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The STAMPEDE2 trial: A site survey of current patterns of care, access to imaging and treatment of metastatic prostate cancer

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Abstract:	Aims The forthcoming STAMPEDE2 trial has three comparisons in metastatic hormone-sensitive prostate cancer (mHSPC). We aim to determine clinical practices amongst STAMPEDE trial investigators for access to imaging and therapeutic choices and explore their interest in participation in STAMPEDE2. Materials and methods The survey was developed and distributed online to 120 UK STAMPEDE trial sites. Recipients were invited to complete the survey between 16th – 30th May 2022. The survey consisted of thirty questions in five sections on access to stereotactic ablative body radiotherapy (SABR), 177Lutetium-PSMA-617 [177Lu-PSMA-617], choice of systemic therapies and use of Positron Emission Tomography/Computerised Tomography (PET/CT) and whole-body magnetic resonance imaging (WBMRI). Results From 58/120 (48%) sites, 64 respondents completed the survey. 55/64 (86%) respondents were interested to participate in SABR, 44/64 (69%) in 177Lu-PSMA-617, and 56/64 (87.5%) in niraparib with abiraterone comparisons. 45/64 (70%) respondents had access to bone, spine, and lymph node metastases SABR delivery, and 7/64 (11%) to 177Lu-PSMA-617. In addition to androgen deprivation therapy (ADT), 60/64 (94%) respondents used androgen receptor signalling inhibitors (ARSI), and 46/64 (72%) used docetaxel. 29/64 (45%) respondents would consider triplet therapy with ADT, ARSI and docetaxel. PET/CT was available to 62/64 (97%) respondents and requested by 45/64 (70%) respondents for disease uncertainty on conventional imaging, and 39/64 (61%) at disease relapse. WBMRI was available to 24/64 (38%) respondents and requested by

	13/64 (20%) respondents in highly selected patients. In low volume disease, 38/64 (59%) respondents requested scans at baseline and disease relapse. In high volume disease 29/64 (45%) respondents requested scans at baseline, best response (at PSA nadir), and disease relapse. 54/64 (84%) respondents requested CT and bone scan for best response assessment. Conclusion There is noteworthy disparity in clinical practice across current study sites, however, the majority have expressed an interest in participation in the forthcoming STAMPEDE2 trial.

Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Author contributions

HA, NJ are guarantors of integrity of the entire study. HA, NJ, GA, LB, CP, WC, NC devised study concept and methodical approach for analysis. LO uploaded the survey online and collated results for analysis. HA analysed the data. HA and NJ wrote first draft of the manuscript. All authors were involved in review of the manuscript.

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The STAMPEDE2 trial: A site survey of current patterns of care, access to imaging and treatment of metastatic prostate cancer

Abstract

Aims

The forthcoming STAMPEDE2 trial has three comparisons in metastatic hormone-sensitive prostate cancer (mHSPC). We aim to determine clinical practices amongst STAMPEDE trial investigators for access to imaging and therapeutic choices and explore their interest in participation in STAMPEDE2.

Materials and methods

The survey was developed and distributed online to 120 UK STAMPEDE trial sites. Recipients were invited to complete the survey between 16th – 30th May 2022. The survey consisted of thirty questions in five sections on access to stereotactic ablative body radiotherapy (SABR), 177Lutetium-PSMA-617 [^{177}Lu-PSMA-617], choice of systemic therapies and use of Positron Emission Tomography/Computerised Tomography (PET/CT) and whole-body magnetic resonance imaging (WBMRI).

Results

From 58/120 (48%) sites, 64 respondents completed the survey. 55/64 (86%) respondents were interested to participate in SABR, 44/64 (69%) in ^{177}Lu-PSMA-617, and 56/64 (87.5%) in niraparib with abiraterone comparisons. 45/64 (70%) respondents had access to bone, spine, and lymph node metastases SABR delivery, and 7/64 (11%) to ^{177}Lu-PSMA-617.
In addition to androgen deprivation therapy (ADT), 60/64 (94%) respondents used androgen receptor signalling inhibitors (ARSI), and 46/64 (72%) used docetaxel. 29/64 (45%) respondents would consider triplet therapy with ADT, ARSI and docetaxel.
PET/CT was available to 62/64 (97%) respondents and requested by 45/64 (70%) respondents for disease uncertainty on conventional imaging, and 39/64 (61%) at disease relapse. WBMRI was available to 24/64 (38%) respondents and requested by 13/64 (20%)

respondents in highly selected patients. In low volume disease, 38/64 (59%) respondents requested scans at baseline and disease relapse. In high volume disease 29/64 (45%) respondents requested scans at baseline, best response (at PSA nadir), and disease relapse. 54/64 (84%) respondents requested CT and bone scan for best response assessment.

Conclusion

There is noteworthy disparity in clinical practice across current study sites, however, the majority have expressed an interest in participation in the forthcoming STAMPEDE2 trial.

Highlights

- STAMPEDE trial investigators have great interest in participation in STAMPEDE2.
- Metastatic prostate cancer management varies significantly across UK trial sites.
- PET/CT imaging is commonly used in various clinical settings.
- Triplet systemic therapy will be considered by clinicians with available funding.

Introduction

Prostate cancer causes around 12,000 deaths per year in the UK [1]. The STAMPEDE platform trial (ISRCTN78818544) is an innovative multi-arm multi-stage (MAMS) platform trial that has tested ten different treatments in advanced prostate cancer, hypothesising improved outcomes with upstream treatment intensification. To date, three treatments added to androgen deprivation therapy (ADT) have improved outcomes: docetaxel, abiraterone acetate and prostate radiotherapy in low burden metastatic disease [2–6], and have become standard of care in international guidelines [7,8]. STAMPEDE2 is a new platform trial continuing on from STAMPEDE and testing three new treatments with the ability to add further treatments in the future.

