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EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel Consensus statements for deferred treatment with curative intent for localised prostate cancer from an international collaborative study (DETECTIVE Study)

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Glossary of terms and acronyms:
EAU: European Association of Urology; EANM: European Association of Nuclear Medicine; ESTRO: European Society for Radiotherapy and Oncology; ESUR: European Association of Urology Section of Urological Research; SIOG: International Society of Geriatric Oncology

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Abstract

Background: There is uncertainty in deferred active treatment (DAT) programmes, regarding patient selection, follow-up and monitoring, reclassification, and which outcome measures should be prioritised.
Objective: To develop consensus statements for all domains of DAT. Design, setting and participants: A protocol-driven, 3-phase study undertaken by the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel in conjunction with partner organisations, including: (1) A systematic review to describe heterogeneity across all domains; (2) A 2-round Delphi survey involving a large, international panel of stakeholders, including healthcare practitioners (HCPs) and patients; and (3) A consensus group meeting attended by stakeholder group representatives. Robust methods regarding what constituted consensus were strictly followed.
Results and limitations: 109 HCPs and 16 patients completed both survey rounds. Of 129 statements in the survey, consensus was achieved in 66 (51%); the rest of the statements were discussed and voted on in the consensus meeting by 32 HCPs and 3 patients, where consensus was achieved in an additional 27 statements (43%). Overall, 93 statements (72%) achieved consensus in the project. Some

uncertainties remained regarding clinically important thresholds for disease extent on biopsy in low risk disease, and the role of mpMRI in determining disease stage and aggressiveness as a criterion for inclusion and exclusion.
Conclusions: Consensus statements and the findings are expected to guide and inform routine clinical practice and research, until higher levels of evidence emerge through prospective comparative studies and clinical trials.
Patient summary: We undertook a project aimed at standardising elements of practice in active surveillance programmes for early localised prostate cancer because currently there is great variation and uncertainty regarding how best to conduct them. The project involved large numbers of healthcare practitioners and patients using a survey and face-to-face meeting, in order to achieve agreement (i.e. consensus) regarding best practice, which will provide guidance to clinicians and researchers.

1. Introduction

Deferred treatment with curative intent (i.e. deferred active treatment, or DAT) has emerged as a feasible alternative to standard radical interventions for low-risk localised prostate cancer. [1-3] This includes active surveillance or active monitoring, whereby patients are not curatively treated immediately but instead are reassessed and monitored at regular intervals, and involves a choice by a patient following counselling with their physician, and alternative treatment options may be considered at a future timepoint. Large, prospective studies are currently underway and medium-term outcomes appear to be promising. [4, 5] However, clinical practice guidelines (CPGs) [6] often acknowledge the significant heterogeneity inherent in deferred treatment strategies, with protocols differing in patient eligibility, selection and recruitment, disease monitoring and reassessment, outcome definition and measurement, and triggers for reclassification and change in management. In short, there is uncertainty regarding the definition of eligible patients, and the optimum follow-up strategies. Although attempts have been made to standardise definitions and terminology via consensus methods, [7] there have been no successful projects which harness clinical and patient expertise aiming to comprehensively standardise practice.

Consequently, the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel in conjunction with partner organisations (Appendix 1) commissioned and undertook a project to develop consensus statements for DAT. The project was unique and novel in its use of protocol-driven consensus methods. [8] The specific objectives were to achieve consensus on the following domains: (1) Criteria for patient selection, inclusion and exclusion; (2) Nature and timing of investigations and assessments during monitoring and follow-up; (3) Criteria and thresholds for reclassification and change in management; and (4) Type of outcome measures which should be prioritised. The study findings will be incorporated into international CPGs issued by the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel and collaborators, and will guide and inform clinical practice and further research.

2. Material and Methods

The protocol outlining the detailed methods underpinning the project has been published. [8] An overview of the study is depicted in Figure 1. The project was divided into 3 phases, lasting 12 months.

Phase 1 was a systematic review of current DAT practice [9] the results of which are summarized in Table 1 and Supplementary Table 1. The review findings were used to inform a list of statements and organised into domains and sub-domains reflecting aspects of DAT (i.e. patient eligibility and recruitment, follow-up and monitoring, reclassification, and outcome measures).

In Phase 2, the list of statements was incorporated into an online questionnaire as part of a two-round iterative Delphi survey. An international panel of participants including healthcare practitioners (i.e. urologists, medical and clinical/radiation oncologists, radiologists, pathologists, and specialist nurses) and patients were purposefully sampled to participate. The list of organisations which participated is included in Appendix 1. These organisations were targeted owing to the expertise of their membership. Organisations provided participants by either nominating individuals or cascading the invitation to their entire membership. Informed consent was assumed if participants registered and completed the survey.

In the online questionnaire, participants were presented with statements and asked to rate their strength of agreement on a scale of 1 (strongly disagree) to 9 (strongly agree). Participants could also suggest additional statements for incorporation into the following round. In Round 2, participants were provided with information regarding their own score from Round 1 as well as a summary of the scores for the entire cohort, and could either revise or retain their original scores. Thresholds regarding what constituted 'consensus agreement' and 'consensus disagreement' were specified *a priori* [8]. 'Consensus agreement' was defined as ≥70% of participants scoring a statement as 'strongly agree' (7-9) **and** <15% of participants scoring 'strongly disagree' (1-3). Conversely, 'Consensus disagreement' was defined as statements scored as 'strongly disagree' (score 1–3) by ≥70% of participants **and** <15% of participants scoring 'strongly agree' (7–9). All other statements not falling in the above categories will be classified as equivocal. The decision to use 70% as a threshold was based on prior studies and consensus methods research. [10-13]

Phase 3 consisted of a one-day, face-to-face consensus group meeting attended by representatives from all stakeholder groups and chaired by a non-voting clinician and non-voting methodologist. Participants were sampled from those who completed both rounds of the Delphi survey. All participants were provided with a personalised print-out containing a reminder of how they scored each statement in both rounds of the Delphi, and were given the summary of group results for all statements. All statements not achieving consensus in Phase 2 were discussed, reviewed and voted upon by participants, using the same consensus thresholds from Phase 2, using live voting software [8]. At the end of Phase 3, a final list of consensus statements organised according to the domains of DAT were ratified by the consensus group participants and project steering group.

