A Summary of Recommendations from PAREXEL® Medical Imaging

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Historically, the design of clinical trials to assess drug effects in prostate cancer has been challenging compared to other solid tumors. Metastases are primarily localized in bones and changes in disease status are therefore often difficult to assess. The majority of metastases involve the spine, with the lumbar spine affected much more often than the cervical spine, presumably because of the route of dissemination. Other metastatic sites include lymph nodes and visceral organs. As a result, the evaluation of prostate cancer with imaging requires the evaluation of bone lesions as well as soft tissue disease. The currently validated and accepted imaging modalities for these disease compartments are radionuclide-based bone scans and CT/MRI scans.

The 2008 publication by Scher, et al. on the “Design and End Points of Clinical Trials for Patients with Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group” has become the current standard for the assessment of advanced and metastatic prostate cancer in clinical trials. Published before the RECIST 1.1\textsuperscript{2} Guidelines, the PCWG2 Guidelines reference the original RECIST 1.0 publication from 1999, however most prostate cancer clinical trials utilize the clarifications of the updated 2009 RECIST 1.1 guidelines.

The following discussion is limited to the imaging-related compartments of bone lesions and soft tissue disease as certain aspects of the corresponding criteria require further clarification.


It is important to note that while the PCWG2 guidelines were intended to be utilized in phase II clinical trials to evaluate agents that have promise for regulatory approval in Phase III, further guidelines specifically for the evaluation of Phase III trials have not yet been provided. Most Phase III clinical trials today rely on the PCWG2 guidelines in order to standardize the criteria for evaluation across multiple clinical sites. There is anticipation, that the data collected on these Phase II and Phase III trials since the publication of the PCWG2 criteria, will provide supportive evidence for a more standardized set of guidelines in the future. The four components of the PCWG2 guidelines are prostate-specific antigen (PSA) test, bone lesions, soft tissues disease and symptoms. From an imaging perspective, only the soft tissue disease and bone lesion components are evaluated.
EVALUATION OF RESPONSE AND PROGRESSION

RECIST is widely used to evaluate response and progression in solid tumor clinical trials. In prostate cancer evaluation, RECIST may be used to derive overall responses based on improvements (Complete Response [CR] and Partial Response [PR]) in addition to the evaluation of disease stability (SD) and disease progression (PD). However, in the evaluation of bone scans by PCWG2 there is not a parallel response outcome for CR or PR. Instead, the evaluation of disease on bone scans seeks to rule out progression. PAREXEL recommends approaching bone scan assessment as No Progression (stability/no change), Unconfirmed progression (PDU) and Confirmed Progression (PDC).

CONFIRMATION CRITERIA AND "FLARE"

As a general rule, a baseline CT and bone scan are recommended at or close to the initiation of therapy. The first post treatment bone scan should not be done before 12 weeks after starting therapy, unless clinically indicated.

Bone Lesions

There is a risk associated with early scanning (<12 week mark) in that the patient may demonstrate pseudo progression on bone scan evident by the appearance of new lesions, or an increase in intensity of existing lesions. Technetium bone scans are reliant on the radiopharmaceutical uptake

WHAT IS FLARE?

Flare may be observed when changes occur on a bone scan soon after starting systemic therapy, illustrated by an increase in size or uptake intensity in known lesions and/or the appearance of new, previously occult lesions. The changes are presumed to be due to active osteoblastic bone depositions that is in essence a healing response as opposed to tumor metastases progression. Flare is generally thought to occur within 12 weeks (i.e. 3 months) of systemic therapy initiation. Progression may be called too early if lesions seen on bone scan are related to flare rather than to actual progression. Consequently, there is a concern that the treating oncologist is at risk of discontinuing the drug prematurely and will switch therapy before it had a chance to take effect. For this reason, an additional scan should be performed no less than 6 weeks from the date of the first follow up scan (i.e. Week 12 and Week 18 bone scans).
in osteoblasts, so the technique is sensitive to osteoblastic activity rather than tumor metabolism. Osteoblastic activity may be induced or supported by systemic treatment and some bone lesions already present at baseline but either indeterminate or undetected, may become visible, larger in size, or more striking, in these initial weeks in response to treatment. This transient increase in bone scan uptake early in the course of successful therapy is commonly referred to as the “flare phenomenon” in the context of prostate cancer treatment.