Radiation-based targeted therapies for metastatic prostate cancer have been of increasing interest. Metastasis directed therapy (MDT) with stereotactic ablative body radiotherapy (SABR) in metachronous oligometastatic disease has been shown to delay recurrence in prospective trials [9–13]. No randomised data exist in synchronous metastatic disease. Comparably, in heavily pre-treated castrate-resistant prostate cancer (CRPC), two randomised trials showed 177Lutetium-PSMA-617 [^{177}Lu-PSMA-617] improved progression-free survival [14,15] with results from the VISION trial [14] leading to the U.S. Food and Drug Administration (FDA) approval of ^{177}Lu-PSMA-617 and subsequently its wider availability[16].

In addition to radiation-based therapies, molecular targeted therapies with poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors (PARPi) in combination with androgen-receptor signalling inhibitors (ARSI) have been investigated in first line CRPC. Phase III randomised trials recently reported on preferential improved survival in men with homologous recombination repair (HRR) deficiency and breast cancer gene (BRCA) mutation subgroups [17–19].

The STAMPEDE2 trial aims to investigate these treatments in three new comparisons in men with metastatic hormone-sensitive prostate cancer (mHSPC). Here, we report on results from the STAMPEDE2 trial site survey conducted to explore the interest and technical

capacities of STAMPEDE investigators to participate in the STAMPEDE2 trial and determine the patterns of current clinical practice for imaging and therapeutic choices.

Materials and Methods

The site survey was designed by the STAMPEDE2 trial team in April 2022. The aims of the survey were to inform the design of the forthcoming STAMPEDE2 trial design and determine consensus on current practices in the UK reflected by the multiplicity of the STAMPEDE trial participating sites. The survey included a summary and rationale of the STAMPEDE2 trial design with three new comparisons in men with mHSPC investigating SABR (comparison S), ^{177}Lu-PSMA-617 (comparison P), and niraparib (PARPi) with abiraterone acetate plus prednisolone [abiraterone] (comparison N). The survey constituted of thirty questions in five sections: general questions, questions on access to novel imaging facilities, questions on use of systemic therapies at the treating site, questions on access to SABR delivery, and questions on access to ^{177}Lu-PSMA-617 (Appendix A, STAMPEDE2 site survey). Multiple responses were permitted for selected questions. The survey was conducted using the online platform survey monkey (http://www.surveymonkey.co.uk) and was distributed via an email link from the Medical Research Council Clinical Trials Unit (MRC CTU) to the 120 UK-based sites participating in the STAMPEDE trial (ISRCTN78818544). Principal investigators and/or first recipients of the survey were invited to complete the survey. The survey was active online between 16th to 30th May 2022. Descriptive analysis was utilised using Stata statistical software version 17.0 (Stata Corporation, College Station, TX, USA).

Results

During the two-week period of the survey being active, 64 respondents completed the survey from 58 of the 120 (48%) STAMPEDE trial participating sites. 55/64 (86%) respondents were interested to participate in comparison S, 44/64 (69%) respondents were interested in comparison P, and 56/64 (87.5%) respondents were interested in comparison N. 62/64 (97%) respondents had access to Positron Emission Tomography/Computerised Tomography (PET/CT) scans. Of those, 35/62 (56%) had access to PET/CT scans at their treating centre, 23/62 (36%) had access at a neighbouring treating centre, and 4/62 (6%) had access at a distance centre with a long referral pathway. 11/64 (17%) respondents did not have direct access to PET/CT scans. Of those, 2/64 (3%) foresaw direct access at their treating centre in less than 12 months, 2/64 (3%) foresaw direct access in 1 to 3 years, 1/64 (1.5%) foresaw direct access in more than 3 years, and 6/64 (9%) were unsure or had no planned direct access to PET/CT scans. The types of PET/CT scans to which respondents had access to is summarised in **Table 1**.

24/64 (37.5%) respondents had access to Whole-body magnetic resonance imaging (WBMRI), and 38/64 (59%) did not have access to WBMRI. The timepoints for when clinicians requested novel imaging with PET/CT or WBMRI scans are summarised in **Figure 1.**

Questions on the frequency of imaging in mHSPC were divided based on disease volume (low volume versus high volume). For these questions, multiple responses were permitted. **Figure 2** summarises the frequency of imaging in low and high volume mHSPC.

For best response assessment scans, 55/64 (86%) respondents selected CT and bone scans as the preferred imaging modality used, 3/64 (5%) respondents selected WBMRI and 2/64 (3%) respondents selected PET/CT.

The choice of systemic doublet therapy in addition to ADT is summarised in **Figure 3A.** The choice of ARSI for systemic doublet therapy, providing all were approved and available on the National Health Service (NHS) is summarised in **Figure 3B.**

47/64 (73%) respondents were likely to commence ARSI therapy together with ADT, and 14/64 (22%) respondents were likely to commence ARSI at any another time after commencing ADT. Of those, 7/14 (50%) start ARSI within 3 months of ADT, 3/14 (21%) started within 6-8 weeks, and 4/14 (29%) started within 1 month of ADT.

29/64 (45%) respondents were likely to use docetaxel chemotherapy as part of triplet therapy, if funding was available, 10/64 (16%) were not likely to use triplet therapy, and 22/64 (34%) were unsure.

