# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Health Technology Appraisal

## Pharmalgen for the treatment of bee and wasp venom allergy

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Definitions:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

**Clinical specialists and patient experts** – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

**Commentators –** Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

## Comments received from consultees

| Consultee | Comment | Response |
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| Royal College of Physicians | The RCP is grateful for the opportunity to respond to the above ACD. Our experts are supportive of the general conclusions and have only a few comments.<br><br>1.2 - How is a specialist centre experienced in venom immunotherapy to be defined? We would suggest adding 'as evidenced by registration with the Royal College of Physicians scheme for registration of allergy services'.<br><br>3.4 - The evidence that being on ACE I inhibitors increases the risk of venom immunotherapy is considered weak and the term contraindicated should be changed to 'should be used with caution'.<br><br>We could not see any discussion of the value of using component resolved diagnosis to distinguish between IgE to venom proteins and carbohydrate moieties in people with dual specific IgE to wasp and bee. This is an important issue which needs to be addressed. We would favour the routine use of IgE testing to distinguish these patterns of specific IgE. | A NICE technology appraisal makes recommendations about the cost effectiveness of new and existing medicines, products and treatments for use in the NHS. NICE makes recommendations within the marketing authorisation (MA) for the products and the MA for Pharmalgen states that it should be provided within a specialist centre. The definition of such a centre is more appropriately considered as part of the decision problem for a clinical guideline, and is outside of the scope of a technology appraisal.<br><br>The FAD section 3.4 describes the contraindications as listed in the summaries of product characteristics (SPC) provided by the manufacturer of Pharmalgen at the start of the appraisal (SPC dated last revision to the text May 2010). NICE can only appraise a medicine within the context of its SPC.<br><br>NICE was requested by the DH to consider the treatment of bee and wasp venom allergy. The diagnosis of bee and wasp venom allergy is outside of the remit and scope for this appraisal. FAD section 4.3.2 describes the Committee's discussions on the current clinical practice for the diagnosis of bee or wasp venom allergy. |
| Royal College of Nursing | **Has the relevant evidence has been taken into account?**<br><br>The evidence considered seems comprehensive. | Comment noted. No changes to the FAD required. |

| Consultee | Comment | Response |
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| | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**<br><br>We would ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by people with venom allergy. The preliminary views on resource impact and implications should be in line with established standard clinical practice. | Comment noted. Sections 4.1 and 4.2 of the FAD include a summary of all the evidence submitted, including evidence from clinical trials and the Assessment Group's economic analysis. FAD sections 4.3.2 -4.3.4 describe the Committee's discussion on the current clinical practice for the diagnosis and treatment of bee or wasp venom allergy. |
| | **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**<br><br>Nurses working in this area have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.<br>The RCN would welcome guidance to the NHS on the use of this health technology. | Comment noted. No changes to the FAD required. |
| | **Are there any equality related issues that need special consideration that are not covered in the ACD?**<br><br>We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate. | Comment noted. The equality impact assessment for this appraisal will be published on the NICE website. |
| Royal College of Pathologists | **Has all of the relevant evidence been taken into account?**<br>Recently published UK guidelines from the British Society for Allergy & Clinical Immunology should be incorporated into the information base for the MTA (Krishna MT, Ewan PW, Diwakar L et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) Guidelines. Clin Exp Allergy 2011; 41: 1201-20). The ACD alludes to these guidelines (page 19) but they are not formally referenced here or in the full Evaluation Report. | The British Society for Allergy and Clinical Immunology (BSACI) guidelines are noted in the background section of the FAD – See FAD sections 2.3 and 2.7. The Committee was aware of the BSACI guidelines and these are discussed in the guidance document - see FAD section 4.3.4. |