**ONE OF THE PRIMARY CHALLENGES IN THE EVALUATION OF PROSTATE CANCER IS, THEREFORE, THE APPROPRIATE INTERPRETATION OF THE BONE SCANS TO REDUCE THE RISK OF A PREMATURE AND/OR INCORRECT CONCLUSION THAT THE TREATMENT HAS FAILED.**

The confirmation requirement of the PCWG2 criteria for the first follow-up scan at ≤12 weeks is designed to address the potential presence of a flare response. If ≥ 2 new lesions are seen within 12 weeks of systemic therapy initiation, this may be considered flare. To differentiate between a flare and the first sign of a progression, it is therefore recommended that a repeat bone scan be performed at least 6 weeks later. If no additional new lesions are detected, then “no progression” has occurred for the subject. If two or more additional lesions are present at the subsequent bone scan and the two previously new lesions are still present, then the progression event is considered “confirmed”. With regard to the date of progression, this will be the date of the first scan with new lesions documented and later confirmed, not the date of the confirmatory scan.

PAREXEL recommends the following guidelines for establishing the flare window based on PCWG2 [Figure 2.]:

<table>
<thead>
<tr>
<th>FLARE WINDOW</th>
<th>Post-Flare Window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 through to the end of Week 12 (i.e. ≤ 84 days Post-First Dose)</td>
<td>Any time after Week 13 (i.e. &gt; 84 days Post-First Dose)</td>
</tr>
</tbody>
</table>

**Figure 2. Flare and post-flare window**
**FLARE PROGRESSION RULE (FlaP)**

At least 2 new lesions are identified on a bone scan within the ‘flare’ window and persist into a subsequent bone scan that is at least 6 weeks later. The subsequent bone scan must also have a minimum of two additional new lesions. Confirmation requirement at the very next available timepoint is not part of PCWG2 recommendations, however PAREXEL recommends this implementation.

**POST-FLARE PROGRESSION RULE (POST-FlaP)**

At least 2 new lesions are identified on a bone scan outside of the ‘flare’ window. The requirement of whether these lesions persist at a subsequent follow-up bone scan should be defined in the study protocol and are not part of PCWG2 recommendations. However, PAREXEL recommends confirmation of these lesions be implemented.

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Figure 3. PAREXEL recommendation for the implementation of the progression determination within and outside of the flare window
Soft Tissue Disease

While the PCWG2 criteria refers to RECIST for the interpretation of soft tissue disease, specific modifications to RECIST are recommended for delay and prevent endpoints (e.g. PFS). For these trials, if soft tissue progression is observed within the flare window PAREXEL recommends that progression is confirmed by a second scan 6 or more weeks later. As the “flare phenomenon” in soft tissue disease may be less common and is less well understood, not all sponsors adopt this recommendation.

PAREXEL does not recommend confirmation of soft tissue disease at timepoints post the flare window. Thus, any evidence of soft tissue disease progression outside of the initial 12 week window would be considered immediate evidence of progression.

Using the examples in Figure 3 and Figure 4, note how the progression determination would differ if the rules around progression specified the ‘first follow-up scan” rather than specifying the rules for scans inside and outside of the flare window. The two new lesions at TP 2 may potentially be flare. Clinical trial protocols should provide clear guidelines on the difference between progression rules based on weeks post-dose versus the first follow-up scan.

Figure 4. Example of progression by bone scan lesions when first follow-up bone scan is done post-flare window
TIMING OF BONE SCAN IMAGING

In clinical trials, decisions about the frequency of bone scan imaging will need to be titrated between necessity, inconvenience/potential radiation burden to the patient, and cost to the sponsor. Both patients and investigators must be comfortable with the bone scan imaging schedule and understand the reasoning behind it. In addition to the reasoning behind bone scan frequency, it may not be intuitive to patients and investigators why they should continue current treatment in the context of a progression confirmation requirement where the bone lesion metastases count appears to have increased. Clearly explaining the treatment plan in the protocol is essential.

As a general rule, the patient should remain on the treatment long enough to allow for a treatment effect. PCWG2 recommends the first follow-up imaging assessment to be scheduled 12 weeks after the first dose of treatment. Often times the first bone scan assessment is not performed on the same day as randomization or dosing, and in some trials may occur as many as 4 weeks prior to the patient’s first dose. This can be a source of confusion for the sites, which may perform the first follow-up assessment at 12 weeks after the baseline/screening scan rather than 12 weeks post-first dose. The impact of this misunderstanding is substantial because imaging 12 weeks after the baseline/screening scan may cause the first follow-up visit to fall within the flare window and the patient may not have been on the trial long enough for the treatment to show a possible effect.

While it is clear that any scans acquired at or prior to Week 12 should be considered in the flare window, what must clearly be defined in the protocol is how long the flare window extends. Most protocols allow a certain time-window for acquisitions (often +/- 3 to 7 days), as patient scheduling will not always be feasible at exactly 12 weeks (i.e. every 84 days). If there is, for example, a +/-7 days acquisition window, all scans acquired up to and including day 91 since the pre-specified start date (e.g. dosing) would need to apply the Flare Progression Rules if potential evidence of progression is observed.

