, radical prostatectomy was less costly and conferred modestly more QALYs compared with intensity-modulated radiotherapy modalities".	Thank you for your comment. In the presence of higher quality and more applicable evidence based on UK and European studies, we excluded less applicable evidence as per the methods outlined in the NICE Guideline Development Manual, Section 7.4.
Janssen-Cilag Limited	Algorithms	3	general	Draft clinical commissioning policy from NHSE is that there is not enough evidence to make docetaxel in combination with androgen deprivation therapy for hormone naïve locally advanced prostate cancer available at this time.	Thank you for your comment. The evidence reviewed for this guideline update showed that clinical progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. This was from the STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014) trials, As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences
Janssen-Cilag Limited	Algorithms	4	general	Evidence from Smith et al. suggest that a PSADT of < 8 months increases the risk of bone metastases. In addition monitoring of PSA is recommended every 6 month. Suggest revision to PSADT of < 6 months J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716. Epub 2013 Sep 16.	Thank you. This update did not review the evidence on biochemical relapse and therefore we are unable to update this section of the algorithm.
Janssen-Cilag Limited	Algorithms	6	General	As per TA387 and TA377 abiraterone or enzalutamide is recommended for "people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated". Current algorithm suggests abiraterone or enzalutamide use only after chemotherapy	Thank you. We have removed the connecting line so that the relevant box is now stand alone.
Janssen-Cilag Limited	Guideline	general	general	Draft clinical commissioning policy from NHSE is that there is not enough evidence to make docetaxel in combination with androgen deprivation therapy for hormone naïve locally advanced prostate cancer available at this time.	Thank you for your comments. The evidence reviewed for this guideline update showed that clinical progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. This was from the STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014) trials, As a result, the committee made a recommendation for clinicians to discuss the

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					benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.
Janssen-Cilag Limited	Guideline	22	26	Evidence from Smith et al. suggest that a PSADT of < 8 months increases the risk of bone metastases. In addition monitoring of PSA is recommended every 6 month. Suggest revision to PSADT of < 6 months J Clin Oncol. 2013 Oct 20;31(30):3800-6. doi: 10.1200/JCO.2012.44.6716. Epub 2013 Sep 16.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
National Osteoporosis Society	Guideline	24	General	The evidence-base is strong regarding the detrimental effects of long-term ADT on bone health. Therefore, it would be beneficial within this section to provide specific recommendations regarding supplementation with calcium and vitamin D and also a recommendation regarding the frequency of DEXA scans.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
National Osteoporosis Society	Guideline	24	General	The guideline makes general recommendations; that fracture risk is considered for all men receiving androgen deprivation therapy and that treatment is offered to all those with osteoporosis. However, there is no mention of bone health assessment at the time of androgen deprivation therapy initiation.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
National Osteoporosis Society	Guideline	24	20	**Do not routinely offer bisphosphonates to prevent osteoporosis in people 20 with prostate cancer having androgen deprivation therapy** The recommendation is reasonable.	Thank you for your comment.
National Osteoporosis Society	Guideline	24	22	**Consider assessing fracture risk in people with prostate cancer who are having androgen deprivation therapy, in line with the NICE guideline on osteoporosis: assessing the risk of fragility fracture** We are concerned that this recommendation is not strong enough. We believe that all people should be assessed as they commence androgen deprivation therapy unless intervention to prevent bone loss and fractures is contra-indicated. The recommendation to use the NICE approach to assessment is reasonable but is inconsistent with the following recommendation to *"offer bisphosphonates to people who are having androgen deprivation therapy and have osteoporosis"* (page 24 Line 25; comment 3). This is because some men will be identified who are at high fracture risk warranting treatment without bone mineral density (BMD) measurement so without a diagnosis of "osteoporosis".	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
National Osteoporosis Society	Guideline	24	25	**Offer bisphosphonates to people who are having androgen deprivation therapy and have osteoporosis** We are concerned, as this recommendation needs to state that bisphosphonates should be offered to all people who are having androgen deprivation therapy and have a **high fracture risk**. This is because some men will be identified who are at high fracture risk warranting treatment without bone mineral density (BMD)	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates

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				measurement so without a diagnosis of "osteoporosis". The inclusion of patients with a high risk of fracture will include those with a T score below -2.5 but should also include those with high FRAX score who reach the National Osteoporosis Guidelines Group (NOGG) threshold and those with vertebral fragility fractures. We would also argue that as these men are at risk of accelerated bone loss, that the threshold for treatment should be lower in the same way as in women with adrenal insufficiency (AI) or glucocorticoid-treated patients. Pragmatically, the BMD thresholds used in the original AI guidance would be reasonable until such time as an evidence-base becomes available. We suggest that the lack of this evidence-base be highlighted as an area for future research.	
National Osteoporosis Society	Guideline	25	1	**Consider denosumab for people who are having androgen deprivation therapy and have osteoporosis if bisphosphonates are contraindicated or not tolerated.** This recommendation is sensible but we believe it may be worth adding advice not to stop denosumab without specialist input if/when androgen deprivation is stopped in order to avoid rebound fracture risk.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
NCRI-ACP-RCP-RCR	General	General	General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and with the Joint Specialty Committee for Nuclear Medicine and would like to make the following comments.	Thank you for your comment.
NCRI-ACP-RCP-RCR	Guideline	General	General	**1.If MRI or biopsy negative - recommendation is MDT review for all Likert lesion 3 and above** **2. Core member of MDT should review all risk factors of patients with negative first biopsy** Currently these patients being managed on case by case basis as per regional guidelines. These new guidelines mean a significant increase in workload for the MDT and core members. Many non-core urologists feel able to make these case by case considerations.	Thank you for your comment. The committee made the recommendation because it is important to have this discussion in an MDT as these cases are difficult to deal with. Reviewed scans may fluctuate by 20% therefore a discussion in an MDT is warranted. The committee pointed out that the recommendation was purposefully open so that local areas could decide what the best configuration for the MDT meeting would be. It did not specify that the MDT meeting should be the cancer meeting, and there is no requirement for core urologist involvement
NCRI-ACP-RCP-RCR	Guideline	General	General	The draft Prostate Cancer Diagnosis and Management guidelines recommend more widespread use of multi-parametric MRI for diagnosis, which is to be commended and we fully concur with. However, there is no mention anywhere in the document about the role of PET-CT in management of patients with prostate carcinoma which is at odds with the literature and Evidence-Based PET-CT guidelines published by the Royal College of Physicians, Royal College of Radiologists and British Nuclear Medicine Society in 2016 (available at: https://www.rcr/acl/uk/publication/evidence-based-indications-use-pet-ct-united-kingdom-2016)	Thank you for your comments and we welcome your support of this guideline update. For this current update, PET-CT was out of scope, therefore no evidence was reviewed during the developmental process. We have now passed your comments and suggestions to the NICE surveillance team to help inform their decisions for future updates of this guideline.
NCRI-ACP-RCP-RCR	Guideline	General	General	The use of bone scintigraphy for staging in high risk patients is mentioned in the draft guidelines but there is now widespread evidence of the superior accuracy of PET-CT using a range of different PET tracers, particularly prostate specific membrane antigen (PSMA) labelled tracers. There is widespread clinical practice within continental Europe, Australia and the United States using this modality in prostate cancer. In particular there is	Thank you for your comments. For this current update, PET-CT was out of scope, therefore no evidence was reviewed during the developmental process. We have passed your comments and suggestions to the NICE surveillance team to help inform their decisions for future updates of this guideline.

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				extensive evidence demonstrating superior accuracy of this technique in comparison to other imaging modalities primarily in the setting of biochemical recurrence of prostate cancer but also in selected high-risk patients for baseline staging in order to inform optimal patient management. We feel this is a major omission from the draft guidance. Within the UK, Choline PET-CT is performed for selected patients in this scenario which is funded by NHS England as part of specialised commissioning. Elsewhere there has been a rapid transition to use of more accurate PSMA PET-CT and within the USA the use of amino acid PET-CT (Fluciclovine). These tracers are not currently funded by NHS England.	
NCRI-ACP-RCP-RCR	Guideline	General	General	A brief summary of the literature supporting PET-CT use in prostate cancer is provided below which we hope will be of use to the committee. We feel that it would be remiss to not make any mention of these techniques and hope the panel will consider making reference to their potential use within the final version of the NICE guideline. At the very least the current clinical use of PET-CT in recurrent prostate cancer should be acknowledged and in the future research section there should be some suggestions made with regard to the potential use of more accurate imaging techniques such as PSMA PET-CT in high risk patients. ***Choline PET-CT in Prostatic Malignancy*** Carbon-11 and Fluorine-18 labelled Choline are precursors for the biosynthesis of cellular membrane phospholipids and as such are markers of membrane metabolism and turnover, which are increased in certain tumours[i]. The use of Choline PET-CT in the assessment of patients with prostatic malignancy has been extensively studied[ii]. The main indication is for assessment of patients with biochemical relapse after prior local treatment with curative intent (radical prostatectomy, radiotherapy or brachytherapy) to differentiate between local, loco-regional and systemic relapse. Current European recommendations advocate the use of Choline PET-CT in this clinical scenario if the serum PSA is > 1 ng/mL if the results would influence patient management e.g. salvage radiotherapy or prostatectomy would be performed if localised recurrence is confirmed[iii]. A number of studies have evaluated how best to stratify the use of Choline PET-CT in this clinical scenario in order to increase the diagnostic utility of the technique, which even when used optimally has a detection rate of 38% (at best) for patients with a PSA of <2 ng/mL[iv]. Specific patient characteristics, which increase the likelihood of a positive Choline PET-CT during the early phase of biochemical relapse include high Gleason score[v], rapid PSA doubling time (< 6 months)[vi], increasing PSA level despite androgen deprivation therapy[vii] or high PSA nadir after radical prostatectomy. Recent expert opinion suggests that Choline PET-CT might be optimally used to identify patients with biochemical relapse who would benefit from salvage radical prostatectomy and/or salvage lymphadenectomy but is unlikely to be clinically useful in patients with a low PSA following radical prostatectomy[viii].	Thank you for your comments. For this current update, Choline PET-CT, Fluorine-18 Fluoride Bone Imaging, Prostate Specific Membrane Antigen (PSMA) in Prostatic Carcinoma were out of scope, therefore no evidence was reviewed during the development process for these areas. We have passed your comments and suggestions to the NICE surveillance team to help inform their decisions for future updates of this guideline.