3. Results

3.1 Delphi survey

Round 1 of the Delphi survey was generated from the systematic review findings (Appendix 2). 127 statements were organised under the following domains and sub-domains: (1) Patient eligibility, inclusion and exclusion criteria: (a) Age and life expectancy; (b) Risk classification (including D'Amico or EAU risk groups, PSA elements, Gleason sum score/ISUP Grade group, clinical stage, etc.); (c)

Histopathological characteristics (including how biopsy is performed, extent of disease, etc.); and (d) Imaging characteristics (including issues regarding multi-parametric MRI, etc.); (2) Monitoring and follow-up criteria (including issues regarding frequency and nature of PSA testing, repeat biopsy, clinical examination by digital rectal examination, and imaging); (3) Reclassification and change in management criteria and triggers: (a) Patient characteristics; (b) PSA kinetics; (c) Histopathology (including change in grade or disease extent); (d) Clinical examination; (e) Imaging; and (f) Patient preference; and (4) Outcome measures which must be prioritised in DAT programmes (including oncological, functional and quality of life [QoL] outcomes).

A total of 180 healthcare practitioners (HCPs) involved with DAT were identified through international specialist societies (Appendix 1) and invited to participate. 50 patients identified through patient advocacy organisations (Appendix 1) were invited to complete the patient-relevant parts of the survey (i.e. outcome measures which should be prioritised). Two additional statements suggested by participants were added to the questionnaire in Round 2 (Appendix 2), bringing the total number of statements to 129. In total, 126 HCPs (70% of those invited) and 29 patients (58% of those invited) completed Round 1, and 109 HCPs (61% of those invited) and 17 patients (34% of those invited) completed both rounds of the survey. The attrition rates between Rounds 1 and 2 were 14% for HCPs, and 41% for patients. Appendix 3 outlines the list of Delphi participants organised by stakeholder group (i.e. HCPs or patients), and including details such as name, speciality and country of residence for HCPs, and previous treatment, age and country of residence for patients.

Table 2 summarises the characteristics of all Delphi participants completing both rounds of the survey, based on stakeholder groups, speciality (or relevant treatment for patients), age (for patients only) and country of residence. Table 3 summarises the survey results for all statements, organised according to consensus status (i.e. consensus, near consensus, divergent opinions, or equivocal/unclear). In summary, there was consensus on 66 statements (51%) from the Delphi survey. The other remaining 63 statements were brought forward for review, discussion and voting in Phase 3, to see if consensus could be achieved on them.

3.2 Consensus group meeting

The consensus group meeting was held in Amsterdam on 9th November 2018 during the 10th European Multidisciplinary Congress on Urological Cancers (i.e. EMUC 2018). The meeting was attended by 35 voting participants (32 HCPs and 3 patients) and chaired by a non-voting clinician and a non-voting methodologist. Table 4 summarises the characteristics of consensus meeting participants based on stakeholder group, speciality and country of residence. Table 5 summarises the results for all statements reviewed, discussed and voted upon, organised according to consensus status 'yes/no' (i.e in summary, 27/63 statements (43%) achieved consensus during the meeting.

3.3 Final consensus statements and recommendations from DETECTIVE Study

Table 6 summarises all the consensus statements obtained from all phases of the study. In total, 93 statements out of a total 129 (72%) achieved full consensus. The majority of these were achieved from the Delphi survey (71%), whilst the consensus group meeting contributed 29% to the consensus

statements. 53% of the consensus statements were 'consensus agree' whilst 48% were 'consensus disagree'. Consensus was achieved in at least 65% of statements across all domains across the Delphi and consensus meeting process. Table 7 lists all clinical practice recommendations based on the consensus statements.

4. Discussion

4.1 Principal findings

This project explored and defined key areas of controversy and uncertainty covering all the main domains of deferred active treatment, a large undertaking not previously attempted on this scale using transparent methodology. A mixed methods approach was used to investigate this pressing problem, incorporating a systematic review, a two-round Delphi survey and a face-to-face consensus meeting with international participation from key stakeholders. The systematic review confirmed the scale and scope of the problem, highlighting significant heterogeneity, inconsistency and variability in clinical practice across all domains in contemporary studies of DAT. Given such heterogeneity, it is not surprising to note that currently, there is no conclusive data on how different DAT strategies compare to one another, and which strategy, definition and threshold should be adopted in clinical practice, and in clinical trials. Although several seminal randomised controlled trials investigating the effectiveness of observation [1, 2]or active monitoring [3] as a management strategy for localised prostate cancer in comparison with active curative treatment have been published, these studies do not represent current practice of deferred active treatment, which has continued to evolve over the past 15 years, especially with the introduction of new technology such as mpMRI scan into the patient care pathway, changes in the reporting of prostate cancer grade, and more accurate ways of performing prostate biopsies (including MRI-targeted biopsies or transperineal template biopsies). There is, therefore, an urgent need to provide guidance to clinicians, patients, researchers and policymakers, and in the absence of high levels of evidence, the only available option is to issue consensus statements using robust, transparent and reproducible methods. Our project set out to achieve this objective, and ultimately consensus was achieved in more than 72% of statements covering all the domains of DAT, and the results will provide the basis for international guidance and drive the research agenda for the immediate future. The main recommendations based on the consensus statements are listed in Table 7.