| Consultee | Comment | Response |
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| | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br>Yes. | Comment noted. No changes to the FAD required. |
| | **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**<br>Yes. Recent BSACI guidelines also indicate that treatment with Pharmalgen may be considered in moderate reactions on the basis of remoteness from medical help, increased age, patient preference and co-morbid cardiac or respiratory conditions. | The Committee noted that Pharmalgen may be offered to people with a history of moderate systemic reactions to bee or wasp venom if they live far from emergency medical care, have certain co-morbid conditions, or request treatment with Pharmalgen. The Committee considered that these people with bee or wasp venom allergies who live far from emergency medical care, request treatment or have certain co-morbid conditions were likely to have heightened awareness of their situation and be anxious about the possible effects of having a systemic reaction from future stings. Therefore the Committee concluded that these groups were covered in its recommendations for people with a history of moderate systemic reactions, who are anxious about future stings –see FAD section 4.3.14. |
| | **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?**<br>None identified. | Comment noted. No changes to the FAD required. |
| | **Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?**<br>None identified. | Comment noted. No changes to the FAD required. |
| | **Specific comments**<br>Page 24, Evidence for clinical effectiveness section, para 2, line 4: insert ‘to’ between ‘…relevant’ and ‘Pharmalgen.’. | The FAD has been amended to reflect this - see FAD summary table page 24. |

| Consultee | Comment | Response |
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| Royal College of Paediatrics and Child Health | This is an excellent appraisal which has appropriately considered the needs of children with venom allergy.<br>While the recommendation is that this should only be used in a specialist centre, it does not define what co-dependencies are required. These must include the immediate proximity of intensive care relevant to the ages of patients being so treated, ie PICU for children.<br>Nothing to add, from a pharmaceutical viewpoint, to those comments already made by RCPCH.<br>Section 1: Recommendations – in view of the conclusions of the evaluation it would be appropriate to recommend that a national data base of the use of this therapy is created. | The Committee discussed comments about the need for specialist centres to have staff appropriately trained in resuscitation or immediate access to age-appropriate resuscitation facilities. It noted that the SPCs specify that Pharmalgen should be provided under supervision of a doctor experienced in specific immunotherapy and that because of the risk of potentially fatal anaphylaxis, treatment with Pharmalgen must be carried out in clinics or hospitals where full facilities for cardiopulmonary resuscitation are immediately available for use by adequately trained personnel. The Committee concluded that although Pharmalgen should be provided within a specialist centre, the details of the provision of resuscitation equipment was sufficiently specified in the SPC – see FAD section 4.3.16. |
| Department of Health | I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation | Comments noted no changes to the FAD required. |

## Comments received from clinical specialists and patient experts

| Nominating organisation | Comment | Response |
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| Anaphylaxis Campaign (David Glaser) | 3 - 1.1 A raised baseline serum is an indication that a future reaction may well be worse but it is also an indication potentially of other immune disease such as mastocytosis. In that context it is potentially more dangerous to use venom immunotherapy and so high baseline tryptase could be regarded by some practitioners as a contraindication for treatment due to the potential risk of anaphylaxis during the course of treatment. | The Committee discussed comments that mastocytosis may be associated with a raised baseline serum tryptase, and that a diagnosis of mastocytosis is a possible contraindication for Pharmalgen. The Committee concluded that this would be identified by the responsible clinician when considering whether to offer treatment with Pharmalgen. The Committee concluded that it was appropriate to include in its recommendations raised baseline serum tryptase as an additional risk factor for people who have had a moderate systemic reaction – see FAD section 4.3.15. |

| Nominating organisation | Comment | Response |
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| | 3 - 1.2 It is also very important that the specialist centre is located near to an ED | The Committee discussed comments about the need for specialist centres to have staff appropriately trained in resuscitation or immediate access to age-appropriate resuscitation facilities. It noted that the SPCs specify that Pharmalgen should be provided under supervision of a doctor experienced in specific immunotherapy and that because of the risk of potentially fatal anaphylaxis, treatment with Pharmalgen must be carried out in clinics or hospitals where full facilities for cardiopulmonary resuscitation are immediately available for use by adequately trained personnel. The Committee concluded that although Pharmalgen should be provided within a specialist centre, the details of the provision of resuscitation equipment was sufficiently specified in the SPC – see FAD section 4.3.16. |
| | 4 - 2.2 The definition of "anaphylactic shock" as per the Resus Council would include Mueller II and III. The August 2011 BSACI venom allergy guideline simply uses the term "systemic reaction" and avoids the thorny problem of the definition of "anaphylactic shock". I would suggest excluding the final sentence of 2.2.<br><br>5- 2.5 The emergency kit would typically only include the adrenaline injector so I think the "one or more" could be replaced by "on occasion" or some similar phrase. I think Pam Ewan confirmed this in the meeting - in fact to my knowledge the prescription of anything other than an adrenaline injector is rare.<br><br>16 - 4.3.3 I do not think this was an accurate reflection of what the clinical specialist said about the content of the emergency kit.<br><br>33 - C My name is spelt David Glaser! | This information was included in the ACD, but has been amended following comments from consultees – see FAD sections 2.2 and 2.3.<br><br>The FAD has been amended to reflect this - see FAD section 2.6<br><br>FAD section 4.3.3 has been amended following comments from consultees and commentators<br><br>Comment noted. The FAD has been amended to reflect this. |