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				[i] Podo F. Tumor phospholipid metabolism. NMR Biomed 1999; 12: 413-414 [ii] Bauman G et al. 18F-fluorocholine for prostate cancer imaging: a systematic review of the literature. Prostate Cancer and Prostatic Diseases 2012; 15: 45-55 [iii] Heidenreich A et al. EAU guidelines on Prostate Cancer. Part 2: screening, diagnosis, and local treatment with curative intent – update 2013. Eur Urol 2014; 65: 467-479 [iv] Rodado-Marina S et al. Clinical utility of 18F-fluorocholine PET-CT in biochemical relapse of prostate cancer after radical treatment. Results of a multicenter study. BJU Int 2015; 115: 874-883 [v] Cimitan M, Evangelista L, Hodolic M el al. Gleason score at diagnosis predicts the rate of detection of 18F-choline PET/CT preformed when biochemical evidence indicates recurrence of prostate cancer: experience with 1,000 patients. J Nucl Med 2015; 56(2): 209-215 [vi] Castellucci P et al. Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med 2009; 50(9): 1394–1400. Erratum in: J Nucl Med 2009; 50(10): 1578 [vii] Beheshti M et al. Impact of 18F-Choline PET/CT in Prostate Cancer Patients with Biochemical Recurrence: Influence of Androgen Deprivation Therapy and Correlation with PSA Kinetics. J Nucl Med 2013; 54: 833-840 [viii] Heidenreich A. Choline-PET/CT in relapsing prostate cancer patients. BJU Int 2015; 115: 849-850 Choline PET-CT also has proven clinical utility for staging of selected untreated patients with prostate carcinoma and high-risk features (e.g. high serum PSA level or Gleason score) with equivocal findings on conventional imaging such as possible nodal disease where confirmation or exclusion of distant disease would directly influence patient management[ix]. [ix] Beheshti M et al. 18 F Choline PET/CT in the preoperative staging of prostate cancer in patients with intermediate or high risk of extracapsular disease: a prospective study of 130 patients. Radiology 2010; 254: 925–933 ***Fluorine-18 Fluoride Bone Imaging*** Fluoride PET-CT has been evaluated against Technetium-99m MDP planar and SPECT bone scintigraphy in patients with suspected or known metastatic bone disease and multiple studies show it to be more sensitive and specific than bone scintigraphy, and the addition of CT increases specificity[x,xi]. Uptake times are	

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				shorter than conventional bone scintigraphy, 15–30 minutes versus 3–4 hours, and imaging times are shorter 15–30 minutes versus 30–60 minutes but the radiation exposure is approximately double with Fluoride PET-CT compared to standard bone scintigraphy[xii]. Advances in iterative CT technology may allow dose reduction and recent studies have proposed the use of dual tracer FDG and Fluoride PET-CT in selected patients with malignant disease e.g. breast carcinoma which could facilitate one-stop evaluation with reduced patient inconvenience, lower overall cost and improved scanner efficiency[xiii]. The main oncological indications for Fluoride PET-CT are identification of bone metastases and/or more accurate assessment of the extent of bony metastatic disease although clinical use remains limited due to the relative paucity of PET-CT scanners compared with gamma cameras, differential cost and lack of validated interpretation criteria. [x] Even-Sapir E et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT. J Nucl Med 2006; 47: 287–297 [xi] Shen CT et al. Performance of 18F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. Clin Nucl Med 2015; 40(2): 103-110 [xii] Beheshti M et al. F-NaF PET/CT: EANM procedure guidelines for bone imaging. Eur J Nucl Med Mol Imaging 2015; 42(11): 1767-1777 [xiii] Mick CG et al. Molecular Imaging in Oncology: 18F-Sodium Fluoride PET Imaging of Osseous Metastatic Disease. Am J Roentgenol 2014; 203: 263-271 There is established evidence of the superiority of Fluoride PET-CT for assessment of response to treatment of bone metastases in various different tumour types but the inclusion of these in routine clinical practice depends on the establishment of practical and effective imaging protocols whose costs are acceptable to funding bodies[xiv]. Data from the United States has shown a significant clinic impact on patient management in the use of Fluoride PET-CT in cancer patients[xv]. [xiv] Lecouvet FE et al. Monitoring the response of bone metastases to treatment with Magnetic Resonance Imaging and nuclear medicine techniques: A review and position statement by the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer 2014; 50: 2519-2531 [xv] Hillner BE el al. 18F-Fluoride PET Used for Treatment Monitoring of Systemic Cancer Therapy: Results from the National Oncologic PET Registry. J Nucl Med 2015; 56: 222-228	

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				Prostate Specific Membrane Antigen (PSMA) in Prostatic Carcinoma PSMA is a cell surface protein up-regulated in a range of malignancies, particularly prostate carcinoma, with low expression in normal tissues, which provides a tumour specific imaging target[xvi]. This has led to the development of PSMA-based ligands for PET imaging in prostate malignancy over the past few years with Gallium-68 labelled PSMA PET-CT rapidly emerging into routine clinical practice in Europe[xvii]. Recent large retrospective studies have reported the efficacy of the technique in patients with biochemical evidence of recurrent prostate carcinoma following radical treatment with detection rates of up to 96% depending on PSA level and Gleason score[xviii,xix,xx]. It has a significantly higher detection rate in this clinical setting when directly compared to Choline PET-CT particularly in patients with a low PSA level[xxi,xxii]. There is growing evidence of superior utility in other clinical scenarios including staging of high-risk patients prior to radical prostatectomy[xxiii] and in guiding radiotherapy planning[xxiv]. This technique is not yet in widespread use in the UK and rapid rollout to many centres may be limited by the complexities of Ga-68 production. A Fluorine-18 labelled PSMA tracer has recently become commercially available in the UK and several reports suggest this is a highly accurate technique for detection of biochemical recurrence in patients after radical prostatectomy with very low PSA level of 0.2< 0.5 ng/ml [xxv,xxvi,xxvii ,xxxviii]. [xvi] Jadvar H. Molecular Imaging of Prostate Cancer with PET. J Nucl Med 2013; 54: 1685-1688 [xvii] Haberkorn U, Kopka K, Hadaschik B. Positron Emission Tomography-Computed Tomography with Prostate-Specific Membrane Antigen Ligands as a Promising Tool for Imaging of Prostate Cancer. Eur Urol 2015 Sept 14. Pii: S-3-2-2838(15)00855-6 [Epud ahead of print] [xviii] Afshar-Oromieh A et al. The diagnostic value of PET/CT imaging with the 68Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015; 42: 197–209 [xix] Eiber M et al. Evaluation of hybrid 68Ga- PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015; 56: 668–674 [xx] Afshar-Oromieh A et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging 2017; 44: 1258-1268 [xxi] Afshar-Oromieh A et al. Comparison of PET imaging with a 68Ga-labelled PSMA-ligand and 18F-choline based PET/CT for the	

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				diagnosis of recurrent prostate cancer. Eur J Nuc Med Mol Imaging 2014; 41: 11–20 [xxii] Morigi JJ et al. Prospective Comparison of 18F-Fluoromethylcholine versus 68Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy. J Nucl Med 2015; 56: 1185-1190 [xxiii] Budäus L et al. Initial Experience of 68Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. Eur Urol 2015 Jun 24. Pii: S0302-2838(15)00513-8 [Epud ahead of print] [xxiv] Sterzing F et al. 68Ga-PSMA-11 PET-CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. Eur J Nucl Med Mol Imaging 2016; 43: 34-41 [xxv] Szabo Z et al. Initial Evaluation of [18F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer. Mol Imaging Biol 2015; 17: 565-574 [xxvi] Rowe SP et al. 18F-DCFBC PET/CT for PSMA-Based Detection and Characterization of Primary Prostate Cancer. J Nucl Med 2015; 56: 1003-1010 [xxvii] Rowe SP et al. Comparison of PSMA-based 18F-DCFBC PET/CT to Conventional Imaging Modalities for Detection of Hormone-Sensitive and Castration-Resistant Metastatic Prostate Cancer. J Nucl Med 2016; 57: 46-53 [xxviii] Giesel FL et al. Detection efficacy of [^{18}F]PSMA-1007 PET/CT in 251 Patients with biochemical recurrence after radical prostatectomy. Nucl Med. 2018 Jul 24. pii: jnumed.118.212233. doi: 10.2967/jnumed.118.212233. [Epub ahead of print] ***Fluciclovine PET-CT*** Fluciclovine is a synthetic amino acid which has high activity in prostate carcinoma. Fluorine-18 Fluciclovine (Axumin) was approved by the FDA and EMA in 2016 for use in biochemically recurrent prostate cancer. A prospective multi-centre study of 213 patients assessing impact of Fluorine-18 Fluciclovine PET-CT on management decisions in patients with biochemical recurrence of prostate carcinoma following previous curative-intent treatment and negative or equivocal conventional imaging (bone scintigraphy and CT or MRI) has recently been published[xxix]. Referring clinicians completed pre- and post- scan questionnaires recording any change in treatment, alteration from one therapy to another e.g. salvage radiotherapy to systemic chemotherapy being considered a major change. The majority of patients (70%) had a major treatment change directly influenced by Fluciclovine PET-CT. These results	

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				are concordant with a similar multi-centre study conducted in the UK in a smaller patient cohort (n = 85) showing a major management change in 60%[xxx] and a prior study evaluating the influence of Gallium-68 PSMA PET-CT on management plans in 126 patients, with a major change in management occurring in 53%[xxxi]. National Comprehensive Cancer Network guidelines published in 2018 state that Fluorine-18 Fluciclovine PET-CT can be considered for recurrence or disease progression after definitive therapy or for disease progression during systemic therapy[xxxii]. [xxix] Andriole GL et al. The Impact of Positron Emission Tomography with 18F-Fluciclovine on the Management of Patients with Biochemical Recurrence of Prostate Cancer: Results from the LOCATE Trial. J Urol 2018 Sep 1: pii: S0022-5347 (18)43798-6 doi: 10.1016/j.juro.2018.08.050 [Epub ahead of print] [xxx] Teoh EJ et al. The FALCON trial: impact of 18F-fluciclovine PET/CT on clinical management choices for men with biochemically recurrent prostate cancer. J Clin Oncol 2018; 36: 165 [xxxi] Hope TA et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. J Nucl Med 2017; 58: 1956 [xxxii] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 2.2018. June 3, 2018; Available online: https://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf ***Summary*** Non-FDG PET tracers (PSMA, Fluciclovine, Choline) are valuable tools for detection of biochemical recurrence especially after radical prostatectomy with negative or equivocal imaging findings and for evaluation of selected high-risk patients before potentially curative treatment or to evaluate equivocal finding on previous imaging where confirmation or exclusion of distant disease would directly influence patient management. There is evolving evidence for use of multimodality PET-CT and/or PET/MRI(multi-parametric) in staging of patients with prostate cancer.	
NCRI-ACP-RCP-RCR	Guideline	6	1.2.1	**Do not routinely offer imaging to people with prostate cancer who are not going to be able to have radical treatment. [2019]** This recommendation will deny many men who may benefit from an MRI pre-biopsy who do not necessarily need or are suitable for radical therapy. We would suggest that the wording is changed to. 'Do not routinely offer MR-imaging to people with prostate cancer who are not going to be able to have active local treatment given with the intent of cure.' The guidance should also state explicitly that multi-parametric MRI should conform to UK Consensus standards or ESUR guidance. (Brizmohun et al, BJUI, 2018)	Thank you for your comment. The recommendation has now been amended to – "Do not routinely offer multiparametric MRI to people with prostate cancer who are not going to be able to have radical treatment. [2019]" The committee retained the term radical treatment because there are some people who will receive radical treatment as life extending treatment and not necessarily for curative intent. The guidance now includes the multiparametric MRI definition and this conforms to the ESUR guidance.

