NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Omalizumab for treating severe persistent allergic asthma (review of TA133 and TA201)
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
Novartis	Novartis is extremely disappointed and surprised that this draft guidance from NICE does not recommend omalizumab, thus effectively proposing to reverse the positive TA 133 recommendation for patients aged 12 years and older that was issued in November 2007. We are concerned that, should NICE's draft recommendation become final guidance, patients of all ages with severe persistent allergic asthma will be left without access to this unique and highly innovative treatment option. We are pleased that the Appraisal Committee has again recognised that omalizumab is a clinically effective treatment for patients with severe persistent allergic asthma. In this respect, the ACD acknowledges the benefits of omalizumab on outcome measures that are relevant to patients with this condition e.g. reductions in asthma exacerbations, reductions in unscheduled use of healthcare resources (e.g. hospitalisations), improvements in health related quality of life (HRQoL) and reductions in exposure to oral corticosteroids (OCS). Such benefits closely align with the scope of the recently announced NHS Mandate which includes national indicators on HRQoL and unplanned hospitalisation in people with long-term conditions, the latter specifically in people under 19 with asthma. We disagree with the Appraisal Committee's view that omalizumab is not a cost-effective use of NHS resources and believe there are potentially important benefits of omalizumab treatment that have not been fully captured in the independent economic evaluation and subsequent 'additional analyses' conducted by the Assessment Group. We strongly believe that omalizumab can be used cost-effectively when it is appropriately targeted towards subgroups of patients with 'very severe' allergic asthma who are at the highest risk of asthma-related mortality and serious OCS-related side effects. We are concerned by the lack of clarity in the ACD on four main points:- **1. <u>Rationale for Proposing to Reverse the TA 133 Recommendation</u>** The ACD offers no clear justification for the proposal to reverse the TA 133 recommendation. The ACD should specify the exact changes to the evidence base that led the committee to consider that plausible cost-effectiveness estimates were, in their opinion, higher (i.e. worse) than in 2007. Having discussed this issue with	Noted. The Committee's final appraisal determination recommends omalizumab as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year) and only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme. Noted. The Committee has concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21) Noted. The reversal of TA133 proposed in the ACD was primarily based on the

Consultee	Comment	Response
	representatives of NICE, we understand the Committee's negative decision to be primarily based on cost-effectiveness grounds due to new evidence on asthma-related mortality (de Vries et al. 2010) that was published since TA 133. If this is the case, this position should be clearly stated in the ACD. Without this justification, stakeholders are left unclear on what specifically led NICE to arrive at their draft decision.	newly available asthma-related mortality data from on de Vries which when applied to the economic model resulted in an ICER of £83,800 per QALY gained for adults and adolescents. (See ACD 4.4.12).
	For future reviews of existing guidance we suggest that NICE includes a dedicated section in the main body of the ACD and the summary table that addresses (i) changes to the evidence base since the previous review (ii) the impact of these changes on the 'most plausible' incremental cost-effectiveness ratio (ICER) and (iii) the rationale for changing the recommendation (if it is different from the recommendation of the previous review). We also suggest that NICE takes steps to ensure that the content of its press releases is completely congruent with the content of its guidance documents. For example, in this case, NICE's press release stated that omalizumab *"was not as clinically effective as was first thought"*. This is not a view stated in the ACD and created considerable confusion for stakeholders regarding the rationale for the draft decision.	Noted.
	2. <u>Patient Population</u> The ACD focuses mainly on three subgroups of patients receiving maintenance OCS but does not appear to arrive at a clear determination on which one is the most appropriate in UK clinical practice. Based on the ACD content and clinical expert opinion in Evaluation Report we strongly believe that the 3rd population defined on p50 of the ACD **i.e. patients on maintenance OCS <u>or</u> >=4 courses of OCS per year)** is the most clinically relevant population in UK practice and offers the most sound basis for positive guidance to the NHS. Hereafter, we refer to this patient population as ***"Subgroup 3".***	Noted.
	3. <u>'Most Plausible' ICERs and 'Most Plausible' Asthma-Related Mortality Rate</u> The ACD is vague on what the Committee considers to be the 'most plausible' ICER and cites a wide range of £31K per QALY (based on Watson et al. 2007 asthma mortality rates +15%) to £42K per QALY (based on de Vries et al. asthma mortality rates + 15%). However, it also states that *"The Committee agreed that the asthma-related mortality rates applicable to this appraisal were likely to be between the Watson et al. and De Vries et al. estimates"* (ACD 4.4.9, p47). In principle, we are pleased the Committee agrees that patients in 'very severe' subgroups are at an elevated risk of asthma-related mortality which exceeds the rate reported by de Vries et al. (2010). However, whilst we	Noted. The Committee considered that there was significant uncertainty as to what could be the most plausible ICER at the time of the ACD. In the FAD, however, the Committee considered that using the asthma-related mortality rate midpoint between Watson et al. and de Vries et al. inflated by 15%, the 4.75%