| Nominating organisation | Comment | Response |
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| British Society for Allergy and Clinical Immunology (Dr Pamela Ewan and Dr Thirumala Krishna) | The recommendations are appropriate overall.<br>However, as pointed out in earlier comments (Aug 2011), areas of concern are inaccuracies in a. some of the clinical assumptions and b. some of the assumptions in the economic model.<br>This appears to arise from assumptions made in the Liverpool Review. Some are not consistent with recommended UK practice. Our concern is that if these are included, without qualification – that they are not representative of the expert view – that at a later stage, any body reviewing the evidence will assume they are correct. Some examples follow (boxes below) but this is not comprehensive.<br>Will the Liverpool Assessment Group report appear in full?<br>Would a solution be to add further qualifying statements, with the expert view [this has already been done in some places]?<br>4.2.3 Example. The logical comparator is venom immunotherapy (VIT) versus no VIT with provision of adrenaline auto-injector (AAI). Avoidance advice alone would not be given (this is a minor component of management with little impact). All treatment groups get the same avoidance advice. Giving 'avoidance advice alone' is not a recommended treatment option. This is covered in 4.3.6 | The MTA process is designed to provide recommendations on the use of new and existing medicines, products and treatments in the NHS. The Committee considers all the available evidence, including its reliability, when formulating its recommendations. The independent Assessment Report is one source of evidence considered by the Committee, and is published independently as an HTA monograph through the NIHR HTA programme. In the guidance document produced by NICE, the Committee's recommendations are detailed in section 1, the evidence as submitted to NICE is summarised in sections 4.1 and 4.2. The consideration of that evidence by the Committee is discussed in section 4.3. The independent Assessment Report does not reflect the recommendations by NICE, nor the Committee's consideration of the evidence. NICE does not respond to comments on the Assessment Report. |
| | 4.2.3 Example. Questionnaire used. A UK survey of allergy clinics offering VIT showed variable clinical practice, variable adherence to good practice and that current international guidelines for the diagnosis and management of hymenoptera venom allergy are not being followed (Diwakar et al Clin Exp Allergy 2008). Indications for VIT were variable. It is therefore questionable whether responses can be used for the economic model. BSACI have updated their guidelines (Krishna et al Clin Exp Allergy Aug 2011). This paper should be considered as the basis of and standard required in UK practice<br>Example. Economic model. In many patients AAI are not required after successful VIT. AAI appear to be included in all patients post VIT. This will falsely increase cost of VIT<br>Example. It is important to distinguish bee from wasp as efficacy and side effects vary. This not does not appear to have been addressed. In the paper it is assumed that bee and wasp venom IT are equally effective. Most VIT in UK is wasp, and this has a significantly higher efficacy rate and fewer side effects (SRs) than bee VIT. | The Committee discussed the consultation comments that some of the inputs in the economic model relating to costs, efficacy and the likelihood of having a systemic reaction while receiving treatment with Pharmalgen were not plausible. The Committee considered that although there are some uncertainties as to the plausibility of assumptions and inputs, the Assessment Group's sensitivity analyses showed that the estimates of cost effectiveness were not sensitive to changes in these parameters, but were sensitive to assumptions about utility and about how frequently a person is stung. On this basis the Committee concluded that the Assessment Group's model was an appropriate basis for decision-making despite uncertainties around the plausibility of some parameter estimates. See FAD section 4.3.9. |

