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<td>Order of Authors:</td>
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Abstract:

Introduction; development and implementation of active surveillance (AS) for low and intermediate risk prostate cancer (PCa) has shifted from an option to almost standard in developed countries. But still many controversies in its management.

Material & Methods; we review data from the Spanish Register in AS (AEU-PIEM/2014/0001, ClinicalTrials.gov Identifier: NCT02865330), a multicenter longitudinal study considering a cohort of AS patients registered between 2014 and 2019, with open inclusion criteria and different follow-up strategies. We review main midterm oncological outcomes

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Conclusions; Midterm oncological results of AS in Spain are comparable to those in...
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<td>Corresponding Author E-Mail:</td>
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Midterm results of Spanish Register on Active Surveillance for Prostate Cancer


tThese authors contribute equally to this work.

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Ethics statement

For human study

The present study protocol was reviewed and approved by the institutional review board of Ethics Committee for Clinical Research of Aragon (Reg. No. PI17/0280).
Conflict of Interest:
The authors have nothing to disclose.

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AUTHOR CONTRIBUTION
Conceptualization: J. R-B, A. B-F. Data curation: All authors. Formal analysis: J. R-B, A. B-F, LM. E-E. Funding acquisition: LM. E-E, A. B-F. Investigation: J. R-B, A. B-F, LM. E-E. Methodology: J. R-B, A. B-F, LM. E-E. Project administration: J. R-B, A. B-F. Resources: J. R-B, A. B-F. Software: does not apply Supervision: J. R-B, A. B-F, LM. E-E. Validation: J. R-B, A. B-F, LM. E-E. Visualization: All authors. Writing – original draft: J. R-B, A. B-F, LM. E-E. Writing – review & editing: All authors have read and agreed to the published version of the manuscript.

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Dear Hyun Jun Park, Editor-in-Chief of The World Journal of Men’s Health,

I would like to submit the manuscript entitled “Midterm results of Spanish Register on Active Surveillance for Prostate Cancer” by J. Rubio-Briones, A. Borque-Fernando and L.M. Esteban-Escañó, on behalf of the Collaborative Group for Active Surveillance in Prostate Cancer (PIEM/AEU/2014/0001, National Clinical Trials NCT02865330) to be considered for publication as original article, in The World Journal of Men’s Health.

We present the midterm results of this real clinical practice study project on active surveillance in prostate cancer. We show the evolution of more than 3000 patients and 50 hospital centers, in a cohort recruited retrospectively between 2014 and 2019 and with an expected follow-up of 15 years, until 2034. ([https://piem.aeu.es/proyectos/VACP/default_en.aspx](https://piem.aeu.es/proyectos/VACP/default_en.aspx) and [https://clinicaltrials.gov/ct2/show/NCT02865330](https://clinicaltrials.gov/ct2/show/NCT02865330)).

We believe that our findings will be of interest to the readers of your journal.

We declare that this manuscript has not been published in part or whole, or is under consideration for publication elsewhere in any language. All authors have agreed to be so listed and have seen and approved the manuscript, its consent and its submission to WJMH.

Yours sincerely,

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Abstract;

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Introduction;
Many men with early prostate cancer (PCa) show an indolent and long natural history of disease(1). In the 90’s, active surveillance (AS) strategies started to gain popularity regardless age in the Urologic community, differentiating it from just watchful waiting (WW) policies. Its rationale and clear objective were reducing overtreatment, side effects and costs of active management(2).
As all world-wide protocols of AS, the Spanish Register on AS (AEU-PIEM/2014/0001(3), ClinicalTrials.gov Identifier: NCT02865330) tried to achieve the goal of postponing curative treatment up to the occurrence of disease progression. Its philosophy was to act as a real-life Register with wide inclusion criteria, different follow-up (FU) strategies and criteria for active treatment, being promotion of AS itself its main rationale. It includes patients with low and intermediate-risk PCa and assume disease progression as tumour size increase or as a worsening in the biopsy score (upgrading of the Grade Group)(4). In fact, it was proposed as a Registry of real world practice of AS in Spain.
The main present study aim is acknowledging midterm data within our Register in terms of different survival endpoints investigating real world data in our country to find room of improvement.