To avoid confusion, PAREXEL recommends clinical trial protocols include very clear instructions with regard to the imaging.

ESTABLISHING CONSISTENT LESION COUNTING RULES

Establishing clear, consistent lesion counting rules for how counted bone scan lesions drive the assessment of progression is one of the most critical components of a successful clinical trial in prostate cancer. Lesion counting is supported by three essential elements:

1. THE CONFIRMATION REQUIREMENTS FOR PROGRESSION INSIDE AND OUTSIDE OF THE FLARE WINDOW.
2. WHETHER LESIONS IDENTIFIED IN THE FLARE WINDOW ARE HELD IN ABYANCE UNTIL CONFIRMATION AT A SUBSEQUENT TIMEPOINT.
3. DEFINING THE LAST DAY OF THE FLARE TIME WINDOW.

Even seemingly minor variances in the Flap and Post-Flap rules can have a significant impact on progression-based endpoints. One of the most critical determinations that must be made when planning how the PCWG2 criteria will be applied in a trial is how new lesions observed on a bone scan in the flare period will be counted at follow-up. Important to this approach is the concept of whether or not lesions in the flare period can be held in abeyance until progression is met.
COUNTING LESIONS WITHIN THE FLARE WINDOW

PAREXEL’s Recommendation: New Lesions in the flare window should not be held in abeyance until later confirmation

Holding flare lesions in abeyance until later confirmation, will typically lead to an earlier date of progression yet not necessarily to the need of more timepoints to confirm the progression [see One Trial: Three Outcomes diagram]. Is this the appropriate “conservative” approach? Or does this lead to a greater discordance of site management and clinical trial determinations? The answer to this key question is in the interpretation of the nature of these early lesions and thus goes to the heart of the flare phenomenon.

Consider the scenario where two “hypothetically” new lesions are observed in the flare window and are actually the visualization of lesions that were present at baseline. At baseline they do not trigger the osteoblastic uptake of radiopharmaceutical yet. Within the initial 12 weeks [the flare window] the osteoblastic activity takes effect or is significant enough to be picked up by the bone scan. In this scenario, while there is a change in hotspots noted on the bone scan the understanding would be that there is no change in the lesion count. In fact, the interpretation would be that one now has a better understanding of the disease burden likely to have been present at baseline. Thus, the patient is considered stable or potentially improving on treatment. One would not expect for the lesion count to change further at the next timepoint. What happens however, when the abeyance rule is applied, is that once there are two new lesions noted in addition to the two lesions that were visualized during the flare window, the determination would be that progression occurred already with the first follow-up during the flare window. In our example this is neither supported by our understanding of the flare phenomenon nor congruent with the patient management as it occurred at the site [in alignment with PCWG2, the site continued treating until there was more substantial evidence of progression].

The key challenge is that one does not know the true nature of these initial lesions and they may have indeed been new and the first indication of progression. However, in the spirit of PCWG2 and a closer alignment of clinical patient management with clinical trial assessment across the treatment arms, our recommendation is to apply the “clean slate rule”.

PAREXEL’s Recommendation: Apply the “Clean Slate Rule”

A ‘clean slate’ approach has been adopted by many sponsors to prevent baseline lesions from being considered prematurely “new.” If lesions observed within the flare window on a post-baseline bone scan are not confirmed at the next subsequent bone scan at least 6 weeks later, the lesion counts are ‘reset’ and any new disease is determined by comparison to the post-baseline bone scan within the flare window.

Variations in the Post Flare Progression Rules-Is Lesion Persistence Required?

Different approaches to the way new lesions observed outside of the flare window can count towards progression may also impact the bone scan imaging schedule and patient treatment schedule. If two lesions seen on a post-flare window bone scan meet progression the first time they are observed, the average time to progression will not necessarily be different from a trial which requires bone lesions post-flare to persist to a subsequent bone scan. However, when the persistence rule is applied, an additional scan would be required and the switch to new treatment may be delayed.

Also, inherent in all confirmation requirements is the risk that the additional scan is not acquired and a potential PD event is lost. For this reason, PAREXEL recommends details in the Statistical Analysis Plan of the trial on the significance of unconfirmed progression at the last timepoint and high quality criteria trainings for sites. Central confirmation of progression before patients are taken off study can also help in reducing site-central discordance on this critical endpoint.
In One Trial: Three Outcomes we illustrate how small changes in the way lesions are counted can make a difference on the date of progression for a subject and the average time to progression in a clinical trial.