4.2 Relevance and impact of study findings on clinical practice and research

Our study, with participation from healthcare practitioners and patients, has provided the basis for conduct of DAT. Consensus statements represent the lowest level of evidence (i.e. level 5) on the evidence-based medicine hierarchy, [14] but in areas where there is low certainty and conflicting evidence, they represent a pragmatic basis for interim guidance. Consensus statements should be regarded as a starting point for clinicians and researchers to guide studies which will provide higher quality evidence and increase certainty. Evidence is never complete; it is ever-evolving, and correspondingly recommendations require updating as necessary. Using our consensus statements as a basis for informing and guiding the conduct of DAT, there is a need for clinicians to prospectively

collect and audit data on DAT in routine clinical practice, and researchers and trialists to conduct clinical trials or prospective comparative studies so that clinical effectiveness data can be obtained. In this context, initiatives such as PIONEER [15] and the Movember Foundation's Global Action Plan Active Surveillance (GAP3) project which aims to establish a global prospective database [16] represent important initial steps.

Our results may be juxtaposed with those of other studies with overlapping aims. Bruinsma *et al.* [7] used consensus methods to develop statements for active surveillance primarily aimed at standardising terms and definitions. The authors published a list of 61 items as a glossary of terms and definitions, whereas our study provides practical guidance for programmes of DAT. Both studies are complementary. MacLennan *et al.* [12] used similar consensus methods in creating a core outcome set applicable across all interventions, including deferred active treatment. The prioritised outcome measures obtained from our study (i.e. core outcomes for DAT) overlap with MacLennan *et al.*'s core outcome set, providing confidence that men with localised prostate cancer and the healthcare practitioners who treat them, regarded the same outcomes as important in two separate samples. More recently, Merriel *et al.* [17] published consensus statements on current best practice of active surveillance in the UK. The statements were developed by a multi-disciplinary group of 27 members consisting of clinical experts and patient experts, informed by a review of the literature, existing guidelines and protocols used by UK Urology departments, and survey data from men with localized prostate cancer. The final consensus statements were then issued by a subgroup of the panel (n=14) at a face-to-face meeting. There are clear similarities between both projects, with both being informed by a review of the literature, and statements were developed by a multidisciplinary panel of clinicians and patients covering similar domains. However, there are major differences. It was unclear if Merriel et al's project was based on an *a priori* protocol for the systematic review (e.g. PRISMA) and for the consensus phases; the methods, processes and rules underpinning the consensus process, its definitions and how they were developed and achieved were not described. Our project was more international in scope, involved a larger multidisciplinary panel (n=125) and was protocol-driven. We believe these are essential elements in any consensus endeavour which minimise bias, arbitrariness and subjectivity, whilst enhancing rigour, transparency and reproducibility. Nevertheless, there is overlap between the findings of both projects across all domains, and there are no major contradictory findings; as such both projects could be regarded as complementary.

4.3 Strengths and limitations

The study used robust, transparent and reproducible methods based on an *a priori* protocol. The study was international and contemporary in scope, involving patients and a large panel of healthcare practitioners purposively sampled from a broad range of disciplines, all of whom are stakeholders in DAT. A two-step, multi-phase consensus building process based on an iterative Delphi survey and consensus group meeting using anonymous voting techniques was employed, all of which enhanced internal validity. High external validity was achieved by ensuring that the survey items were informed by a systematic review of the literature, which was undertaken according to PRISMA guidelines. In terms of limitations, the project was designed to be pragmatic and practical for participants. Statements had to be brief and concise, and although participants rated their judgements on a scale, decisions were essentially binary in nature (i.e. disagree or agree). Consequently, it was not possible

to address all elements of uncertainty regarding DAT. In particular, the decision-making process regarding patient inclusion or exclusion or reclassification often involves a complex interplay between multiple factors and variables. The relative weighting placed on each variable as one or more variables change within and across patients, and how this affects the decision-making process for patients and clinicians is difficult to conceptualise and address meaningfully in a consensus-finding study. Secondly, within the healthcare practitioners' group, there was a higher ratio of urologists compared with other specialists, in both the Delphi survey and consensus group meeting. However, this reflects contemporary practice, whereby patients within DAT programmes are managed mostly by urologists. Additionally, there was an unusually high attrition rate within the patient group between Rounds 1 and 2 of the Delphi survey (41%). However, the outcome of all statements rated by patients remained stable between Rounds 1 and 2, hence suggesting that the attrition had minimal impact on the consensus outcome. There is also a small risk of introducing sampling error in terms of failure to achieve a balance between contrasting attitudes regarding active surveillance. However, through purposive sampling of a large number and a wide range of clinical practitioners involved in active surveillance, diverse opinions regarding active surveillance would have been achieved and hence minimising this risk.