Consultee	Comment	Response
	accept that there is inherent uncertainty, we suggest that the Committee should reach a judgement on where the asthma mortality rate is most likely to fall within this range, and hence where the 'most plausible' ICER is most likely to fall in the £31K-£42K per QALY range. The ACD also indicates that the 2.2% proportion of children in the Assessment Group's weighted average cost-effectiveness analyses may be an underestimate. However, employing alternative proportions of children in the Assessment Group model has little impact on the 'overall' age-weighted ICERs. **4. <u>Rationale for Lack of Consideration of 'Additional' OCS Side-Effects and HRQoL Benefits</u>** There is strong qualitative evidence highlighted in the ACD and Evaluation Report that chronic treatment with OCS increases the risk of a number of serious adverse effects which are not currently accounted for in the economic modelling due to a paucity of empirical data. The ACD also notes that frequent OCS courses are likely to adversely impact patients' lives but this impact is also not quantified in the OCS-sparing analyses. In a similar vein, we also note that '*The Committee agreed that there could be additional health-related benefits conferred to carers as a result of omalizumab use but that these were currently not quantifiable'* (ACD 4.4.7, p45). On each of these points, we question whether having no empirical evidence despite likely benefit is reasonable grounds for assuming no benefit at all. By not capturing these benefits, we believe that the £31K-£42K per QALY range cited in the ACD underestimates the cost-effectiveness of omalizumab. These and other issues are discussed in detail in our response which is structured as follows:- *A. Main Comments on the ACD* *B. Supplementary/Minor Comments on the ACD* *C. Comments on the Evaluation Report* *D. References* In summary, we accept that there is some uncertainty regarding asthma-related mortality rates in the economic model but feel that, with a mortality rate that is plausible in patients with 'very	proportion of children aged 6 to 11 in the overall population eligible for omalizumab and incorporating the patient access scheme for omalizumab resulted in a most plausible ICER of £23,200 per QALY gained for adults, adolescents and children on maintenance or frequent courses of oral corticosteroids defined as 4 or more courses in the year before receiving omalizumab. (See FAD 4.4.20) Noted. The Committee has acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.22)

