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Stakeholder	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Academic Urology Group University of Cambridge	General		There is a very strong pro-MRI lobby that justifies MRI for all use by claiming that a negative scan does not need biopsies. This is not supported by the many papers from the UK that have consistently shown a significant risk of 10-20% of harbouring clinically significant disease in MRI negative men. NICE needs also to consider what is "clinically significant disease". This is currently not clear by the current risk stratification model NICE uses but may be informed by revising this (see below).	Thank you for your comment. We will be undertaking an update on the use of mpMRI in the diagnosis and staging of prostate cancer. NICE undertakes a systematic search of the literature for each topic area; this evidence is then critically appraised and the findings are presented to the decision-making committee for their consideration when making recommendations. When making recommendations, the committee take into account the strengths and limitations of the evidence base. More detail on this can be found in section 9 of 'Developing NICE guidelines: the manual'.
			We must be very careful that NICE does not mandate tests and treatments that NHS hospitals cannot afford or which needs significant skills and personnel in place to deliver. NICE must also ensure that any cost analysis does not assume that a higher risk for patients in terms of missed cancer diagnosis is acceptable to increase diagnostic accuracy. This may open clinical teams to a high risk of complaints and litigations as patients expectations are raised and their tolerance of risk reduced. Thus decisions to not biopsy (because of a negative MRI) must be made with patients and with data specific to a centre and not mandated by trusts to save costs.	Thank you for this information. Health economic reviews are undertaken for each area of the guideline update. We will consider this information during development. Please see section 9 of 'Developing NICE guidelines: the manual' for more information on incorporating economic evidence into guidelines. No large national patient survey has been identified in the scoping searches for this update. The

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			Has there been any large national patient survey to ask what actually men feel about not being biopsied but with a 10-20% risk of harbouring undetected cancer? This needs to be done in men who don't have cancer not men with prostate cancer.	perspective of people affected by the guideline is key in developing NICE guidance. As stated in section 3.4 of Developing NICE guidelines: the manual, 'All Committees have at least 2 lay members with experience or knowledge of issues that are important to people using services, family members and carers, and the community affected by the guideline. This helps to ensure that the guideline is relevant to people affected by the recommendations and acknowledges general or specific preferences and choice'.
Academic Urology Group University of Cambridge	General		There is an urgent need for NICE to overhaul its recommendation for risk stratification as using the 1997 D'Amico criteria as a basis is very out-dated and has never been tested in UK populations. Moreover it does not include the new 5 strata WHO histological grade groups. A crucial need is to have a prognostic model that can more accurately predict prostate cancer mortality which is the key outcome of interest for patients and clinicians. Any new model must also have been tested in the UK setting and have relevance to practice in this country. It is notable that even the recent USA AUA guidelines and NCCN guidelines are not based on data but instead on consensus expert opinion. NICE must look and consider the evidence for the UK and not simply adopt	Thank you for your comment. We understand that there are issues around the criteria for risk stratification in prostate cancer. We did not identify any new published evidence, or evidence that is due to be published during the guideline update that would

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			practice in the US or elsewhere (as was done with the 2014 risk classification model).	impact the current recommendations on risk stratification. We will highlight this area to the surveillance team for consideration at the next surveillance review.
Academic Urology Group University of Cambridge	3	22	NICE must consider that many MRI - biopsy studies have limitations that make generalisations of their results problematic. For example in the PROMIS study – the MRI was not used to target the biopsies. Indeed the real comparison was between a TRUS biopsy (12 biopsies) and a grid based transperinal template biopsy (estm 30-50 biopsies). An MRI was considered to be positive if any cancer was found on the grid base biopsy (even if the MRI suggested the image lesion was elsewhere). PROMIS also used a very high threshold for clinical significant cancer (Grade 4+3 or >6mm) to make a claim of saving the need for biopsies. To most urologists this is very risky and any Grade 3+4 is considered clinically significant. Hence the case to not biopsy after an mpMRI is not made. Instead PROMIS does (in addition to many other studies) support the use of mpMRI to guide biopsies to increase accuracy and obtain correct histological assessment. Certainly a negative MRI reduces the risks of harbouring cancer but not enough to exclude a biopsy need at this time and the accuracy and sensitivity of MRI reading varies from place to place (65-95%).	Thank you for your comment. We will take into account the information that you have provided during the updating of this guideline. When considering the evidence, the committee assess the strengths and limitations of the evidence base. For detail on how NICE develops it recommendations please see section 9 of 'Developing NICE guidelines: The manual'. The manual states that when making recommendations 'The Committee must use its judgement to decide what the evidence means in the context of the guideline referral and decide what recommendations can be made to practitioners, commissioners of services and others.

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			There are many UK and international studies which have shown that image guided biopsies are much better than non-image guided to get a diagnosis and accurate grading.	The evidence is assessed for validity, reliability and bias, but also requires interpretation, especially an assessment of its implicit and explicit value base. Evidence also needs to be assessed in light of any conceptual framework and theories relating to individual and organisational behaviour change'.
Academic Urology Group University of Cambridge	3	24	NICE must consider that treatment stratification studies have limitations that make their applicability to contemporary practice problematic in addressing and answering the questions NICE is asking. As an example the recent PROTECT study did not use any risk stratification in their randomisation or treatment assignments. This would never happen in current practice. Moreover the cohort in the study was overwhelmingly low risk as the study was sourced from a screened population (which is not current practice in the UK). Thus NICE needs to also look at other more contemporary and relevant studies (albeit not prospective and in a trial) to inform their new review of the risk stratification guidelines. NICE should do a comprehensive search of what data there is on the use of risk stratification models in UK populations or at least unscreened non-USA cohorts and which have shown the ability of new risk or prognostic classification categories to predict outcome in men with non-metastatic disease.	Thank you for your comments. A systematic literature search is undertaken for each clinical area being updated. When considering the evidence, committees take into account the strengths and limitations of the evidence base. We will take this information into consideration during development of the guideline update. Please see 'Developing NICE guidelines: the manual' for more details on how guidelines are developed.

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Astellas Pharma Ltd	general	general	Docetaxel is recommended for patients with mHSPC, but the product does not have licence in the UK for the use for these patients. Furthermore, the STAMPEDE data supporting the use of docetaxel in this patient population specify high volume disease; will the guidance be limited to this subpopulation? And will the guidance define clearly high volume vs low volume disease. (In contrast to high risk vs low risk)	Thank you for your comment. Docetaxel is included in the scope of the guideline update for use in men with hormone sensitive locally advanced or metastatic prostate cancer. As you correctly highlight, Docetaxel is licensed for use in men with hormone resistant refractory prostate cancer. As stated in the scope: 'Note that guideline recommendations for medicines will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended'. The update of this section was prompted by the publication of new evidence in men with locally advanced hormone sensitive prostate cancer and hormone sensitive metastatic prostate cancer, therefore it is appropriate to assess the use of

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				docetaxel in this population. The exact details of the population will be set out in the review protocol that will be finalised during development. We will take into account the information you have provided.
Astellas Pharma Ltd	4	10	Treatment decisions also depend on access and availability of treatment options at local hospital level	Thank you. NICE recognises that guidance is implemented on a local level and has processes in place to assist with this.
Astellas Pharma Ltd	7	7	When writing the guidance on MRI use and diagnosis, will you include guidance on what to do for patient who have negative MRI scan, how to monitor them and how frequently they should be re-scanned?	Thank you for your comment. We have added a review question on 'What is the most clinically- and cost-effective follow-up protocol for men who have a raised PSA, negative MRI and/ or negative biopsy?'
Astellas Pharma Ltd	7	12	For risk stratification: clearly define the risk categories	Thank you for your comment. Risk stratification is not included in the scope of the guideline update, because no evidence was identified that would impact current recommendations.
Astellas Pharma Ltd	7	16	Define locally advanced prostate cancer	Thank you for your comment. The definition of locally advanced prostate cancer is that used in CG175: 'For the