The choice of a threshold for defining consensus (i.e. 70% in our study) merits a brief discussion. It may be argued that this is an arbitrary figure. However, our decision to use this threshold was informed by the methodological literature and through experience in previous consensus research conducted by members of the project steering group [12, 13, 18]. Many consensus projects define consensus as ≥70% of the participants choosing scores 7-9 and <15% choosing scores 1-3 (or vice versa) on a 9-point Likert scale, in order to account for the majority opinion whilst not dismissing divergent opinions [10, 11, 19]. The major emphasis in consensus methodology resources is that any threshold must have been judiciously selected, justified and described *a priori* [20, 21]. A higher threshold of 80% or 90% gives undue influence to outlier opinions and would have significantly reduced the number of items reaching consensus which seriously impairs the study's usefulness in clinical practice and research.

Lastly, the study did not achieve consensus on all statements, with 36 items (28%) failing to reach consensus, although 24 items from this group (i.e. 67% out of the total number of statements not reaching consensus) achieved near-consensus (Table 5). This reflects persisting uncertainty even amongst experts and specialists in the field, which can only be resolved through assessment of robust data from comparative studies from which higher levels of evidence can be obtained.

4.4 Areas for further research

We highlight persisting uncertainly and areas for further study. Firstly, for DAT eligibility, there is a need to improve determination of life expectancy more accurately and on an individualised basis. Presently a combination of approaches and strategies are employed, but they apply on a general rather than an individual level. A potential way forward may include studies exploring the creation of nomograms or actuarial tables integrating essential elements influencing life expectancy, such as age, ethnicity, social class, occupation, family history, specific co-morbidities, smoking status, and so on. Secondly, as our project has shown, certain thresholds remain contentious. For instance, thresholds beyond which disease extent on biopsy ought to lead to exclusion of patients with low-risk disease, or

the role of mpMRI in determining disease stage and aggressiveness as a criterion for inclusion or exclusion into DAT programmes, require data from prospective, well-designed studies, incorporating diagnostic accuracy elements and allowing synthesis of evidence regarding clinical effectiveness. In particular, the definition of 'high disease extent' based on biopsy characteristics remains problematic, although there was consensus on its importance. The role of a negative confirmatory biopsy was also not adequately explored in our study and hence deserves further study. In addition, since decision-making for clinicians and patients regarding DAT should be individualised, there is a need to better understand how the complex interaction between multiple factors influences decision-making, especially in terms of relative weighting placed on different variables and their trade-offs; this could be explored through studies utilising discrete choice experiments. [22] In terms of monitoring and follow-up, there was no consensus regarding the role of per-protocol mpMRI nor per-protocol repeat biopsies (i.e. untriggered), nor on its frequency and timing. The lack of consensus on the need for protocol-mandated (i.e. untriggered) repeat biopsies is particularly striking because many contemporary prospective studies on DAT do include them. Although we found consensus regarding repeat biopsy being required if there was a change in mpMRI, DRE progression or PSA progression, it has to be acknowledged that the sensitivity of these triggers for higher grade disease remains unproven. The evolving role of mpMRI in detecting clinically significant disease in place of biopsy is promising, as are new biomarkers (reviewed in [23]), including serum markers (e.g. Prostate Health Index and 4K score), urinary markers (e.g. Prostate Cancer Antigen 3, or PCA3), and tissue markers (e.g. genomic profiling). Once data on these promising diagnostic interventions mature, future studies should integrate them into nomograms predicting the probability of reclassification. In addition, given the current heterogeneity in practice, there is a need to standardise the risk categories and follow-up strategies in large prospective studies. Lastly, the findings from our study will improve and direct the standardisation of undertaking DAT in routine clinical practice and research. Clinicians should use them to carefully design their DAT protocols such that comparative clinical effectiveness data can be prospectively collected, and the results audited regularly. Researchers should follow our guidance and perform clinical trials or prospective cohort studies comparing different DAT protocols against each other and against immediate curative interventions.

5. Conclusions

The EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel, in partnership with other leading guideline authorities and patient advocacy organisations (Appendix 1), undertook an ambitious project using a novel and transparent approach in this setting to develop consensus statements for all domains relating to DAT to standardise clinical practice and research. Protocol-driven, robust and transparent methods were utilised. Consensus was achieved on 93 out of 129 statements (72%), covering the domains of criteria for patient selection, inclusion and exclusion (including patient and disease characteristics, imaging criteria, and type of biopsies), nature and timing of investigations and assessments during period of monitoring and follow-up (including PSA measurements, clinical examination, repeat imaging and repeat biopsies), criteria and thresholds for reclassification and change in management, and type of outcome measures which should be prioritised. The findings will guide and inform routine clinical practice and research by being incorporated into guidelines issued by the EAU-EANM-ESTRO-ESUR-SIOG Prostate Cancer Guideline Panel and partner organisations, until higher levels of evidence emerge through prospective comparative studies and clinical trials.

Collaborators: *The following organisations participated in the DETECTIVE Study:*

EAU – EANM - ESTRO - ESUR - SIOG Prostate Cancer Guidelines Panel
European Association of Urology Research Foundation (EAU RF)
European Urology
EAU Section of Oncological Urology (ESOU)
American Society of Clinical Oncology (ASCO)
American Urological Association (AUA)
European Society for Radiotherapy and Oncology (ESTRO)
European Association of Urology Nurses (EAUN)
Canadian Urological Association (CUA)
International Society of Urological Pathology (ISUP)
Urological Society of Australia and New Zealand (USANZ)
European Society of Urogenital Radiology (ESUR)
Urological Association of Asia (UAA)
American Society for Radiation Oncology (ASTRO)
Europa UOMO
Red Sock Campaign
Movember Foundation