Consultee	Comment	Response
	severe' asthma, this uncertainty could be offset by the unquantifiable benefits of omalizumab on the reduction of 'additional' OCS side-effects and the improvement of carer quality of life. We acknowledge, however, that empirical data are limited in these areas and that this represents a challenge for the Appraisal Committee. Therefore, as you are aware, and to attempt to fully address any remaining empirical uncertainty around the cost-effectiveness of omalizumab, Novartis has submitted a confidential simple discount Patient Access Scheme (PAS) for consideration by the Department of Health and NICE's Patient Access Scheme Liaison Unit (PASLU). A formal submission of the PAS to NICE will follow in due course, subject to ministerial approval. We believe it is important (assuming approval from the relevant bodies mentioned above), that this PAS is considered alongside our comments on the ACD at the next Appraisal Committee meeting on 22nd January 2013. Also provided with this ACD response is a document entitled ***'Additional Cost-Effectiveness Analyses'***. Further to the agreement obtained from NICE, this document provides some scenario analysis based on the issues raised in points 2 and 3 of this letter. It also provides estimated ICERs with and without the proposed PAS. Please note that this ACD response should only be read in conjunction with the document entitled ***'Additional Cost-Effectiveness Analyses'*** and should not be considered in isolation. I hope that our comments are of value. If you require clarification on any aspects of our response, please do not hesitate to contact me.	
Asthma UK	Asthma UK is pleased to have the opportunity to respond to the consultation document and evaluation report. Our response includes a small selection of the dozens of views that have been shared with us by people with asthma and their families since the consultation was launched (a comprehensive set of comments is included as an appendix). The people who would typically be treated with omalizumab in the UK are seriously ill because of their asthma. We know from the APEX study from clinical experts and most importantly from patient experience that many of them have frequent severe asthma attacks and almost constant breathlessness which makes it impossible for them to do things that other people take for granted. They also suffer terrible side effects from treatments which they have felt compelled to take for years because there was no more effective alternative until omalizumab became available. Denying access to omalizumab now will lead to a lot of unnecessary suffering among a small group of people who are very severely affected by asthma. **On behalf of these people, Asthma UK would like to see a positive recommendation for omalizumab in a subgroup of patients aged 6 and above who are on maintenance or**	Noted. The Committee has concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab should be recommended as an option for add-on treatment to optimised standard therapy for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year). (See FAD paragraph 4.4.21) The Committee has acknowledged the uncaptured benefits of reducing

Consultee	Comment	Response
	frequent courses of oral corticosteroids. We would like to draw the committee's attention to three key issues which are of concern to patients before moving on to address the consultation questions where we elaborate in more detail. These are: A. **Change of recommendation in the absence of significant new evidence.** People with asthma, especially those who currently benefit from omalizumab, find it difficult to understand the rationale for reversing NICE's previous recommendation in favour of omalizumab for adults (TA 133). In 2010, NICE published an explanation that it had recommended omalizumab despite a cost per QALY of >£30,000 because of the severity of the illness, the strength of stakeholder feeling and the degree of innovation from the treatment. All of these circumstances remain unchanged; severe asthma remains a very serious condition, people with asthma very much want omalizumab to remain available and there are no other options for many of the people who use it. 'It's amazing, I started 6 years ago and it totally changed my life around, I was told there was nothing more they could do and was basically going to die, then I started this and I'm here today living a life. It's so sad for people in the position I was in as it could be their last life line.' Neither has there been significant change in the evidence of effectiveness of omalizumab. Instead, the main change in cost-effectiveness estimates has been driven by the use of different mortality rates in the model. The committee has acknowledged that there are flaws with both available estimates of asthma mortality, so Asthma UK does not feel that it is fair to patients to move towards using a mortality estimate which generates a higher ICER. 'Xolair has saved my son's life. He is stage 5 and very severe – he's been using singular for years. I will be very concerned if it's stopped as we've been told by doctors his asthma will kill him.' **B. Inadequate consideration of the side-effects of oral corticosteroids** Side effects of oral corticosteroids are frequently described by people with severe asthma as one of the worst things about their condition, and we know that omalizumab can help to	dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.21) Noted. The reversal of TA133 proposed in the ACD was primarily based on the newly available asthma-related mortality data from on de Vries which when applied to the economic model resulted in an ICER of £83,800 per QALY gained for adults and adolescents. (See ACD 4.4.12). See above.