**ONE TRIAL: THREE OUTCOMES**

One trial in prostate cancer with a progression-based primary endpoint can result in very different outcomes depending on how lesions are counted towards progression determinations. In this example, we demonstrate how minor variances have significant impact on the time to progression. The variables applied to this analysis include:

<table>
<thead>
<tr>
<th>FlaP RULE VARIATIONS</th>
<th>POST-FlaP RULE VARIATIONS</th>
</tr>
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<tbody>
<tr>
<td><strong>Clean Slate</strong>: Flare window lesions only count towards progression if confirmed at the next timepoint that is at least 6 weeks later. Otherwise, the lesion count is reset and lesions post-flare are only considered new if not seen on flare window bone scan (PAREXEL’s recommendation)</td>
<td><strong>Persistence</strong>: At least 2 new post-flare lesions must persist to a subsequent timepoint (PAREXEL’s recommendation) OR <strong>No confirmation required</strong>: 2 new lesions post-flare meet progression the first time they are observed</td>
</tr>
<tr>
<td><strong>Abeyance</strong>: Flare window lesions are held in abeyance and contribute to the new lesion count without a time limit</td>
<td></td>
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**OUTCOME A**

- FlaP with abeyance
- Post-FlaP with persistence

**OUTCOME B**

- FlaP with clean slate
- Post-FlaP with no confirmation required

**OUTCOME C**

- FlaP with clean Slate
- Post FlaP with persistence
LESION COUNTING SCENARIO 1

Each outcome is the same in this scenario. The FlaP rule results in progression and the timepoint confirming the progression is the first timepoint post flare window, so the outcome of FlaP with abeyance and Flap with clean slate are the same.

**OUTCOME A**
Progression at TP2

Progression by FlaP with abeyance occurs at TP2 and is confirmed at TP3.

**OUTCOME B**
Progression at TP2

Progression by FlaP with clean slate occurs at TP2 and is confirmed at TP3. Progression by Post-FlaP with no confirmation required is also evident at TP3, but the earliest timepoint of progression is TP2.

**OUTCOME C**
Progression at TP2

Progression by FlaP with clean slate occurs at TP2 and is confirmed at TP3.

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**KEY**

- Unique new lesions
This scenario demonstrates the different progression determinations that result from FlaP with abeyance vs. FlaP with clean slate and Post-FlaP with persistence vs. Post-FlaP with no confirmation requirement.

**OUTCOME A**
Progression at TP2
Progression by FlaP with abeyance occurs at TP2 and is confirmed at TP4.

**OUTCOME B**
Progression at TP4
Progression by post-FlaP with no confirmation required occurs at TP4, which is the first timepoint post the flare window with 2 new lesions (triangle and square).

**OUTCOME C**
No Progression
FlaP with clean slate does not cause progression because the new lesions that appeared within the flare window (circle and star) are not confirmed at the next visit with two additional new lesions and are therefore taken out of the lesion count.

Post-FlaP with persistence does not support progression because the post-flare new lesions (triangle and square) at TP4 do not persist to the next bone scan.
**LESION COUNTING SCENARIO 3**

This scenario demonstrates the different progression determinations that result from Post-FlaP with persistence vs. Post-FlaP with no confirmation requirement.

**OUTCOME A**
Progression at TP4

Progression by Post-FlaP with persistence occurs at TP4 and is confirmed at TP5 when the 2 new post-flap lesions (star and square) are confirmed.

**OUTCOME B**
Progression at TP3

Progression by Post-FlaP with no confirmation required occurs at TP3 when 2 new lesions appear post flare window (star and triangle).

**OUTCOME C**
Progression at TP4

Progression by Post-FlaP with persistence occurs at TP4 and is confirmed at TP5 when the 2 new Post-FlaP lesions (star and square) are confirmed.

**KEY**

- Unique new lesions
Lesion Counting Scenario 4

This scenario demonstrates how a new lesion that appears within the flare window does not count towards progression according to either Post-FlaP rule.

### OUTCOME A
**No Progression**

The single lesion that appeared within the flare window (circle) does not count towards progression because FlaP with abeyance is not triggered. There are 2 new post-flare lesions at TP4 (star and triangle), however they would need to persist to a subsequent timepoint for progression by Post-FlaP with persistence.

### OUTCOME B
**Progression at TP4**

Progression by Post-FlaP with no confirmation required occurs at TP4 when 2 new lesions appear post flare window (star and triangle).

### OUTCOME C
**No Progression**

The single lesion that appeared within the flare window (circle) does not count towards progression because FlaP with clean slate is not triggered. There are 2 new post-flare lesions at TP4 (star and triangle), however they would need to persist to a subsequent timepoint for progression by Post-FlaP with persistence.