45/64 (70%) respondents had access to SABR to treat spinal, non-spinal bone and nodal metastases at their treating centre, and 22/64 (34%) had access through a neighbouring centre. For those who did not have direct access, 8/64 (12.5%) foresaw direct access at their treating centre in less than 1 year, and 5/64 (8%) in 1 to 3 years. **Figure 4** summarises the frequency of each imaging modality used for SABR planning for bone (non-spinal, figure **4A**), spine (figure **4B**) and lymph node metastases (figure **4C**).

For the delivery of prostate radiotherapy and SABR in comparison S, the majority of respondents were participating sites in other NIHR portfolio prostate trials, this included 39/64 (61%) respondents who participated in the PACE umbrella trial (ISRCTN17627211), 37/64 (58%) in the PIVOTALboost trial (ISRCTN80146950), and 17/64 (26.5%) in the CORE trial (ISRCTN45961438). In oligometastatic disease, 48/64 (75%) respondents would treat lymph nodes if were found to be involved on conventional imaging, and 47/64 (73%) if involved on PET/CT.

7/64 (11%) respondents had direct access to ^{177}Lu-PSMA-617. 18/64 (28%) respondents had access through a neighbouring centre. For respondents with no direct access to ^{177}Lu-PSMA-617, 16/64 (25%) foresaw access in less than 1 year, 18/64 (28%) foresaw access in 1 to 3 years, 1/64 (2%) foresaw access in more than 3 years, 8/64 (12.5%) had no access planned, and 21/64 (33%) were unsure.

Discussion

The STAMPEDE platform trial is a MAMS trial that has recruited 11,992 patients across 120 sites in the UK and Switzerland since its ethical approval in 2005. Responses to our survey were from UK-based participating sites only and have shown great interest for participation in the three new comparisons of the forthcoming STAMPEDE2 trial. Results from the survey have informed the final design of the STAMPEDE2 trial by concluding current practices in the UK related to access to novel imaging and choice of treatment in advanced prostate cancer.

We acknowledge that our survey received only a 48% response rate which is moderate but not high and thus our findings cannot be regarded as fully representative of all STAMPEDE sites. The survey was conducted at a time of particular pressures within the NHS due to Covid-19 when there were limited staff for completion of the survey. One year on from this, the STAMPEDE2 trial is in set-up and enthusiasm from sites to take part in STAMPEDE2 is evident with a more responsive recent request eliciting strong interest to take part.

Our results demonstrated the wide accessibility for PET/CT imaging. The majority of respondents requested PET/CT imaging at the time of disease relapse (61%) or disease uncertainty on conventional imaging (70%) given the greater accuracy of PET/CT for the detection of metastases when compared with suboptimal conventional imaging [20–22]. This practice reflects the established role of PET/CT imaging, in particular PSMA PET/CT in biochemically recurrent disease [23,24] and the initial staging of prostate cancer [22]. Results from these prospective trials have subsequently led to the endorsement of PSMA PET/CT imaging in updated international guidelines [7,8].

The improved sensitivity and specificity of PSMA PET/CT imaging for staging prostate cancer may redefine disease extent with potential stage migration and subsequent change in the patient's treatment plan. Significant implications may arise from treatment alteration, leading to the omission of evidence-based treatment or overtreatment of what would otherwise be considered "microscopic" disease. Evidence on clinical outcomes following PSMA PET/CT directed treatment in mHSPC remains limited, in addition, current evidence from clinical trials for the management of prostate cancer is based on conventional imaging.

In non-metastatic prostate cancer, the survival benefit from combination treatment with ADT and radical doses of prostate radiotherapy is known [25,26]. Staging men in this group with PSMA PET/CT scans may detect occult metastatic disease resulting in the delivery of palliative doses of prostate radiotherapy or it's omission. Similarly, the detection of low volume metastatic disease may persuade the treating clinician to deliver SABR to metastatic sites with no real added benefit to men who will inevitably have excellent outcomes.

In low burden metastatic disease detected on conventional imaging, the STAMPEDE M1:RT comparison demonstrated improved failure-free and overall survival with prostate radiotherapy[2,3]. Exploratory analysis showed that there was a continuum of benefit from prostate radiotherapy beyond 3 bone metastases seen on bone scans [27]. Additionally, bone scans were predictive of response to prostate radiotherapy [28]. Oligometastatic disease has been defined as an intermediary metastatic state [29]. Its current definition is largely driven by the imaging modality used to describe the presence of limited number of macroscopically visualised lesions [30–33]. In metachronous oligometastatic disease, SABR combined with standard of care improved progression free survival [9–13]. A post-hoc analysis from the ORIOLE trial reported improved outcomes when all lesions visualised on PSMA PET/CT were treated with SABR [9].

WBMRI is a novel imaging modality with improved sensitivity than conventional imaging for bone metastases detection [34,35]. Standardised reporting guidelines have been published [36]. WBMRI can assess the cellularity of bone lesions and measure changes in apparent diffusion coefficient (ADC) values, which has been correlated with treatment response [37–39]. The STAMPEDE2 trial comparison S eligibility will be determined by conventional imaging as per current clinical evidence. Considering the current status quo with access to novel imaging, an imaging sub-study will be integrated in STAMPEDE2 comparison S, and treatment decisions using novel imaging will be stratified (Appendix B, comparison S imaging sub-study flowchart). The sub-study aims to explore patterns of treatment decisions and clinical outcomes for each imaging modality in the context of a large prospective clinical trial.