Consultee	Comment	Response
	reduce the need for long-term high doses of these treatments. Asthma UK respects the efforts made by the Committee to take the impact of these side-effects into account and recognises that the evidence that was presented had some limitations. However, we do not agree with the Committee's judgment that it is implausible for the unquantified adverse effects to exceed the quantified adverse effects. The unquantified effects are among those most commonly reported by patients as having a major impact on their quality of life and there is published evidence of significant DALY losses and NHS costs from these conditions in the general population. We therefore feel it is highly plausible that these adverse effects would be enough to bring the ICER below NICE's informal £30,000 threshold. 'As a severe asthmatic - I've relied HEAVILY on Xolair since 2007 - when it gave me my life back. Although my asthma is still classed as severe - it certainly helped me - and I doubt I would still be here without it. I worry that it will be withdrawn from me - and I will have to rely on steroids even more than I do now - which is a terrifying concept - with all the side effects. In my view - this is just a cost cutting exercise, but sadly it's hitting the most vulnerable - the chronically sick.' **C. Lack of consideration of family and carer benefits** People with severe asthma and parents of children with severe asthma often tell us about the impact of the condition on family life and on the health and wellbeing of the family members who are indirectly affected. Asthma UK was therefore disappointed that no attempt was made to quantify the health and personal social services impact of omalizumab on the families and carers of people who are taking it. This could have had a favourable impact on the ICER. **Consultation questions** **1. Has all of the relevant evidence been taken into account?** No. From the patient perspective, there are two major gaps in the evidence that has been considered. These are evidence of side effects of oral corticosteroids and evidence of family and carer benefits. In addition, it is important to note that there is evidence from patients of some important benefits which fall outside NICE's usual scope for consideration. For example, many people with severe asthma have been able to return to work or education as a result of this treatment. **1.1 Evidence of the impact of side effects from oral corticosteroids**	See above. See above.

Consultee	Comment	Response
	The strength of feeling among people with asthma about the negative impact of long-term, high-dose oral corticosteroids cannot be exaggerated. NHS Evidence-accredited asthma guidelines state that 'patients on long term steroid tablets… or requiring frequent courses of steroid tablets (eg three to four per year) will be at risk of systemic side effects'. This is also widely recognised by clinicians, but many of the adverse effects – even those which are well-evidenced in the literature - have not been fully taken into account. 'I think NICE just does not realise what difference it makes talking Xolair instead of high level steroids. They may think its not cost effective - but that is looking at it very short sightedly! They are not considering the fact that Xolair patients are usually able to "contribute to society" as they are able to work, look after their families and live pretty normal lives ...whereas life on high level steroids is everything but normal. Apart from dealing with the "soft" side effects (hair loss, weight gain, thin skin) there are also heavy long term issues - like heart disease and osteoporosis, etc to look at this is not taking in to consideration that one is feeling "poorly" most of the time and is not able do as much as one likes or wishes.' There is good evidence that the side effects of oral corticosteroids include mental health impacts, obesity, skin problems and many other conditions (listed in Table 1) which have not been incorporated into the cost-effectiveness model used in this appraisal. Many of these side effects from systemic corticosteroids are in areas which lead to major public health concern, significant utility losses and high financial cost to the NHS – particularly obesity and mental illness (including depression and anxiety). We feel that evidence in this area has not been adequately considered. **1.2 Evidence of the impact of severe asthma on family and carers and of potential benefits of omalizumab in reducing this** 'My son is a severe asthmatic not well controlled and had been told he would have to wait until he was at least 12 to get it (he's 9). This is really bad news for us. It seems severe asthma is seen as very low priority, despite the fact it has such a devastating effect the quality of life of the asthmatic and their family. Most people perceive it as being a bit wheezy. They should spend a week in the life of an asthmatic and see something as basic as breathing is so hard.'	See above.

Consultee	Comment	Response
	Unfortunately, severe asthma affects entire families, not just the person who is ill. In particular, childhood severe asthma can have a very important impact on parents. Qualitative research and the stories of people in contact with Asthma UK demonstrate a pervasive impact of childhood asthma on daily life, with significant emotional burdens for those affected. Parents – particularly mothers - are more likely to suffer from depression if their child has asthma - and the severity of a child's asthma symptoms is also associated with the likelihood of maternal depression. A US study found that mothers of children with persistent asthma were 2.77 times as likely to have depression as the mothers of those with intermittent asthma. Asthma symptom persistence and severity also has a more general impact on parental quality of life, impacting both emotional function and activity limitation. This suggests that successful treatment to reduce asthma symptoms should have an important impact on quality of life. Omalizumab does this; the committee has already heard from a patient expert about the benefits that it can have for a family. While it may not have been possible to quantify this impact in the cost-effectiveness model, we would urge that it ought to be taken into consideration as a special factor. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Not entirely. The threshold analysis conducted for the appraisal by the assessment group found that between 47% and 58% of the negative health consequences of oral steroids would need to have been unquantified in the cost-effectiveness model in order for omalizumab to be cost-effective at £30,000 per QALY (ie that the unquantified consequences would need to be between 0.9 and 1.4 times the quantified consequences). The Committee judged that this was not plausible. Based on what patients say to Asthma UK, we strongly disagree. Table 1 identifies side effects of oral steroids that are reported by patients to Asthma UK and which of these side effects have been incorporated into to the cost-effectiveness model that was presented to the committee. Of the 16 people who we interviewed for our initial submission to the committee, all had taken oral steroids either as maintenance medication or for multiple short bursts and 14 of them reported side effects without prompting. Many commonly-reported side-effects have not been included in the cost-effectiveness model, including some of those which have been recognised in systematic reviews of literature and which patients feel have a very significant impact on their quality of life. Mental health problems and weight gain are the side effects which are most often highlighted by people with	See above. See above.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>asthma as having a significant impact on their quality of life; neither of these is considered in the cost-effectiveness analysis, which leads us to believe that the quantified adverse effects of oral corticosteroids are a serious underestimate of their overall impact on patients.