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NCRI-ACP-RCP-RCR	Guideline	6	1.2.3	**Offer multiparametric MRI-influenced prostate biopsy to people whose Likert score is 3 or more. [2019]** This recommendation does not take into account a number of publications which have shown that men with a Likert or PIRADS 3 score that have a PSA density of 0.15ng/ml/ml or less have a risk that is close to equivalent to men with Likert / PIRADS 1 and 2 (ie., 5-10%). This recommendation therefore should stipulate a PSA Density threshold for advice to proceed to biopsy. Refs: Distler et al. J Urol. 2017. Venderink et al. Eur Urol. 2017. Boesen, Lars et al. European Urology Oncology 2018 [epub] The guidance also has an absence of recommendations on the route of biopsy. Transperineal targeted and systematic biopsy reflecting the same histological burden as a TRUS biopsy is now possible under pure local anaesthetic using either the grid method or other freehand techniques in a non-theatre setting. The lower risk of infection and sepsis that results from transperineal compared to transrectal should be encouraged in the guidance especially with our duty towards antibiotic stewardship.	Thank you for your comment. We are not sure where the figure that the risk of significant prostate cancer within people with Likert score 1 or 2 is 5 – 10% that you highlight comes from. In Distler et al, the risk of clinically significant prostate cancer (CSPC), based on the definition they used (Gleason 3+4), within people with PIRADS<3 is 71/344 = 21%. In PROMIS this risk is 11% and 28% using the primary and secondary definitions respectively. The papers you cite would have been excluded from our review as their populations are mixed including both biopsy naïve men and those with at least one previously negative biopsy. We could not identify evidence that compares the clinical and cost-effectiveness of different types of prostate biopsies. Thus, the recommendation has been left broad as prostate biopsy to allow for clinician's discretion.
NCRI-ACP-RCP-RCR	Guideline	6	Table 1 and 1.2.4	Whilst these figures reflect the presence of any Gleason 3+4=7, the guidance give no consideration to the fact that a) such disease is prevalent in the general population as well as causes no problems and b) there is no absolute consensus that any Gleason 3+4=7 is absolutely significant. The guidance should reflect this uncertainty and state what this. Further, with both the NIHR-HTA, peer review and The Lancet journal and peer review accepting the PROMIS trial definition of clinical significance, the guidance should also quote rates of clinical significance based on using a volume threshold as used in PROMIS to reflect this uncertainty around what the definition of clinical significance is. The Table should also state that a number of men with insignificant cancer will inappropriately choose active treatment and stand to not benefit from this in terms of survival and have harms of treatment. The guidance is somewhat inconsistent. It chooses to quote rates of clinically significant and insignificant disease based on transperineal mapping biopsy and TRUS biopsy whilst in 1.2.5 mandate absolutely that the former not be used at all in the first biopsy setting, yet the language permits a share decision making process for TRUS biopsy. The language for non-suspicious mpMRI either needs to be as tight as 1.2.5 or the language for 1.2.5 allow clinician and patient shared decision making.	Thank you for your comment. The definition of clinically significant prostate cancer is not certain, and there is not a clear and widely accepted agreement about a specific definition. We selected the secondary definition reported by PROMIS study in our economic model, as it accords with the other pieces of evidence that we use in our economic model. The following is quoted from the economic report page 6: "PROMIS reports results using 2 definitions of clinically significant prostate cancer. The committee advised that the 'secondary' definition is more relevant for our decision-space, both because it corresponds with the definition of disease of at least intermediate grade in the risk stratification used in the guideline and also because it is more representative of the approach to risk stratification that will have informed the treatment decisions for people in the evidence we use to estimate the treated history of true positive disease (see below). This is not to say that it is a better definition of disease that truly is clinically significant; rather that is a definition that accords well with the other evidence in the model." We agree with your comment. Table 1 has been modified.
NCRI-ACP-RCP-RCR	Guideline	7	1.2.11.	Currently these patients are being managed on case-by-case basis as per regional guidelines. These new guidelines mean a significant increase in workload for the MDT and core members. Many non-core urologists feel able to make these case-by-case considerations. There are certain criteria that can be agreed as per	Thank you for your comment. The committee made the recommendation because it is important to have this discussion in an MDT as these cases are difficult to deal with. Reviewed scans may fluctuate by 20% therefore a discussion in an MDT is warranted. The committee pointed out that the recommendation was purposefully open

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				UK consensus MRI guidelines such as offering repeat biopsy if there are no findings on histology (atrophy, inflammation, ASAP) that would account for the suspicious MRI changes. The guidance, if still insistent on multidisciplinary review should stipulate that these reviews are not cancer MDT reviews and therefore need only urology and radiology presence.	so that local areas could decide what the best configuration for the MDT meeting would be. It did not specify that the MDT meeting should be the cancer meeting, and there is no requirement for core urologist involvement
NCRI-ACP-RCP-RCR	Guideline	7	1.2.13	This group of patients are likely to benefit from a better form of repeat biopsy than TRUS biopsy. It makes no sense to apply the same 'blind' biopsy again and a strategy of transperineal sectoral or mapping biopsy are a strong evidential rationale in this setting.	Thank you for your comments. The committee has made a recommendation for prostate biopsy and did not specify which route to take. They have left this decision to the clinician. The committee agree that one may not wish to repeat the same biopsy at repeat biopsy. The committee are not recommending mapping biopsy but acknowledge that transperineal biopsy under LA may be an alternative option
NCRI-ACP-RCP-RCR	Guideline	11	1.3.7	The guidance item should reflect the fact that the recommendation for offering all options (AS, radical radiotherapy and radical prostatectomy) on an equal weighting is incorrect and especially in the setting of a non-suspicious or Likert / PIRADS 3 score on mpMRI the finding of low risk cancer (any Gleason 6) on biopsy is a more stable finding compared to a finding of low risk cancer based on TRUS biopsy that has no pre-biopsy mpMRI. Low risk disease in the new diagnostic paradigm should be managed with active surveillance.	Thank you. The committee agreed that active surveillance was an appropriate way to manage low risk prostate cancer but was also aware that a shared decision needed to be made with patients about the most appropriate management strategy for them.
NCRI-ACP-RCP-RCR	Guideline	14	1.3.11	Disease progression should be more clearly defined in the setting of a the new diagnostic paradigm especially as making a decision for disease progression purely on PSA kinetics is likely incorrect.	Thank you for your comment. We apologise that the disease progression definition from the ProtecT study was omitted in the draft guideline. The definition now reads as follows: "The trial defined disease progression as-: • Evidence of metastases • Diagnosis of clinical T3 or T4 disease, • Long term androgen deprivation therapy, • Rectal fistula or the need for a urinary catheter owing to local tumour growth Disease progression was suspected if -: • any rise in prostate-specific antigen (PSA) >20% between consecutive measures at any time during follow-up or • any rise in PSA level of 50% or greater in any 12 month period confirmed by repeat tests or • any indication of the appearance of symptomatic systemic disease "
NCRI-ACP-RCP-RCR	Guideline	16	1.3.2.4	Strongly endorse the advice to offer chemotherapy to people with high risk locally advanced disease	Thank you for your comment, we welcome your support of this guideline update.
NCRI-ACP-RCP-RCR	Guideline	28	1.5.18	Consider clarifying if this advice is restricted to those with bone metastases (rather than all people with metastases)	Thank you for your comment. The committee believe the recommendation is clear as it refers to prevention and reduction of skeletal events.
NHS England	General	General	General	The guidance is in the right direction and important for wider adoption of pre-biopsy MRI which is the key change from 2014. I have limited comments to 2019 changes.	Thank you for your comment. We welcome your support for this guideline
NHS England	General	General	General	1.2.1 Do not routinely offer imaging to people with prostate cancer who are not going to be able to have radical treatment. [2019] This item needs to remove the term 'suitable for radical therapy' and include provisions based on life-expectancy and the likelihood of any active therapy impacting positively on life expectancy.	Thank you for your comment. The item does not include "suitable". The recommendation now reads:- "Do not routinely offer multiparametric MRI to people with prostate cancer who are not going to be able to have radical treatment. [2019]". The committee explained there are some men who will receive radical treatment as life extending

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				The specification for mpMRI is also obviously key and should be consistent with national and international recommendations.	treatment and not necessarily for curative intent. The committee thinks this is clear. The guidance has now included the multiparametric MRI definition and this conforms to the ESUR guidance.
NHS England	General	General	General	1.2.3 Offer multiparametric MRI-influenced prostate biopsy to people whose Likert score is 3 or more. [2019] A number of studies have now shown that not all score 3 areas need to be biopsied and that PSA density can be used safely in the setting. A PSA Density threshold for biopsy in score 3 areas of 0.15 has good evidence. Mention should be made of offering local anaesthetic transperineal biopsies as an alternative to avoid infection/sepsis. These are not always mapping or sectoral biopsies and can be done in outpatient settings without increasing the number of cores.	Thank you for your comment. We have looked at evidence suggesting this, but the studies included mixed populations including people who were biopsy naïve and those who had at least one negative prior biopsy. Therefore, this evidence is not certain for either population group. The included evidence did not specify this. The guidance only mentions prostate biopsy, and this is defined in the guidance to mean either LA transperineal biopsy or transrectal biopsies.
NHS England	General	General	General	Table 1 and 1.2.4 There is no absolute agreement that all Gleason 7 lesions are clinically significant and a number are being monitored as the NICE recommendations themselves show that intermediate risk cancer can be actively monitored. Therefore, it is important for the guidance to state that other definitions of clinical significance using amount of cancer on biopsy when used have lower rates of presence of cancer in non-suspicious mpMRI cases. The transparency of the table is great but should go further to reflect uncertainty of what is important to find.	The committee was aware that the definition of significant disease is controversial In light of stakeholder comments, we have now included both the UCL1 and UCL2 definitions in Table 2, but have kept recommendation 1.2.4 as it is.
NHS England	General	General	General	1.2.13 In this setting of negative TRUS biopsy and ongoing suspicion, it is probably better to recommend a transperineal sectoral or mapping biopsy if a further repeat biopsy is offered. Also, if image-fusion targeting was not done at the first biopsy and a clinical suspicion is that the lesion might have been missed, referral to a centre that conducts image-fusion might also be prudent.	The committee has recommended prostate biopsy – which is defined as either transperineal (not mapping) or transrectal biopsy. The committee did not specify so that the clinician can use their own judgement. The committee did not review any evidence comparing which technique is appropriate for repeat biopsy as this was out of scope for this guideline update.
NHS England	General	General	General	I have a major concern with one of the recommendations in this draft clinical guideline. It suggests that providers should continue to use the trans-rectal prostate biopsy route, and that the trans-perineal route should only be used in a research setting. The urology colleagues that I have spoken to about this feel that this is well behind the curve of current practice and carries additional risks to patients of infection and sepsis (including Gram-negative blood stream infections) since the biopsy is done through the faeces-lined bowel and even where antibiotic prophylaxis is used it does not always protect the patient. From an infection point of view the PHE is clear that the trans-perineal route is safer. I am told that over 100 hospital trusts are already using the trans-perineal route successfully. The draft guidance says that this is more resource intensive because it needs general anaesthesia. However this is not necessarily the case. Recent developments have enabled a local anaesthetic approach for trans-perineal prostate biopsy, pioneered at Guys and St Thomas' Hospital and being spread rapidly now. The best practice timed pathway for diagnosis of prostate cancer	Thank you for your comment. The committee was aware that practice is varied across the country with some centres now using transperineal biopsy under local anaesthetic, however the best available evidence was based on TRUS biopsy, though the PROMIS study also included some participants who had transperineal biopsies. To address this, the committee used the term prostate biopsy - as a term to encompass both transperineal (not mapping) and trans-rectal biopsy. The committee was clear that transperineal mapping biopsy should only be used for research as it is too resource intensive for routine use.

