### Template 2. NHMRC- Assessing the body of evidence form

#### Question R8: What is the toxicity of unsealed radioisotopes for treatment of metastatic prostate cancer?

<table>
<thead>
<tr>
<th>Evidence table ref: Table 12, 13 in radioisotope report</th>
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</thead>
</table>

#### 1. Volume of evidence (quantity level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)

- **Most of the randomised studies compare Strontium against another active control arm, and so that there is scant evidence on adverse effect of strontium compared with a “best supportive care” treatment. There are a number of studies comparing strontium against other active treatment arms such as hemi-body irradiation or chemotherapy, but these are heterogeneous in choice of comparison, and so provide low volumes of evidence about any specific treatment. C.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>Excellent (several level I or II studies with low risk of bias)</td>
</tr>
<tr>
<td>B</td>
<td>Good (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)</td>
</tr>
<tr>
<td>C</td>
<td>Satisfactory (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)</td>
</tr>
<tr>
<td>D</td>
<td>Poor (Level IV studies or Level I to III studies with high risk of bias)</td>
</tr>
</tbody>
</table>

#### 2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group forms a judgment as to the overall direction of the evidence)

- **Thrombocytopenia and leucopenia are observed to some extent in a number of studies. Strontium tends to show a similar or better effect on haematological endpoints than other active treatments such as hemi-body or local irradiation or non taxane chemotherapy, but more effect than “best supportive care”, and statistically significantly more when added to localised radiation. One study (Dearmaley) of modest quality suggested a trend for worse rates of adverse effects in the patients treated with radiation, compared with strontium. This was inconsistent with the trend noted in most of the other randomised trials. There is no good evidence that strontium causes significant adverse effects other than haematological. C.**

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<td>C</td>
<td>Satisfactory (some inconsistency, reflecting genuine uncertainty around question)</td>
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<tr>
<td>D</td>
<td>Poor (evidence is inconsistent)</td>
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#### 3. Clinical impact (the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)

- **The potential clinical impact would be high if strontium were to be associated with life-threatening haematological toxicity, particularly when other treatment options for palliation are available. This a potentially large patient group - given the mortality from prostate cancer - emphasizing a need to ensure the safety of strontium. The small numbers in these studies mean that the trials are unlikely to sufficiently powered to exclude a meaningful increase in fatal adverse events.**

<table>
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<th>Description</th>
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<tbody>
<tr>
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<tr>
<td>B</td>
<td>Good (substantial clinical impact)</td>
</tr>
<tr>
<td>C</td>
<td>Satisfactory (moderate clinical impact)</td>
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<tr>
<td>D</td>
<td>Poor (slight or restricted clinical impact)</td>
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associated with the use of strontium A

4. Generalisability (how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)

<table>
<thead>
<tr>
<th>Component</th>
<th>Descriptor</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Volume of evidence</td>
<td>Satisfactory</td>
<td>C</td>
</tr>
<tr>
<td>Consistency</td>
<td>Satisfactory</td>
<td>C</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>Excellent</td>
<td>A</td>
</tr>
<tr>
<td>Generalisability</td>
<td>Satisfactory</td>
<td>C</td>
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<tr>
<td>Applicability</td>
<td>Good</td>
<td>B</td>
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Patients in Australia considered for Strontium treatment now are likely to be more heavily pretreated with chemotherapy than those entered into these strontium studies. The haematological toxicity is possible much more marked in these pretreated patients C.

A Excellent (directly generalisable to the target population)
B Good (directly generalisable to target population with some caveats)
C Satisfactory (not directly generalisable to the target population but could be sensibly applied)
D Poor (not directly generalisable to target population and hard to judge whether it is sensible to apply)

5. Applicability (the extent to which the body of evidence is directly applicable to Australian healthcare context)

Strontium is reasonably widely available in metropolitan Australia, but patients from regional or rural areas might be compelled to travel for some distance for treatment. B.

A Excellent (directly applicable to Australian healthcare context)
B Good (applicable to Australian healthcare context with few caveats)
C Satisfactory (probably applicable to Australian healthcare context with some caveats)
D Poor (not applicable to Australian healthcare context)

Other factors
Indicate here any factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)

EVIDENCE STATEMENT
Please summarise the development group's synthesis of the evidence relating to the key question, taking all of the above factors into account. Please indicate any dissenting opinions

At the doses administered, and in a population of patients who were not pretreated with chemotherapy, strontium 89 appears associated with mild haematological toxicity. The possibility of significant serious adverse events cannot be excluded by the published trials, compared with the use of best supportive care or localised radiation.
<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
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<tbody>
<tr>
<td><strong>What recommendation(s) does the guideline development group draw from this evidence?</strong></td>
<td>The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B</td>
</tr>
</tbody>
</table>