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Supplementary material

Appendix 1: List of collaborators

EAU – EANM - ESTRO - ESUR - SIOG Prostate Cancer Guidelines Panel

European Association of Urology Research Foundation (EAU RF)

European Urology

EAU Section of Oncological Urology (ESOU)

American Society of Clinical Oncology (ASCO)

American Urological Association (AUA)

European Society for Radiotherapy and Oncology (ESTRO)

European Forum for Primary Care (EFPC)

European Association of Urology Nurses (EAUN)

Canadian Urological Association (CUA)

International Society of Urological Pathology (ISUP)

Urological Society of Australia and New Zealand (USANZ)

European Society of Urogenital Radiology (ESUR)

Urological Association of Asia (UAA)

American Society for Radiation Oncology (ASTRO)

Europa UOMO

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Appendix 2: Studies included in systematic review (DETECTIVE Study) (n=282)

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Appendix 3: DETECTIVE Delphi survey*

***NOTE all participants saw the same questions in round 1 and round 2 of the Delphi. Two additional questions (suggested by participants in round 1) were included in round 2. These can be seen at the end of this appendix.**

MAIN QUESTIONS PAGE

Please complete the following section which relates to background information.

Part 1: Background information

Name	
What is your main area of speciality? (please tick one that best apply to you)	Urology Clinical or Radiation Oncology Medical Oncology Radiology Pathology General Practitioner Specialist Nurse Other – please specify
What treatment for localised prostate cancer do you specialise in? (you may tick more than one)	Active surveillance Open radical prostatectomy Laparoscopic radical prostatectomy Robot-assisted radical prostatectomy External beam radiotherapy Three dimensional conformal radiotherapy (3D-CRT)

	Intensity modulated radiotherapy (IMRT) Volumetric modulated arc therapy (VMAT) Brachytherapy High Intensity Focussed Ultrasound (HIFU) Cryotherapy (cryosurgery) Focal therapy (including all types of energies and techniques) Other – please specify Not directly involved with treatment for localised prostate cancer Unable to answer

Part 2: Main questions regarding statements concerning deferred active treatment/active surveillance/active monitoring

Please state your level of agreement for each of the following statements. On each page you will see a list of statements organised under the different domains in the patient management pathway for deferred active treatment/active surveillance/active monitoring. These include: (1) Patient eligibility, inclusion and exclusion criteria; (2) Monitoring and follow-up criteria; (3) Reclassification criteria; and (4) Outcome measures, definitions and thresholds. Each domain is sub-divided into the relevant sub-domains. You will be asked to score your agreement on a scale of 1-9, with 1 being 'Strongly disagree' and 9 being 'Strongly agree'. If you feel you are unable to answer, please select 'Unable to score'. Please specify any other important statements/outcomes that you strongly believe should be included in this survey in the space provided in Section E (Domain 5: Additional statements) on the final page and remember to score any new statements that you suggest.

A. Domain 1: Patient eligibility, inclusion and exclusion criteria

I. Age and life expectancy

		Strongly disagree	**Neither agree nor disagree**	**Strongly agree**	

Statement		1	2	3	4	5	6	7	8	9	Unable to score
1. There is no lower nor upper age limit for inclusion as long as the appropriate life expectancy criterion is fulfilled											
2. The appropriate life expectancy criterion for inclusion is:	i. ≥10 years										
	ii. ≥15 years										
3. Life expectancy in everyday practice is best evaluated by:	i. Performance status (e.g. ECOG, Karnofsky)										
	ii. Co-morbidity index measure (e.g. Charlson)										
	iii. Health status screening (e.g. Geriatric 8 screening tool)										
	iv. Combination of performance status, co-morbidity index and health status screening										

II. Risk classification (e.g. D'Amico, EAU, etc.)

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
1. Low-risk disease:	i. is an automatic inclusion criterion regardless of other disease factors										
	ii. is excluded if the extent of disease is high based on biopsy core volume, length or number or proportion of core positivity										
	iii. is excluded if the extent and/or stage of disease is high based on mpMRI										
	iv. is excluded if mpMRI suggests biologically-aggressive disease										
2. Gleason 3+4=7 (ISUP grade 2):	i. is an automatic exclusion criterion										
	ii. can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a) and biopsy characteristics (low core positivity)										
3. Gleason 4+3=7 (ISUP grade 3):	i. is an automatic exclusion criterion.										
	ii. can be included only if favourable characteristics are present, including PSA (<10), clinical stage (≤cT2a) and biopsy characteristics (low core positivity)										

4. PSA:	i. >10ng/ml is an automatic exclusion criterion, regardless of other disease characteristics										
	ii. >20ng/ml is an automatic exclusion criterion, regardless of other disease characteristics										
5. PSA density:	i. is an important inclusion criterion										
	ii. for inclusion should be ≤ 0.15ng/ml per g										
	iii. for inclusion should be ≤ 0.20ng/ml per g										
6. Clinical stage:	i. ≥cT2b is an automatic exclusion criterion, regardless of other disease characteristics										
	ii. ≥cT2c is an automatic exclusion criterion, regardless of other disease characteristics										