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**KEY**

- Unique new lesions
In a clinical trial setting both computerized Tomography (CT) scans and bone scans must be evaluated to determine if progression has occurred. PCWG2 relies on both bone lesion assessment and soft tissue disease assessment for determination of progression and CT for any evidence of response to treatment.

It has become standard practice for sites to acquire CT scans with contrast using a slice interval of 5mm and save them in Digital Imaging and Communications in Medicine (DICOM) format. This standard is ideal for central collection and evaluation of CT scans.

When it comes to bone scans, clinical sites do not routinely apply standard methods for acquisition or archiving. The quality of bone scans is at times limited by inadequate scan delay, insufficient scanning time, urine contamination and missing anatomy. Furthermore, bone scans may be saved in a variety of file formats other than DICOM, which degrade the quality of the bone scan. A particular problem seen by

<table>
<thead>
<tr>
<th>Scanning Methodology</th>
<th>Inadequate scan delay (waiting time after injection)</th>
<th>2-4 hours (preferably 3) after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insufficient scanning time/speed (collecting insufficient counts)</td>
<td>Normally 10-14cm/min</td>
</tr>
<tr>
<td></td>
<td>Poor image resolution</td>
<td>500k-800k counts spots</td>
</tr>
<tr>
<td></td>
<td>Variable tracer dose</td>
<td>Low energy high resolution collimator</td>
</tr>
<tr>
<td></td>
<td>20-30 mCi</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Positioning</th>
<th>Patient’s head turned to the side/ inconsistent head position baseline to follow-up</th>
<th>Use pillow to support head and lower back when necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Missing anatomy/ inadequate spot views</td>
<td>Detailed instructions on required views and labelling</td>
</tr>
<tr>
<td></td>
<td>No side markers</td>
<td>Have patient void right before the exam start</td>
</tr>
<tr>
<td></td>
<td>Urine contamination in the pelvis (may be mistaken for osseous metastatic disease)</td>
<td>Use foot band to keep feet close together</td>
</tr>
<tr>
<td></td>
<td>Detector head not in close proximity to the patient</td>
<td>If patient has any type of monitor attached unplug or move it so out of Field of View (FOV) (if possible)</td>
</tr>
<tr>
<td></td>
<td>Use of too large lead covers (to cover bladder) can exclude anatomy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Image Formatting</th>
<th>Screenshots</th>
<th>Send files in DICOM format</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JPEG file format</td>
<td>Be sure that whoever is sending images from the site has been well trained and understands how to send the images correctly</td>
</tr>
</tbody>
</table>
PAREXEL is that sites save the bone scan image as a screenshot, which cannot be manipulated as one would in a DICOM format to achieve the best possible display intensity for evaluating presence of bone lesions, particularly if the patient has multiple lesions. Sometimes screenshots are converted to DICOM which will also have insufficient quality. To avoid inconsistent bone scan evaluation and “not evaluable” assessments it is important that sites involved in a clinical trial follow standardized image acquisition guidelines for the acquisition and archiving of bone scan imaging. PAREXEL image acquisition guidelines include recommendations for improving scan quality as explained by Table 1.

Another challenge for evaluation of bone scans according to PCWG2 is the superscan effect. While a superscan cannot be corrected by changing image acquisition or archiving procedures, it may still be considered to be an image quality concern.

A Superscan is a bone scan which exhibits diffuse skeletal uptake with little or no uptake in the soft tissues, including kidneys or bladder. This results in the characteristic high bone to soft tissue ratio and discrete lesions may not be visible. Patients with extremely diffuse metastatic disease often exhibit a superscan but some patients with extensive disease may approach but not meet all the hallmarks of the true superscan. Making an evaluation using PCWG2 guidelines on patients with extensive, diffuse disease or patients with superscans is at best difficult, often impossible.

The absence of discrete lesions on bone scans due to superscan effect may be misleading for investigators during patient enrollment. The appropriate and well standardized disease status determination of a patient that has diffuse disease at baseline and a superscan on follow-up yet no lesions to count is equally challenging. Also, patients with superscans are often not evaluable at follow-up and as such impact the Progression Free Survival (PFS) analysis in the intent-to-treat population.

Figure 5. Bone scan demonstrating superscan effect
PAREXEL RECOMMENDATIONS FOR CENTRAL REVIEW OF PROSTATE CANCER DATA IN CLINICAL TRIALS

CENTRAL REVIEW WORKFLOW

Central evaluation of bone scans and CT/MRI scans for prostate cancer clinical trials is implemented by many sponsors. Often, the central review workflow is an important discussion. There are a number of different approaches; one of the first decisions to make is whether the soft tissue assessments and bone lesion assessments should be performed by the same reader[s] using a composite read model or by different reader(s) using a decoupled read model.