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				purposes of this guideline, this includes: high-risk localised prostate cancer (as defined in chapter 4); T3b and T4, N0 prostate cancer; and any T, N1 prostate cancer'.
Barts Health NHS Trust	General	General	These guidelines do not cover the process of **staging adequately**.	Thank you for your comment. No new evidence was identified in the scoping searches that would impact current recommendations on staging; therefore this area of the guideline will not be updated at this time.
Barts Health NHS Trust	General	General	**Use of PET CT in** staging / restaging has been completed missed from this document.	Thank you for your comment. No new evidence on the use of PET/CT in staging was identified in the scoping searches, therefore it is not included in this update. We understand that PET/CT in staging is an emerging area with ongoing trials, and we will highlight this to our surveillance team for their consideration during the next guideline surveillance review.
Barts Health NHS Trust	General	General	There is no mention of role **of biomarkers** eg. Choline and PSMA when the diagnosis of prostate cancer is not clear and there has been over emphasis on the use of multiparametric MRI.	Thank you for your comment. We understand that the role of biomarkers in the diagnosis of

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				prostate cancer is an emerging area with ongoing trials, however no evidence on biomarkers was identified through the scoping process and therefore it is not included in this update. We will highlight this area to the surveillance team for specific consideration at the next surveillance review of this guideline.
Barts Health NHS Trust	General	General	Role of functional imaging has not been mentioned in the detection of **nodal metastases** which are not adequately detected by multi parametric MRI.	Thank you for your comment. The role of MRI in the diagnosis of prostate cancer will be updated. No new evidence on the use of other imaging modalities for the diagnosis of prostate cancer was identified through the scoping process and therefore they will not be included in this update. With regards to the limitations of MRI in the detection of nodal metastases, we will take this information into account when developing the guideline if evidence on this is identified. Furthermore, no new evidence on the use of imaging in staging was identified in the scoping

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				searches, therefore it is not included in this update
Barts Health NHS Trust	General	General	**Musculoskeletal lesions** are not adequately characterised on multi parametric MRI and use of PET/CT has been completed missed from this document.	Thank you for your comment. The role of MRI in the diagnosis of prostate cancer will be updated. No new evidence on the use of PET/CT for the diagnosis of prostate cancer was identified through the scoping process. With regards to the limitations of MRI in the detection of musculoskeletal lesions, we will take this information into account when developing the guideline if evidence on this is identified. Furthermore, no new evidence on the use of imaging in staging was identified in the scoping searches, therefore it is not included in this update.
Barts Health NHS Trust	General	General	**British Nuclear Medicine Society** should be consulted about the use of PET/CT in the diagnosis of Prostate cancer.	Thank you for your comment. We would welcome the British Nuclear Medicine Society to register as a stakeholder for this guideline. Section 10.1 of Developing NICE guidelines: the manual states that 'The draft version of the guideline is posted on the NICE website for consultation with

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				registered stakeholders and respondents. Stakeholders can register at any point during guideline development. NICE informs registered stakeholders and respondents that the draft is available and invites them to comment by the deadline'.
Barts Health NHS Trust	General	General	**UKRG (United Kingdom Radiopharmacy Group) should** be given representation in drafting guidelines and use of Radio-isotopes in diagnostic pathway of Prostate Cancer	Thank you for your comment. We would welcome the UKRG to register as a stakeholder for this guideline. Section 10.1 of Developing NICE guidelines: the manual states that 'The draft version of the guideline is posted on the NICE website for consultation with registered stakeholders and respondents. Stakeholders can register at any point during guideline development. NICE informs registered stakeholders and respondents that the draft is available and invites them to comment by the deadline'.
Barts Health NHS Trust	General	General	Role of **Radionuclide Therapy** has been completely missed from this document	Thank you for your comment. NICE has Technology Appraisal guidance on the use of radium 223 in

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				metastatic prostate cancer (TA412), which we will cross- refer to in the guideline update. No additional new evidence on radionuclide therapy was identified in the scoping search for this update, therefore this section will not be included in the update of this guideline.
Bayer HealthCare	6	16	When reviewing the role of multiparametric or functional MRI in the diagnosis and active surveillance of prostate cancer, the following should be considered. 1) Pre-contrast T2 2) Diffusion weighted imaging (DWI) 3) Dynamic contrast enhanced (DCE).	Thank you for your comment. We will take into account the information you have provided when writing the detailed review protocols for this topic area.
Bayer HealthCare	6	19	When reviewing the role of multiparametric or functional MRI in the active surveillance of prostate cancer, managing relapse after radical treatment should be considered.	Thank you for your comment. Not enough new evidence was identified to impact on current recommendations for the section of 'managing relapse after radical treatment', therefore this section will not be updated at this time.
Bayer HealthCare	8		It is not currently proposed that the section on staging should be updated, however we suggest it would be relevant to consider the PI-RADS v2 in	Thank you for your comment. No evidence on staging was identified in the scoping searches, therefore this will not be updated at this time. The

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			conjunction with PSA and Gleason score in relation to the risk stratification for newly diagnosed men with localized prostate cancer.	PI-RADS scoring system for multiparametric MRI will be covered by that section of the update scope.
Bayer HealthCare	10		The draft scope for this update of the prostate cancer clinical guideline has identified related published technology appraisal guidance in accordance with the guidelines manual (2014) www.nice.org.uk/process/pmg20, but has not stipulated which of the 'possible approaches' will be followed in each case. Technology appraisal guidance [TA412]: Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases was published in September 2016. The recommendations from this technology appraisal should therefore be incorporated verbatim in this clinical guideline, and this should be made explicit in the scope. Failure to incorporate the TA recommendations in the clinical guideline may cause confusion amongst commissioners and clinicians.	Thank you for your comment. We have updated the scope to say that TA412 will be cross-referred to in the guideline and prostate cancer pathway, thus ensuring clear guidance on it place in the management of prostate cancer.
Beckman Coulter	3	3	The clinical and health economic evidence related to the use of new serum biomarkers or combination of biomarkers such as indexes as an aid for prostate cancer risk stratification and the decision to perform an initial or a repeated trans-rectal ultrasound guided biopsy (TRUS) should be considered for review.	Thank you for your comment. No new evidence regarding biomarkers was identified in the scoping search, therefore this area will not be updated at this time.
Beckman Coulter	3	22	The clinical evidence related to the use of new serum biomarkers or combination of biomarkers such as indexes as an aid for prostate cancer risk stratification and the diagnosis of prostate cancer in conjunction with multiparametric or functional MRI should be considered for review.	Thank you for your comment. No new evidence regarding biomarkers was identified in the scoping search, therefore this are will not be updated at this time.

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Beckman Coulter	4	10	The clinical and health economic benefits of the use of new serum biomarkers or combination of biomarkers such as indexes in selection of patients that would benefit the most of multiparametric or functional MRI for prostate cancer detection should be considered for review.	Thank you for your comment. No new evidence regarding biomarkers was identified in the scoping search, therefore this are will not be updated at this time.
Beckman Coulter	6	22	The evidence related to the use of new serum biomarkers or combination of biomarkers such as indexes as an aid for localized low risk prostate cancer treatment decision in particular for active surveillance should be considered for review.	Thank you for your comment. No new evidence regarding biomarkers was identified in the scoping search, therefore this are will not be updated at this time.
British Association of Urological Surgeons	general		BAUS would advise that caution must be applied if switching Active Surveillance (AS) programs to only biopsying if MRI shows a lesion as there is little evidence to support that this is safe. There were three presentations at the recent BAUS annual scientific conference showing cost savings by only biopsying AS patients if MRI shows a lesion and one of them clearly showed that significant upgrading of disease in 21% of patients could be missed by this method. We request that evidence in relation to this be reviewed and this issue addressed in the guideline. The abstracts were: P11-16 Introducing mpMRI into contemporary UK active surveillance for localised prostate cancer **Bryant R[1], Yang B[1], Philippou Y[1], Lam K[1], Obiakor M[1], Ayers J[1], Gleeson F[2], MacPherson R[2], Verrill C[3], Roberts I[3], Leslie T[1], Crew J[1], Sooriakumaran P[1], Hamdy F[1], Brewster S[1]**	Thank you for your comment. The role of multiparametric MRI and biopsy in active surveillance is included in the scope of the guideline update. We will take into account the information you have provided during the development of the guideline. . When making recommendations, the committee take into account the strengths and limitations of any intervention. Please refer to Developing NICE Guidelines: the manual, section 9 Developing and wording recommendations and writing the guideline, for more details on how recommendations are made.