III. Pathology characteristics

		Strongly disagree			**Neither agree nor disagree**			**Strongly agree**			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
1. Targeted biopsies should be reported separately from systematic biopsies											
2. The extent of disease should be reported in:	i. mm										
	ii. % tumour volume (as a proportion of total volume of core)										
3. ISUP grade (Gleason score) should be reported for each positive core											
4. Percentage of Gleason pattern 4 carcinoma should be provided for each biopsy site with Gleason score 7 carcinoma											
5. Intraductal and cribriform histology are exclusion criteria											
6. When systematic biopsies are performed, the extent of disease based on histological characteristics (e.g. core length, core volume, core positivity, etc.) is an important inclusion/exclusion criterion											
7. Extent of disease on histology is important even for Gleason 3+3=6/ISUP Grade 1 disease because it may lead to patients being excluded											
8. The threshold of disease extent **beyond which patients are automatically**	i. Core positivity >20%										

excluded based on systematic biopsy regardless of other disease characteristics for Gleason 3+3=6/ISUP Grade 1 disease is:	ii. Core positivity >33%										
	iii. Core positivity ≥50%										
	iv. Positive cores >2										
	v. Positive cores >3										
	vi. Core length >3mm										
	vii. Core length >5mm										
9. The threshold of disease extent **beyond which patients are automatically excluded** based on systematic biopsy regardless of other disease characteristics for Gleason 3+4=7/ISUP Grade 2 disease is:	i. Core positivity >20%										
	ii. Core positivity >33%										
	iii. Core positivity ≥50%										
	iv. Positive cores >2										
	v. Positive cores >3										
	vi. Core length >3mm										
	vii. Core length >5mm										
	viii. Any disease extent (because Gleason 3+4=7/ISUP Grade 2 is an automatic exclusion)										

IV. Imaging characteristics

		Strongly disagree			**Neither agree nor disagree**			**Strongly agree**			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
1. If a patient has had upfront mpMRI followed by systematic and targeted biopsies, there is no need for confirmatory biopsies											
2. If targeted biopsies based upon mpMRI images are performed, the number of positive cores is not an indicator of extent of disease nor tumour volume											

3. The number of positive sextants based on systematic and/or targeted biopsies should be taken into account as an indicator of tumour volume											
4. The volume of the dominant lesion seen on mpMRI (PI-RADS V2 ≥3) should be taken into account as an indicator of tumour volume											
5. For inclusion, prostate biopsies should be performed by:	i. MRI-guided targeted biopsies (including in-bore, cognitive guidance or MRI fusion) without systematic biopsies										
	ii. MRI-guided targeted biopsies (including in-bore, cognitive guidance or MRI fusion) with systematic biopsies										
	iii. Transperineal template biopsies instead of MRI-guided biopsies										
	iv. TRUS-guided systematic biopsies only										
6. Tumour volume (for ≤T2 disease) based purely on mpMRI characteristics is an important inclusion/exclusion criterion											
7. Disease aggressiveness (for ≤T2 disease) (e.g. low ADC value) based purely on mpMRI characteristics is an important inclusion/exclusion criterion											
8. For inclusion, all patients need an mpMRI at some point											

B. Domain 2: Monitoring and follow-up criteria

I. Monitoring and follow-up

		Strongly disagree			**Neither agree nor disagree**			**Strongly agree**			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
During active surveillance in the first 2 years, men should have their PSA checked:	i. Every 3 months										
	ii. Every 6 months										
	iii. Not checked at all										
During active surveillance after the first 2 years, men should	i. Every 6 months										

have their PSA checked:	ii. Every 12 months											
	iii. Not checked at all											
During active surveillance, men should have a digital rectal examination (DRE):	i. Every 3 months											
	ii. Every 6 months											
	iii. Every 12 months											
	iv. Not needed											
During active surveillance, repeat biopsy should be performed:	i. Every 12 months											
	ii. Every 24 months											
	iii. Every 48 months											
	iv. At 1 year, 4 years and 7 years											
	v. Not routinely pre-planned unless triggered											
	vi. Triggered by a change in mpMRI (i.e. increase PI-RADS score, lesion volume or radiological T stage)											
	vii. Triggered by PSA doubling time <3 years											
	viii. Triggered by DRE progression											
If repeat biopsies are needed, they should be performed by:	i. 10-12 core TRUS-guided											
	ii. MRI-guided targeted biopsies (including in-bore, cognitive guidance or MRI fusion) without systematic biopsies											
	iii. MRI-guided targeted biopsies (including in-bore, cognitive guidance or MRI fusion) with systematic biopsies											
	iv. Transperineal template biopsies instead of MRI-guided biopsies											
	v. TRUS-guided systematic biopsies											

C. Domain 3: Reclassification (i.e. leaving active surveillance for an active treatment) criteria

I. Reclassification – Criteria based on patient characteristics

	Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Reclassification should only apply to patients with a life expectancy of ≥10 years at the time of assessment										
Reclassification should only apply to patients with a life expectancy of ≥15 years at the time of assessment										
Active surveillance should only be continued in patients with life expectancy of ≥10 years										
Active surveillance should only be continued in patients with life expectancy of ≥15 years										
Patient anxiety or depression is a valid reason for triggering reclassification (including active treatment)										
Patient reluctance to undergo repeat biopsies or repeat imaging is a valid reason for triggering reclassification (including active treatment)										

II. Reclassification - Criteria based on PSA

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
PSA progression is sufficient to indicate reclassification in the absence of other factors.											
A rise in PSA mandates re-biopsy irrespective of other findings.											