The survey concluded that almost half clinicians (43%) used docetaxel as doublet therapy, despite approval of National Institute for Clinical Excellence (NICE) for enzalutamide and apalutamide in mHSPC following the COVID-19 pandemic [40,41]. Results from the STAMPEDE, CHAARTED and LATITUDE trials have shown that the addition of abiraterone or docetaxel to long-term ADT improves survival [4–6,42,43], however, no trials have directly compared the two treatments to determine superiority of one over the other. A post-hoc analysis from the STAMPEDE trial compared outcomes from the abiraterone and docetaxel contemporaneous comparisons where recruitment overlapped. The results of which favoured abiraterone for improved failure-free survival and progression-free survival, with no significant difference with regards to other outcomes [44]. Subsequent exploratory analysis from the STAMPEDE trial reported on quality-of life differences between the two treatments. Results after 2 years of treatment showed an improved global quality of life score with abiraterone [45]. In STAMPEDE2, based on our own patient reported outcome data [46], we have adopted ARSI as the doublet treatment of choice. The choice of ARSI doublet treatment aligns with the investigational treatment in the trial, additionally, by offering biomarker testing prior to commencing ARSI, there is opportunity for a second randomisation in comparison N for patients with a positive biomarker status (Appendix C, STAMPEDE2 trial schema).

Triplet therapy was likely to be used by 45% of respondents. At the time of the survey, the PEACE-1 and ARASENS trials had reported on the improved overall and progression-free survival with triplet therapy [47,48]. Subgroup analysis from the ARASENS trial confirmed the survival benefit was consistent among all comers regardless of the disease volume and risk, with no increased toxicity from the addition of ARSI [49]. Since the survey, darolutamide has recently become available on the NHS for men with mHSPC through the “fast-track access for life-extending drugs” scheme [50]. In the STAMPEDE2 trial design, provision has been made for triplet therapy use across all comparisons. The decision to treat with triplet therapy will be stratified and will be at the treating clinician’s discretion.

Best response assessment scans may be useful when the clinical trial primary endpoint is radiographic progression as per the RECISTv1.1 criteria [51]. In the STAMPEDE2 trial, we strongly recommend undertaking best response assessment scans at 24 weeks from

randomisation to correspond with the PSA nadir. The preferred choice of scans would be CT and bone scan to facilitate a validated like-for-like comparison with baseline and progression scans.

Radiotherapy quality assurance for the STAMPEDE2 trial comparison S will be led by the national Radiotherapy Clinical Trials Quality Assurance (RTTQA) group and will be streamlined through the SABR expansion programme (SEP) and other National Institute for Health and Care Research (NIHR) portfolio prostate cancer trials (PACE: ISRCTN17627211, PIVOTALboost: ISRCTN80146950, and PEARLS: ISRCTN36344989 trials). The survey results have demonstrated most centres had access to SABR. We, therefore, anticipate a smooth set-up and start to recruitment in comparison S.

Following the FDA approval for ^{177}Lu-PSMA-617 in castrate-resistant prostate cancer (CRPC) [16], ^{177}Lu-PSMA-617 became available in the UK through the Early Access to Medicines Scheme (EAMS) [52], potentially expanding access across the UK. At the time of writing, the therapy is no longer available pending a NICE review. Treating centres with an infrastructure to support radioactive ligand therapy (RLT) delivery will be prioritised to open for recruitment in the STAMPEDE2 trial comparison P. Additionally, this comparison is part sponsored by Advanced Accelerator Applications USA, Inc (AAA, a Novartis company; Millburn, NJ, USA) who will supply ^{177}Lu-PSMA-617 and support additional trial costs.

Conclusion

The STAMPEDE2 trial will open three new investigative treatment comparisons for men diagnosed with mHSPC. There is significant variation in clinical practice across current study sites regarding access and application of novel imaging and choice of therapy combinations at treatment initiation. Despite this, the majority of existing trial centres have expressed great interest in participation in the STAMPEDE2 trial.

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Tables

Table 1. Type of available PET/CT imaging. PSMA= prostate specific membrane antigen. Ga= Gallium. F= Fluorinated.

Figures

Figure 1. Timepoints for when clinicians request PET/CT and WBMRI.

Figure 2. Frequency of imaging in low volume and high volume metastatic disease.

Figure 3. Systemic treatment. A) Choice of doublet therapy with ADT. B) Choice of ARSI.

Figure 4. Frequency of each imaging modality requested for SABR planning to A) Bone (non-spinal), B) Spine and C) Lymph node metastases.

Table 1. Type of available PET/CT imaging. PSMA= prostate specific membrane antigen. Ga= Gallium. F= Fluorinated.

Access to PET/CT imaging	n/N	% [95% CI]
PET/CT	62/64	97 [89 - 99]
^{18}F - Choline PET/CT	36/62	58 [45 - 70]
^{18}F - PSMA PET/CT	25/62	40 [28 - 54]
^{68}Ga - PSMA PET/CT	23/62	37 [25 - 50]

Figure 1. Timepoints for when clinicians request PET/CT and WBMRI.