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			[1]*Urology Department, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom,* [2]*Radiology Department, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom,* [3]*Pathology Department, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom* P11-17 P11-17 Impact of introducing an intensive mpMRI based protocol on active surveillance outcomes **Thurtle D[1,2], Thankappan-Nair V[1], Barrett T[1], Koo B[1], Warren A[1], Kastner C[1], Saeb-Parsy K[1], Kimberley-Duffell J[1,2], Gnanapragasam V[1,2]** [1]*Cambridge University Hospitals NHSFT, Cambridge, United Kingdom,* [2]*Academic Urology Group, Department of Surgery, University of Cambridge, Cambridge, United Kingdom* P11-18 The impact of repeat prostate biopsy after MP-MRI on subsequent management of patients on active surveillance for low risk prostate cancer **Gallagher K[1], Christopher E[1], Cameron A[1], Perumal R[1], Little S[1], Laird A[1], Keanie J[1], Bollina P[1], McNeill A[1]** [1]*Western General Hospital, Edinburgh, United Kingdom,* [2]*University of Cambridge, Cambridge, United Kingdom* All abstracts were published in the Journal of Clinical Urology, Volume 10, Issue 2_suppl, June 2017.	
British Association of	general		In terms of initial diagnosis we seek reassurance that the review will consider the role of mpMRI in the diagnostic pathway. BAUS supports mpMRI in the	Thank you for your comment. As outlined in section 3.3 and 3.5 of the

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Urological Surgeons (BAUS)			pathway but would not encourage that it be considered the only triage test, as per our comments above changing to a policy of only biopsying visible lesions would mean significant delays in diagnosis in many men. mpMRI is an important part of the diagnostic pathway, it vastly improves the diagnostic yield avoiding repeat biopsies but we would urge that great caution should be exercised regarding no biopsy if mpMRI is negative.	draft scope, we will be assessing the role of mpMRI in the diagnostic pathway. When making recommendations, the committee take into account the strengths and limitations of any intervention. Please refer to Developing NICE Guidelines: the manual, section 9 Developing and wording recommendations and writing the guideline, for more details on how recommendations are made.
Department of Health			Thank you for the opportunity to comment on the draft scope for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
Frimley Health NHS Foundation Trust	General	General	Please can transperineal template biopsies as a diagnostic tool also be examined as part of the guidance. They are more accurate than a Trus biopsy, enable targeting of the anterior prostate (where 20%) of cancers occur) and have a reduced rate of sepsis when compared with Trus biopsies.	Thank you for your comment. We have added transperineal template biopsy and MRI-influenced TRUS biopsy as comparators in the section on the diagnosis of prostate cancer.
Frimley Health NHS Foundation Trust			If using MRI to help decide on performing biopsies, should systematic biopsies of the whole prostate be taken in addition to targeted biopsies of the visualised lesion on MRI. In other words, is it OK just to biopsy the abnormal area seen on MRI and leave everything else?	Thank you for your comment. We have added transperineal template biopsy and MRI- influenced TRUS biopsy as comparators in the section on the diagnosis of prostate cancer.

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Frimley Health NHS Foundation Trust			Is it possible to accredit individuals and locations to perform and report high quality mpMRI scans of the prostate?	Thank you for your comment. NICE does not accredit individuals and locations in its guidelines; recommendations are made on the basis that those providing the intervention or procedure are trained and competent. If a quality issue is identified during the development of the guideline this will be documented in committee considerations and if required will be passed on to NICE's implementation team following publication of the updated guideline.
Frimley Health NHS Foundation Trust			Is focal therapy a reasonable treatment option for well characterised small and significant tumours?	Thank you for your comment. By the term 'focal therapy' we understand you are referring to vascular targeted photodynamic therapy (VTP), as well as high intensity focused ultrasound (HIFU) and cryoablation. VTP is currently the subject of NICE technology appraisal guidance in development 'Prostate cancer (localised) – padeliporfin' which is due to be published in August 2018. Therefore VTP will not be included in this guideline update but cross-

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				reference will be made to the TA guidance (once published), in the pathway. Both High-intensity focussed ultrasound and cryoablation are the subject of NICE Interventional Procedure Guidance (IPG424 and 423 respectively). We did not identify any new evidence that would impact the current recommendations on either HIFU or cryoablation, Therefore we will not be including them in the scope for the guideline update.
Frimley Health NHS Foundation Trust			Define follow up strategy for men referred at risk of prostate cancer and found to be negative after mpMRI and or biopsy e.g. a man with high PSA, abnormal MRI and negative biopsy - can we discharge to GP for follow up and if so what strategy should the GP follow?	Thank you for your comment. We have added a question about follow up strategy in this group of people, please see section 3.5, question 3.1. When making recommendations, the committee take the care pathway into consideration and will make relevant recommendations to capture how the evidence relates to clinical practice.

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Myriad Genetics	8	1.1	This draft scope currently indicates that there will be no review of the evidence on Decision Support – retaining the recommendations from the existing guideline. We feel that consideration should be given for the methodology utilised to stratify risk for prostate cancer based on the aggressiveness of the disease and effectively assign patients to the appropriate treatments – Active Surveillance or Radical Prostatectomy. NICE recognises that since 2014 developments in the area of 'risk stratification and treatment of localised prostate cancer; active surveillance, radical prostatectomy or radical radiotherapy' (page 3) NICE has recognised that there are limitations to the current method of classifying risk and commissioned the following Medtech Innovation Briefing document on Prolaris, a gene expression test which provides prognostic information for risk stratification. https://www.nice.org.uk/advice/mib65 'Despite the routine use of risk classification and nomograms to categorise prostate cancer, these tools have some limitations. These include the lack of patient specificity, which may lead to misclassifications and to over- or under-treatment. A more personalised approach for assigning risk categories to people diagnosed with prostate cancer may improve accuracy and, therefore, appropriateness of treatment.' (page 5). Based on this information we respectively request consideration for a review of the evidence around decision support tools to be in scope for this evaluation.	Thank you for your comment. No new evidence on decision support was identified in the scoping searches and therefore this area was not included in the scope for the guideline update. The area of 'treatment of localised prostate cancer; active surveillance, radical prostatectomy or radical radiotherapy' is included in the scope of the guideline update. Thank you for the information regarding Prolaris, we will pass this information on to the diagnostic assessment programme.
National Institute for Health Research	General	General	The guideline scope should consider the results of the UK NIHR ProtecT trial. The median 10-year primary analysis results in terms of mortality, clinical progression, and a wide range of patient-reported outcomes were published in the New England Journal of Medicine in September 2016 (see below). These results have implications for the diagnosis and treatment of clinically localised	Thank you for your comment. We are aware of the ProTecT trial, and this was discussed in the exceptional surveillance review which led to the update of sections on the treatment of

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Collaboration for Leadership in Applied Health Research and Care West			prostate cancer, and decision-making for men considering having a PSA test or being diagnosed with clinically localised prostate cancer. The results are available from the following papers: Hamdy FC, Donovan JL, Lane A et al. Mortality and Clinical Outcomes at 10 years' Follow-up in the ProtecT Trial. New England Journal of Medicine. 2016; 375:1415-1424; and Donovan JL, Hamdy FC, Lane A et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. New England Journal of Medicine. 2016; 375:1425-1437.	localised prostate cancer: active surveillance, radical prostatectomy or radical radiotherapy. Thank you for providing references to the relevant studies. A systematic search of the literature is undertaken for each area for update during the development of the guideline.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	General	General	The guideline scope should consider the recent systematic review and draft recommendations produced by the US prostate cancer task force. This group has assembled and synthesised the world literature on prostate cancer screening, diagnosis and treatment. It is available at: https://screeningforprostatecancer.org/	Thank you for your comment. Screening for prostate cancer is not within the remit of NICE clinical guidelines, it is reviewed by the UK National Screening Committee (UKNSC). The next review date is 2018/19 and the UKNSC will consider any new evidence for prostate cancer screening at that time. With regards to the systematic review of treatment and diagnosis for prostate cancer developed by the task force, NICE will consider any relevant evidence that meets the review

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				protocols for the areas to be updated in the guideline.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	1	15-18	There have been important publications that should lead to a reconsideration of the current narrow scope of the guideline update, specifically to include a wider range of issues. The publication of the ProtecT trial, PROMIS study, updates from the STAMPEDE and CHHIP trials, and publications from the ERSPC and PLCO screening trials, mean that there is a lot of new evidence to consider in relation to screening, diagnosis and treatment of prostate cancer. In addition, the publication of the primary outcomes of the UK CRUK/DH CAP prostate cancer screening trial will also occur in 2017. Further publications from the ProtecT trial are also expected. This guideline update needs to be able to consider important new evidence outside its current very narrow scope.	Thank you for your comment. Screening for prostate cancer is not within the remit of NICE clinical guidelines, it is reviewed by the UK National Screening Committee (UKNSC). The next review date is 2018/19 and the UKNSC will consider any new evidence for prostate cancer screening at that time. We are aware of the publication of the ProtecT, PROMIS, STAMPEDE and CHHIP studies. We are updating the areas of the guideline that these studies are related to, these are: treatment of localised prostate cancer, mpMRI for diagnosis and surveillance of prostate cancer, radiotherapy for localised prostate cancer and the scheduling of docetaxel + standard treatment in hormone sensitive metastatic prostate cancer and hormone sensitive locally advance prostate cancer. The studies that you