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				that is being adopted by NHS England also uses trans-perineal rather than trans-rectal biopsy. I am content with the other recommendations in the draft NICE guidance but would be very keen for them to re-consider the statement regarding biopsy route – ideally to favour transperineal biopsy, but at least to support its use as a low infection risk alternative to trans-rectal biopsy.	
NHS England	General	General	General	This guidance is currently in draft form for consultation, however the draft guidance has already been highlighted in the national press for its major recommendation on pre-biopsy MRI.	Thank you for your comment.
NHS England	General	General	General	NICE itself publicised this recommendation in www.nice.org.uk.news and in the article it highlights that "the incidence of prostate cancer is 40,488. From 1st April 2015 until 31 March 2016, 21,730 people newly diagnosed with prostate cancer in England received an mpMRI. Last year, 15,243 Transperineal Template Biopsies and 35,267 Transrectal Ultrasound Guided Biopsies were performed	Thank you for this information.
NHS England	General	General	General	I have read the guidance in detail and I am concerned that there is a lot of inconsistency in the descriptions and definitions of prostate biopsy. There is a very specific new recommendation for 2019 on Pg 8 1.2.5 "Do not offer mapping transperineal template biopsy as part of an initial assessment, unless as part of a clinical trial. [2019] However, current HES data and the NICE news article indicates that over 1/3 of all prostate biopsies are actually transperineal but the draft guidance recommends that Transperineal Mapping Biopsy should be a research tool.	Thank you for your comments. We have now addressed these inconsistencies and made sure that the definitions are clear. Prostate biopsy refers to both transrectal and transperineal (non-mapping) biopsy. We are not recommending transperineal mapping biopsies (defined as 18-24 and can be upto 60-90 biopsies), the evidence showed this is not the best use of resources.
NHS England	General	General	General	In the definitions of the Terms used in this guideline Pg 31 there is no definition for transperineal mapping template biopsy but there is a definition for Systematic Prostate Biopsy on Pg 32 Ln 19 - "For the purposes of this guideline, this included 12 core biopsy by transrectal or transperineal biopsy". The section of definitions should include a definition for transperineal mapping template biopsy originally described by Barzell & Whitmore and provides the reference standard for the PROMIS study highlighted in the Evidence Section. A template mapping biopsies is certainly a resource heavy procedure and require 1 – 2 biopsies per ml of prostate collected from over 24 separate zones and analysed separately. This procedure therefore requires a minimum of 24 cores and often up to 60 – 90 cores are taken in larger prostates (60 – 90 cc in volume). I am certain that this type of biopsy protocol is not the standard transperineal biopsy approach used for the majority of the 15,243 transperineal biopsies identified through the HES data. These transperineal biopsies are most likely a more systematic biopsy protocol involving 18 – 32 cores and are clearly being managed by the current NHS resources.	Thank you for your comments. We have now addressed these inconsistencies and made sure that the definitions are clear.
NHS England	General	General	General	The guidance in Table 1, illustrates the Factors to consider when discussing the options for people whose multiparametric MRI Likert score is 1 or 2. The table then describes the advantages and disadvantages of undergoing TRUS Biopsy. It is then followed by the recommendation 1.2.5 Do not offer mapping transperineal template biopsy as part of an initial assessment, unless as part of a clinical trial. [2019].It is far more appropriate that patients should be	Thank you for your comments. We have amended Table 1 The "do not offer" recommendation refers to the template/template mapping procedures that requires a minimum of 24 cores and often up

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				offered a choice between TRUS and transperineal biopsy. It is not appropriate that the 2019 guidance refer to the 2006 guidance on prostate biopsy which was part of the Prostate Cancer Risk Management Program. At that time the majority of all prostate biopsies were transrectal but that was over 12 years ago and also the 2006 guidance predates the advent of pre – biopsy MRI and the options for targeted biopsies be they transrectal or transperineal. Given that the NICE reported HES data indicates that over 30% of biopsies are transperineal. I am sure that the 2019 NICE guidance should at least acknowledge that there has been a paradigm shift in biopsy techniques such that a 1/3 of biopsies are now done transperineally. There are a number of centres in the UK particularly in London (Imperial, UCLH & Guy's & St Thomas that have already abandoned transrectal biopsy in favour of transperineal biopsy. Less invasive transperineal biopsy techniques and the use of effective local anaesthetic to facilitate outpatient MRI targeted biopsies will undoubtedly drive an increasing uptake of TP biopsy as a primary diagnostic procedure and in that regard I welcome the recommendation against Transperineal Template Mapping Biopsy as an initial diagnostic procedure.	to 60 – 90 cores taken in larger prostates. The committee has retained the recommendation to encourage a change in practice. The committee are not referring to the LA transperineal biopsy. The committee is aware that some centres are now using the LA transperineal biopsies, this is why the recommendations state prostate biopsy. However, there was no evidence of this techniques performance. This is why the recommendation has been left purposely open with the term prostate biopsy – allowing for clinicians to have a choice. The recommendation that referred to the Prostate Cancer Risk Management programme has now been removed.
NHS England	General	General	General	I appreciate that NICE has formulated some research questions for investigation particularly with regard to its section on Other Recommendations for Research Pg 30 Ln 40 In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer? What is the diagnostic accuracy of transperineal mapping biopsy compared with transperineal non-mapping biopsy in the diagnosis of clinically significant prostate cancer? These are important questions and I hope that the guidance will stimulate urologists to formulate studies to address these questions.	Thank you for your comments. We welcome your support for this guideline
NHS England	General	General	General	When a patient is discharged to primary care and there are expectations for follow up or prescribing, the responsibility should be clearly described and transferred under local shared care arrangements.	Thank you for your comment. The committee has made recommendations on follow up strategies and has stressed the need for local agreements. There is very little evidence in this area therefore the committee was unable to make far reaching or strong recommendations.
NHS England	Guideline	15	16-19	Commissioners of urology services should base robotic systems in centres that are both geographically and financially appropriate.	Thank you for your comment. The recommendation you refer to was outside the scope of this update and therefore we are unable to change it.
NHS England	Guideline	28	13	The guideline suggests the use of zoledronic acid. Whilst they have accepted that this is now off patent and less expensive there is no thought to the actual administration. It is not available in all areas and will require additional funding/staff.	Thank you for your comments. In the review, we acknowledge that there may be a cost to implementation, but we believe this would be limited.
NHS Horsham and Mid Sussex CCG	Evidence review D	General	General	I'd be most grateful for your clarification & feedback on the following points please; • Will this guideline replace or over-ride the existing NICE (NG12) guidance on referrals for suspected prostate cancer?	Thank you for your comment. This guideline will neither replace nor override the existing NG12 guideline, it will update the current CG175 - Prostate Cancer Diagnosis and Management. The sections of the guideline that are being updated do not address the issue of referrals for suspected prostate cancer. We will pass your comments on to the NICE surveillance team for consideration. The NG12 guidance is

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				• At present, there is a lot of confusion within CCGs and Cancer Alliances about the PSA-related thresholds for GP referrals for suspected prostate cancer. For example, NG12 makes it clear that a single elevated and unexplained age-specified PSA should trigger a GP 2WW (two week wait) referral. Contrary to this, many urologists are advocating that any raised age-specified PSA should be repeated in Primary Care and a 2WW referral should only be made if the second PSA is also abnormal. As this opens the door to patients getting 'lost' in the system and it conflicts with NG12 guidance, there has been some resistance to this approach but it would be enormously helpful if the new guideline gave us clarity on the correct procedure for managing patients with an unexplained and elevated age-specified PSA. • It is unclear which 'age-specified reference range' should be used for PSAs (i.e. should it be the latest Prostate Cancer Risk Management Programme's reference range or the British Association of Urological Surgeons reference range or possibly even a different range altogether)? As NG12 sheds no light on this, may I ask that this is also covered in the new guideline, to avoid a post-code lottery situation for patients in England? Many thanks.	earlier in the care pathway and covers referral for suspected cancer. This guideline begins when that referral has happened.
NICE GP Reference Panel	General	General	General	The GP reference panel was asked to comment on these draft recommendations having given input to an earlier stage of the update in June 2017. The members responding this time were not necessarily the same ones who commented in 2017. As this is guideline is mainly aimed at secondary care, we asked panel members to give input into three areas likely to be relevant to primary care: Active surveillance of localized prostate cancer (1.3.7), the role of DRE (Table 4 p14) and follow up after treatment (1.3.42-47). As always, members could comment on other aspects if they wish. 8 responses were received in total. In keeping with previous feedback, I have collated comments and summarised. Unedited comments are included in the final line with numbers for reference. JT.	Thank you for your comment. We welcome your support during the consultation on this guideline update.
NICE GP Reference Panel	guideline	General	General	2 respondents (4+5) made broadly positive comments about the guideline in general.	Thank you for your comments, we welcome your support of this guideline update
NICE GP Reference Panel	guideline	11	1.3.1	1 respondent (7) felt the language in sections 1.3.1-6 was very one-sided, medico-legally defensive and doesn't address patient priorities well.	Thank you for your comment. This section of the guideline was out of scope, and the committee did not amend this section. We have passed your comments to the NICE surveillance team and editors for consideration in any future guideline updates
NICE GP Reference Panel	guideline	11	1.3.7	One respondent (3) commented positively on Table 3 and felt it would be helpful for discussions with patients. They wondered if the format could be improved.	Thank you for comment. We welcome your support for this guideline update. We have made some amendments to the table. Disease progression is a lot more severe than rising PSA, the table now reads as follows -:

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				I would add additional comments on table 3, which is a very positive and important inclusion: The definition of disease progression is in the footnotes only. It would be valuable to have this in the main body of the table as there is a risk people might interpret disease progression as being more severe than just rising PSA. "Problems with urinary continence" is vague. Surely the severity of this is key to decision making. Could more detail be given? Similar issue with faecal incontinence. Are there plans to develop a visually clear decision aid (in partnership with patients)? This was also suggested by respondent 7	The trial defined disease progression as-: • Evidence of metastases or • Diagnosis of clinical T3 or T4 disease, or • Long term androgen deprivation therapy, • Rectal fistula or the need for a urinary catheter owing to local tumour growth Disease progression was suspected if -: • any rise in prostate-specific antigen (PSA) >20% between consecutive measures at any time during follow-up or • any rise in PSA level of 50% or greater in any 12 month period confirmed by repeat tests or • any indication of the appearance of symptomatic systemic disease We apologise for the omission in the draft. Due to resource constraints, NICE will not be producing a decision aid to support this guideline.
NICE GP Reference Panel	guideline	14		<u>1.3.8 and Table 4 Active surveillance protocol and DRE</u> Two respondents (8) requested more detail on what GPs should do regarding PSA monitoring (agreed protocols, clarity on timing and when to re-refer), but agreed it was appropriate to do in primary care. Workload concern and dumping of responsibility rasied as a concern by two respondents (1+8). I note that footnote 2 in table 4 mentions agreed shared care protocols, but this would be worth highlighting strongly as a recommendation in it's own right (it came through as a concern in the panel's initial responses). The message to secondary care should be: don't pass on this work without setting up a proper system. DRE was questioned by 5 respondents (2,3,4,5,6) with 2 questions emerging: Is it a valuable test in the first place? Doubt about the competence/confidence/skills of GPs to do this adequately. Although this seems like a simple routine examination, if done badly in primary care it may lose its value (if it has any) and also adds an additional procedure into busy GP consultations, or creates the need for an additional dedicated appointment. How do we define who has expertise and confidence? This recommendation might lead to hospital appointments solely for the purpose of DREs (if GPs aren't expert of confident enough). How acceptable is repeated PR examination to patients?	Thank you for your comments. There was very little evidence in this area, hence the weaker recommendation to "consider" table 4 for active surveillance protocol. The committee believes areas will have their own protocols and more detail may be provided at local level. The committee decided to leave DRE as part of the surveillance protocol because they did not see any evidence in this review to challenge its role. In 2014, the committee used evidence from a range of surveillance protocols from across the country that showed that people were using DRE as part of the protocol. In addition, the committee noted that the active monitoring in ProtecT trial also included DRE as part of the protocol.