While PCWG2 advocates reporting bone lesions separately from soft tissue disease it does not address how this recommendation is applied in a central review setting. PAREXEL recommends a decoupled read model.

Decoupled Read Model

With a decoupled read model, central radiologists with expertise in prostate cancer evaluate CT/MRI scans for soft tissue disease according to RECIST and central nuclear medicine physicians evaluate bone scans for bone lesions according to PCWG2. PAREXEL’s experience has shown that the interpretation of the bone scans is the more challenging piece in the PCWG2 patient status determination and recruiting the expertise of a nuclear medicine physician will improve the quality of the interpretations.

The decoupled read model is typically more expensive with two sets of readers and potentially more complex imaging case report forms used to record independent reviewers’ assessments. However, the decoupled read model offers the most accurate interpretation of both bone scans and CT/MRI by using reviewers with the correct expertise. The decoupled read model also adheres to the PCWG2 recommendations, which suggest that soft tissue disease should be reported separate from bone lesions and keeps the radiologist blinded to bone lesion progression, reducing bias. Additionally, for some trials, the decoupled read model allows for a better understanding of the effectiveness of the treatment in the different disease compartments and may preserve endpoint integrity by distinguishing progression events on CT/MRI separate from bone scan (radiological progression due to increasing or new soft tissue disease separate from radiological progression due to new bone lesions). Occasionally, patients may present with a purely lytic bone lesion that will not be apparent on the technetium bone scan. Such lesions are rare and may not be documented in this decoupled reading model.
**Composite Read Model**

With a composite read model, one central reader evaluates both CT/MRI scans and bone scans. CT/MRI scans are evaluated for progression or response of soft tissue disease according to RECIST. Bone scans are evaluated for progression of bone lesions according to PCWG2. Generally, the readers performing reads according to a composite read model are radiologists with some expertise in bone scan evaluation, but given the extent of the soft tissue evaluation required, not a nuclear medicine physician.

The composite read model is more cost and time efficient, because the same reader can assess CT/MRI and bone scan in one review session. Some key challenges with the composite read model are:

- Identification of readers that have sufficient experience with bone scans in addition to CT/MRI expertise in prostate cancer.
- The distinct assessment criteria for bone lesions vs. soft tissue disease result in complex rules that the reader must follow to accurately determine disease status.
- The joint evaluation of bone scan and CT/MRI can introduce bias into the soft tissue evaluation leading to more sensitivity in the determination of progressive disease.

While the composite read model has time and cost benefits, PAREXEL does not recommend it because of these challenges and the resulting impact on data.

**CENTRAL INDEPENDENT REVIEW: VALUE OF CT SCAN IN BONE SCAN EVALUATION**

When a study adopts the decoupled read model, a particular area of discussion in the assessment of bone scans is the value added by having access to the correlating CT scans. While there is value in establishing bone scans as a standalone surrogate endpoint for the evaluation of bone metastases in prostate cancer, the benefit of having access to the correlating CT scans can be critical. The CT scan often provides critical diagnostic information on the nature of bone scan findings (e.g. fractures and degenerative changes), and it can validate the presences of true metastases. This approach is also consistent with the PCWG2 criteria recommendations.

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**Figure 6. Non-metastatic bone scan finding with correlative CT.** Focusing on the encircled red areas, the image on the left shows a bone scan with a non-metastatic finding on the vertebral body. Using a CT scan (right) acquired in close proximity to the date the bone scan was performed, allows for an accurate anatomical location that is not available when using a standalone bone scan. This results in a better understanding of the nature of the finding (consistent with metastatic disease or a benign cause).
SUMMARY OF PAREXEL’S KEY RECOMMENDATIONS

There are many challenging aspects of assessing prostate cancer in clinical trials, ranging from protocol design, imaging schedules, and image acquisition to implementation of criteria, lesion counting rules, and read models. PAREXEL recommends the following design for a clinical trial in prostate cancer:

- Clearly define the imaging schedule and flare window in the protocol. When possible, do not require sites to acquire a follow-up bone scan until after the flare window.
- Educate sites about scan acquisition and archiving (Table 1), especially for bone scans.
- Consider the impact of superscans when developing protocol inclusion and exclusion criteria. If subjects are allowed on study with superscans, or if superscans are to be expected on-study, train the sites on what a superscan is and the downstream impact this may have on the endpoint [i.e. patient may be not evaluable at follow-up]. Use RECIST 1.1 clarifications for the evaluation of soft tissue disease.
- Provide sites with clear guidelines on bone scan lesion counting rules:
  - FlaP with clean slate (recommended) or FlaP with abeyance
  - Post-FlaP with persistence (recommended) or FlaP with no confirmation requirement
  - The reporting date of progression (providing examples)
  - Application of lesion counting rules (providing examples)
- Additional recommendations for implementing central review:
  - Use a decoupled read model
  - Provide correlative CT/MRI scan to the bone scan reviewer
  - Provide clear rules on reporting baseline disease and marking new disease at follow-up
  - To foster harmonization, establish a threshold for determining whether a lesion is metastatic
  - Clearly define the determination of skeletal related events in protocol, typically these are better determined by the sites

PAREXEL’s experience in prostate clinical trials and further recommendations for a successful trial can be found in Table 2, Table 3, and Table 4.
## RECOMMENDATIONS FOR ASSESSMENT OF PROSTATE CANCER DATA IN CLINICAL TRIALS

| Reporting Disease | • Provide clear rules on reporting baseline disease and new disease at follow-up:  
|                   | - How to mark baseline disease. PAREXEL recommends that baseline lesions can be grouped and that individual lesions do not need to be marked.  
|                   | - Reporting of ‘missed’ lesions.  
|                   | - If a new lesion was not obvious at a previous follow-up timepoint, determine how to report when the lesion is considered unequivocal.  
|                   | - How image quality may impact the ability to identify and report lesions at baseline and how this may limit assessment options at follow-up timepoints.  
| Define Clear Progression Rules | • Specifically define the flare window taking the acquisition window into account  
|                              | • Define how new lesions that appear within the flare window cause progression (FlaP) and how new lesions that appear after the flare window cause progression (Post-FlaP).  
|                              | • Prevent early or incorrect progression determinations due to differences in application of the PCWG2 criteria – the spirit of PCWG2 is that the patient should be kept on study until progression is unequivocal.  
| Requirements on Date of Progression | • Define how the date of progression is reported.  
|                                    | - Typically, the date of progression is the date two new lesions were first seen together, not the confirmatory timepoint.  
| Establish a Threshold for Determining whether a Bone Lesion is Metastatic | Establish a threshold for what is considered a metastatic lesion:  
|                                    | 1. Highly likely to be negative/not malignant  
|                                    | 2. Likely to be not malignant  
|                                    | 3. Reasonably likely to be malignant  
|                                    | 4. Likely to be malignant  
|                                    | 5. Highly likely to be malignant  
|                                    | • At baseline, lesions should be recorded when reasonably likely to be malignant (score 3, 4 or 5).  
|                                    | • At follow-up timepoints, lesions should be recorded when likely to be malignant (score of 4 or 5).  
| Skeletal Related Events Endpoint Contributions | Clearly define the determination of skeletal related events in the protocol. Skeletal related events can present in many ways:  
|                                              | • Changes to antineoplastic therapy and on-study radiation to treat bone pain  
|                                              | • Pathological fractures  
|                                              | • Spinal cord compression  
|                                              | • Surgery to bone  
|                                              | These events are most often documented by site investigator teams even when central review is part of the trial design.  
| Train the Clinical Sites | Use examples to demonstrate lesion counting rules and teach sites how to apply these rules (see lesion counting logic, Table 4).  

Table 2. Recommendations for assessment of prostate cancer data in clinical trials
### RECOMMENDATIONS FOR CONSISTENT APPLICATION OF THE PCWG2 CRITERIA

<table>
<thead>
<tr>
<th>Soft Tissue Assessment on CT/MRI</th>
<th>Bone Lesion Assessment on Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Use RECIST version 1.1 for soft tissue assessment.</td>
<td>• Providing access to CT/MRI during the bone scan review can be helpful in the interpretation of indeterminate bone findings.</td>
</tr>
<tr>
<td>• Perform the soft tissue assessment using CT and MRI separate from bone scan lesion assessment. We call this a decoupled read model: The soft tissue reviewer assesses CT and MRI without knowledge of the bone scan assessment.</td>
<td>• Clearly define the flare window for bone scan (e.g. up to Week 13, Day 0 (91 days from dosing).</td>
</tr>
<tr>
<td>• When performing the soft tissue assessment, bone lesions seen on CT or MRI should not be evaluated.</td>
<td>• PAREXEL recommends the following bone lesion counting rules:</td>
</tr>
<tr>
<td>• Lesions extending from the prostate bed should be considered disease but should be followed qualitatively not by measurement. Typically such lesions are not considered metastases.</td>
<td>- FlaP with clean slate</td>
</tr>
<tr>
<td></td>
<td>- Post-FlaP with persistence</td>
</tr>
<tr>
<td></td>
<td>- Confirmation requires a minimum of 6 weeks between scans.</td>
</tr>
<tr>
<td></td>
<td>• The timepoint of progression is the timepoint where two new bone lesions are seen together for the first time, not the confirmatory timepoint.</td>
</tr>
</tbody>
</table>