A rise in PSA mandates re-imaging of the patient.											
A shortening of PSA doubling time:	1. is sufficient to indicate reclassification in the absence of other factors										
	1. Should only indicate reclassification if it falls below a defined threshold										
	2. of < 36 months indicates reclassification										
	3. of < 24 months indicates reclassification										
	4. even if minimal would indicate reclassification if accompanied by other PSA-based parameter changes										
A rise in PSA above an absolute threshold:	1. of > 10 would indicate reclassification										
	2. of > 20 would indicate reclassification										
A PSA velocity:	1. of > 0.75/year would indicate reclassification										
	2. of > 1.0/year would indicate reclassification										
An increase in PSA density:	1. is sufficient to indicate reclassification in the absence of other factors										
	2. would indicate reclassification if accompanied by other PSA-based parameter changes										
A change in PSA parameters which by itself is not sufficient, would indicate reclassification if accompanied by:	1. changes in histology										
	2. changes in imaging										

III. Reclassification - Criteria based on histopathology

(a) Criteria based on grade

		Strongly disagree			**Neither agree nor disagree**			**Strongly agree**			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
A higher Gleason score (or ISUP grade) on re-biopsy is required for reclassification											

(b) Criteria based on histopathological extent

		Strongly disagree					Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
An increase in the number of positive cores on re-biopsy:	1. indicates re-classification (i.e. no threshold needed)										
	2. if > 2 cores on re-biopsy indicates reclassification										
	3. If > 3 cores on re-biopsy indicates reclassification										
An increase in the extent of core involvement:	1. indicates re-classification (i.e. no threshold needed)										
	2. If > 20% of a core indicates reclassification										
	3. If > 33% of a core indicates reclassification										
	4. If > 50% of a core indicates reclassification										
	5. Is not important for Gleason 3+3=6/ISUP Grade 1 disease										

IV. Reclassification - Criteria based on clinical examination

		Strongly disagree					Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
An increase in the clinical T-category based on DRE , as the sole criterion:	1. If increase to cT2a, indicates reclassification										
	2. If increase to cT2b indicates reclassification										
	3. If increase to cT2c indicates reclassification										

V. Reclassification - Criteria based on imaging

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Radiological evidence of disease progression is sufficient to reclassify in the absence of other factors.											
Radiological evidence of progression mandates an image-directed biopsy.											
A new focus of cancer on repeat imaging indicates re-classification	1. Always										
	2. Only if accompanied by a re-biopsy										
Increase in tumour volume (for ≤T2 disease) on imaging alone (i.e. in the absence of re-biopsy, PSA, etc.) indicates re-classification.											
An increase in the PI-RADS score indicates reclassification in the absence of other features.											

VI. Reclassification - Criteria based on patient preference

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Patient preference to switch to active treatment, regardless of other factors, should trigger reclassification.											

D. Domain 4: Outcome measures * NOTE this is the subset of questions which patients were asked also

I. Primary outcome measures which must be measured and prioritised by all active surveillance programmes

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
The following outcomes are critically important for active surveillance programmes to measure:	Overall survival (i.e. a measure of survival or death from all causes, including natural causes)										
	Prostate cancer-specific survival (i.e. a measure of survival or death from prostate cancer only, excluding other causes)										
	Progression to metastatic disease (i.e. cancer spreading to other organs)										
	Local progression (i.e. cancer getting bigger or more advanced locally)										
	Symptomatic progression (i.e. cancer progressing locally to cause symptoms such as pelvic pain, bleeding in urine, difficulty in urinating, etc.)										
	Re-classification (i.e. coming off active surveillance for active curative treatment e.g. surgery or radiotherapy)										
	Urinary function (i.e. function relating to urinating)										
	Sexual function (i.e. function relating to erection, libido, ejaculation, etc.)										
	Overall quality of life (i.e. quality of life relating to general health and well-being)										
	Anxiety										
	Depression										

E. Domain 5: Additional statements or important outcomes included by survey participants (*NOTE asked to ALL PARTICIPANTS, INCLUDING PATIENTS)

I. **If you feel <u>strongly</u> that important statements or outcomes are missing from the survey, please include them below and include your judgement. They will be included in the next round of the survey. However, please restrict to critically important statements or outcomes only, as there is a limit to the number of statements allowable on the survey.**

	Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**

Additional statements included in round 2 of the survey (for HCPs only).

		Strongly disagree			Neither agree nor disagree			Strongly agree			
Statement		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Unable to score**
Biomarkers are useful in stratifying risk of disease progression for men undergoing active surveillance											
Men known to carry the BRAC2 mutation are ineligible for active surveillance											

ADC = apparent diffusion coefficient; BRAC2 = DNA repair associated gene; 3D-CRT= external beam radiotherapy three dimensional conformal radiotherapy; DRE = digital-rectal examination; ECOG = Eastern Cooperative Oncology Group (performance status); HCP = healthcare professional; HIFU = high intensity focussed ultrasound; IMRT = intensity modulated radiotherapy; ISUP = International Society of Urological Pathology; mpMRI = multi-parametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS = transrectal ultrasound; VMAT =Volumetric modulated arc therapy.