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NICE GP Reference Panel	Guideline	21	1.3.42-47	2 respondents (4+5) commented that this section was clear and looked feasible. 1 respondent (8) asked for guidance on when to STOP monitoring and follow up 1 respondent (7) felt strongly that follow-up should be specialist responsibility, citing GP skills/confidence as a barrier. Respondent 7 said: 1.3.45 is not clear. Does it refer to patients who were on active treatments? Or does this imply that some patients will no longer be on active surveillance after some time?	Thank you for your comments, we welcome your support for this guideline update. The committee did not make any recommendations on when to stop monitoring and follow up because prostate cancer is thought to progress – in some people very slowly. There was no evidence to guide where stopping monitoring was safe. This is therefore agreed locally based on the follow up and monitoring protocols in place. Recommendation 1.3.45, says that DRE should only be used as part of active surveillance. Some people with localised prostate cancer may opt for treatment. We have further clarified by expanding the section title to be clear the follow up is for people on watchful waiting and radical treatment regimes.
NIHR CLAHRC West		14	Table	Table at top of p14. The definition of progression is incorrect. This is not the definition of progression in ProtecT - it is the active monitoring protocol. When referring to ProtecT in relation to non-radical treatment, it should say 'active monitoring' not active surveillance.	Thank you for your comment. We have now amended the definition. The committee decided to refer to active surveillance since this is the term used most commonly - our definition of active surveillance is similar to the active monitoring. A definition is given in the Terms used in this guideline.
NIHR CLAHRC West	All	ProtecT		There are several examples (at least) of incorrect reporting of the ProtecT trial. There was insufficient time to document these in the very short consultation period.	Thank you for your comment. We have gone through the relevant chapters, and we hope we have managed to identify and amend all your concerns.
NIHR CLAHRC West	Decision	Patient-reported outcomes	Table 3 p12	It is disappointing that the information on functional side effects based on patient-reported outcomes in the main table to facilitate decision-making is quite unclear and sometimes inaccurate: Should say 'Median 10 years' not 10 years. Table 3 on p.12 on effects of treatment: Patient-reported outcomes (PROMs) It is unclear where the numbers that have been extracted and reported have come from within the ProtecT analysis. They do not reflect the main findings reported in the NEJM paper. The source of the numbers should be clarified and checked. If this relies on EPIC measures, this should be stated. If the EPIC measure for urinary function has been used, this is not a simple measure of urinary incontinence as stated. This measure of urinary function conflates several urinary symptoms and so the finding is misleading. The diagrams reported in the ProtecT NEJM paper focus on the key issues. At the very least it needs to be clear where these reported numbers come from. They are not presented in a helpful manner.	Thank you for your comments. We are sorry that you did not find the table helpful. We have made some amendments to the table to improve how it reads. The numbers were obtained from Appendix papers of the ProtecT NEJM publication. We have made that clearer and included the reference.
NIHR CLAHRC West	Evidence statements	Patient-reported outcomes		It is unclear why the quality of the evidence of studies varies across comparisons of treatments. Also unclear why PROMs analyses were termed subgroup analyses – they were not subgroups or analysed as such.	Thank you for your comment. We use GRADE to assess the quality of the evidence for each outcome. GRADE stands for Grading of Recommendations Assessment, Development and Evaluation. This takes into account the 1. Risk of bias of the evidence considering the risk of bias from each paper included in the meta-analysis, 2, Heterogeneity - how different the evidence is from each paper contributing to the evidence

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					3. Imprecision - how precise the confidence intervals are in relation to the predetermined minimal important difference 4. Directness – how directly applicable the study is. Following this assessment, the evidence for the outcome is then rated as high, moderate, low or very low, this forms the basis of how the evidence statement are constructed. This is included in detail in the methods section B of each chapter. These were termed subgroup analysis where there is truly a subgroup analysis of the meta-analysis,
NIHR CLAHRC West	General	General	General	It is good to see the change in this guideline to encourage a choice between active surveillance, radical surgery and radiotherapy for people with low risk localised prostate cancer	Thank you for your comment. We welcome your support for this guideline update.
NIHR CLAHRC West	Health economic modelling			The vast quantity of work is to be admired. However, the layouts of the report and appendices make it very difficult to identify where the primary evidence on the sensitivity and specificity of all 190 diagnostic strategies in 11 different populations have come from. So many strategies and populations are difficult to consider. Assumptions are difficult to discern. Conclusions are difficult to find.	Thank you for your comment. The accuracy data of the components of a diagnostic strategy is sourced from the clinical evidence review, **Table HE09** in the economic report. We had to simulate this number of diagnostic strategies (190) to address procedures taken place in primary care settings. A diagnostic strategy consists of a screening test at a defined threshold with a defined frequency and, if the screening test reaches that threshold, a further and more invasive diagnostic procedure i.e. prostate biopsy is required. Some strategies include MRI before biopsy. We also addressed a strategy that does not include any screening test. This is a symptoms-based strategy, where people are directed to prostate biopsy once they experience urinary symptoms or skeletal-related events. Further details are in the section of economic report titled "**Follow-up strategies**". As the population of interest in this decision problem is people at risk of prostate cancer who have had previous negative diagnosis using MRI and/or biopsy, we had to categorise this population into 11 sub-populations. This is mainly to address potential heterogeneity in terms of true prevalence estimates and prostate biopsy sensitivity to capture the disease within people with different previous diagnosis. Further details are in the section of the economic report titled "**Modelling approach to define the baseline population based on previous diagnosis**". A list of assumptions made in the analysis is reported in **Table HE04**. The "**Results**" section of the main report shows the findings for each sub-population. The main findings are discussed in the "**Discussion**" section showing that the use of PSA density test at a threshold of 0.15 ng/ml/ml, the PSA velocity at a threshold of 0.75 ng/ml/year and the percentage of free PSA at a threshold of 15% as screening tests within a follow-up protocol to trigger further diagnosis is reliable. The frequency of the screening tests varies based on the baseline risk (i.e. the sub-population). No screening strategy that is the symptoms-based strategy is optimal to follow-up people with the lowest risk of prostate cancer. The uncertainty surrounding the results is considerable. In particular, the results are sensitive to the hazard assigned to the prostate cancer death (constant over time vs proportional to general mortality). The

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					disease progression within people with occult disease is also a key drive for uncertainty.
Northern Ireland Cancer Network	Guideline	General	General	The review of the guidance has shown appraisal of transperineal template biopsy of the prostate vs TRUS only. More recently there is work and evidence supporting LA transperineal biopsy of the prostate (using precision point or freehand) with in particular a lower rate of post-operative sepsis complications. **Will there be a technology appraisal or interim NICE assessment of this technique vs TRUS between now and the next revision of the guidelines?**	Thank you. We have been in contact with the other guidance producing teams at NICE and none of them has the topic on their list for future guidance. We have passed this information on to the NICE surveillance team for consideration.
Prostate Cancer UK	Guideline	11	26	Suggest changing 'them' to 'patients'.	Thank you for your comment. The 'them' is referring to the 'people' in the previous sentence and so it isn't necessary to use that term again or 'patients' here.
Prostate Cancer UK	Guideline	15	1	Suggest NICE considers further risk stratification or moves away from the D'Amico scale (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4970710/)	Thank you for your comment. Re-classification of disease was out of scope for this guideline update. We have passed your comment to the NICE surveillance team for consideration in any future guideline updates
Prostate Cancer UK	Guideline	21	20	Paragraph 1.3.47 on page 21 does not align with paragraph 1.3.47 on page 45. We would suggest that the text on page 45 should be used to highlight potential strategies that can be considered for non-hospital based follow up.	Thank you for tor comments. We have now amended the numbering. The committee decided that highlighting potential strategies may lead to confusion. It discussed various strategies, but as detailed on p.45 did not recommend specific strategies as it had not examined the evidence for these and therefore it
Royal College of Nursing	General	General	General	This is just to let you know that the feedback I have received from nurses caring from people with Prostate cancer: diagnosis and management suggests that there is no additional comments to submit to inform on the consultation of the above draft guidelines. Thank you for the opportunity to review this document.	Thank you for your comment. We welcome your support for this guideline update.
Royal College of Pathologists	Guideline	General	General	Key recommendations for research: Add "refine definition of clinically significant prostate cancer"	Thank you for your comments, this is already one of the research recommendations
Royal College of Pathologists	Guideline	9	14/15	Change to "multifocal HGPIN" and add IDCP (Intraductal carcinoma of the prostate)	Thank you for your comment. The committee did not review any evidence on HGPIN and IDCP as this was out of scope. As a result we are unable to make any changes to this section on this occasion. We have referred this to the NICE surveillance team.
Royal College of Pathologists	Guideline	10	23	Please use Grade Groups instead of Gleason (4+3 could be intermediate while 3+4 PSA,10, Tic could be low-risk) We do not have good evidence in this area : D'Amico is obsolete due to grade shifts and grade groups. A lot of 3+3 would now be graded as 3+4	Thank you for your comment. Re-classification of disease was out of scope for this guideline update. We have passed your comment to the NICE surveillance team for consideration in any future guideline updates
Royal Surrey County Hospital NHS Foundation Trust		11	35	Using NHS (England) data, the treatment pathway and associated resource use provided by the economic review cited (Ramsey et al 2015), were compared to the 4D LDR brachytherapy technique performed in our service, by means of micro-costing exercise.* Our paper published in 2018 reports that the reduction in time and resource use decreased the cost of LDR brachytherapy by 40% compared to the data provided by Ramsey et al. **Langley SEM et al PubMed PMID: 29054374*.	Thank you for your comment. We do not think the reduction in costs associated with brachytherapy performed in one stage would have an impact on the recommendations, which suggest hypofractionated RT for those eligible for EBRT. For people with intermediate to high risk, the combination of BT and EBRT is considered. The evidence review related to this question shows that based on Ramsay et al 2015, brachytherapy produced slightly more QALYs but at a higher cost with the ICER at more than £80,000 per QALY. If we applied the reduction in costs of brachytherapy you reported (40%) at the cost reported by Ramsay et al, then the ICER will be about £40,000 per QALY, which is