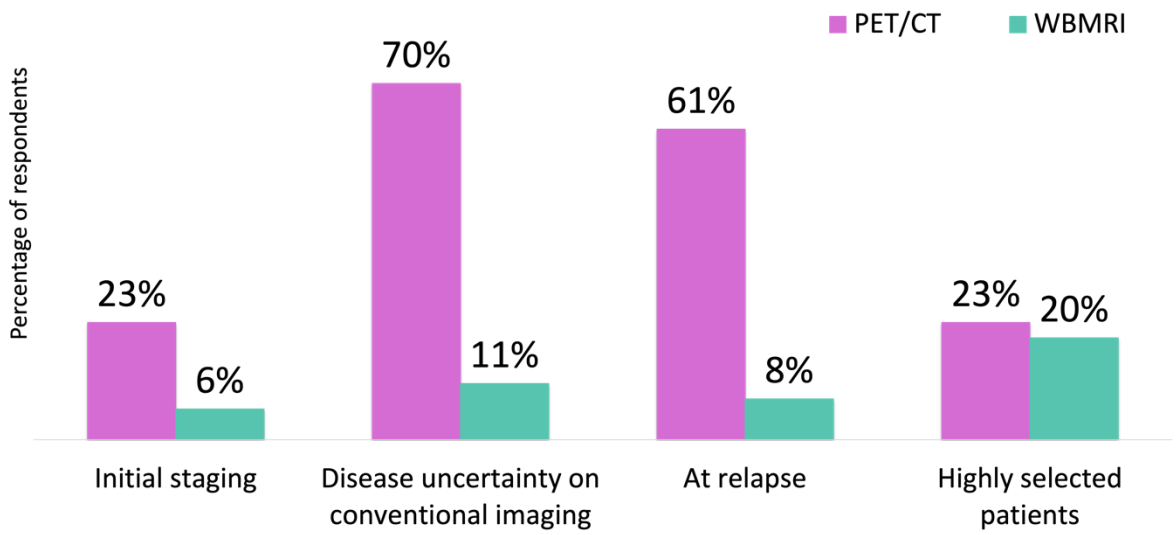


Figure 2. Frequency of imaging in low and high volume metastatic disease.

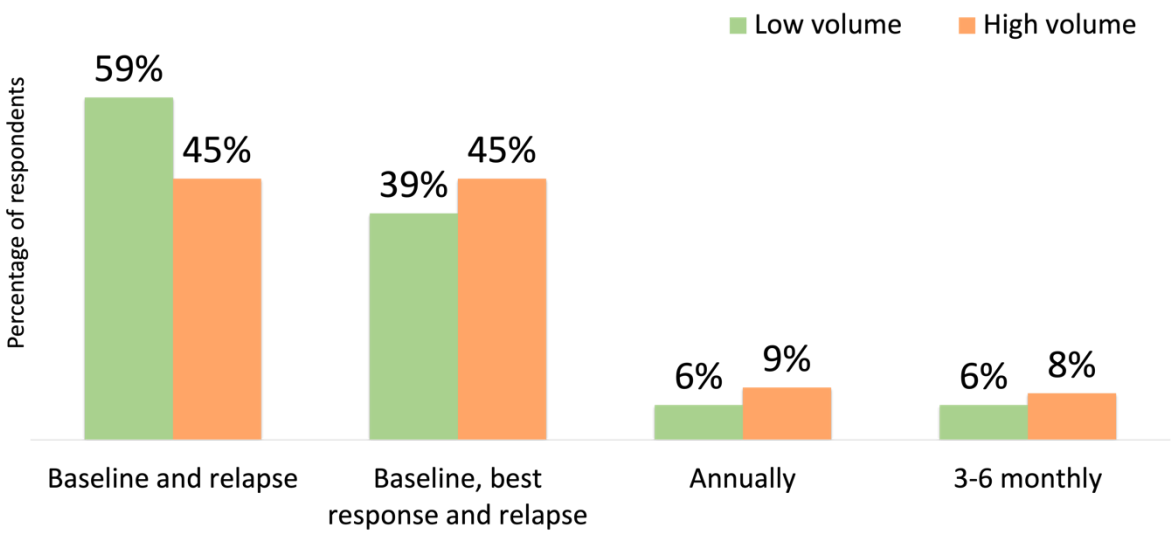


Figure 3. Systemic treatment. A) Choice of doublet therapy with ADT. B) Choice of ARSI with ADT.

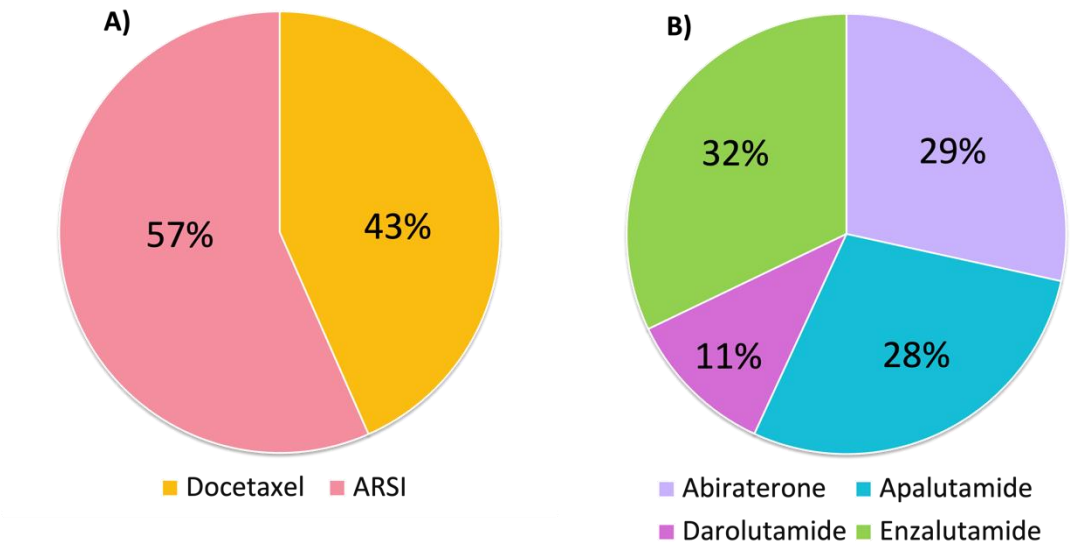


Figure 4. Frequency of each imaging modality requested for SABR planning to A) Bone (non-spinal), B) Spine and C) Lymph node metastases.