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				have identified will be considered alongside others in the systematic literature search during the guideline development if the meet the criteria in the review protocol.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	2	12-16	These figures on mortality rates could be updated with much greater detail based on the results of the ProtecT trial.	Thank you for your comment The figures that you refer to on this page are taken from the most recent available overall figures from the UK, rather than a specific study as they are intended to give a broad overview of the topic under consideration for update.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	3	15-19	The patient-reported outcomes from the ProtecT trial provide definitive evidence about the impact of the major contemporary treatment modalities (surgery, radiotherapy and active monitoring) on urinary, sexual and bowel function and specific and generic aspects of quality of life. These factors are likely to affect a man's choice of treatment but are not included here.	Thank you for your comment. We are updating the section on treatment of localised prostate cancer: active surveillance, radical prostatectomy or radical radiotherapy. As outlined in sections 1, 3.3 and 3.5. With regards to the outcomes for the review, these will be defined in the review protocol that will be developed for that specific clinical question, and may include patient important outcomes in addition

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				to the main outcomes identified in section 3.6.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	4	1-3	Clarity over follow up in primary care for men undergoing active surveillance or monitoring is also required. There is evidence, for example, from the ProtecT trial about nurse-led clinics for follow up of men following active surveillance or monitoring protocols, or after radical treatment (Wade et al. BMJ Open 2015;5:e008953).	Thank you for your comment. As part of the update of the section on treatment of localised prostate cancer, we will be looking at the different active surveillance protocols used in the included studies, and making recommendations when and if appropriate.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	4	11	MRI may also be used in the follow up of men on active surveillance or monitoring protocols.	Thank you for your comment. The role of MRI in excluding the clinically significant progression of prostate cancer in men with low to intermediate risk is included in the scope for the guideline update.
National Institute for Health Research	6	1	The imminent publication of the UK CAP prostate cancer screening trial and US prostate cancer task force recommendations will likely require reconsideration of the evidence in relation to population screening.	Thank you for your comment. Screening for prostate cancer is not within the remit of NICE clinical guidelines, it is reviewed by the UK

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Collaboration for Leadership in Applied Health Research and Care West				National Screening Committee (UKNSC). The next review date is 2018/19 and the UKNSC will consider any new evidence for prostate cancer screening at that time.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	6	19	Key areas that are missing from this update, where there is new high quality evidence to consider, include: The development of evidence-based protocols for active surveillance or monitoring of men with clinically localised prostate cancer. There is new evidence about the inclusion/exclusion criteria for such programmes, and the strategies for surveillance or monitoring that can be employed. The adverse effects of radical surgery, radical radiotherapy and active surveillance/monitoring in men with clinically localised prostate cancer.	Thank you for your comment. The scope of the guideline update includes treatment options after risk stratification in localised prostate cancer: active surveillance, radical prostatectomy or radical radiotherapy. The systematic review for this question will take into account the adverse effects of each treatment as well as the benefits. When undertaking the review, the development team will note the protocols for active surveillance which will help form the basis of any recommendation.
National Institute for Health Research	8	1.1 in the Table	Information and decision-support should be considered in relation to recent publications.	Thank you for your comment. We did not identify any new evidence that would impact current recommendations on decision support

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Collaboration for Leadership in Applied Health Research and Care West				in the scoping searches, therefore this area will not be updated at this time.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	8	1.3 in the Table 'Low risk' and 'intermediate risk'	It is not clear whether the wording here will allow consideration of the new evidence mentioned above. A full review of the evidence related to active surveillance and monitoring is warranted as the current guidance is based on weak evidence.	Thank you for your comment. As outlined in section 3.3 'key areas that will be updated', the area of treatment of localised prostate cancer: active surveillance, radical prostatectomy or radical radiotherapy will be updated. Therefore, both 'low risk' and 'high risk' parts of 1.3 in the table 'proposed outline of the guideline' will be updated.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	8	1.3 in the Table 'locally advanced'	It is stated that other than docetaxel, no other evidence will be considered for locally advanced prostate cancer. This should be reconsidered in light of new evidence, including, for example, Johnston TJ, Shaw GL, Lamb AD et al. Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial. European Urology. 2017, 71; 3: 381–388.	Thank you for your comment. Not enough comparative evidence for other treatments for locally advanced prostate cancer was identified during the surveillance process or scoping searches. Therefore no other interventions for locally advanced prostate cancer will be included in this update.

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National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	9	1.3 in the Table 'managing adverse effects of radical treatment'	It is stated that there will be no review of the evidence in this area. However, there have been several important publications of high quality patient-reported outcomes that should change the guideline – for example Donovan et al NEJM, 2016; 375:1425-1437; Barocas et al JAMA 2017, 317:1126-40; Chen et al JAMA 2017, 317:1141-50; Yaxley et al Lancet 2016, 388: 1057-66). Some of this evidence relates to the effects of active surveillance and monitoring as well as radical treatments mentioned here.	Thank you for your comment and for providing these references. Yaxley (2016) reports the early results of a comparison between open vs laparoscopic prostatectomy. It concludes that these two techniques yield similar functional outcomes at 12 weeks and that longer term follow-up is needed, so we will look for further evidence about this during the next surveillance review. With regards to the other papers that you refer to, these are related to clinical questions that are being updated in this guideline. If this evidence meets the review protocol, this will be considered by the guideline committee during the update. No new evidence that would impact current recommendations on how to manage sexual dysfunction, urinary incontinence and radiation- induced

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				enteropathy, therefore this section will not be updated at this time.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	9	2	Evidence about screening may need to be reconsidered following the publication of the US task Force, updates from ERSPC and PLCO, and the CAP trial.	Thank you for your comment. Screening for prostate cancer is not within the remit of NICE clinical guidelines, it is reviewed by the UK National Screening Committee (UKNSC). The next review date is 2018/19 and the UKNSC will consider any new evidence for prostate cancer screening at that time.
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West	9	1.4 and 1.5 in Table	New evidence has been published about androgen deprivation therapy that should be considered.	Thank you for your comment. Not enough new evidence was identified to impact on current recommendations on the use of Androgen Deprivation Therapy (ADT) in prostate cancer and therefore this area will not be included in the scope for the guideline update and the current recommendations will stand.
National Institute for Health Research	12 13	24-29 1-21	These key issues and questions will need updating in relation to the issues raised above.	Thank you for your comments. As outlined in responses to your previous comments, we will not be updating sections on ADT or screening. We

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Collaboration for Leadership in Applied Health Research and Care West				have included treatment of localised prostate cancer in the update Abiraterone in locally advanced hormone sensitive prostate cancer will not be included in the scope of the update because not enough evidence was identified during the scoping process.
NCRI-ACP-RCP-RCR	General	General	Our experts would welcome consideration of biopsy technique. In particular, the role of transperineal, rather than transrectal , biopsy and the role of systematic, as well as targeted, biopsies	Thank you for your comment. We have added transperineal template biopsy and MRI- influenced TRUS biopsy as comparators in the section on the diagnosis of prostate cancer.
NCRI-ACP-RCP-RCR	General	General	New evidence from the STAMPEDE and LATITUDE trials suggest a role for abiraterone in hormone sensitive disease. Our experts understand that this will be a subject of a NICE TA for men with metastatic disease. The role of abiraterone in locally advanced disease should also be assessed. Indeed, it is in the locally advanced setting where the benefits may be particularly large.	Thank you or your comment. Abiraterone for men with metastatic disease is the subject of technology appraisal guidance 259, 387 and ID 945 (due to be published September 2018). Not enough evidence on abiraterone in locally advanced hormone sensitive prostate cancer was identified in the scoping searches to include this area in the update.
NCRI-ACP-RCP-RCR	General	General	Our consumer representative suggested paying attention to the needs of men with prostate cancer who also have impaired hearing	Thank you for your comment. The related NICE guidance Patient