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				Langley SEM, Uribe J, Uribe-Lewis S, Money-Kyrle J, Perna C, Khaksar S, Soares R, Laing R. Comparative Analysis of Clinical Outcomes and Procedural Costs between the Conventional Two-stage Technique and 4D Brachytherapy for Early Prostate Cancer. Clin Oncol (R Coll Radiol). 2018 Jan;30(1):57-64. Epub 2017 Oct 18. PubMed PMID: 29054374.	still greater than the conventional cost-effectiveness thresholds (£20,000 to £30,000 per QALY). Thus, the recommendation has not changed.
Royal Surrey County Hospital NHS Foundation Trust		21 Table	XIV	"Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. **[new 2014]"** This recommendation will be affected by the updated evidence relating to Low Dose Rate Brachytherapy from ASCENDE RT. A long term follow up of the RCT by Sathya et al., which was presented as evidence of HDR boost efficacy in the prior guidelines, was published in 2017.* Findings from this long-term follow-up study of brachytherapy for patients with prostate cancer failed to provide evidence that the HDR boost treatment leading to improvements of early biochemical control, translated into superior disease specific or overall survival. It should be noted that this involved an open surgical technique that has subsequently been superseded by TRUS guided source placement and moreover the EBRT prescription doses were less than those currently recommended by NICE. ** Dayes IS et al. PubMed PMID: 28816169* *Dayes IS, Parpia S, Gilbert J, Julian JA, Davis IR, Levine MN, Sathya J. Long-Term Results of a Randomized Trial Comparing Iridium Implant Plus External Beam Radiation Therapy With External Beam Radiation Therapy Alone in Node-Negative Locally Advanced Cancer of the Prostate. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):90-93. PubMed PMID: 28816169.*	Thank you, we agree, this recommendation was affected by the ASCENDE trial, and therefore now reads as "Consider brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer". The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose. The committee also noted that some centres only use HDR and evidence from the ASCENDE trial is not robust enough to warrant a change in practice from HDR to LDR. The study suggested was excluded because EBRT did not meet the levels stated in our protocol - conventional fractionation arm should be between 70 and 80 Gy total dose of external beam radiotherapy in 1.8–2.0 Gy fractions. We have passed this reference to our surveillance team for consideration in future updates.
Royal Surrey County Hospital NHS Foundation Trust	Algorithms	Page: Treatment localised PCa		Recommendation for treatment pathway for intermediate and high risk localised Prostate Cancer is "consider high dose brachytherapy and EBRT". This is a misnomer as "high dose brachytherapy" is not a treatment modality. In the light of recent evidence from the ASCENDE RT trial this should be modified to "Low Dose Rate" brachytherapy.	Thank you, we agree, this recommendation was affected by the ASCENDE trial, and therefore now reads as "Consider brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer". The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR as there was evidence for its efficacy in the earlier version of this guideline, therefore the committee recommended brachytherapy and left it for the centres to choose the dose rate. The algorithm has been updated accordingly.
Royal Surrey County Hospital NHS Foundation Trust	Evidence review C	26	14	C2. Consider brachytherapy in combination with external beam radiotherapy for people with intermediate- and high-risk localised prostate cancer. [2019] Should be "consider Low Dose Rate brachytherapy in combination with EBRT" in view of the evidence base.	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
Royal Surrey County Hospital	General	General	General	The incorporation of Real World Data in evidence reviews will be an important addition to Guideline Development. We are aware that	Thank you for your comment. NICE is currently exploring how enhanced use of real-world data can inform our guidelines. However,

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NHS Foundation Trust				the NICE Guidelines committee is studying this approach. Many treatments are delayed and patient care is set back because randomised evidence is lacking. This has been the case for LDR brachytherapy where its effectiveness was not previously supported by an RCT. A PubMed search for "prostate AND brachytherapy AND (low dose rate OR LDR or iodine*)" shows over 1800 entries dating back as far as the 1950s. Similarly, a search using the terms "prostate AND brachytherapy AND (high dose rate OR HDR OR iridium*)" revealed over 1100 entries.	this is still under consideration and was not applicable for this current guideline update. NICE does not rely only on RCT evidence and, depending on the nature of the question, uses observational and qualitative studies.
Royal Surrey County Hospital NHS Foundation Trust	Guideline	16	20	*"Consider brachytherapy in combination with EBRT in intermediate and high risk localised prostate cancer."* We consider that the term "brachytherapy" should specify whether LDR or HDR is being recommended by the committee in this guideline based on the Evidence Review. LDR and HDR brachytherapy are different techniques. The former being permanent seed implantation in a single session and the latter being the temporary application of a stepping source in a number of sessions. The evidence that supports use of brachytherapy and describes clinical outcomes is not transferable from one technique to the other. The dose prescription of the two techniques is different. The Evidence Review C question related to "optimal dose" and the evidence admitted for "brachytherapy" was the ASCENDE RT trial. This randomised trial compared a Low Dose Rate, (LDR) iodine 125 seed, permanent implant boost with an EBRT boost.	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
Royal Surrey County Hospital NHS Foundation Trust	Guideline	36	25	The ASCENDE - RT RCT is **new evidence** that affects the previous recommendations for treatment of high risk localised prostate cancer i.e. combination of EBRT and LDR brachytherapy boost.	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
Royal Surrey County Hospital NHS Foundation Trust	Guideline	45	Table 1	"Consider brachytherapy in combination with external beam radiotherapy for people with intermediate- and high-risk localised prostate cancer (1.3.23)." Please see comment number 1.	Thank you for your comment. Please see response for comment 1.
Society and College of Radiographers	General	General	General	The Society and College of Radiographers felt the document could possibly be more prescriptive on the evidence base in terms of imaging recommendations. There is guidance from ESUR and/or PIRADS from the USA regarding field strength and minimum technology requirements that this is missing from this documentation and is an area that needs to be standardised to ensure appropriate quality in diagnosis.	Thank you for your comments, the committee has added the definition of multiparametric MRI in the "terms used in the guideline" section of the guideline and this reflects the same imaging from the ESUR consensus recommendations.
Society and College of Radiographers	General	General	General	Also, is there any evidence to support timeframes from presentation of symptoms (LUTS +/- DRE/PSA) to scanning?	Thank you for your comment. We did not look for any evidence on timeframes from presentation of symptoms to scanning, because this was out of scope.
TACKLE Prostate Cancer	Guideline	General		These comments are written on behalf of TACKLE Prostate Cancer, a national federation of patient-led support groups. The comments not only reflect the patient viewpoint but have additional input from our Clinical Advisory Board	Thank you for your comment. We appreciate you taking the time to consult on this guideline update

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TACKLE Prostate Cancer	Guideline	General		Broadly there is agreement on the new and updated recommendations. We are particularly pleased to see positive support for the use of multi-parametric MRI (mpMRI) prior to biopsy	Thank you for your comment. We welcome your support for this guideline update
TACKLE Prostate Cancer	Guideline	General		Research recommendations are quite broad and lacking in detail, but are in line with that which most patients would wish to see in the future	Thank you for your comment. We welcome your support for this guideline update. The committee purposely left the research recommendation broad to avoid being too prescriptive for researchers.
TACKLE Prostate Cancer	Guideline	General		It is disappointing that this guideline does not address the use of PSA testing / screening in the early stages of diagnosis of Prostate Cancer. This is an aspect of diagnosis and treatment that many patients find confusing. They are subjected to very conflicting opinions from experts, the media and other sources. There is a great need for robust and positive statements and guidance in this area.	Thank you for your comments. The current update only focussed on the diagnosis and management of prostate case, as a result screening was out of scope. We have passed your concerns and suggestions for reviews on screening and PSA testing to the NICE surveillance team to help inform their decisions for future updates of this guideline.
TACKLE Prostate Cancer	Guideline	General		The guidance conflates LDR and HDR brachytherapy. They are different treatments. The indications are different. Where brachytherapy is mentioned the guidance should make it clear which type they are referring to.	Thank you for your comment. The committee recommends brachytherapy - LDR or HDR. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what it available at each centre. The committee agree that these are different treatments, they explained that centres tend to only do one or the other but the end result is the same. Since there is evidence for both treatments the committee did not specify.
TACKLE Prostate Cancer	Guideline	8	1	ADD: However, if the mpMRI suggests an anterior prostate cancer, transperineal biopsy is preferred to transrectal biopsy, as the anterior prostate is difficult to access transracially.	Thank you for your comment. This current update did not include the review of evidence on techniques as a result of prostate cancer location, as result these elements are out of scope. The recommendation has been left broad as prostate biopsy to allow for clinician's discretion. We are therefore unable to add you suggested recommendation. We have forwarded your suggestion to the NICE surveillance team for consideration during future updates
TACKLE Prostate Cancer	Guideline	9	19	ADD: The repeat biopsy should be a transperineal biopsy (Not a repeat transrectal biopsy)57	Thank you for your comment. We preferred not to be specific when referring to prostate biopsy in the majority of this guideline update, due to the lack in evidence on the accuracy data of transperineal biopsies. The way the recommendation is worded should allow clinicians some discretion.
TACKLE Prostate Cancer	Guideline	11	23	Low dose rate brachytherapy (LDR 'seed' brachytherapy) should be listed as an option. It is a radical radiotherapy treatment, It is unclear if this is included under radical radiotherapy	The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.
TACKLE Prostate Cancer	Guideline	12	1 onwards	Table 3 gives a comprehensive overview of the data. Sadly the main 'sound bite' that has come from this is that the 10 year survival rate is the same irrespective of whether treatment has been given or not and has encourage a belief in some patients that Prostate Cancer does not need to be treated. The effects on quality of life – both positive and negative need to be more widely disseminated.	Thank you for your comment.
TACKLE Prostate Cancer	Guideline	16	20	The recommendation should be more specific and state 'LDR brachytherapy'	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre.