Appendices

Appendix A- STAMPEDE2 site survey

STAMPEDE2 SITE SURVEY

We would be very grateful if you could take some time to complete this survey for the development of STAMPEDE-2 trial platform. It consists of 6 parts and will take approximately 10 minutes.

PART 1 – General questions

1. Please provide which site you are based at e.g., Somewhere General Hospital

2. Please provide your job title

3. Please provide your name (optional)

4. Would you participate in a comparison that randomises oligometastatic patients to SABR vs no SABR in addition to SOC?
    - Yes
    - No
    - Unsure
    - If No or Unsure, please explain in the comments box

5. Would you participate in a comparison that randomises polymetastatic patients to PSMA Lutetium-617 vs no PSA Lutetium-617 in addition to SOC.?
    - Yes
    - No
    - Unsure
    - If No or Unsure, please explain in the comments box

6. Would you participate in a comparison that randomises DDR positive patients to Abiraterone and Niraparib vs SOC?
    - Yes
    - No
    - Unsure
    - If No or Unsure, please explain in the comments box

Part 2- Questions relating to imaging facilities at your site

7. Do you have access to PET/CT imaging?
    - Yes, PET/CT is available at my centre
    - Yes, PET/CT is available at a neighbouring centre
    - Yes, PET/CT is available at a distant centre with a long referral pathway
    - No

8. What type of PET/CT imaging do you use currently (use numbers or vague estimates for proportion if more than one)?
    - Choline PET/CT
    - 68-Gallium-11 PSMA PET/CT
    - 18-Fluoride PSMA PET/CT
    - Other, please specify

9. If you currently have access to PET/CT, when are you likely to request this for your patient?
    - At the Initial staging
    - If there is disease uncertainty on conventional imaging
    - At time of relapse
    - In highly selected patients, please specify

10. If you don't have access to PET/CT imaging, do you foresee this happening in
    - less than 1 year
    - 1-3 years
    - >3 years
    - No access planned
    - Unsure (please explain in comments)

11. For non- spinal bone lesions in SABR planning, which imaging modality do you use and at what frequency (you may select multiple responses)?
    - MRI
        - Always
        - Sometimes
        - Rarely
        - Never
    - PET/CT
        - Always
        - Sometimes
        - Rarely

        - Never
    - CT and bone scan
        - Always
        - Sometimes
        - Rarely
        - Never
    - Other modalities, please specify

12. For spinal bone lesions in SABR planning, which imaging modality do you use and at what frequency (you may select multiple responses)?
    - MRI
        - Always
        - Sometimes
        - Rarely
        - Never
    - PET/CT
        - Always
        - Sometimes
        - Rarely
        - Never
    - CT and bone scan
        - Always
        - Sometimes
        - Rarely
        - Never
    - Other modalities, please specify in comments box

13. For lymph node lesions in SABR planning, which imaging modality do you use and at what frequency (you may select multiple responses)?
    - MRI
        - Always
        - Sometimes
        - Rarely
        - Never
    - PET/CT
        - Always
        - Sometimes
        - Rarely
        - Never
    - CT and bone scan
        - Always

    - Sometimes
    - Rarely
    - Never
- Other modalities, please specify in comments box

14. Do you have access to Whole body MRI imaging?
    - Y/N
15. If you currently have access to Whole body MRI imaging, when are you likely to request this for your patient?
    - At the Initial staging
    - If there is disease uncertainty on conventional imaging
    - At time of relapse
    - In highly selected patients, please specify
16. How often do you currently scan as standard of care in men with low volume mHSPC? (You may select multiple responses)
    - At baseline (pre-ADT) and PSA/clinical progression only
    - At baseline, best response (corresponding to PSA nadir), and PSA/clinical progression
    - On a yearly basis
    - At regular time intervals, please specify
    - Other, please specify
17. How often do you currently scan as standard of care in men with high volume mHSPC? (You may select multiple responses)
    - At baseline (pre-ADT) and PSA/clinical relapse only
    - At baseline, best response (corresponding to PSA nadir), and PSA/clinical progression
    - On a yearly basis
    - At regular time intervals, please specify
    - Other, please specify
18. What imaging modality do you use to assess best response to treatment?
    - MRI

- PET/CT
- CT and Bone scan
- Other, please specify in comments box

Part 3- Questions relating to your use of systemic therapies

19. In addition to ADT, which systemic treatment are you currently using for metastatic HSPC? You can tick both.
    - ARSi
    - Docetaxel

20. If funded, are you likely to use docetaxel in addition to ADT and ARSi, as part of triple therapy?
    - Y/N
    - Unsure
    - Please specify in the comments box reasoning for your response

21. The trial will require ADT + one ARSi. If all were approved, what would be your ARSi of choice? (Please use vague estimates for proportion if more than one)
    - Abiraterone
    - Apalutamide
    - Enzalutamide
    - Darolutamide

22. When are you likely to start ARSi therapy in metastatic patients?
    - At the time of commencing ADT
    - At the time of radiotherapy/PSMA Lu
    - Any other time, please specify

Part 4- Questions relating to the SABR comparison

23. Do you have access to SABR at your centre to treat bone, lymph nodes and spinal metastases?
    - Y/N (if Y, please specify which of the above sites of disease)

24. If no to question 23 (SABR access), do you foresee this happening in
    - less than 1 year
    - 1-3 years
    - >3 years
    - Not planned
    - Unsure (please explain in comments box)

25. If no to question 23, is there a neighbouring centre that you currently refer to for SABR delivery?
    - Y/N (if Y, please specify referral site)

26. If you don't have RTTQA approval for SABR, are you prepared to get benchmark approval to deliver SABR to bone, lymph nodes and spinal metastases?
    - Y/N

27. Was/Is your site participating in the following trials (you may select multiple responses)?
    - CORE trial
    - PACE trial
    - PIVOTAL Boost trial
    - None

28. In oligometastatic disease, do you plan to treat pelvic lymph nodes with radiotherapy?

    i. If LN involved on conventional imaging:
    - Y/N

    ii. If LN not involved on conventional imaging:
    - Y/N

    iii. If LN involved on PSMA PET/CT
    - Y/N

    iv. If LN not involved on PSMA PET/CT
    - Y/N

29. We recommend a moderately hypofractionated RT schedule for pelvic LN RT (60Gy in 20#, 47Gy in 20# to LN), do you plan to use this dose fractionation?