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				experience in adult NHS Services CG138 has the following recommendation which takes account of people with impaired hearing: 1.1.2 Ensure that factors such as physical or learning disabilities, sight, speech or hearing problems and difficulties with reading, understanding or speaking English are addressed so that the patient is able to participate as fully as possible in consultations and care. This will be cross-referred to in the guideline update.
NHS England			Thank you for the opportunity to comment on the above Clinical Guideline. We can confirm that there are no comments to be made on behalf of NHS England.	Thank you for your comment.
Prostate Cancer UK	General	General	We anticipate this review of the NICE Guidelines for prostate cancer: diagnosis and management will necessitate an update to the quality standards for prostate cancer through the Quality Standards Advisory Committee. If this is the case, we believe this is the opportunity to provide guidance to ensure that mpMRI before biopsy is delivered to a consistent set of standards. Prostate Cancer UK is working with mpMRI before biopsy experts from University College Hospital, London and other centres to develop a clinical consensus that will set these standards. The intention is to	Thank you for your comment. NICE Quality Standards are based on NICE Clinical Guidelines, so there is a possibility that the QS will be updated if there are changes to the guideline. We will pass this information onto the Quality Standards team for their consideration.

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			publish this consensus in autumn 2017 and we would welcome it if the Quality Standards could signpost to it.	
Prostate Cancer UK	General	General	Research has recently been published showing clinical benefit from the use of abiraterone in combination with ADT for men newly diagnosed with locally advanced and advanced metastatic prostate cancer.[i] The draft scope should be mindful of these results and the results from the LATITUDE trial so that it can incorporate the NICE Technical Appraisal decision given for this treatment in February 2018, should abiraterone in combination with ADT be recommended for baseline commissioning.	Thank you for your comment. We have listed the relevant related Technology Appraisal (in development) 'Abiraterone for treating newly diagnosed metastatic hormone-naive prostate cancer' in the 'related NICE guidance' section of the scope. This is due to publish in September 2018. We will cross-refer to this guidance in the updated guideline. TA259 'abiraterone for treating metastatic castration- resistant prostate cancer will be incorporated unchanged into the guideline subject to a review proposal. Not enough evidence was identified in the scoping searches on the use of abiraterone in hormone-sensitive locally advanced prostate cancer for it to be included in this update.

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Prostate Cancer UK	General	General	There is an increasing body of medical research that we would like the NICE Committee to have on its radar. This includes: • Optimum use of cabazitaxel showing that a lower dose delivered equal overall survival and reduced toxicity. Professor Johann de Bono at the Institute of Cancer Research can make the unpublished findings available under non-disclosure • Evidence on Focal Therapies, best accessed from Professor Mark Emberton at UCL • Ga-PSMA PET/CT impact on prostate cancer management, accessible via Dr Jamshed Bomanji at UCL In addition, there needs to be a place holder for sequential biopsy of men with metastatic disease either through bone biopsies or liquid biopsies looking at CTCs or cfDNA. Professor Johann de Bono at the Institute of Cancer Research can provide expert witness.	Thank you for providing this information. NICE has Technology Appraisal guidance (TA391) on the use of Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. This guidance is due for review in May 2019. We will pass this information onto the technology appraisals team for their consideration. By the term 'Focal therapies' we understand that you are referring to vascular targeted photodynamic therapy (VTP), high-intensity focussed ultrasound (HIFU) and cryoablation. VTP is currently the subject of NICE technology appraisal guidance (in development) 'Prostate cancer (localised) – padeliporfin' which is due to be published in August 2018. Therefore VTP will not be included in this guideline update but cross-reference will be made to the TA guidance once published, in the pathway.

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				Both High-intensity focussed ultrasound and cryoablation are the subject of NICE Interventional Procedure Guidance (IPG424 and 423 respectively). We did not identify any new evidence that would impact the current recommendations on either HIFU or cryoablation, Therefore we will not be including them in the scope for the guideline update. With regard to the use of Ga-PSMA-PET/CT, we understand that this an emerging area in the diagnosis of prostate cancer. Not enough new evidence was identified during the scoping phase to include it in this update. We will notify the surveillance team of this emerging area for their attention at the next surveillance review. For CTC and cfDNA, we note that these are also emerging areas in the diagnosis and staging of prostate

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				cancer, with large ongoing trials that will not publish during the development time of this guideline update. We will notify the surveillance team of this emerging area for their attention at the next surveillance review.
Prostate Cancer UK	3	6	"TRUS biopsies can miss up to 1in ~~5~~ 4 clinically significant cancers." According the results of the Prostate MRI Imaging Study (PROMIS) trial, trans-rectal ultra sound (TRUS) biopsies can miss up to 1 in 4 clinically significant cancers, not 5.[ii]	Thank you for highlighting this. This has been amended as per your comment.
Prostate Cancer UK	4	8	Incorrect data. TRUS is used in 85% not 92% of cases. Although 92% does exist in the document cited in the text, it is the figure for Wales.	Thank you. We have checked the information and amended as per your comment.
Prostate Cancer UK	4	9	Incorrect data. Of the 44% of men in England who had an multi-parametric MRI (mpMRI), 55% of this group had an MRI before biopsy.[iii]	Thank you. We have checked the information and amended as per your comment.
Prostate Cancer UK	6	17	A health economics study by York University has investigated the potential cost-effectiveness of the PROMIS trial's results and is currently being reviewed for publication. This analysis should be included in the scope for assessment by the Committee.	Thank you for this information, we will take it into consideration during the development of the guideline update. We do not specify details of particular studies in the scope.

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				A systematic search is undertaken for clinical and health economic evidence for each area of the update. All relevant studies that fit the specified review protocol will be included in the analysis presented to the decision making committee.
Prostate Cancer UK	6	17	Any consideration of the use of mpMRI before biopsy as a triage test should include a consideration of the definition of the sequences that comprise mpMRI. This should be based on the sequences used in the PROMIS trial, which is the only current level one evidence of best practice. By including this in the draft scope, there is the potential to make sure that wherever a man is scanned it is done to the same high standard. Sequences used in the PROMIS trial include: T2, diffusion weighted imaging using 4 b values to produce ADC maps and a separate high b value sequence, as well as dynamic gadolinium contrast enhancement. These are also the minimum set of requirements set by international uro-radiology expert groups.[iv]	Thank you for your comment. It is beyond the remit of the scope to include the level of detail that you suggest. We will take this information into consideration during guideline development in the context of assessing the quality of the evidence against best practice.
Prostate Cancer UK	6	22	Assessments of risk stratification of localised disease, and especially the rate of progression of Gleason 6 (grade group 1) cancers, may be confounded by the reliance on TRUS biopsy within clinical trials (including Prostate Testing for Cancer and Treatment (ProtecT) trial to detect and then to grade tumours. TRUS biopsy performs poorly at identifying the highest grade cancers and therefore often misses cancer completely or finds only a lower grade tumour when a higher grade one is present.	Thank you for your comment. When considering the evidence the committee consider the strengths and limitations of the evidence base. We will take this information into consideration during the development of the guideline update when undertaking the literature review.