Table 1: side effects of oral corticosteroids

<table>
<tr><th>Side effect</th><th>Ever reported by patients to Asthma UK?</th><th>Number of times reported by patients interviewed for current MTA (n=16)</th><th>Recognised in systematic review of literature</th><th>Included in cost-effectiveness analysis</th></tr>
<tr><td>Fracture/osteoporosis</td><td>Yes</td><td>5</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Diabetes</td><td>Yes –reported in 2010</td><td>0</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Peptic ulcer</td><td>No</td><td>0</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Stroke</td><td>No (though weight gain and increased blood pressure are reported)</td><td>0</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Cataract</td><td>Yes</td><td>1</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Myocardial infarction</td><td>No (though weight gain and increased blood pressure are reported)</td><td>0</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Glaucoma</td><td>No</td><td>0</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Non-Hodgkin’s</td><td>No</td><td>0</td><td>Yes</td><td>Yes (but the</td></tr>
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Consultee	Comment					Response
	lymphoma				analysis did not include NHS costs saved, only QALYs gained)	
	Sleep disturbance	Yes	5	Yes	Yes (but the analysis did not include NHS costs saved, only QALYs gained)	
	Adrenal insufficiency	Yes	2	Yes	Yes (but the analysis did not include NHS costs saved, only QALYs gained)	
	Mental health problems (categorised in assessment report as 'mood disturbance')	Yes - depression, anxiety, aggression and one case of psychosis	9	Yes	No	
	Weight gain	Yes – and patients also mention this worsening other conditions such as sleep apnoea	9	Yes	No	
	Abnormal hair loss/growth	Yes – reported in 2010	0	Yes	No	
	Skin conditions	Yes – reported in 2010	0	Yes	No	

Consultee	Comment	Response

Lethargy/weakness	Yes	1	Yes	No
Pain	Yes	2	Yes	No
'Moon face' or Cushing's Syndrome	Yes	2	Yes	No
Headaches/migraines	Yes	2	Yes	No
Reflux	Yes	2	Yes	No
Growth impairment	Yes – reported in 2010	0	Yes in children	No
Nausea/vomiting	Yes	2	Yes in children	No
Menstrual problems	Yes	1	Yes, but low quality study	No
Oral thrush	Yes – reported in 2010	0	No	No
Dental problems	Yes – reported in 2010	0	No	No
Carpal Tunnel Syndrome	Yes	1	No	No
Hot flushes	Yes	1	No	No
Tremors and palpitations	Yes	1	No	No
Liver damage	Yes	1	No	No

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. Asthma UK would like to see a positive recommendation for omalizumab in a subgroup of patients aged 6 and above who are on maintenance or frequent courses of oral corticosteroids.