Unsealed radioisotopes alone may be associated with higher haematological adverse events compared with supportive care or localised radiation although these rates overall are low. Unsealed radioisotopes in combination with other treatments such as radiotherapy have higher rates of serious toxicity than radiotherapy alone. The toxicity of unsealed radioisotopes in combination with modern chemotherapy (taxanes) has not yet been defined and caution should be exercised if such combinations are considered.

| GRADE OF RECOMMENDATION | C |
**Template 2. NHMRC- Assessing the body of evidence form**

**Question R8: What is the toxicity of unsealed radioisotopes for treatment of metastatic prostate cancer?**  
*Samarium 153*

<table>
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<th>Evidence table ref: Table 16 in radioisotope report</th>
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### 1. Volume of evidence (quantity level, methodological quality and relevance to patients of the body of evidence for this question, based on critical appraisal of each individual study according to Minimum Requirements)

- **There are only two randomised trials comparing samarium with placebo containing 118 and 150 patients (the smaller study included 38 non prostate cancer patients). Two further studies compared different doses of samarium providing a small amount of additional information. There are no randomised trials comparing samarium with other radio-isotopes, chemotherapy or external beam irradiation. (C)**

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- **Excellent (several level I or II studies with low risk of bias)**
- **Good (one or two Level II studies with low risk of bias or SR/multiple Level III studies with low risk of bias)**
- **Satisfactory (Level III studies with low risk of bias or Level I or II studies with moderate risk of bias)**
- **Poor (Level IV studies or Level I to III studies with high risk of bias)**

### 2. Consistency (the degree of consistency demonstrated by the available evidence. Where there are conflicting results indicate how the group forms a judgement as to the overall direction of the evidence)

- **Considering relatively small size, all trials are remarkably consistent. All demonstrate consistent reduction in platelets and white cell count but the development of grade III/IV neutropaenia is uncommon (<15%) and clinically significant toxicity is rare (B)**

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- **Excellent (all studies consistent)**
- **Good (most studies consistent and inconsistency can be explained)**
- **Satisfactory (some inconsistency, reflecting genuine uncertainty around question)**
- **Poor (evidence is inconsistent)**

### 3. Clinical impact (the potential impact of recommendation i.e. size of patient population, relevance of outcomes to the question, balance of risks and benefits, relative benefit over other management options, resource and organisational implications)

- **Available data suggests that the tolerability of samarium in this patient population is good with low rates of significant toxicity and is unlikely to impact on patient’s quality of life (B)**

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- **Excellent (very large clinical impact)**
- **Good (substantial clinical impact)**
- **Satisfactory (moderate clinical impact)**
- **Poor (slight or restricted clinical impact)**

### 4. Generalisability (how reasonable it is to generalise from the results of the studies used as evidence to the target population for this guideline?)

- **Care must be made extrapolating these results to prostate cancer patients who have been pre-treated with chemotherapy or who have significant marrow infiltration prior to starting samarium (C)**

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- **Excellent (directly generalisable to the target population)**
- **Good (directly generalisable to target population with some caveats)**
- **Satisfactory (not directly generalisable to the target population but could be sensibly applied)**
5. Applicability (the extent to which the body of evidence is directly applicable to Australian healthcare context)

Patients in Australia are more likely to be heavily pre-treated with chemotherapy, pamidronates and external beam irradiation limiting applicability. Also the tolerability of chemotherapy after giving samarium has not been studied (C)

Other factors
Indicate here any factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)

EVIDENCE STATEMENT
Please summarise the development group’s synthesis of the evidence relating to the key question, taking all of the above factors into account. Please indicate any dissenting opinions

The limited evidence demonstrates that Samarium 153 results in falls in white cell counts and platelets. However, in patients with adequate marrow reserve, the development of grade III/IV neutropaenia or thrombocytopenia is uncommon (<15%) and clinically significant toxicity is rare. There is no randomised evidence comparing samarium with other radio-isotopes such as strontium.

RECOMMENDATION
What recommendation(s) does the guideline development group draw from this evidence?

Unsealed radioisotopes alone may be associated with higher haematological adverse events compared with supportive care or localised radiation although these rates overall are low. Unsealed radioisotopes in combination with other treatments such as radiotherapy have higher rates of serious toxicity than radiotherapy alone. The toxicity of unsealed radioisotopes in combination with modern chemotherapy (taxanes) has not yet been defined and caution should be exercised if such combinations are considered.

The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both either A or B

GRADE OF RECOMMENDATION
C