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			We recommend that any analysis of outcomes of "Gleason 6 tumours" identified by TRUS biopsy are also likely to contain a significant proportion of higher grade (and therefore higher risk) cancers. Long term follow up cohorts with either template biopsy identified cancers or cohorts that compare performance of TRUS biopsy to identify cancers by examining excised whole prostates, may be able to help in modelling and adjusting for this discrepancy. Professor Hashim Ahmed and Dr Laurence Klotz can provide expert witness on this.	
Prostate Cancer UK	6	26	Docetaxel in combination with Androgen Deprivation Therapy (ADT) in for men newly diagnosed with locally advanced prostate cancer is not currently commissioned by NHS England. This is because the data for overall survival for this stage of the disease is currently immature. However, the STAMPEDE trial has shown that use of docetaxel in this indication can help to stop disease progression. We anticipate that information on the cost-effectiveness of this intervention will be shown by the soon to be published York University Health Centre health economics analysis. We therefore recommend that this evidence is included in the draft scope to enable it to be reviewed.	Thank you for your comment. The area of the use of docetaxel in hormone-sensitive locally-advanced prostate cancer and hormone-sensitive metastatic prostate cancer is included in the scope for this update, prompted in part by data from the STAMPEDE trial. A systematic search for clinical and health economic evidence will be undertaken for each topic area and relevant studies that match the protocol will be included in the review and presented to the committee for their consideration.
Prostate Cancer UK	6	30	Follow up protocols after radical treatment must distinguish between the side-effects that are the result of radical prostatectomy and those associated with radical radiotherapy across all of their types. For the latter, a further distinction	Thank you for your comments. The detailed review protocols will be drafted during development, using the

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			is required between short-term and late effects. The draft scope must include questions that enable these distinctions to be made. The clinical and cost-effectiveness assessment must include those side-effect treatments that are made available to men with prostate cancer treatment-induced side effects in Schedule 2.[v] Not doing so could deny men access to treatments that are not cost-effective, but that they are entitled to.	key areas in the scope. We will take this information into consideration during protocol development.
Prostate Cancer UK	13	1	The draft scope should investigate the guidance needed to manage men who have a negative MRI scan having had an mpMRI scan before a biopsy. This is because, while mpMRI can exclude the diagnosis of clinically significant disease, the PROMIS results showed that 1 in 10 clinically significant cancers were missed. To make sure that men are safeguarded to the same extent as those who have a negative TRUS biopsy result (NICE guides for these men to have a MRI scan to make sure that a clinically significant cancer has not been missed).[vi] We would like men with a negative MRI scan to be managed in the following ways: • For men that have low probability of clinical significant cancer and a low risk histiopathology we would like the draft scope to set out an intention to explore a programme of PSA monitoring in primary care. • For those men whose histiopathology suggests a higher than average risk of prostate cancer - this could include a family history of the disease and / or an abnormal digital rectal examination or abnormal PSA density for their age - the draft scope should include a question about whether these men should be considered for a transperineal	Thank you for your comment. After considering stakeholder feedback, we have added the area of 'Follow up protocols for people with raised PSA, negative MRI and/ or negative biopsy' to the section on key areas that will be covered in this update'.

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			template biopsy. This is important because mpMRI before biopsy can miss 1 in 10 clinically significant cancers.[vii] As such, we recommend that a positive answer to question 1.2 is followed by a question related to the effective management of men that receive a negative MRI result.	
Prostate Cancer UK	13	2	The draft scope should assess a definition of clinically significant cancer so that it is clear which men can be safely ruled out of an unnecessary biopsy. The PROMIS trial results provide two definitions: 1. Gleason ≥4 + 3 or more, or a maximum cancer core length (MCCL) involvement of 6 mm or more in any location 2. Gleason ≥3 + 4 or any grade with cancer core length 4 mm or greater.[viii] The scope should include a question to determine which of these definitions it recommends.	Thank you for your comments. There will not be a specific question to determine which definition of clinically significant cancer is recommended. However, the committee will take into account the information you have provided when addressing the topic on the most clinical an cost-effective pathway for diagnosis of prostate cancer.
Prostate Cancer UK	13	4	While comparisons of cost and clinical effectiveness of the three treatment options for localised disease (active surveillance, radical surgery and radical radiotherapy) will necessarily be based on the results of the ProtecT trial, the assessment of the ProtecT trial results should take into account and attempt to model the difference between how all three of those treatments are now administered compared to the trial protocols. In particular the surveillance protocol now used for active surveillance is significantly tighter than that used for the surveillance arm of the trial, with more frequent and more extensive monitoring of men on active surveillance.	Thank you for providing us with this information. The clinical and cost-effectiveness of treatment options for localised disease (active surveillance, radical surgery and radical radiotherapy) is included in the scope for the guideline update. We will take into account the information you have provided. It is worth noting that a full systematic search will be undertaken

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				for both clinical and economic reviews; and quality, applicability and any limitations of the included studies will be considered during consideration of the evidence. For more details on the development of the guideline and economic aspects of the guideline, please refer to Developing NICE guidelines: the manual.
Prostate Cancer UK	13	7	We believe that the draft scope should consider the role of mpMRI as a safe surrogate for biopsy in active surveillance. Research has shown reliability between stability on an MRI and stability in Gleason score, and therefore mpMRI could rule out or make clear any progression. There is potential for additional evidence to support this from the Prostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance or Not? (PRECISION) trial when it publishes.[ix]	Thank you for your comment and for highlighting this study. The area of mpMRI in active surveillance has been identified as an area for update in the guideline. A systematic literature search is undertaken for each topic, and studies that match the review protocol will be included and appraised for committee consideration in order to make recommendations.
Prostate Cancer UK	13	22	We would like 'prevention of symptomatic skeletal related events' added to the list of outcomes in section 3.6. This is because these events are significantly life limiting for patients, and extremely costly for the NHS. Emerging evidence from the health economics of the health economics for the docetaxel arm of the STAMPEDE trial suggests that treatments that reduce symptomatic skeletal related events are likely to drive significant savings to the system and improve patient outcomes.	Thank you for your comment. The outcomes listed in 3.6 are the main outcomes. Other outcomes can be added to individual review protocols if these outcomes are deemed important for a particular systematic review. We will take into account the

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				information you have provided. Please see Developing NICE guidelines: the manual, section 2 for more information on this.
Prostate Cancer UK	13	28	The list of outcomes in section 3.6 negates biochemical relapse and as such, we would like 'failure-free survival' added in above 'metastasis-free survival'.	Thank you for your comment. The outcomes listed in 3.6 are the main outcomes. Other outcomes can be added to individual review protocols if these outcomes are deemed important for a particular systematic review. We will take into account the information you have provided'. Please see Developing NICE guidelines: the manual, section 2 for more information on this.
Royal College of Nursing			This is to inform you that the Royal College of Nursing have no comments to submit to inform on the above draft scope. Thank you for the opportunity, we look forward to participate in the next stage of the consultation.	Thank you for your comment.
Royal College of Pathologists	General	General	The RCPath would like clarification on when a template/transperineal (and the extent of this) should be done as part of primary diagnosis and in active surveillance. The number of these biopsies has vastly increased over the last 3 years since the last NICE guidance. There is no standard protocol leading to variation in practice across the country – and presumably cost.	Thank you for your comment. We have added MRI- influenced TRUS and transperineal template biopsy as comparators to multiparametric/ functional MRI in the diagnosis and staging of prostate cancer.

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Royal College of Pathologists	7	7	Please add – The role of template biopsies	Thank you for your comment. We have added transperineal template biopsies as a comparator to mpMRI in the diagnosis and staging of prostate cancer.
Royal College of Pathologists	7	11	Please add – the role of template biopsies	Thank you for your comment. We have added transperineal template biopsies as a comparator to mpMRI in the diagnosis and staging of prostate cancer.
Royal College of Pathologists	8	Table 1.2	You state Biopsy – please clarify what type is advised – eg template vs TRUS	Thank you for your comment. We have added transperineal template, MRI- influenced TRUS biopsy and TRUS biopsy alone to this section to clarify what areas will be reviewed.
Royal Surrey County Hospital NHS Trust	General		Indications for Low Dose Rate Brachytherapy have been evaluated and updated in the following recent guidelines *1.Chin et al. 2017 PMID 2834680: Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update* *2.Davis et al. 2017 PMID 27964905: ACR appropriateness criteria: Permanent source brachytherapy for prostate cancer*	Thank you for your comment and for providing these references. We did not identify any new evidence that would impact the current recommendations on low dose rate brachytherapy through the surveillance or scoping process. The combination of low dose rate brachytherapy and external beam radiotherapy would be allowed under

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			3.Spratt et al.2017 PMID 27771243: American Brachytherapy Society Task Group Report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer *4.NCCN Clinical Practice Guidelines in Oncology: Prostate cancer. Version 2:2017* *https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf*	the existing recommendation 1.3.23 in CG175. Low dose rate brachytherapy for localised prostate cancer is the subject of a NICE Interventional Procedures Guidance (IPG132, 2005) and this is included in the related guidance list.
Royal Surrey County Hospital NHS Trust	3	24-25 & 29-30	Low dose rate brachytherapy (LDRBT) for localised prostate cancer Interventional Procedures Guidance [IPG132] published in 2005 stated, **"Radiation therapy can take the form of External Beam Radiotherapy (EBRT) or brachytherapy. Low Dose Rate Brachytherapy can be used alone or in combination with EBRT. Low Dose rate brachytherapy is not recommended for men with high-risk prostate cancer"**. Subsequently LDRBT was included in the Clinical Guidelines for Prostate Cancer as an option for low and intermediate risk localised prostate cancer. In light of the results from the **ASCENDE RT trial** and other publications, clinical guidelines should be re-evaluated. The **ASCENDE-RT trial** (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) trial is a randomized comparison of 2 methods of dose escalation in the context of combined modality therapy for	Thank you for your comment and for providing details of the ASCENDE-RT trial. The current recommendations in IPG132 and CG175 do not exclude the use of Low dose rate Brachytherapy (LDRBT). We understand that the results from ASCENDE-RT would not impact current recommendations on LDRBT, and therefore this area will not be included in the scope for the guideline update.