Consultee	Comment	Response
	Omalizumab is an innovative treatment for a serious condition – indeed, it is the only treatment that has succeeded for some people who are so severely affected by their asthma that they would otherwise be virtually housebound. We strongly urge the Committee to reconsider its recommendation for this small subgroup of patients. Making it treatment available to these people under specialist supervision would be a pragmatic approach which ensures access to an important treatment while limiting the total financial burden on the NHS. 'My 11 year old just [read] a newspaper article about this and burst into tears. She is on week 9 of a 16 week trial for Xolair and she has been able to do PE for the first time in 2 years. She has also not had any hospital admissions since being on it which is a miracle. She still suffers some symptoms but not nearly as bad as she was.'	
British Thoracic Society	The British Thoracic Society notes the provisional recommendation that: 1.1 Omalizumab is not recommended within its marketing authorisation for treating severe persistent allergic asthma. 1.2 People currently taking Omalizumab should be able to continue treatment until they and their clinician consider it appropriate to stop. For children and adolescents, this decision should be made jointly by the clinician, the child or adolescent, and their parents or carers. It is the experience of clinicians working with those who have severe asthma that in the small number of patients for whom it is suitable and effective, it is life transforming. * Has all of the relevant evidence been taken into account? We note that the manufacturer did not perform studies in the population for whom the drug was made available by NICE. * Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We note the different assumptions made by the NICE Assessment Group in their model compared to that of the Manufacturer. We agree with some of their changes, for example in using a lower mortality rate than the perhaps unrealistically high figure derived from the Watson paper. However, we would like clarification around the assumption that "people in the state of day-to-day asthma symptoms (and not only the state of clinically significant severe exacerbation) have an elevated risk of asthma-related death compared with people without asthma and could die because of asthma" (para 4.2.18). It is true that people with asthma do not always recognise or act on a deterioration in symptoms and may therefore appear to die suddenly "out of the blue", but asthma mortality studies show that in the majority of deaths	Noted. The Committee has concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21)

Consultee	Comment	Response
	there is a discernible period of time in which action might have been taken i.e. in a large majority of cases, death is preceded by clinically severe exacerbation. This is important in terms of translating Omalizumab's effect on reducing exacerbations into a mortality benefit in the cost-effectiveness analysis.	
	We are not convinced that the manufacturers were wrong in their model to use AQLQ data mapped to EQ-5D. AQLQ is a disease specific QOL measure with well validated responsiveness to change data, and the AQLQ data used by Novartis was taken from a superior study (INNOVATE) whilst the Assessment Group used EQ-5D data from the open-label EXALT study. In this instance we think the manufacturer made a better choice than the NICE Assessment group.	Noted. The Committee preferred the Assessment Group's method of using direct estimates of EQ-5D values to the manufacturer's approach of mapping Asthma Quality of Life Questionnaire scores collected in the INNOVATE trial onto EQ-5D values as it is in line with the NICE reference case to use direct estimates of EQ-5D values. (See FAD 4.4.10)
	We note that the Scottish Medicines Consortium, in reviewing the same data, approved Omalizumab and made the drug available to patients who were dependent on oral steroids. This would be the substantial majority of patients in the UK for whom the drug is used and the current NICE position will introduce significant inequity in this severe asthma population within the UK, where therapeutic options are extremely limited.	
	We also note that the NICE models assess only direct costs, which excludes any indirect cost such as lost work days and potentially more significantly, the cost of systemic steroid induced morbidity. While there may be no good reliable data at this point, there are almost certainly longer term economic benefits in reducing steroid burden.	The Committee acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.22)
	We do not feel that the impact of oral corticosteroids has been taken into account sufficiently when deciding on cost effectiveness of Omalizumab. This clinically effective treatment should not be withheld due to the inability of health economists to accurately cost the undoubted morbidity attached to long term oral corticosteroid use. Using the ICER per QALY is inappropriate in a patient population with lifelong severe disease, but an overall low mortality.	
	* Are the provisional recommendations sound and a suitable basis for guidance to the NHS?	
	The provisional guidelines are not sound, nor suitable. Omalizumab is a well established treatment for severe asthma across Europe and the USA.	Noted. See above.
	The loss of this effective therapy, which is steroid sparing in this population, would be a significant backward step in severe asthma care and is significantly out of step with established best practice for severe asthma.	
	The document is long and complicated and would benefit from being simplified.	Noted.
Department of Health	The Department of Health has no substantive comments to make, regarding this consultation	Noted.

