**SPECIALISED COMMISSIONING - CLINICAL EVIDENCE EVALUATION CRITERIA FOR A PROPOSITION FOR A CLINICAL COMMISSIONING POLICY FOR ROUTINE COMMISSIONING**

URN: F01X08
TITLE: Treatments for Graft versus Host disease (GvHD) following Haematopoietic Stem Cell Transplantation

Note: GvHD is acute Graft versus Host disease and cGvHD is chronic Graft versus Host disease

CRG: Blood and Marrow Transplant
NPOC: Blood and Infection
Lead: Claire Foreman

Date: 17th February 2016

The panel were presented a policy proposal for routine commissioning

**Extracorporeal photopheresis (ECP) for aGvHD and cGvHD**

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>1. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of effectiveness considered in the evidence review | The panel noted that evidence for use in acute GvHD is less well developed than for chronic GvHD and is based on a small number of studies with relatively small numbers of patients. The results showed a significant clinical benefit, but with a wide confidence interval. The most likely response rate (partial and complete) probably lies between half and two thirds of patients. There was a trend for increased overall survival. Complete response was less likely in more severely affected patients.<br><br>Responses were probably highest in GvHD affecting |

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| | | the skin, gut and liver. |
| <u>Population subgroups</u><br>2. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | The population subgroups defined in the policy are the same or similar as those for which there is evidence in the evidence review | The policy criteria identifies the group of patients with GvHD for whom first line treatments are no longer appropriate. |
| <u>Outcomes - benefits</u><br>3. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review support the eligible population and/or subgroups presented in the policy | The benefits include reduced symptoms, reduced steroid dose and there may be a survival benefit. |
| <u>Outcomes – harms</u><br>4. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are reflected in the eligible population and/or subgroups presented in the policy | ECP is generally considered to be a relatively safe intervention. |
| <u>The intervention</u><br>5. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review | |
| <u>The comparator</u><br>6. Is the comparator in the policy the same as that in the evidence review? | No comparator<br><br>No comparator | The ‘comparators’ are other second line treatments and these are widely used in the NHS at present although the evidence supporting their use is often less robust than for ECP and |

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| 7. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | | their cost may be significant. |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | Advice is to routinely commission ECP for acute and chronic GvHD. |

**Infliximab for aGvHD**

The panel were presented a policy proposal for routine commissioning

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>8. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is | The evidence available is very weak and harms appear very significant. |

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| evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | evidence of effectiveness considered in the evidence review. | |
| <u>Population subgroups</u><br>9. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | No subgroups defined | |
| <u>Outcomes - benefits</u><br>10. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review do not support the eligible population and/or subgroups presented in the policy. | The panel noted that the very limited evidence available for the use of Infliximab in patients with Acute GvHD. The evidence that was available did not show clear evidence of benefit. |
| <u>Outcomes – harms</u><br><br>11. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are not reflected in the eligible population and/or subgroups presented in the policy. | The panel noted the significant risk of infection in the use of Infliximab in this patient group, and were concerned at the likely reduction in quality of life and length of life for those patients for whom the treatment was not very effective and serious infection occurred. |

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| <u>The intervention</u><br>12. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review. | |
| <u>The comparator</u><br><br>13. Is the comparator in the policy the same as that in the evidence review?<br><br>14. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator<br><br>No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the | | The clinical panel noted that the clinical pressure to use infliximab would be removed if ECP were routinely available.<br><br>The evidence to support the effectiveness of infliximab is particularly weak. The evidence base is poorly developed and the net benefits reported appear to be so marginal that infliximab cannot be supported for routine commissioning. The panel advised that rituximab should not be routinely commissioned for aGvHD. |

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| need for policy review. | | |

**Etanercept for Acute GvHD**

The panel were presented a policy proposal for routine commissioning.

| Question | Conclusion of the panel | If there is a difference between the evidence review and the policy please give a commentary |
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| <u>The population</u><br>15. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of effectiveness considered in the evidence review. | The evidence for entercept tended to show some benefit in aGvHD in combination with steroids and for steroid refractory patients. A small study in steroid refractory patients showed a 50% response rate, but no complete responses. |
| <u>Population subgroups</u><br>16. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | No subgroups defined | |
| <u>Outcomes - benefits</u><br>17. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review do not support the eligible population and/or subgroups presented in the policy. | The panel noted that the very limited evidence available for the use of Etanercept in patients with Acute GvHD. The evidence that was available tended to show some evidence of benefit. |

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| <u>Outcomes – harms</u><br><br>18. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are not reflected in the eligible population and/or subgroups presented in the policy. | The panel noted the possible risk of infection in the use of Etanercept in this patient group. The small studies available reported that there may be no increased risk of infection or a significant increased risk of infection. |
| <u>The intervention</u><br>19. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review. | |
| <u>The comparator</u><br><br>20. Is the comparator in the policy the same as that in the evidence review?<br><br>21. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator<br><br>No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in | | The clinical panel noted that the clinical pressure to use Etanercept would be removed if ECP were routinely available.<br><br>The evidence to support routine commissioning is weak. However, the evidence base is poorly developed and it is possible that entercept |

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| clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | could be effective in a proportion of patients where other treatment options are lacking. |

**Alemtuzumab for Acute GvHD**

The panel were presented a policy proposal for routine commissioning.