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TACKLE Prostate Cancer	Guideline	16	23	It is not correct to offer LDR brachytherapy as sole treatment. But high dose rate brachytherapy (HDR brachytherapy) can be offered in intermediate and high risk disease as a sole treatment.	Thank you for your comment. This update only considered the use of brachytherapy as an adjunct to external beam therapy. Brachytherapy alone is outside of the remit of this update and therefore we cannot make recommendations about it.
TACKLE Prostate Cancer	Guideline	20	1	The use of PDE5 inhibitors is now becoming more accepted and known in General Practice. However, no comment is made about the early prophylactic use of regular low-dose PDE5 inhibitors in people who have undergone radical therapy. There may be insufficient evidence for this, but there is an increasing body of opinion that believes this may be helpful in accelerating recovery of sexual function.	Thank you for your comment. PDE5 inhibitors were out of scope, therefore we did not review any evidence on this topic. We have forwarded this comment to the NICE surveillance for consideration in future updates.
TACKLE Prostate Cancer	Guideline	22	5	Not just if in a clinical trial. Those with locally recurrent disease can be offered salvage local therapy, for example salvage radical prostatectomy, salvage HIFU, salvage cryotherapy outside a clinical trial. Such clinical trials are few and far and far between, if indeed any exist. Men should not be denied a chance of cure. So, men should be be biopsied.	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
TACKLE Prostate Cancer	Guideline	24	22	Bone health for men on androgen deprivation therapy is a major concern. We would like to see bisphosphonates offered to all men receiving androgen deprivation therapy	Thank you for your comment. However, this section was out of scope and therefore changes cannot be made without reviewing evidence. We have forwarded your comment to the NICE surveillance team for consideration in future updates
TACKLE Prostate Cancer	Guideline	26	14	The early use of combination therapy of docetaxel and Androgen Deprivation Therapy (ADT) is becoming more known to patients. This is a useful addition to the recommendations. A similar use of Abiraterone and ADT is currently under review.	Thank you for your comment. We welcome your support for this guideline update.
TACKLE Prostate Cancer	Guideline	33	24	Transperineal biopsy can be done under local anaesthesia especially if a targeted biopsy is done as opposed to a full mapping biopsy.	Thank you for your comment, The definitions of the different ways to biopsy the prostate have been expanded and clarified.
TACKLE Prostate Cancer	Guideline	35	17	This is a very reasonable statement. mpMRI is not the panacea for all diagnosis of Prostate Cancer but is undoubtedly an extremely useful additional tool. Patients with low-risk disease from mpMRI results may still have malignancy present and this may not always be detected by standard biopsy techniques currently in use.	Thank you for your comment
TACKLE Prostate Cancer	Guideline	38	27	Should specify 'High Dose Rate Brachytherapy'	Thank you for your comment. The ASCENDE trial provided evidence for LDR, it was out of scope to compare LDR VS HDR, the committee therefore did not rule out HDR, and they recommended brachytherapy and left it for the centres to choose, based on what is available at each centre
United Lincolnshire Hospitals NHS Trust	Guideline	10	23	T2c disease is not considered High Risk in other recognised guidelines (NCCN https://www2.tri-kobe.org/nccn/guideline/urological/english/prostate.pdf) , even currently recruiting large Phase 3 trials (PIVOTALboost for example) are using NCCN rather than NICE. I think it would send a more consistent message if T2c would not be consider a single feature that label diease as high risk	Thank you for your comment. Re-classification of disease was out of scope for this guideline update. We have passed your concerns and comment to the NICE surveillance team for consideration in any future guideline updates
University Hospital Southampton NHS Foundation Trust	1.2.6	n/a	n/a	With respect to PSA measurement the age specific reference ranges for PSA have been lowered for men in the age range 60-69 yrs of age from an upper limit of 4 to 3. This will increase the number of men being referred to urology OPDs across the UK at a time when over-diagnosis of CaP is a known problem. Why has this been done and what is the rationale for it?	Thank you for your comment. The committee has not made any changes to the PSA levels. Recommendation 1.2.6 has not been changed since 2008. It was out of scope to do so in this current update

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University Hospital Southampton NHS Foundation Trust	Guideline	5	5	1.1.6 The guidelines recommend the use of a validated, up-to-date decision aid – I am not aware that this is currently available for patients with prostate cancer in a form that reflects **current** prostate cancer management.	Thank you for your comments. For this current update, this section of the guideline was not reviewed as it was out of scope. We have however removed the defunct link. We have passed your comments and suggestions to the NICE surveillance team to help inform their decisions for future updates of this guideline.
University of Cambridge	Evidence Review E	35, 39 and 41	16, 37 and 49	There is a major discrepancy with the stated conclusions from the analysis on the use of PHI in biopsy and MRI negative men. As a conflict of interest, I have to declare that there is one of my own papers cited in this review (Gnanapragasam et al 2016). The NICE guidelines states in this review page 39 line 37 that the outcome of most important is identifying or excluding clinically significant prostate cancer in people who had at least one negative initial biopsy. On page 35 line 16 it states that the PHI test at a threshold of <30 and <35 (taken from Gnanapragasam et al 2016) resulted in a large decrease in probability that a person persistently suspected of prostate cancer after a negative initial mpMRI (and also a negative biopsy) has prostate cancer Yet on page 41 line 49 the committee decide that it was not a useful test to help identify prostate cancer in people with at least one negative TRUS biopsy and MRI negative. This is inconsistent and not following the statements on the evidence review. In addition, of the 3 other studies referenced in this conclusion: one did not use MRI at all, one other was comparing MRI with PHI and not PHI in the context and of a negative MRI and none used template mapping as a reference standard (which NICE considered a reference index test). Thus, the basis of this conclusion is significantly flawed and conflates many different studies into one. The only study which addressed the statement is the UK study by our group. Could this please be corrected and hence amended to reflect NICE own evidence review?	Thank you for your comment. The Gnanapragasam study was the only study that carried out PHI in MRI negative population. Some of the other studies were deviations from protocol and were only included due to a lack of evidence in this area. The study provided evidence that at thresholds 30 and 35, a negative PHI decreases the probability that someone has cancer but a positive PHI does not significantly affect the probability that a person has cancer. So PHI is only useful if it is negative and therefore the committee was not confident about its usefulness overall as a test. The economic model did not find PHI to be cost-effective at the conventional cost-effectiveness thresholds. Based on this evidence, the committee decided there was limited evidence and concluded that PHI did not represent an effective use of NHS resources in the follow-up of people who have had a negative transrectal ultrasound guided prostate biopsy, and therefore did not make any recommendations on these technologies, this is consistent with NICE DG17 which did not recommend PHI. We have amended this within the review chapter to make this clearer.
University of Cambridge	Evidence Review F	Title and evidence used 15 onwards	19 onwards	1. There is a major problem with this evidence review. There has to be a distinction made between re-classification (i.e. when a repeat biopsy shows that the original disease classification was wrong and in fact there is a higher risk or higher volume tumour) and true disease progression (i.e. when a known tumour grows and becomes of a higher risk). The title of this evidence review is about progression yet the papers reviewed are about early reclassification. Note that the papers included have follow up less than 6 months with only one with a median of 38 months. This is not enough to make any recommendations about follow up schedules. **Thus, this review should instead be retitled as "Evidence reviews for identifying prostate cancer reclassification"** NICE in fact acknowledge this on page 16 line 28 onwards. All the evidence on MRI is actually about how using MRI improves disease classification and not about its use in detecting progression. This	Thank you for your comments: 1. The review question was "Which of the following, alone or in combination, constitutes the most clinical and cost- effective pathway for excluding the clinically significant progression of prostate cancer in people with low to intermediate risk (as defined in NICE CG175): Multiparametric/ functional MRI, TRUS biopsy, Transperineal template biopsy?". We were not able to identify papers on disease progression. We cannot retroactively change the title or the question. As you note, we have acknowledged the lack of evidence in the review and pointed out that the majority of the evidence relates to reclassification. In spite of that, the committee made recommendations on the best available evidence. 2. Thank you for the suggested study, we have looked at it and have now included it in our review. However, the committee felt that this study used biparametric MRI and not multiparametric MRI as

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				evidence review appears to infer that better disease characterisation and progression are the same thing. 2. The review does not take advantage of the published data on the rates of progression when men do have MRI at the outset and accurate early reclassification. I offer this paper from the UK which does not appear on the reviewed paper list which address this and shows the true rates of progression in men with well characterised disease: Thurtle D, et al doi: 10.1111/bju.14166. This paper also examined the role of MRI as a tool to monitor men on AS and how useful it was. 3. Table 3 therefore is outdated and does not reflect evidence-based practice. If there is no good recommendations based on evidence on the best follow up schedule then this should be left unstated rather than offering a recommendation for follow up which is at best an opinion at worse a reason to not explore better surveillance regimes as centres adopt this as NICE endorsed practice. As an example of this discrepancy: in Evidence review E, NICE states that PSA velocity has no value in predicting detection of clinically significant cancer, yet in Table 3 here it is recommended as a method pf monitoring men on AS? Similarly, DRE in in Evidence review E has no vale in ruling out clinically significant disease but is recommended here as a tool in monitoring men? In many centres MRI is now replacing DRE and DRE itself is an unnecessary and invasive examination with very low sensitivity, specificity and repeatability. Oddly the document states that they referenced evidence review E on page 18 line 11 but infer something different from the conclusions in E. Perhaps this needs a relook 4. Table 3 also suggests that you can step down follow up with time yet it is very very clear that progression in prostate cancer occurs after some time and not in the short term – see the protect study which NICE cites. Again, this suggests that these guidelines are not about follow up but about reclassification. If anything, follow up can be less intense in the early years and more needed in the later years. These recommendations therefore are not based on evidence and are more hinderance than help to evidence-based practice in AS as centres are reluctant to stray from what is printed in the guidelines. 5. If NICE are recommending an MRI for anyone on AS (page 18 Line 39) who has not had one, then why repeat it at 12-18 months again? And then why not in subsequent follow up? 25 Surely the most important research question is when should AS stop and what construes disease that absolutely needs treatment? Also, what is the best way to monitor men and detect progression without invasive examinations and is also cost-effective	suggested by the authors because the MRI protocol was T2W and diffusion weighted but had no dynamic contrast enhancement. The inclusion of the paper is a deviation of the protocol. Nevertheless, the committee considered the evidence and concluded that most of the pathological progression were identified on MRI and only a small proportion were missed. The committee retains its recommendation. 3 & 4. Thank you for your comments. The current review did not set out to investigate the role of DRE in active surveillance. In evidence review E, the population is people with a prior negative biopsy but still suspected of prostate cancer. The committee decided to leave DRE as part of the surveillance protocol because they did not see any evidence in this review to challenge its role. In 2014, the committee used evidence from a range of surveillance protocols from across the country that showed that people were using DRE as part of the protocol. In addition, the committee noted that the active monitoring in ProtecT also included DRE as part of the protocol. There is currently no evidence on the best follow up – the committee made a research recommendation, to highlight the lack of evidence. The committee considered PSAV and concluded that based on the sensitivity and specificity of 69% and 56% respectively, their opinion also matched the results from the economic analysis that looked at the best follow-up strategies that showed that PSA measures based on density and velocity performed better than other PSA measures. 5. We agree PSA density is not one of the PSA kinetics; this has been corrected. The committee advised that the volume of prostate gland identified during the diagnosis will be used as a reference to calculate the PSA density. Evidence review E shows that the use of PSA density test at a threshold of 0.15 ng/ml/ml and the PSA velocity at a threshold of 0.75 ng/ml/year as screening tests within a follow-up protocol to trigger further diagnosis is reliable.