Material and Methods;
Briefly as previously published(3), the Spanish Register in AS started recruitment in July/15/2014, admitting patients included in AS protocols retrospectively. It closed recruitment 5 years later July/15/2019 and its FU is prospectively assured for a minimum of 15 years. Patients for any of the 49 participating Centers all along the country were included if PSA was ≤ 20 ng/ml, digital rectal examination (DRE) dictated clinical stage (cT) of cT1a-b-c or cT2 a-b-c, and primary Gleason pattern was 3 and secondary 3 or 4. Prostate volume was calculated from hypogastric or transrectal ultrasound. Initial magnetic resonance imaging (MRI) was not mandatory as per the studied period but was registered in FU biopsies when used. A minimum of 10 diagnostic cores were mandatory to be included, and patients could harbour 1, 2 or 3 positive cores. No central pathological review was considered. FU strategies were open with no pre-determined timing for FU biopsies (Bx) nor type of Bx approach, mirroring real-life practices in our country.
Pathological progression was defined as any increase in Gleason Grade Group (GG) or within the same GG if any core had a PCa length > 5mm or 50% in cores at least 1cm in length, 3 or more affected cores in any FU transrectal ultrasound guided Bx (TRUS-Bx) or 3 or more affected cores and more than 2 affected prostatic zones if FU Bx had a transperineal approach (TP Bx). Local progression was defined as increase by FU DRE cT or MRI from
cT1-2 to cT3. To define metastatic progression, metastasis had to be diagnosed by bone scan, computed tomography (CT) or MRI scan or next generation imaging techniques such as positron emission tomography (PET) with choline or PSMA as radiotracers.

Characteristics of the whole cohort and by risk categories were described using median and interquartile range (percentile 25th-percentile 75th) or absolute and relative frequencies, for continuous and categorical variables respectively. Differences by low and intermediate risk groups were analysed using Mann-Whitney or Fisher exact test as appropriate. Registered data sometimes are missing due to open label and not central research office guided implementation; thus, when we refer to percentages we take in account reliable registered data.

The period time between biopsies were reported using violin plots and the results of the follow-up biopsies were described using bar plots. The patient status at the time of analysis were analysed by pie chart.

The pathological, local progression, active treatment, overall mortality, and cancer specific free survival probabilities were calculated and displayed using Kaplan-Meier survival curves.

Data analysis were carried out using version 4.0.3 of the R statistical software, through version 1.3.1093 of the RStudio development environment (RStudio Team (2021). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA, USA, URL http://www.rstudio.com/).

The study was reviewed and approved by the institutional review board of Ethics Committee for Clinical Research of Aragon (Reg. No. PI17/0280), registering with the code AEU-PIEM/2014/0001. The present study protocol.

Results;

Along the recruitment period of 5 years, 3337 patients were included in the Register. Median age was 67 years (P25-74, 61-71), 99.6 % caucasian, 83.92 % from urban living and just 17.01 % with university studies. Most of them had stable partner (92.63 %) and 43.55% played some sport sporadically or regularly. 326 (9.77%) of patients only conducted the diagnostic visit. Among those questioned for familial PCa, 13.78 % recognized relatives with PCa. Main clinico-pathological variables at inclusion are shown in table 1. Using National Comprehensive Cancer Network (NCCN) prognostic groups, 436 (13.06%) and 2901 (86.93%) patients corresponded to intermediate and very low & low risk groups. At recruitment, median PSA was 6.05 (IQR: 4.75-7.94) ng/ml. cT1c was the most frequent cT (87.83%) and 268 patients with cT2 were included (8.03%). Most of them were minimally or mildly symptomatic with a mean IPSS of 9.34 (SD 6.30) and quality of life final question with a mean of 1.86 (SD 1.38). Patients taking medical treatment for lower urinary tract symptoms (LUTS) were 40.74%, while just 6.90 % had been operated for LUTS.
For initial diagnosis, TRUS-Bx was used in 96.6% of men and TP-Bx just in 3.4%. Just 371 patients (out of 1843, 20.13%, in whom those data were available) had their diagnostic Bx guided by MRI. When performed, PI-RADs 3-5 lesions were observed in 206 patients (55.52%). Use of MRI increased to 824 patients (out of 1843, 44.69%) for the confirmatory Bx. At inclusion, Gleason Grade group 1 (3+3) was the most frequent in up to 3235 patients (96.7%).