Table 3. Recommendations for consistent application of PCWG2 criteria
### RECOMMENDATIONS ESTABLISHING LESION COUNTING LOGIC FOR CONSISTENT APPLICATION OF THE CRITERIA

For the following example cases assume the following:

- Flare window = up to Week 12
- TP2 = Week 10 (within flare window) and TP3 = Week 16 (post flare window)
- Interval between follow-up scans is at least 6 weeks

- PDu = Progressive Disease Unconfirmed
- PDC = Progressive Disease Confirmed
- No PD = No Progression
- NE = Not evaluable
- Flare with clean slate and Post-Flare with Persistence are applied (PAREXEL’s recommendations)

<table>
<thead>
<tr>
<th>CASE 1</th>
<th>TP2</th>
<th>TP3</th>
<th>TP4</th>
<th>TP5</th>
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</thead>
<tbody>
<tr>
<td>Overall Timepoint Response</td>
<td>AB</td>
<td>ABCD</td>
<td>No bone scan</td>
<td>No bone scan</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>TPMT 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Timepoint Response</td>
<td>PDu</td>
<td>PDC</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>NO PROGRESSION</td>
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<th>TP4</th>
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<tbody>
<tr>
<td>Overall Timepoint Response</td>
<td>AB</td>
<td>AB</td>
<td>ABCD</td>
<td>No bone scan</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>TPMT 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Timepoint Response</td>
<td>PDu</td>
<td>No PD</td>
<td>PDU</td>
<td>N/A</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
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<th>TP2</th>
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<th>TP4</th>
<th>TP5</th>
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<tbody>
<tr>
<td>Overall Timepoint Response</td>
<td>No lesions</td>
<td>AB</td>
<td>AB</td>
<td>No bone scan</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>TMPT 3</td>
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<tr>
<td>Overall Timepoint Response</td>
<td>No PD</td>
<td>PDu</td>
<td>PDc</td>
<td>N/A</td>
</tr>
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<td>Timepoint of Progression</td>
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<td>AB</td>
<td>ABC</td>
<td>ABCD</td>
<td>No bone scan</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>TMPT 4</td>
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<td>Overall Timepoint Response</td>
<td>PDu</td>
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<td>PDU</td>
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</tr>
<tr>
<td>Timepoint of Progression</td>
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<tbody>
<tr>
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<td>A</td>
<td>A</td>
<td>ABCDEF</td>
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<td>Timepoint of Progression</td>
<td>TMPT 4</td>
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<tr>
<td>Overall Timepoint Response</td>
<td>No PD</td>
<td>No PD</td>
<td>No PD</td>
<td>PDU</td>
</tr>
<tr>
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<td>NO PROGRESSION</td>
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<td>BC</td>
<td>BC</td>
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<td>Timepoint of Progression</td>
<td>TMPT 4</td>
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<tr>
<td>Overall Timepoint Response</td>
<td>No PD</td>
<td>PDu</td>
<td>PDu</td>
<td>PDC</td>
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<tr>
<td>Timepoint of Progression</td>
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<td>No lesions</td>
<td>A</td>
<td>A</td>
<td>AB</td>
</tr>
<tr>
<td>Timepoint of Progression</td>
<td>TMPT 4</td>
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</tr>
<tr>
<td>Overall Timepoint Response</td>
<td>No PD</td>
<td>No PD</td>
<td>PDU</td>
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</tr>
<tr>
<td>Timepoint of Progression</td>
<td>NO PROGRESSION</td>
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<td>Overall Timepoint Response</td>
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<td>A</td>
<td>AB</td>
<td>AB</td>
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<tr>
<td>Timepoint of Progression</td>
<td>TMPT 4</td>
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<td></td>
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<tr>
<td>Overall Timepoint Response</td>
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<td>No PD</td>
<td>No PD</td>
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<tr>
<td>Timepoint of Progression</td>
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</thead>
<tbody>
<tr>
<td>Overall Timepoint Response</td>
<td>AB</td>
<td>Not Evaluable (image quality)</td>
<td>ABCD</td>
<td>No bone scan</td>
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<td>Timepoint of Progression</td>
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<td>PDu</td>
<td>NE</td>
<td>PDC</td>
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<tr>
<td>Timepoint of Progression</td>
<td>NO PROGRESSION</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Recommendations for consistent application of PCWG2 criteria
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