Article:
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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 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

Appendix 2: 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.

Appendice 3: 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	Country of residence	Current treatment
Patient #1	No active surveillance	61-70	Belgium	No Active surveillance
Patient #2	Active surveillance	51-60	The Netherlands	Active surveillance
Patient #3	Active surveillance	>70	United Kingdom	No active surveillance
Patient #4	No active surveillance	>70	Belgium	No active surveillance
Patient #5	No active surveillance		Belgium	No active surveillance
Patient #6	No Active surveillance	>70	Portugal	No Active surveillance
Patient #7	No active surveillance	61-70	Sweden	No active surveillance
Patient #8	No active surveillance	> 70	Switzerland	No active surveillance
Patient #9	Active surveillance	61-70	United Kingdom	Active surveillance
Patient #10	Active surveillance	> 70	United Kingdom	Active surveillance
Patient #11	Active surveillance	61-70	United Kingdom	No active surveillance
Patient #12	Active surveillance	> 70	United Kingdom	Active surveillance
Patient #13	Active surveillance	61-70	United Kingdom	Active surveillance
Patient #14	No active surveillance	>70	United Kingdom	No active surveillance
Patient #15	Active surveillance	>70	United Kingdom	Active surveillance
Patient #16	Active surveillance	51-60	United Kingdom	Active surveillance
Patient #17	No active surveillance	>70	United Kingdom	No active surveillance

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