Appendix 4: List of participants completing Rounds 1 and 2

Name	Role	Country of residence
Monique Roobol	Epidemiologist	The Netherlands
Gwendolyn Hooper	Family and Urology nurse practitioner	United States
Russo Russo	Nurse specialist	Italy
Helen Attard Bason	Nurse specialist	Malta
Brian Corr	Nurse specialist	United Kingdom
Foroozan Atashzadeh-Shoorideh	Nursing associate professor	Iran
Alberto Bossi	Oncologist	France
Maria De Santis	Oncologist	Germany
Caroline Moore	Oncologist	United Kingdom
Chris Parker	Oncologist	United Kingdom
Silke Gillessen	Oncologist	United Kingdom, Switzerland
Ronald Chen	Oncologist	United States
Glen Kristiansen	Pathologist	Germany
Maurizio Colecchia	Pathologist	Italy
Arno Van Leenders	Pathologist	The Netherlands
Murali Varma	Pathologist	United Kingdom
Peter A. Humphrey	Pathologist	United States
Lawrence D. True	Pathologist	United States
Theo van der Kwast	Pathologist	the Netherlands, Canada
Brett Cox	Radiation oncologist	United States

Geert Villeirs	Radiologist	Belgium
Raphaele Renard-Penna	Radiologist	France
Olivio Donati	Radiologist	Switzerland
Anwar Padhani	Radiologist	United Kingdom
Francesco Giganti	Radiologist	United Kingdom
Olivier Rouvière	Radiologist	France
Stefano Fanti	Radiologist	Italy
Ivo Schoots	Radiologist	The Netherlands
Jonathan Richenberg	Radiologist	United Kingdom
Thomas M. Pisansky	Radiologist	United States
Tom Pickles	Radiation oncologist	Canada
Michel Bolla	Radiation oncologist	France
Thomas Wiegel	Radiation oncologist	Germany
Gemma Sancho Pardo	Radiation oncologist	Spain
Malcolm D. Mason	Radiation oncologist	United Kingdom
Ann Henry	Radiation oncologist	United Kingdom
Mark Buyyounouski	Radiation oncologist	United States
John Yaxley	Urologist	Australia
Damien Bolton	Urologist	Australia
Niall Davis	Urologist	Australia
Mark Frydenberg	Urologist	Australia
Jeremy Grummet	Urologist	Australia
Declan Murphy	Urologist	Australia
Shomik Sengupta	Urologist	Australia
Philip Stricker	Urologist	Australia
Ian Vela	Urologist	Australia
Henry Woo	Urologist	Australia
Laurence Klotz	Urologist	Canada
Luke Lavallee	Urologist	Canada
Chris Morash	Urologist	Canada

Frederic Pouliot	Urologist	Canada
Patrick Richard	Urologist	Canada
Christopher Wallis	Urologist	Canada
Sebastien Crouzet	Urologist	France
Alexandre Ingels	Urologist	France
Jacques Irani	Urologist	France
Nicolas Mottet	Urologist	France
Nikolaos Grivas	Urologist	Greece
Michael Lardas	Urologist	Greece
Maurizio Brausi	Urologist	Italy
Paolo Dell'Oglio	Urologist	Italy
Giorgio Gandaglia	Urologist	Italy
Hiroshi Sasaki	Urologist	Japan
Antonio Alcaraz	Urologist	Spain
Maria J. Ribal	Urologist	Spain
Anders Bjartell	Urologist	Sweden
Christian Fankhauser	Urologist	Switzerland
Tobias Gross	Urologist	Switzerland
Yeong-Shiau PU	Urologist	Taiwan
Roderick van den Bergh	Urologist	The Netherlands
Max Bruins	Urologist	The Netherlands
Peter-Paul Willemse	Urologist	The Netherlands
Rakesh Heer	Urologist	United Kingdom
William Cross	Urologist	United Kingdom
James Donaldson	Urologist	United Kingdom
Thomas B. Lam	Urologist	United Kingdom
Matthew Liew	Urologist	United Kingdom
Karl Pang	Urologist	United Kingdom
Justine Royle	Urologist	United Kingdom
Hashim U. Ahmed	Urologist	United Kingdom

Philip Cornford	Urologist	United Kingdom
Marcus Cumberbatch	Urologist	United Kingdom
Alastair D. Lamb	Urologist	United Kingdom
James Eastham	Urologist	United States
Peter Albertsen	Urologist	United States
Daniel A. Barocas	Urologist	United States
Pail Crispen	Urologist	United States
Scott Eggener	Urologist	United States
Daniel Lin	Urologist	United States
Steven Joniau	Urologist	Belgium
Anil Kapoor	Urologist	Canada
Philippe Violette	Urologist	Canada
Derya Tilki	Urologist	Germany
Alberto Briganti	Urologist	Italy
Nicola Fossati	Urologist	Italy
Piotr Chlosta	Urologist	Poland
Chris Bangma	Urologist	The Netherlands
Michiel Sedelaar	Urologist	The Netherlands
Henk Van der Poel	Urologist	The Netherlands
Konstantinos Dimitropoulos	Urologist	United Kingdom
James N'Dow	Urologist	United Kingdom
Stacy Loeb	Urologist	United States
Lisa Moris	Urologist in training	Belgium
Thomas Van den Broeck	Urologist in training	Belgium
Catherine Paterson	Urology nurse consultant & Research fellow	United Kingdom
Sau-loi Ng	Urology specialist nurse	Hong Kong
Corinne Buckett	Urology specialist nurse	United Kingdom
Karen Wilkinson	Uro-oncology nurse specialist	United Kingdom

Patient ID	Prior treatment	Age
Patient #1	No active surveillance	61-70
Patient #2	Active surveillance	51-60
Patient #3	Active surveillance	>70
Patient #4	No active surveillance	>70
Patient #5	No active surveillance	
Patient #6	No Active surveillance	>70
Patient #7	No active surveillance	61-70
Patient #8	No active surveillance	> 70
Patient #9	Active surveillance	61-70
Patient #10	Active surveillance	> 70
Patient #11	Active surveillance	61-70
Patient #12	Active surveillance	> 70
Patient #13	Active surveillance	61-70
Patient #14	No active surveillance	>70
Patient #15	Active surveillance	>70
Patient #16	Active surveillance	51-60
Patient #17	No active surveillance	>70