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			National Comprehensive Cancer Network high- and intermediate-risk prostate cancer. Sixty nine percent of the patients were high risk. The protocol included 12 months of androgen deprivation therapy and whole pelvic irradiation to 46 Gy. Compared with an iodine 125 LDR brachytherapy boost, men randomized to an external beam radiation therapy boost to a total of 78 Gy were twice as likely to have experienced biochemical failure at a median follow-up of 6.5 years PubMed PMID number has been used to identify the relevant publications. *Morris et al. 2017 PMID 28262473: ASCENDE RT, Clinical outcomes* *Rodda et al. 2017 PMID 28433432: ASCENDE RT, Morbidity outcomes* *Rodda et al. 2017 PMID 28581398: ASCENDE RT, QOL outcomes*	
Society and College of Radiographers	Page 2 and Pages 8 & 9	Line1 (1.3&1.4)	This requires further exploration of this issue for transgender and ensure representation. Sexual dysfunction for Gay & bisexual men has also been highlighted as a potential area that is not widely discussed in terms of treatment pathway and informed consent. The Society and College of Radiographers can ensure dissemination of the document for comment.	Thank you for your comment. Gender reassignment and sexual orientation are protected characteristics under Government legislation, and are considered under the Equalities Impact Assessment. We will take this information into consideration during guideline development.
Society and College of Radiographers	Page 3 and Page 6 and Page 8	Lines 7-12, 22 Line17 1.2	Multiparametric / functional MRI and image based assessment is indicated in some settings (Biopsy) so it is important to liaise with the full clinical imaging team. Key questions to be addressed:	Thank you for your comment. We have amended the questions slightly, and they now say:

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			Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer? Can multiparametric/functional MRI, instead of TRUS biopsy exclude a diagnosis of clinically significant disease? Can multiparametric/functional MRI, instead of TRUS biopsy, exclude the clinically significant progression of prostate cancer in men with low to intermediate risk (as defined in NICE CG175)? The Society and College of Radiographers can ensure dissemination of the document for comment.	Which of the following, alone or in combination, is the most clinical and cost-effective pathway for diagnosing prostate cancer: • Multiparametric/ functional MRI • TRUS biopsy • Transperineal template biopsy? Which of the following, alone or in combination, is the most clinical and cost-effective pathway for excluding the clinically significant progression of prostate cancer in men with low to intermediate risk (as defined in NICE CG175) • Multiparametric/ functional MRI • TRUS biopsy • Transperineal template biopsy?
Society and College of Radiographers	Page 4	Line 23	Statement…'This is not reflected by current recommendations' The Society and College of Radiographers is unsure what is meant by this statement and feels additional clarity is required.	Thank you. We have amended the wording to 'This is not reflected by the current recommendations on radiotherapy in CG175'.

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Tackle Prostate Cancer	General	General	One of the most important aspects of this review has been ignored. For men on long term ADT, this is a major problem as Zoladex (and equivalents)) is known to cause osteoporosis. Although the TRAPEZE trial showed no benefit in overall survival, it showed important benefits to quality of life for patients. The results show: Zoledronic acid significantly delayed the amount of time before men presented with a new bone problem due to their prostate cancer; The total number of unpleasant bone complications were reduced by about a third in men who had zoledronic acid. These include: • the need for radiotherapy to relieve bone pain • bone fractures • surgery for bone problems On these findings alone, advanced prostate cancer patients on ADT should be given either bisphosphonates or denosumab. This is standard practice in every other metastatic cancer.	Thank you for your comment. After consideration of your comments we have added the area of 'The use of bisphosphonates in bone-targeted therapy' to the key areas that will be updated.
Tackle Prostate Cancer	8	1.2	With the ever increasing threat of MRSA, MRI should become the standard for diagnosing prostate cancer. It clearly shows where the tumour is, thus removing the need for multiple needle biopsies	Thank you for your comment. We will be updating the section on using multiparametric MRI in diagnosis and surveillance of prostate cancer. For detail on how NICE develops it recommendations please see section 9 of 'Developing NICE guidelines: The

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				manual'. The manual states that when making recommendations 'The Committee must use its judgement to decide what the evidence means in the context of the guideline referral and decide what recommendations can be made to practitioners, commissioners of services and others. The evidence is assessed for validity, reliability and bias, but also requires interpretation, especially an assessment of its implicit and explicit value base. Evidence also needs to be assessed in light of any conceptual framework and theories relating to individual and organisational behaviour change'.
Tackle Prostate Cancer	9	1.5	As the STAMPEDE trial has shown, Docitaxel is even more useful if 6 cycles are given on diagnosis (or within 12 weeks). On average, this has extended life expectancy by 2 years.	Thank you for providing this information. A systematic evidence search and systematic review will be undertaken for each clinical question and the committee will consider all the evidence before making a recommendation.

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Tackle Prostate Cancer	10	1.3	There is insufficient acknowledgement of one of the key changes that have happened since the last version of the guidance was developed, namely the increasing use of active surveillance for low risk prostate cancer. Because over-diagnosis and treatment are the main arguments against screening, we all want to see active surveillance as working, but there is conflicting evidence of the safety of this approach, and it is important that the review should grasp this nettle, and not gloss over it as if active surveillance were just another management modality of proven effectiveness.	Thank you for your comment. As set out on the scope for the guideline update, treatment of localised prostate cancer: active surveillance, radical prostatectomy or radical radiotherapy will be updated. We will consider the information that you have provided when the review protocols are developed.
Tackle Prostate Cancer	12	4	The draft scope currently excludes the use of denosumab or bisphosonates for bone health. We feel as spinal compression and SREs are major causes of distress for men on long term hormone therapy, this is a serious omission and should be rectified. Both denosumab and bisphosonates are allowed in all other metastatic cancers, so why should prostate cancer be the poor relation?	NICE Technology Appraisal guidance on Denosumab in hormone refractory prostate cancer was suspended as the company decided not to pursue licensing for this indication. Denosumab is also the subject of TA265 'Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours'. After considering stakeholder feedback, the use of bisphosphonates in bone-targeted therapy for men with hormone-relapsed metastatic prostate cancer has been included in the key

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				areas that will be covered in this guideline.
University College London	general	general	The draft scope does not include the advances in Positron Emission Tomography (PET) imaging in the evaluation of patients with prostate cancer. We propose that consideration should be given to the radiotracer 'Gallium-68 Prostate Specific Membrane Antigen (68Ga-PSMA)', which has been used clinically in the UK since 2015 and has had a major impact on the management of patients with prostate cancer. 68Ga-PSMA PET has been included in 'RCR/RCP Evidence-based indications for the use of PET-CT in the United Kingdon 2016', which recognized '68Ga -PSMA is a rapidly emerging alternative tracer for assessment of prostate malignancy with superior diagnostic accuracy compared to choline' (1). Recently, the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging have jointly published guidelines for 68Ga-PSMA PET/CT imaging (2) Indications are as follows (1): •Evaluation of high-risk patients before curative treatment or to evaluate equivocal findings such as possible nodal or metastatic disease in patients with prostate cancer where confirmation or exclusion of distant disease would directly influence patient management •Suspected recurrence in patients with a rapidly rising PSA and negative or equivocal conventional imaging where the results would directly influence patient management The target of this tracer, Prostate Specific Membrane Antigen (PSMA) is is a type II transmebrane protein which undergoes considerable (100-1000 fold)	Thank you for your comment. We are aware that the use of PSMA – PET/CT in the diagnosis and staging of prostate cancer is an emerging area with ongoing trials. We did not identify enough relevant evidence on PSMA-PET in the scoping searches to include it in the update of this guideline. We will highlight this specific area to the surveillance team for their attention at the next surveillance review.