Median time elapsed between FU visits was 6.03 months (Q1-3: 4.13-7.93). This time frame between FU visits was stable along most FU in different Centers. In figure 1 we display time elapsed between FU Bx, observing that the first (confirmatory) Bx had a median of 11 months (IQR: 8-14) and the median between the following was around 24 months. Taking in account those 2705 patients with FU Bx, 1410 (52.13%) had just one, and then 826 (30.54%), 344 (12.72%), 96 (3.55%) and 29 (1.17%) had 2, 3, 4 and 5 or more respectively. During the first year of FU, 1414 men were biopsied (42.37%), progressively reducing the percentage of biopsied men in the following years. When focusing on type of Bx in FU, TP-Bx approach was more frequently used (16.5%), but still far from TRUS-Bx. In figure 2, we can see pathological results of the FU Bx; the percentage of non PCa results was 35.88% in first FU Bx, slowly increasing to 43.33% in fifth FU Bx. The percentage of GG 2 or higher was stable in the three first FU Bx, but increasing between posteriorly up to 20% at the 5th, figure 2B.

In figure 3 we can see final stage of the whole series after excluding 187 patients lost to follow-up. With a median FU of 53.13 months (Q1-3: 34.37-75.58), we observed that just 1577 patients (50.06%) remain in AS, while 1151 have been actively treated (36.54%). Two hundred fifty-four (8.06%) have been transferred to a watchful waiting (WW) strategy due to aging or intercurrent disease. Death occurred in 168 patients (5.33%), 2 per PCa progression and 166 for intercurrent disease.

Pathological progression occurred in 1308 (46.63%) out of 2805 available FU data patients, resulting in a pathological progression free survival at 2 and 5 years of 69% and 50.4% respectively (figure 4A). Local progression occurred in 315 patients (15.33%), and local progression free survival at 2 and 5 years were 92.3% and 83.5% (figure 4B). Metastasis occurred in 19 patients out of 1864 (1.01%), with corresponding metastasis free survival rates at 2 and 5 years of 99.4% and 98.6% respectively (figure 4C). Active treatment free survival at 2 and 5 years were 72.7% and 51.5% respectively, as 1351 were treated somehow (45.73%) (figure 4D). Just 2 patients died from PCa. Finally, overall survival at 2 and 5 years were 98.98% and 94.82% respectively (figure 4E).

Among the 1144 active treatments performed, radical prostatectomy was the most frequent used in 580 patients (50.69%), followed by radiotherapy (401, 35.05%), brachytherapy (100, 8.74%), hormonotherapy (32, 2.79%),
focal treatment (24, 2.09%) and cryotherapy (7, 0.61%) (Figure 5A); in figure 5B we show second active rescue treatments in 40 patients after progression from the first active treatment in row numbers and percentages.

Discussion;

In 2022, the better understanding of the highly varied natural behaviour(5) of low risk PCa and the morbidities associated with PCa treatments(6) has led to increasing embracement of AS protocols. So AS is now considered the preferred management strategy for low-grade (ie, GG 1) PCa. But that was not so clear when our Registry was planned in 2012-13, a time frame where AS data started to be considered in major Guidelines. It prompted urologist in our country to take AS into consideration as one of the first options, if not mandatory, in very low and low risk PCa patients. As mentioned, its main aim was to promote AS use and attending to its wide implementation today, it was successfully accomplished mirroring what has happened in many developed countries(7).

The previous was the reason to allow as much Centers as possible avoiding closed and strict FU protocols that just had hampered recruitment and consequently, AS promotion. This concept maybe still relevant today as AS embracement is poor in underdeveloped countries. Ten years after its start, oncological figures in Spain mirror major AS in the literature, with just 19 and 2 out of 3337 having had metastasis and died due to PCa(8).

In this paper we just want to show the most relevant and general figures describing the diagnosis and follow-up of patients, trying to find out where management of AS might be improved. Recognizing that a median FU of 53.13 months (Q1-3: 34.37-75.58), is not enough for PCa specific mortality (PCS), we had liked to observe a perfect overlapping between pathological progression and active treatment free survivals curves (figures 4A and 4D).

Attending to results of a recent metanalysis, highlighting the role of GG 3 or higher as the “real fail” in an AS programme (14), due to its relationship with a worse oncological behaviour, we find our active treatment rates somehow worrisome, as we had 10.01% GG 3 in FU Bx when we split combined Gleason 7 in our FU Bx in 3+4 vs 4+3 (data not shown). We and others think that progression in GG1 volume or an isolated non massive upgrading to GG2 has to be deeply discussed with the patient before moving to active treatment, considering other recognized factors of bad behaviour such as MRI visibility(9) and PSA-density (10).