    - Y/N
    - If N, please specify why and describe your preferred fractionation schedule

Part 5- Questions relating to the 177Lu-PSMA-617 comparison

30. Do you currently have access to 177Lu-PSMA-617 treatment at your centre?
    a. Y/N

31. If you currently don't have access to 177Lu-PSMA-617 at your centre, is there a neighbouring centre that you could refer to?
    - Y/N
    - if Y please specify referral site
    - NA

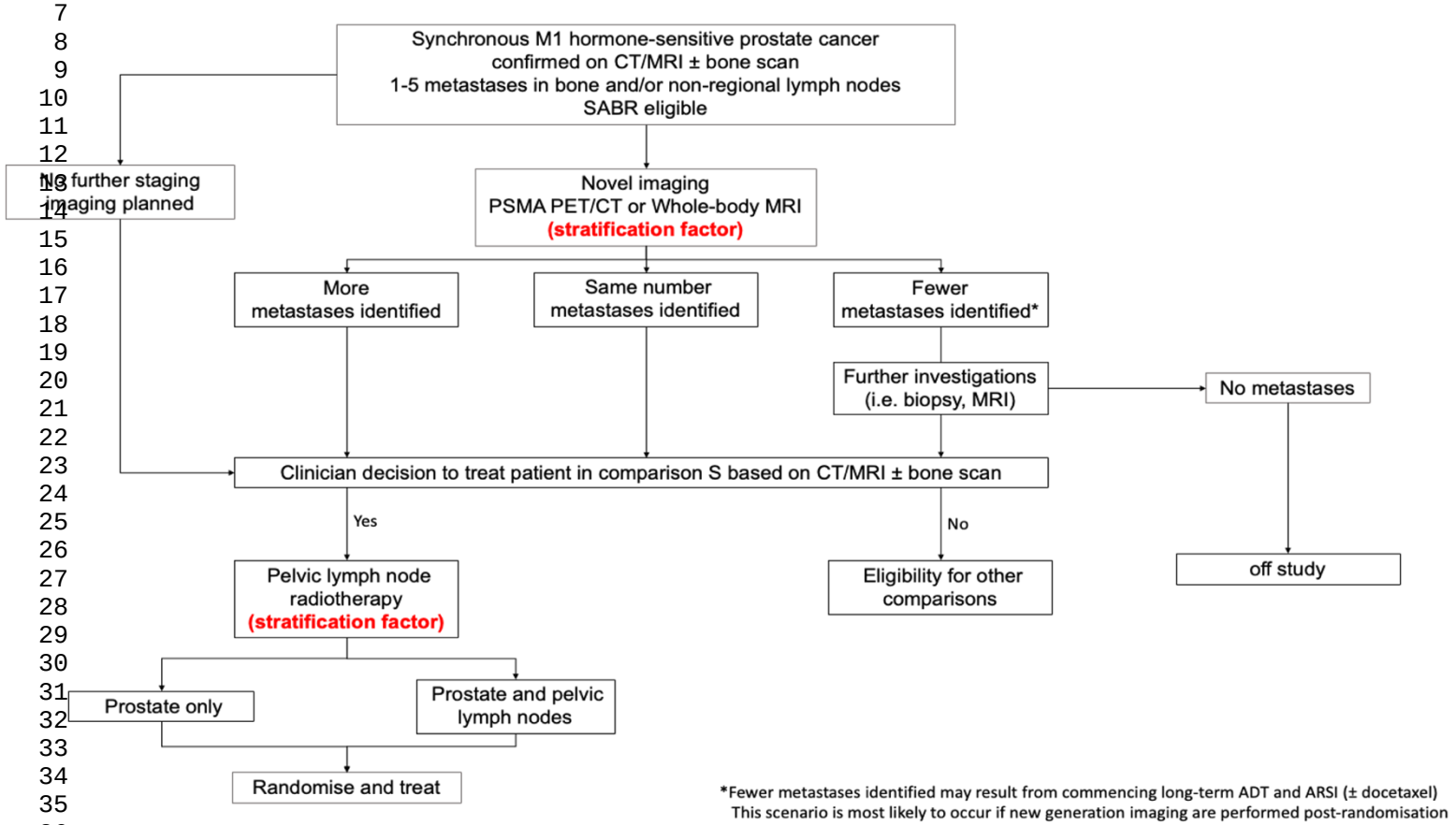
32. If you currently don't have access to 177Lu-PSMA-617 at your centre, do you foresee this happening in
    - less than 1 year
    - 1-3 years
    - >3 years
    - No access planned
    - Unsure (please explain in comments)

33. **Please feel free to provide any other comments in the box below:**

Thank you for taking the time to complete this survey.