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>22. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of effectiveness considered in the evidence review. | The evidence showed possible benefit for Alemtuzumab in aGvHD. Studies showed variable outcomes with some significant response rates but one study showed a 100% mortality at 40 days in the 5 patients who responded initially. |
| <u>Population subgroups</u><br>23. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | No subgroups defined | |
| <u>Outcomes - benefits</u><br>24. Are the clinical benefits | The clinical benefits | The panel noted that the |

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| demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | demonstrated in the evidence review do not support the eligible population and/or subgroups presented in the policy. | very limited evidence available for the use of Alemtuzumab in patients with Acute GvHD. The evidence that was available did not show clear evidence of benefit. |
| <u>Outcomes – harms</u><br><br>25. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are not reflected in the eligible population and/or subgroups presented in the policy. | The panel noted the significant risk of infection in the use of Alemtuzumab in this patient group and severe harms identified in the evidence, including very high mortality. |
| <u>The intervention</u><br>26. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review. | |
| <u>The comparator</u><br><br>27. Is the comparator in the policy the same as that in the evidence review?<br><br>28. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator<br><br>No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to | | The clinical panel noted that the clinical pressure to use Alemtuzumab would be |

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| the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | removed if ECP were routinely available.<br><br>The evidence to support routine commissioning is weak. However, the evidence base is poorly developed and it is possible that alemtuzumab could be effective in a proportion of patients where other treatment options are lacking. Access to ECP would be preferable. |

**Pentostatin for Acute GvHD**

The panel were presented a policy proposal for not routine commissioning.

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>29. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | The ineligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of lack of effectiveness or inadequate evidence of effectiveness demonstrated in the evidence review. | |
| <u>Population subgroups</u><br>30. Are any population | No subgroups defined. | |

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| subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | | |
| <u>Outcomes - benefits</u><br>31. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | A2: The lack of benefit or absence of evidence of benefit demonstrated in the evidence review is consistent with the ineligible population and/or subgroups presented in the policy. | |
| <u>Outcomes – harms</u><br><br>32. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | A: The clinical harms demonstrated in the evidence review are reflected in the eligible and / or ineligible population and/or subgroups presented in the policy. | |
| <u>The intervention</u><br>33. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | A: The intervention described in the policy is the same or similar as in the evidence review. | |
| <u>The comparator</u><br><br>34. Is the comparator in the policy the same as that in the evidence review?<br><br>35. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS | No comparator<br><br>No comparator | |

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| and are they suitable for informing policy development. | | |
| Advice<br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | |

**Mesenchymal stem cells for Acute GvHD**

The panel were presented a policy proposal for not routine commissioning.

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| The population<br>36. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations | The ineligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of lack of effectiveness or inadequate evidence of effectiveness demonstrated in the evidence review. | |

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| considered in the evidence review? | | |
| <u>Population subgroups</u><br>37. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | No subgroups defined. | |
| <u>Outcomes - benefits</u><br>38. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The lack of benefit or absence of evidence of benefit demonstrated in the evidence review is consistent with the ineligible population and/or subgroups presented in the policy. | |
| <u>Outcomes – harms</u><br>39. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are reflected in the eligible and / or ineligible population and/or subgroups presented in the policy. | |
| <u>The intervention</u><br>40. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy is the same or similar as in the evidence review. | |
| <u>The comparator</u><br>41. Is the comparator in the policy the same as that in the evidence review? | No comparator | |

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| 42. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | |

**Pentostatin for Chronic GvHD**

The panel were presented a policy proposal for routine commissioning

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>43. Are the eligible and ineligible populations defined in the policy consistent with the | The eligible population(s) defined in the policy are the same or similar to the population(s) for which | There is evidence of effectiveness in refractory cGvHD. The studies are |