| Nominating organisation | Comment | Response |
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| | **Yes all the relevant evidence been taken into account ?**<br>– Yes, but see above.<br><br>**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence ?**<br>– No<br>a. Page 5 and 22-23: Given that recommendations are based on 'moderate' and 'severe' systemic reactions, the classification of mild, moderate and severe systemic reactions should be clearly defined. We suggest the committee refers to recent BSACI guideline (Krishna MT et al. Clin Exp Allergy 2011;41:1201-20; Page-1206 [Table-5]).<br><br>b. Page 5 & 6: Diagnosis: Skin testing should be performed in all cases unless there is a reason they cannot be performed (this is rare; eg generalised severe eczema or unable to stop antihistamine therapy). Skin tests should be the primary diagnostic tool. Serum specific IgE can occasionally generate false positive results. | Comments noted. See response above.<br><br>The FAD has been amended to reflect this - see FAD section 2.3.<br><br>NICE was requested by the DH to consider the treatment of venom allergy. Issues relating to the diagnosis of venom allergy are outside of the remit and scope for the appraisal. Section 2.5 of the FAD is provided as brief background information. |

| Nominating organisation | Comment | Response |
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| | c. Page 6, section 3.4, Contraindications: This section is requires greater clarity.<br><br>i. Absolute contraindications include chronic severe/brittle asthma, heart failure or patients with 'poor' lung reserve. In other chronic heart and lung conditions, decision on venom immunotherapy (VIT) is based on a careful 'risk-benefit analysis' by the specialist. Mild/moderate chronic asthma and seasonal asthma are not absolute contraindications.<br><br>ii. Similarly, immunological disorders (immunodeficiency, systemic autoimmunity), malignancy, beta blockers, angiotensin converting enzyme (ACE) inhibitors are not absolute contraindications and decision on venom immunotherapy is based on a careful 'risk-benefit analysis' by the specialist. However, as far as possible beta blockers and ACE inhibitors should be withdrawn prior to commencing VIT.<br><br>iii. Pregnancy – VIT should not be initiated in pregnancy but may be continued if the patient has tolerated treatment and is in maintenance phase and there is a significant risk of insect sting/s. VIT does not have teratogenic effects. | FAD section 3.4 describes the contraindications as listed in the summary of product characteristics. The summary of product characteristics was provided by the manufacturer at the start of the appraisal (dated as having the last revision to the text May2010). NICE can only appraise a technology within the context of its marketing authorisation. Clinicians are referred to the Summary of Product Characteristics for further details on adverse events and contraindications. |
| | d. Page 8, section 4.1.3: Adverse reactions: Systemic reactions (SRs) reported in previous studies are influenced by dosage protocols and patient selection criteria and these data have to be interpreted cautiously. The range of SRs stated in the document are too broad (0-36.4%), and in routine clinical practice, SRs, in particular, grade 3 and 4 are extremely rare, particularly with the conventional (slow) 12 weekly up dosing. SRs are relatively more common with bee VIT and with 'ultra-rush/rush' protocols, the latter rarely employed in UK practice. | Sections 4.1and 4.2 of the FAD describes the evidence submitted, including evidence from clinical trials and the Assessment Group's economic analysis. The plausibility of the inputs in the economic model was considered by the Committee. The Committee, noting the Assessment Group's sensitivity analyses, considered that the cost effectiveness were not sensitive to changes in these parameters. See FAD sections 4.3.8 and 4.3.9. |