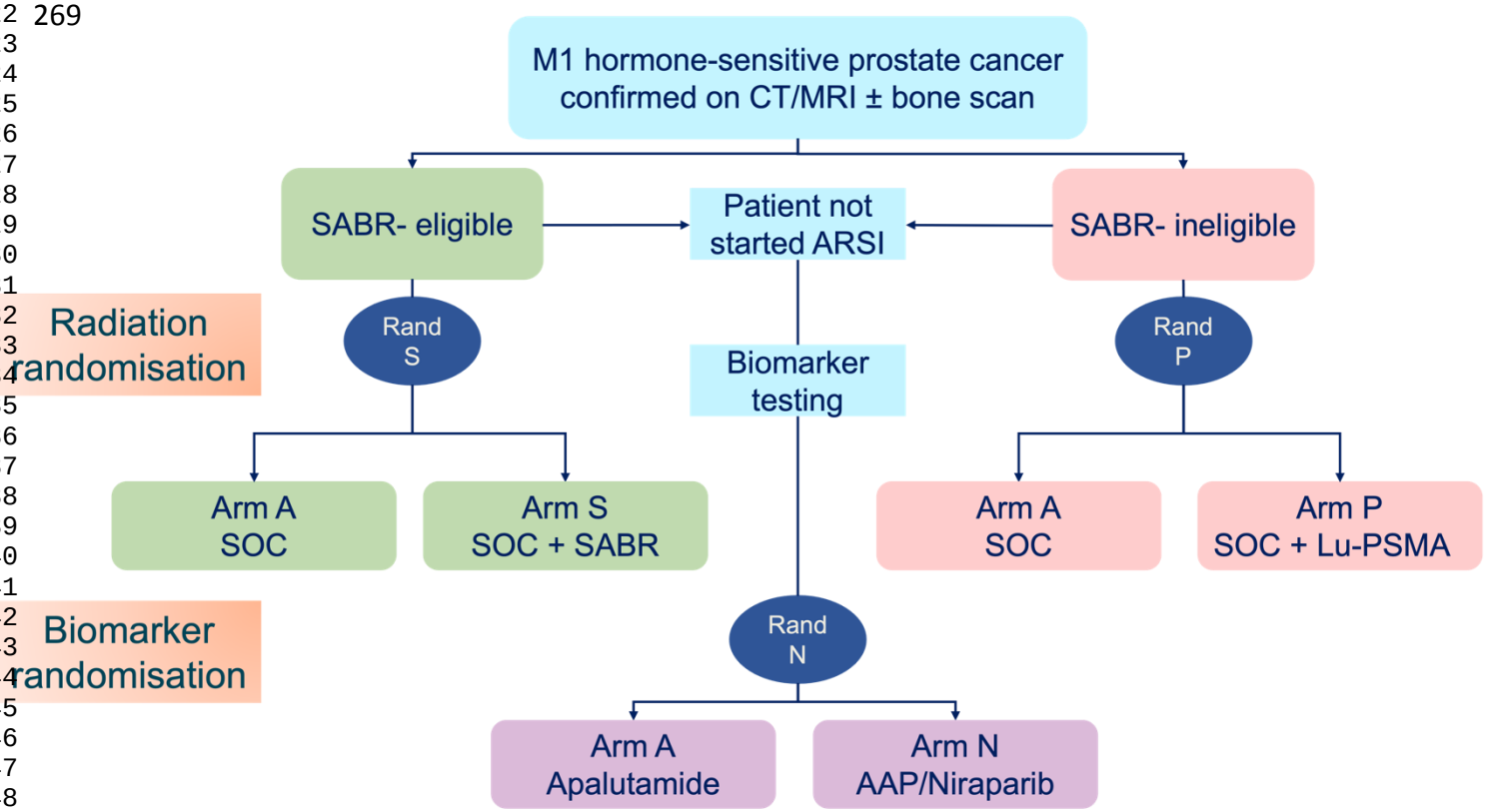
Appendix B- Comparison S imaging sub-study flowchart

Comparison S imaging flowchart. Integration of novel imaging sub-study with PSMA PET/CT and WBMRI. Treatment decisions will be stratified based on the imaging modality used. This applies to treatment decision for radiotherapy treatment to pelvic lymph nodes.



Appendix C- STAMPEDE2 trial schema

STAMPEDE2 trial schema. Two-by-two co-enrolment design. Confirmation of eligibility based on conventional imaging (CT/MRI and bone scan). Upfront radiation-based randomisation dependent on SABR eligibility as specified in the protocol. Randomisation in comparison S if SABR eligible and comparison P if SABR ineligible. Upfront biomarker status testing for men who have not commenced on ARSI. For biomarker status positive patients, they will be offered a second biomarker randomisation in comparison N to abiraterone plus niraparib.



Thursday, 18 May 2023

Dear Editorial Team

We present results of the STAMPEDE2 trial site survey to determine patterns of care amongst current STAMPEDE trial investigators. In this manuscript we explore the interest and technical capacities of STAMPEDE investigators to participate in the three new comparisons of STAMPEDE2 testing SABR, 177Lutetium-PSMA-617 and Niraparib. We aim to determine current access to SABR and 177Lutetium-PSMA-617, novel imaging with PSMA PET/CT and Whole-body MRI, and determine current practices for therapeutic choices in the management of metastatic hormone-sensitive prostate cancer.

Our survey results reflect the rapidly evolving practices in this space and informed the final STAMPEDE2 trial design.

We hope that this submission will be of interest to the Clinical Oncology audience and look forward to hearing from you.

On behalf of all authors

Yours sincerely,

Dr Hoda Abdel-Aty

Clinical Research Fellow, The Institute of Cancer Research and Royal Marsden Hospital.

STAMPEDE Fellow, The MRC Clinical Trials Unit, University College London.