Acknowledging debate of intermediate risk definition(11), our 13.06% of patients recruited as intermediate risk group mirrors what occurs in other collaborative groups. We are aware that pathological progression to GG2 should be further discussed with the patient, as many of them still not clinically significant. Maybe we should keep in mind that when managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year PCSM rates of 13.0% and 19.6 %(12)(13), so probably age at progression is a matter. Huge efforts are being
displayed nowadays in what we understand as a “second wave” AS era pursuing new biomarkers or algorithms that could split tigers from pussy cats.

The main strength or our Registry is the representation of real-world data in our country, assuming many limitations inherent to its nature and design. Not under the scope of this paper, we will embrace comparisons between low and intermediate risk groups and subgroup analysis in future work. Our shared results allow real data for urologists to inform new candidates for AS today. MRI use is similar to our series in many AS published reviews(14). Although use of MRI and TP Bx increased in our FU Bx, these tools still are not available in every Center in Spain, so our data confer reliable information to clinicians. Future research will evaluate the results of AS patients by incorporating the latest tools such as MRI, genomic testing, or new biomarkers. We think these tools may optimize AS protocols and maybe allow more patients to be enrolled in AS, but if its use does improve oncological figures of classic AS protocols without them, their role will remain to be proven.

Conclusions;
Midterm oncological results of AS in Spain do mirror those in major series worldwide. We denote underuse of Guideline recommendations such as use of MRI or TP Bx for initial PCa characterization. We probably face same problems of over treatment due to lack of reliable tools to differentiate those progressions that need treatment as from those that could safely stay in AS. We prompt collaborative work searching for algorithms, new imaging or new biomarkers that could shed some light in this increasing dilemma.

Acknowledgments;
The authors thank Mr. Manuel Espárrago, Spanish Association of Urology; Mr. Sergio Lara, Ms. Paula Jiménez Serrano and Ms. Silvia Lladosa, Clinscience; and Ms. Concepción Herrando and Mr. Raúl López Blasco, GIIS071-Grupo de Urología, Hospital Universitario Miguel Servet (URO-SERVET), for their technical assistance for this study.

Bibliography:


**Table 1: characteristics of the series at inclusion**

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<tr>
<td>III; 2 (0.1%)</td>
<td>III; 1 (0.06%)</td>
<td></td>
<td>III; 1 (0.41%)</td>
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<tr>
<td><strong>BMI</strong></td>
<td>Median 27.34</td>
<td>Q1-Q3; 25-29.93</td>
<td></td>
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</tr>
<tr>
<td>Min/Max: 15.8/72</td>
<td>Median 27.4</td>
<td>Q1-Q3; 25-29.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min/Max: 15.8/72</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>PSA (ng/ml)</strong></td>
<td>Median 6.05</td>
<td>Q1-Q3; 4.75-7.94 Min/Max: 0.5/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median 5.08</td>
<td>Q1-Q3; 4.63-7.26 Min/Max: 0.5/10</td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>cT</strong></td>
<td></td>
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<tr>
<td>cT1a; 77 (2.31%)</td>
<td>cT1a; 70 (2.43%)</td>
<td></td>
<td>cT1a; 7 (1.63%)</td>
<td>0.183</td>
</tr>
<tr>
<td>cT1b; 34 (1.02%)</td>
<td>cT1b; 31 (1.08%)</td>
<td></td>
<td>cT1b; 3 (0.7%)</td>
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<tr>
<td>cT1c; 2931 (87.83%)</td>
<td>cT1c; 2570 (89.24%)</td>
<td></td>
<td>cT1c; 361 (83.95%)</td>
<td></td>
</tr>
<tr>
<td>cT2a; 236 (7.07%)</td>
<td>cT2a; 209 (7.26%)</td>
<td></td>
<td>cT2a; 27 (6.28%)</td>
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<tr>
<td>cT2b; 17 (0.51%)</td>
<td>cT2b; 15 (0.45%)</td>
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<td>cT2b; 17 (3.95%)</td>
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<tr>
<td>cT2c; 15 (0.45%)</td>
<td>cT2c; 15 (0.45%)</td>
<td></td>
<td>cT2c; 15 (3.49%)</td>
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</tr>
<tr>
<td>N.A; 27 (0.81%)</td>
<td>N.A; 27 (0.81%)</td>
<td></td>
<td>N.A; 6 (1.38%)</td>
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<tr>
<td><strong>Prostate volume (cc)</strong></td>
<td>Median 45</td>
<td>Q1-Q3; 33-61</td>
<td></td>
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</tr>
<tr>
<td>Min/Max: 9/250</td>
<td>Median 44</td>
<td>Q1-Q3; 33-60</td>
<td></td>
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<tr>
<td></td>
<td>Min/Max: 9/250</td>
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<tr>
<td><strong>PSA density</strong></td>
<td>Median 0.13</td>
<td>Q1-Q3; 0.09-0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min/Max: 0.01/1.09</td>
<td>Median 0.13</td>
<td>Q1-Q3; 0.09-0.18</td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td></td>
<td>Min/Max: 0.01/1.09</td>
<td></td>
<td></td>
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<tr>
<td><strong>Positive cores (%)</strong></td>
<td>Median 8.33</td>
<td>Q1-Q3; 8-16.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median 8.33</td>
<td>Q1-Q3; 8.33-16.67</td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td><strong>GG 1</strong></td>
<td>Grade 6; 3231 (97.11%)</td>
<td>Grade 6; 2901 (100%)</td>
<td></td>
<td>&lt; 0.001*</td>
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<tr>
<td><strong>GG 2</strong></td>
<td>Grade 7; 96 (2.89%)</td>
<td>Grade 7; - N.A.</td>
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<tr>
<td><strong>PCa length / core (mm)</strong></td>
<td>Median; 1.6</td>
<td>Q1-Q3; 1-3</td>
<td></td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>Median; 1.7</td>
<td>Q1-Q3; 1-3</td>
<td></td>
<td></td>
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<tr>
<td><strong>Percentage PCa / core (%)</strong></td>
<td>Median; 10</td>
<td>Q1-Q3; 5-20</td>
<td></td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>Median; 10</td>
<td>Q1-Q3; 5-20</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Median; 1.2</td>
<td>Q1-Q3; 1-3</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Median; 9.19</td>
<td>Q1-Q3; 5-20</td>
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</tbody>
</table>