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			overexpression on the cell membrane of nearly all prostate cancer cells (3). 68Ga-PSMA on binding to prostate cancer cells, gets internalized and high accumulation occurs, even in small metastases (3). The technique is safe and has been used clinically now for several years.	
University College London	general	general	References for comment 1. 1. RCP/RCR Evidence-based indications for the use of PET-CT in the United Kingdon 2016' 2. Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hope TA, Kopka K, Krause BJ, Mottaghy FM, Schöder H, Sunderland J, Wan S, Wester HJ, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017 Mar 10. doi: 10.1007/s00259-017-3670-z. [Epub ahead of print] 3. Maurer T, Eiber M, Schwaiger M, Gschwend JE (2016).Current use of PSMA-PET in prostate cancer management. Nat Rev Urol. 13(4):226-35.	Thank you for providing these references. We note that they are guidelines, or narrative reviews of use of PSMA- PET. They would therefore be unlikely to be included in any systematic review on the topic, because we use best available evidence published evidence (such as diagnostic test accuracy or cross-sectional studies), rather than referring to other guidelines. Please see Developing NICE guidelines: the manual, Section 8.2 for further information.
University College London	general	general	Sites of disease which are not detectable with bone scan or on CT (such as within normal sized lymph nodes) are now being identified with 68Ga-PSMA PET/CT (4). In order to provide most effective management options, it is important to identify localized disease as early as possible/ at the lowest PSA level. Salvage radiotherapy in recurrence post-prostatectomy is most effective at serum PSA <0.5ng/ml. (5,6)	We are aware that the use of PET/CT with choline or 68Ga-PSMA in the diagnosis and staging of prostate cancer is an emerging area with ongoing trials. We did not identify enough relevant evidence on PSMA-PET in the scoping searches to include it in the guideline update. We

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			However, 18F-Choline PET tracers have a detection rate ranging from 19-36% when serum PSA is below 1.5ng/mL (7,8,9) In a study of 319 patients with biochemical recurrence, 82.8% of 68Ga-PSMA scans were positive and probability of detecting disease increased with higher PSA levels. For example, a 50% likelihood of positive scan at PSA <0.5 and 60% when PSA was 0.5-1 (10) Afshar-Oromieh et al found PSMA PET was able to detect all lesions demonstrated on Choline PET as well as additional sites of disease, identifying 86.5% of patients with at least one site of disease characteristic for prostate cancer, compared with 70.3% (11) On lesion-based analysis, Morigi et al found 68Ga -PSMA detected significantly more lesions than (18)F-fluoromethylcholine (59 vs. 29 respectively, P < 0.001) (12)Tumour to background ratio is higher in 95% of lesions compared to 18F-choline.	will highlight this specific area to the surveillance team for their attention at the next surveillance review.
University College London	general	general	References for comment 3. 4. Afaq A, Batura D, Bomanji J (2017) Int J Urol Nephrol 49(5):803-810. 5. Pfister D, Bolla M, Briganti A, Carroll P, Cozzarini C, Joniau S, van Poppel H, Roach M, Stephenson A, Wiegel T, Zelefsky MJ (2014).Early salvage radiotherapy following radical prostatectomy. Eur Urol. 65(6):1034-43.	Thank you for providing these references. The studies here have not prompted an update of the area of PET/CT and Ga-PSMA for the following reasons:

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			6. King CR (2012).The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiat Oncol Biol Phys. 84(1):104-11. 7. Castellucci P, Fuccio C, Rubello D, Schiavina R, Santi I, Nanni C, Allegri V, Montini GC, Ambrosini V, Boschi S, Martorana G, Marzola MC, Fanti S (2011). Is there a role for ^{11}C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? Eur J Nucl Med Mol Imaging.38(1):55-63. 8. Castellucci P, Picchio M (2013).11C-choline PET/CT and PSA kinetics. Eur J Nucl Med Mol Imaging. 40 Suppl 1:S36-40. 9. Graute V, Jansen N, Ubleis C, Seitz M, Hartenbach M, Scherr MK, Thieme S, Cumming P, Klanke K, Tiling R, Bartenstein P, Hacker M (2012).Relationship between PSA kinetics and [18F]fluorocholine PET/CT detection rates of recurrence in patients with prostate cancer after total prostatectomy. Eur J Nucl Med Mol Imaging. 39(2):271-82. 10. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, Eisenhut M, Boxler S, Hadaschik BA, Kratochwil C, Weichert W, Kopka K, Debus J, Haberkorn U (2015).The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 42(2):197-209.	4. This paper is a non-systematic review which is not of sufficient quality to prompt an update on this topic. 5. This study was a review of retrospective studies on early salvage radiotherapy, not specifically focused on the use of PET-CT 6. As above, this study was about timing of salvage radiotherapy, not directly focused on the use of PET-CT 7. This is a case series of 102 people undergoing PET-CT imaging; whist it is related to the area of PET-CT, it is not a sufficient evidence base to prompt an update of this area. 8. This study is a brief review of choline kinetics, and would not prompt an update of the area of PET-CT because it is neither a high quality study, or directly related to the area proposed for update.

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				9. This study is a case series to identify prostate-specific antigen (PSA) threshold level. It would not prompt an update of the area of PET-CT because it is not directly related to the area proposed for update. 10. This study is a retrospective analysis of the ability of (68)Ga-PSMA-ligand PET/CT to detect recurrent prostate cancer. This study is directly relevant to the area you propose for update, but is not sufficient quality evidence to prompt an update of PET-CT imaging.
			11. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, Holland-Letz T, Hadaschik BA, Giesel FL, Debus J, Haberkorn U (2014).Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 41(1):11-20.	11 This study is a retrospective analysis of the ability of (68)Ga-PSMA-ligand PET/CT to detect prostate cancer. This study is directly relevant to the area you propose for update, but is not sufficient quality evidence to prompt an update of PET-CT imaging.

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			12. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, Hruby G, Fogarty G, Jagavkar R, Kneebone A, Hickey A, Fanti S, Tarlinton L, Emmett L (2015).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. 56(8):1185-90.	12. This is a small case series that is directly relevant to the area of PET-CT, but is not sufficient quality or evidence to prompt an update of PET-CT imaging.
University Hospital Southampton NHS Foundation Trust	General	General	The draft scope does not detail the intention to include percutaneous or minimally invasive prostate cancer treatments as part of the guidance update. With ongoing product innovation, trials and registries in the UK, and importantly at the request of some patients, we would like to highlight that less invasive, image-guided techniques such as HIFU and cryoablation are set to play an increasing role in intermediate risk disease. As a part of a multi-disciplinary team and with clinical governance, University Hospital Southampton is one of a few sites in the UK with large volume, multimodality, image-guided ablation expertise and currently offering ultrasound-guided cryotherapy and high-intensity focused ultrasound to appropriate patients, and have recently become the first UK centre to perform MRI-guided prostate cryoablation. With the potential for a reduction in the deleterious effects of established treatment we feel that these evolving therapies should form part of the scoping exercise.	Thank you for your comment. Both High-intensity focussed ultrasound and cryoablation are the subject of NICE Interventional Procedure Guidance (IPG424 and 423 respectively). We did not identify any new evidence that would impact the current recommendations on either HIFU or cryoablation, Therefore we will not be including them in the scope for the guideline update.

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			Should you wish to include these techniques in the consultation we would like to offer our own local experience and perspective of treating patients with these therapies.'	

[i] http://www.stampedetrial.org/87548/87552/ASCO_abiraterone_comparison_results
[ii] http://thelancet.com/journals/lancet/article/PIIS0140-6736(16)32401-1/fulltext
[iii] National Prostate Cancer Audit Third Year Annual Report – Results of the NPCA Prospective Audit and Patient Survey 2016 - Available at https://www.npca.org.uk/content/uploads/2016/12/NPCA-2016-Annual-Report-Final.pdf
[iv] http://thelancet.com/journals/lancet/article/PIIS0140-6736(16)32401-1/fulltext
[v] https://www.engage.england.nhs.uk/consultation/clinical-commissioning-wave8/user_uploads/urolgcl-cancrs-spec-kidny-blddr-prstte-service-spec.pdf
[vi] NICE Clinical Guideline 175 – Prostate Cancer: Diagnosis and Management. Available at https://www.nice.org.uk/guidance/cg175
[vii] Negative predictive value of 89%. Ahmed, H.U. *et al.* 2017. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet.*, Volume 389 , Issue 10071 , 815 – 822
[viii] Ibid.
[ix] https://clinicaltrials.gov/ct2/show/record/NCT02380027