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| evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | there is evidence of effectiveness considered in the evidence review | small and the effect size varies. |
| <u>Population subgroups</u><br>44. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | The population subgroups defined in the policy are the same or similar as those for which there is evidence in the evidence review | |
| <u>Outcomes - benefits</u><br>45. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review support the eligible population and/or subgroups presented in the policy | |
| <u>Outcomes – harms</u><br><br>46. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are reflected in the eligible population and/or subgroups presented in the policy | There is a significant risk of infection. |
| <u>The intervention</u><br>47. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review | |
| <u>The comparator</u><br><br>48. Is the comparator in the policy | No comparator | |

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| the same as that in the evidence review?<br><br>49. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | |

**Rituximab for Chronic GvHD**

The panel were presented a policy proposal for routine commissioning

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy please give a commentary** |
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| <u>The population</u><br>50. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of | There is evidence suggesting effectiveness from a number of small studies. There is a wide range of possible response rates and overall the |

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| evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | effectiveness considered in the evidence review | evidence is of poor quality. However, studies all report a probable benefit in terms of partial or complete responses in a proportion of patients. |
| <u>Population subgroups</u><br>51. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | The population subgroups defined in the policy are the same or similar as those for which there is evidence in the evidence review | |
| <u>Outcomes - benefits</u><br>52. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review support the eligible population and/or subgroups presented in the policy | |
| <u>Outcomes – harms</u><br><br>53. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are reflected in the eligible population and/or subgroups presented in the policy | There is an increased risk of infection. |
| <u>The intervention</u><br>54. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review | |

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| <u>The comparator</u><br><br>55. Is the comparator in the policy the same as that in the evidence review?<br><br>56. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator<br><br>No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | Clinical Panel advises that the use of rituximab restricted to subgroup where effective. Note that if ECP is available, use of rituximab would be limited. |

**Imatinib for Chronic GvHD**

The panel were presented a policy proposal for routine commissioning

| **Question** | **Conclusion of the panel** | **If there is a difference between the evidence review and the policy** |
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| | | **please give a commentary** |
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| <u>The population</u><br>57. Are the eligible and ineligible populations defined in the policy consistent with the evidence of effectiveness, and evidence of lack of effectiveness; and where evidence is not available for the populations considered in the evidence review? | The eligible population(s) defined in the policy are the same or similar to the population(s) for which there is evidence of effectiveness considered in the evidence review | Studies of Imatinib are small and the evidence limited. There appears to be some benefit that is probably limited to patients with mild pulmonary disease and may be effective in patients with skin disease. |
| <u>Population subgroups</u><br>58. Are any population subgroups defined in the policy and if so do they match the subgroups considered by the evidence review? | The population subgroups defined in the policy are the same or similar as those for which there is evidence in the evidence review | |
| <u>Outcomes - benefits</u><br>59. Are the clinical benefits demonstrated in the evidence review consistent with the eligible population and/or subgroups presented in the policy? | The clinical benefits demonstrated in the evidence review support the eligible population and/or subgroups presented in the policy | |
| <u>Outcomes – harms</u><br><br>60. Are the clinical harms demonstrated in the evidence review reflected in the eligible and / or ineligible population and/or subgroups presented in the policy? | The clinical harms demonstrated in the evidence review are reflected in the eligible population and/or subgroups presented in the policy | There are adverse effects although risk of infection was not highlighted in the small studies reported. |

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| <u>The intervention</u><br>61. Is the intervention described in the policy the same or similar as the intervention for which evidence is presented in the evidence review? | The intervention described in the policy the same or similar as in the evidence review | |
| <u>The comparator</u><br><br>62. Is the comparator in the policy the same as that in the evidence review?<br><br>63. Are the comparators in the evidence review the most plausible comparators for patients in the English NHS and are they suitable for informing policy development. | No comparator<br><br>No comparator | |
| <u>Advice</u><br>The Panel should provide advice on matters relating to the evidence base and policy development and prioritisation. Advice may cover:<br>• Uncertainty in the evidence base<br>• Challenges in the clinical interpretation and applicability of policy in clinical practice<br>• Challenges in ensuring policy is applied appropriately<br>• Issues with regard to value for money<br>• Likely changes in the pathway of care and therapeutic advances that may result in the need for policy review. | | |

Overall conclusions of the panel

The following indications should progress for routine commissioning: Extracorporeal photopheresis (ECP) for patients with acute GvHD and ECP, pentostatin, rituximab and imatinib for patients with chronic GvHD.

The following indications should progress for not routine commissioning: infliximab, etanercept, inolimomab, alemtuzumab, pentostatin or mesenchymal stem cells for patients with acute GvHD.

The policy should be updated to reflect the conclusions of the panel for each of the interventions for GvHD and progress to stakeholder testing

Report approved by:
David Black
Clinical panel chair (panel B)
17/2/16