| Nominating organisation | Comment | Response |
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| | e. Page 11, section 4.2.5: Probability of SR to bee/wasp sting/s following Pharmalgen treatment: The figure of 38.5% for grade-1 in the 'Pharmalgen' group is incorrect. VIT reduces both severity and incidence of SRs to bee/wasp stings and this figure is significantly greater than the 2 comparative groups considered i.e., advice only and advice and AAI and this would have significantly affected the calculations for cost effectiveness against the 'Pharmalgen' group. Similarly, the figure of 54% for grade-2 SRs in Pharmalgen group appears relatively high. Wasp VIT is effective in about 95% of patients; bee VIT efficacy is lower 80-85%. | Comment noted; see response above. |
| | f. Page 12, section 4.2.6: SRs during VIT: SR rates of 12.5% for grade 3 and 4 reactions are unacceptably high, particularly for UK practice, where over 92% centres employ the 12 week up dosing protocol. | Comment noted; see response above. |
| | g. Page 12, section 4.2.7: Whilst dual sensitisation is common, dual clinical reactivity of 7% is unacceptably high. | Comment noted; see response above. |
| | h. Page 12, section 4.2.11, Costs to treat SRs during VIT: Patients developing grade 1-3 reactions are treated in the out patients department and the costs involved are covered with the 'standard tariff' for a follow up appointment. Grade-4 reactions are uncommon/rare and such patients are likely to be admitted for observation/treatment for a period of 12-24 hours. Therefore, the costing of £32.81 to treat grade 1-3 SRs would have significantly affected the calculations against the cost effectiveness of Pharmalgen. | Comment noted; see response above. |
| | i. Page 14, section 4.2.15, QALY/ICERs: There are additional costs for patients in the advice + AAI group which has not been factored into the model. Patients carrying AAI would require annual training (indefinitely, i.e., for life time) in nurse led clinic (£120 approx. per year). This would significantly increase overall costs for the advice + AAI group, i.e., not including these costs would have influenced the cost effectiveness of the Pharmalgen group adversely. | Comment noted; see response above. |

| Nominating organisation | Comment | Response |
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| | j. Page 17, section 4.3.3 Immunity: There is no data in the literature to support the statement that Pharmalgen induces 'lifelong immunity' in children. Observational studies in children have been up to 20 years only. It is suggested a similar statement (as currently stated for adults) is given for both adults and children. | Comment noted. This has been amended in the FAD. |
| | **Are the provisional recommendations sound and suitable for guidance to the NHS ? –**<br><br>These are acceptable but we recommend that patients with moderate SRs who live in remote rural areas with no immediate access to emergency medical care are also offered VIT (in addition to the groups already identified). | The Committee noted that Pharmalgen may be offered to people with a history of moderate systemic reactions to bee or wasp venom if they live far from emergency medical care. The Committee considered that these people with bee or wasp venom allergies who live far from emergency medical care were likely to have heightened awareness of their situation and be anxious about the possible effects of having a systemic reaction from future stings. Therefore the Committee concluded that this group was covered in its recommendations for people with a history of moderate systemic reactions, who are anxious about future stings. –see FAD section 4.3.14. |
| | **Are there any aspect of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief ?**<br><br>– No | Comment noted. No changes to the FAD required. |
| | **Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document ?**<br><br>- No | Comment noted. No changes to the FAD required. |
| Anaphylaxis Campaign (Moira Austin) | My comments are that:<br>• All of the relevant evidence has been taken into account.<br>• The summaries of clinical and cost effectiveness are reasonable interpretations of the evidence.<br>• The provisional recommendations are sound and are a suitable | Comment noted. No changes to the FAD required. |

| Nominating organisation | Comment | Response |
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| | basis for guidance to the NHS? | |

## Comments received from commentators

| Commentator | Comment | Response |
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| Healthcare Improvement Scotland | **Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results?**<br>NO - I would say that optimal alternative medical therapy should also include regular prophylactic therapy with histamine/leukotriene antagonists ,in addition to acute rescue therapy with high dose antihistamines ,corticosteroids and adrenaline . Such comparative data does not exist . | The Committee discussed the relevant comparator for Pharmalgen. It heard from the clinical specialists that people with a history of systemic reactions to bee or wasp venom are offered an adrenaline auto-injector (and training in its use) to carry and use following a bee or wasp sting that is accompanied by symptoms of a systemic reaction. The Committee concluded that an adrenaline auto-injector given alongside avoidance advice was the most appropriate comparator for Pharmalgen treatment. See FAD section 4.3.6. |
| | **Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations?**<br>YES | Comment noted. No changes to the FAD required. |
| | **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound?**<br>YES with the pro viso that in addition to Pharmalgen regular allergic mediator blockade should be considered during periods of high risk such as the summer months –the latter may modify the acute response to sting and allow more time to use adrenaline and seek medical help. | Comment noted. The technology in the appraisal is Pharmalgen. NICE can only make recommendations about the use of the intervention under appraisal. |
| | **Are the patient pathways and treatment options described in the assessment applicable to NHS Scotland? If not, how do they differ in Scotland?**<br>YES | Comment noted. No changes to the FAD required. |