BMI: body mass index; cT: clinical stage; GG: Gleason Grade Group; N.A: not available, PCA: prostate cancer, PSA: prostatic specific antigen; Q: quartile
Figure 3; final stage of the whole series after excluding 187 patients (5.6%) loss of follow-up. Median follow-up of 53.13 months (Q1-Q3: 34.37-75.58)

Patient status at the time of analysis:
- 1577 (50.06%) Active Surveillance
- 1151 (36.54%) Active Treatment
- 254 (8.06%) Watchful Waiting
- 166 (5.27%) Death due to intercurrent disease
- 2 (0.06%) Death due to PC

Click here to access/download;Figure;Figure 3 final stage of the whole series_ABF (3).docx
Figure 4; Survival oncological outcomes. A) Pathological progression free survival, B) Local progression free survival, C) Metastatic progression free survival, D) Active treatment free survival and E) Overall survival
Figure 5; Active treatments

A; First active treatments performed after AS (row numbers and percentages), 1144 patients treated:

- Prostatectomy: 580 (50.7%)
- Brachytherapy: 100 (8.74%)
- Radiotherapy: 401 (35.05%)
- Focal treatment: 24 (2.1%)
- Hormone therapy: 32 (2.8%)

B; Second active treatment performed after progression to the 1st active treatment performed (row numbers and percentages), 40 patients.

- Androgen deprivation therapy: 14 (35%)
- Prostatectomy: 3 (7.5%)
- External Radiotherapy: 17 (42.5%)
- Other: 5 (12.5%)
Manuscript title: Midterm results of Spanish Register on Active Surveillance for Prostate Cancer

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Examples of Conflict of Interest: Source of Funding, Paid consultant to Sponsor, Study Investigator Funded by Sponsor, Employee of Sponsor, Board membership with Sponsor, Stock Holder for Mentioned Product, Patent Inventor for Mentioned Product, Any Financial Relationship to Competitors of Mentioned Product, and others (please specify).

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<th>No conflict involved</th>
<th>Conflict (specify)</th>
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<td>1) All authors have nothing to disclose.</td>
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Date: 28th January, 2023

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Authors name (printed) and signature (below name):

José Rubio-Briones Ángel Borque-Fermando Luis M. Esteban-Escaño

on behalf of the Collaborative Group for Active Surveillance in Prostate Cancer

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   □ In lieu of a formal ethics committee, the principles of the Helsinki Declaration (2013) were followed.
   □ All human subjects provided written informed consent with guarantees of confidentiality.

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