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		16	3 onwards	It concerns me that the follow up regime was changed based on the committee's expertise (i.e. opinion) and not any real evidence base. As an example, the evidence on using PSA kinetics is not clear (using kinetics to diagnose is not the same as using it to monitor) and I don't understand how PSAd is a kinetic? This is calculated from the PSA divided by the prostate volume – using it as a kinetic means how it changes with time yet NICE is not recommending repeated prostate volume measurements so how is a clinician supposed to use it? Also what PSA velocity is important, what rate, what speed – this cannot be the same as for diagnostics where the evidence there is also not very strong?	
University of Cambridge	Evidence review G	10 onwards	7	1. I am concerned that these recommendations are based on now outdated studies and over reliance on solely RCT data. ProtecT (the newest study) is now over 15 years old and the practice and biopsy methods has completely changed. Also note that it did not attempt to stratify patients by risk whereas NICE has inferred this in their recommendations. There is an over reliance on this trial and the other mentioned, much which do not represent the disease we now see in practice. Table 2 in particular is not representative in the better biopsies and staging in current practice and AS data from long term studies now show no extremely low risk of metastatic spread. 2. There is a strange contradiction that NICE suggests in Evidence review D that it is not desirable to detect clinically insignificant disease (by its own definition <Gleason 7 i.e. low risk disease) yet here it recommending radical therapy as an option. Either one or the other is correct but both cannot be? 3. The risk groupings NICE are using here is completely outdated – the terms low and intermediate risk have been replaced by different subgroups in the AUA and NCCN classifications and there is strong UK data to show how these subgroups have very significantly different outcomes (see below). This review also ignores the major changes that have happened in grade migration following changes in histopathological review by ISUP. 4. The types of cancers picked up here are different from what will be detected by what NICE is recommending with the new MRI pathways - so is a low risk cancer detected by a random 12 core biopsy back in 2000 the same as one from a MRI and then targeted biopsy in 2019? This is not mentioned or discussed or caveated and appears a divergence in what NICE is recommending in both evidence reviews. 5. Disease progression in Table 2 seems be mainly about PSA rises but PSA rises were not corrected for prostate size nor correlated with outcome in Protect and hence must be interpreted with caution. It is very well known that PSA is a poor correlate with survival outcome. While it was suitable at the time of Protect, it is a	Thank you for your comments: 1. ProtecT was categorised as directly applicable evidence with moderate to high quality that recruited participants with different risk groups (Evidence review G page 132). If a study provides long term follow-up data, it is inevitable that the study will be older. 2. Radical treatments for people with low-risk are offered to people who opt for it. This is based on a shared decision between clinicians and patients that have to be well informed of the benefits and harms of a radical treatment for their disease. 3. The scope of the current update does not include the re-consideration of the staging system for prostate cancer. However, we understand your concerns and we will pass this to the NICE surveillance team. 4. Whilst the new pathways are designed to be more appropriate there will still be people diagnosed with low risk prostate cancer who need recommendations for their management and therefore this needs to be acknowledged. The risk distribution of cancers detected in ProtecT may be different from those detected in 2019 but ProtecT provides the only prospective randomised evidence of treatment versus surveillance. 5. Our apologies regarding the disease progression in table 2, this has

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				poor surrogate now and is unsuitable as an endpoint to base a national guideline. How does it impact on prognosis and what is the evidence for it? All cancers will progress as that is what cancers do – but does this mean it affects mortality or spread? Also, is moving from low to intermediate risk mean more deaths or more spread? Considering NICE states here that it does not differentiate between the 2 in its recommendations then why is this a reason to change from AS to treatment? 6. Overall, I think this guideline will result in serious over-treatment of low-risk (and indeed what is now accepted as favourable intermediate risk-disease) and more ambiguity on what to do for clinicians and patients. I would strongly urge NICE to review this and marry up the different recommendations on diagnostics versus treatments and not review them separately. 7. Most crucially I strongly urge NICE to look at the data on how classifications of disease need to be changed and updated. I offer these 2 papers for review in this area which is derived from UK data and validated in 2 international series (total of 86,000 men included) : Gnanapragasam et al 2018 doi: 10.1186/s12916-018-1019-5 and Gnanapragasam et al 2016 doi: 10.1371/journal.pmed.1002063 (NICE have actually used this paper in a different evidence review) and I also recommend the committee look at the new AUA and NCCN guidelines. Indeed, the words risk need to be abandoned and using disease prognosis would be much better. 8. I cannot see that the NICE have recognised and accepted the well-established new Grade Grouping system instead of the now out-dated Gleason scoring system? Indeed, adoption of newer classifications as above will account for this.	been amended. The initial definition was the criteria for suspecting progression. The definition is now stated as – *The trial defined disease progression as-* • *Evidence of metastases* • *Diagnosis of clinical T3 or T4 disease,* • *Long term androgen deprivation therapy,* • *Rectal fistula or the need for a urinary catheter owing to local tumour growth* *Disease progression was suspected if -:* • *any rise in prostate-specific antigen (PSA) >20% between consecutive measures at any time during follow-up or* • *any rise in PSA level of 50% or greater in any 12-month period confirmed by repeat tests or any indication of the appearance of symptomatic systemic disease* 6, 7 and 8. Thank you for your comment, we are not able to review risk stratification in this current review. We have forwarded your comment to the NICE surveillance team for consideration in future updates
University of Cambridge	Evidence review H	Whole document		This entire document review does not consider the very different mechanisms and tumour responses to radical surgery and radical radiotherapy. Not least as the PSA thresholds for each after treatment are very different. Thus, the value of this review and any updates is very unclear. As an example, the effect of ADT on PSA with radiotherapy is not considered and it takes up to a year or more for the true new post treatment PSA hence recommending discharge to primary care within 6 months will result in many men referred back. This review needs to consider different follow up in different treatment settings and recommendations accordingly. A one size fits all is practically unworkable and means the guidelines are unlikely to be ever taken up. I wholly agree with a risk based follow up approach and this is actually already available for use.	Thank you for your comment. The purpose of this review was to investigate different follow up strategies after radical treatment. We were unable to find any evidence to make recommendations. Your suggestion to consider the different mechanisms and tumour responses to radical surgery and radical therapy would have been out of scope. The committee is aware that there are variations in follow up protocols across the country, the recommendations made were meant to reflect that and be broad to allow for centres to formulate their own protocols.
University of Southampton	Guideline	6	5	Although not invited to comment on the grey shaded areas, there are some word changes that we would recommend to ensure that incontinence is fully understood as a risk for men and that they are properly supported following treatment: There is evidence from interview data that men sometimes make treatment decisions without fully appreciating the risks for bladder	Thank you for your comments. This current update did not include the review of evidence on bladder and/or bowel incontinence, as a result these elements are out of scope. We did however report on adverse events in Table 3 to be included as part of the decision making discussion between clinician and patient. Unfortunately we are unable to add your suggested recommendation.

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				and bowel function and that, when severe and/or intractable, incontinence can lead to a severe reduction in quality of life and regret about treatments made. We are concerned that men should fully understand that this could affect bladder and /or bowel function and recommend that this bullet point be amended to: *bladder and/or bowel continence*	We have forwarded your suggestion to the NICE surveillance team for consideration during future updates
University of Southampton	Guideline	6	10	For the reason given in comment 1, we would recommend an additional point: *Offer people with prostate cancer, and their partners or carers, the opportunity to talk to a healthcare professional experienced in dealing with continence issues at any stage of the condition and its treatment.*	As explained above, we are unable to add your suggested recommendation
University of Southampton	Guideline	11	11	For the reason given in comment 1, we would amend this point to: *Warn people undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function, specifically the risk of urinary and/or faecal incontinence.*	Thank you for your comments. We have included the information in table 3 outlining the adverse events associated with each treatment. As this is a preference sensitive decision, the committee decided that people choosing radical treatment would have discussed the pros and cons with their clinician.
University of Southampton	Guideline	11	13	Offer men a consultation with a urology nurse specialist or continence nurse to ensure they have suitable knowledge and products for management of post radical treatment incontinence. After 1.3.4, we would recommend an additional point signposting to the Prostate Continence Website www.prostatecontinencewebsite.org for evidence-based, impartial and comprehensive product information.	Thank you for your comment. The committee did not review any evidence on the best plan on managing incontinence as this is out of scope. We have passed this information to the NICE surveillance team for consideration in future updates of this guideline
University of Southampton	Guideline	14	9	Given the risk of incontinence from radical prostatectomy and radical radiotherapy, suggest word change as follows "....person's preferences, comorbidities, the likelihood of side effects and life expectancy."	Thank you for your comment. This is covered in depth in table 3.
University of Southampton	Guideline	20	7	The substantial majority of men having their catheter removed after radical prostatectomy will have urinary incontinence in the immediate post catheter removal period and will require containment advice and products before the catheter is removed (see comment above). We suggest an additional point after 1.3.36 such as: *Ensure that people with prostate cancer having a catheter removed after surgery have been referred beforehand to a urology nurses specialist or continence nurse and have containment devices available to take with them to the catheter removal appointment.*	Thank you for your comment. We have made reference to adverse events in Table 3. The committee did not review the impact of catheters as this was out of scope. We will not be able to add your suggested recommendation. We have forwarded this comment to the NICE surveillance for consideration in future updates.
University of Southampton	Guideline	20	8	We agree that people with incontinence after radical treatment should be offered conservative treatments but they must have access to containment products while awaiting treatment to take effect and in the event that treatment fails. We would recommend an additional point after 1.3.36:	Thank you for your comment. We have made reference to adverse events in Table 3. The committee did not review containment products as this was out of scope. We will not be able to add your suggested recommendation. We have forwarded this comment to the NICE surveillance for consideration in future updates.

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				Refer men with urinary incontinence to a continence nurses for advice about containment while undergoing conservative treatments and in the event that these are unsuccessful. 20 *Refer men to appropriate information sources such as the Prostate Continence Website www.prostatecontinencewebsite.org to make informed decisions about managing their incontinence*.	
University of Southampton	Guideline	20	25	Men who have radiation are at risk from faecal incontinence. We therefore recommend an additional section called 'Faecal Incontinence' within which the following point is made: *Refer men with faecal incontinence to a continence nurses for advice about containment while undergoing conservative treatments and in the event that these are unsuccessful. 20* *Refer men to appropriate information sources such as the Prostate Continence Website www.prostatecontinencewebsite.org to make informed decisions about managing their incontinence*.	Thank you for your comment. We have made reference to adverse events in Table 3. The committee did not review any evidence on management of faecal incontinence as this was out of scope. We will not be able to add your suggested recommendation. We have forwarded this comment to the NICE surveillance for consideration in future updates.
University of Southampton	Q3 on comments form			Clear signposting to evidence-based web information for management of incontinence provides men with the resources to self-manage their incontinence, giving them confidence in selection of combinations of products. To this end use of a validated tools for product selection reduces decision conflict. Please see www.prostatecontinence.org and www.continenceproductadvisor.org	Thank you for your comment.
Wales Cancer Network	Guideline	31	21	**The Prostate cancer: diagnosis and management (update) consultation** document was considered by the Clinical specialists within the Urological Cancer site Group of the Wales Cancer Network and the following comments received: We are grateful for the panel's time and effort in producing the latest draft guideline for diagnosis and management of prostate cancer. In particular, we note the recommendation for wider incorporation of multiparametric MRI into the diagnostic pathway of patients with suspected prostate cancer. However, we feel that the definition of multiparametric MRI should be more specific to facilitate justification of the additional contrast material and scanner time cost, for implementation into clinical practice. The current definition in the draft document is as below for your reference: **Multiparametric MRI** A magnetic resonance imaging study that incorporates anatomical and functional information about a body part. The functional information may include one or more sequences based on diffusion-weighted imaging, dynamic contrast enhanced imaging or magnetic resonance spectroscopy. If the committee's decision is to recommend multiparametric MRI, including diffusion-weighted imaging and dynamic contrast	Thank you for your comment. The definition for multiparametric MRI has now been amended and we have aligned it with the ESUR guidance.

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				enhanced imaging, as patient's first investigation, the definition should ideally be more specific. Additionally, since magnetic resonance spectroscopy is only performed within trial setting, consideration can also be made to remove this component from the definition. An updated example definition has been draft below for your consideration. **Multiparametric MRI** A magnetic resonance imaging study that incorporates anatomical and functional information about a body part, where the functional information includes	