Consultee	Comment	Response
Primary Care Respiratory Society	The Primary Care Respiratory Society supports Asthma UK's objections to the ACD recommendation that omalizumab is not to be used for people with severe asthma. We have seen that omalizumab has had truly dramatic results in a small group of patients with severe allergic asthma and are very concerned that these patients will not have the benefits of this treatment any longer. The negative effects of high dose steroids are considerable in patients' lives and removal of omalizumab from the armamentarium will result in omalizumab patients returning to a life dominated by the difficulties and side effects associated with high dose inhaled and oral steroids. It appears that this product has been used responsibly and in line with NICE guidance from 2007 and in line with the licensed indications, and initiated by specialists in the relevant patients. In the absence of any significant new evidence on the effectiveness of omalizumab, it is puzzling how NICE has arrived at a different decision from its previous review of the evidence on adults. We must draw the conclusion that either the first decision in 2007 or this decision is therefore not sound. We urge NICE to consider carefully the content of the submission from AsthmaUK, and to reconsider the proposal not to recommend omalizumab. The Primary Care Respiratory Society has also reviewed and supported the submission by the British Thoracic Society.	Noted. The Committee has concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21)
Royal College of Nursing	The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults (review of TA133 and TA201). Nurses caring for people with asthma were invited to review this consultation document on behalf of the RCN. **Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Omalizumab for the treatment of severe persistent allergic asthma in children aged 6 and over and adults (review of TA133 and TA201). The RCN's response to the questions on which comments were requested is set out below:	

Consultee	Comment	Response
	i) **Has the relevant evidence been taken into account?** This seems reasonable. ii) **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?** In summary and in response to the Appraisal Committee, we consider that from a professional and clinical perspective, the Committee has made the wrong decision in not recommending omalizumab for the treatment of severe persistent allergic asthma. Our clinical expert gave her opinion based on the evidence and clinical effectiveness of the drug submitted to the Appraisal Committee and clinical experience of using omalizumab in children attending a demanding asthma service in Leicester over the last 4 years. In this trust, they initiated treatment with this health technology in eight children. Over this time frame; after careful consideration and assessment they deduced that these children were suitable candidates for this treatment and where all other licensed medications had been tried. To date seven out of the eight children continued with the treatment past the sixteen week assessment and there has been considerable improvement not only in their asthma control but also in theirs and their family's quality of life. The feedback from these children and their families is that treatment with omalizumab has been life changing in not only reducing exacerbations and hospital admissions but also in allowing them to reduce or stop their oral steroid treatment which is of extreme importance considering the potential and actual side-effects of corticosteroids. We note that that this concern was recognized by the Committee who concluded 'that some adverse effects of oral corticosteroid use, such as obesity, hypertension, mood changes, depression, psychosis, thinning skin, delayed wound healing, reduced growth in children, and increased risk of infection were additional important factors' but that these 'had not been captured when calculating the QALY'. (4.4.13) As healthcare professionals involved in the care and management of children with severe allergic asthma, reducing the actual and potential risk of the corticosteroids and reducing the risk of acute and potentially life threatening asthma attacks is paramount.	Noted. The Committee concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21) The Committee acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.21) Noted. See above.

Consultee	Comment	Response
	The feedback from the families and children also showed improvements to their quality of life based on the Juniper Paediatric Quality of Life Questionnaire (PAQLQ) scores, and carers' quality of life questionnaire score. Again, this is in line with the Committee's view that there could be additional health-related benefits conferred to carers as a result of omalizumab use 'but that these were currently not quantifiable.' (4.4.17) iii) **Are the provisional recommendations of the Appraisal Committee sound and suitable basis for the preparation of guidance to the NHS?** In summary, we consider that the decision not to support the use of omalizumab is going to deny a small but important and vulnerable group of children and adults the opportunity to have treatment with a drug that has been shown to be clinically effective and has undoubtedly changed and improved the quality of lives for those that have had the opportunity to have this treatment in the last four years. iv) **Are there any aspects of the recommendations that need particular consideration to ensure avoidance of unlawful discrimination against any group of people on grounds of gender, race, disability, age, sexual orientation, religion or belief?** None that we are specifically aware of at this stage. v) **Are there any equality related issues that need special consideration that are not covered in the ACD?** This health technology has a positive impact on a vulnerable group of children and adults. We would ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Noted. The Committee made a recommendation across all age groups. No equality issues relevant to the Committees recommendations were raised throughout the appraisal process.
Royal College of Paediatrics and Child Health	We strongly disagree with the proposal by NICE not to recommend omalizumab within its marketing authorisation for treating severe persistent allergic asthma. The use of omalizumab in children has been limited to those with severe disease. The majority of paediatric prescribers will be British Paediatrics Respiratory Society (BPRS) members. A recent survey (carried out in November 2012) of BPRS members indicates that at present there are 120 children in England currently using omalizumab. Approximately 50 children per year are started on omalizumab, of which between 50% and 75% will have a good or very good	Noted. The Committee concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated

Consultee	Comment	Response
	response and continue with treatment. Children with the severest form of asthma frequently require long term oral prednisolone treatment to keep their disease under control. The health consequences of long term oral prednisolone use in children are significant and include adrenal suppression, growth failure, weight gain, behavioural problems, osteoporosis, diabetes and cataracts. Every possible alternative to long term oral steroids for the management of severe asthma in children should be considered. RCPCH would like NICE to consider recommending the continued use of omalizumab in children requiring long-term (more than 3 months daily use) maintenance oral steroids for asthma control who in addition: 1. Fulfil the existing requirements of omalizumab use 2. Have been evaluated in a tertiary level paediatric respiratory clinic 3. Have had all alternative therapies considered 4. Have had their adherence to therapy assessed and confirmed as satisfactory The outcome for continued use should be a significant symptomatic improvement at 16 weeks as per the existing guidance and at least a 50% reduction in maintenance of oral steroid use by 12 months. "Are the recommendations sound and suitable….?" No "Do aspects to avoid discrimination need particular attention?" Yes The 2 recommendations, 1.1 and 1.2 are incompatible. Either, NICE should judge that omalizumab should not be prescribed or even continued for those already receiving it or it should continue to be available for those with nightmare asthma. The 1.2 recommendation is a clear admission that this treatment is highly effective and has revolutionised the lives of a small number of very severe asthmatic patients and it would be unethical to withdraw treatment. However, those individuals who have yet to start the therapy are being discriminated against in being denied this opportunity for a dramatically improved quality of life exclusively on the basis of cost. This should state not only that asthma can be severe but it can also be life-threatening. This should state that the consequences of asthma in childhood include increased school absences, compromised educational attainment and exam results with an effect on career	asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21)

Consultee	Comment	Response
	prospects and therefore the future life of the individual. It is sad to say that despite the guidelines, good control is not achieved in a high percentage of cases. Step 5 of the guidelines includes considering omalizumab. The list of side effects of oral corticosteroids which are considerable and life crippling are the alternative future on offer for patients who might otherwise benefit from omalizumab. The evidence is that FEV 1% predicted at baseline has no influence on clinical response to treatment particularly in children. NICE have conceded that omalizumab has evidence of efficacy from a large number of relatively high quality trails in adults and young people and less but still equivalent evidence in children down to 6 years of age. It is important to emphasise that conclusions are based on mean responses and conceal the fact that some patients have spectacular improvements while others have none. The recommendation is that response is reviewed at 16 weeks with the opportunity for reimbursement of costs if the response is deemed inadequate. The key to the whole evaluation is the model which is used to calculate QALYs. As indicated in this section the range from different studies is very wide. The NICE choice of model has put the costs above their bar for recommendation but this is clearly open to dispute. No QALY has taken fair account of the burdens of severe disease in children. This was admitted by the head of NICE during a meeting with RCPCH. The summary is that NICE reject the use of omalizumab based exclusively on cost while admitting the following; – It is highly effective in a sub-group of very severe asthmatics – Its side effects are mild by comparison with the alternatives – The alternative of long term oral steroids or other immunosuppressives have extensive, severe and life modifying side effects	The Committee acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.21)
	In the UK omalizumab is used very selectively and less than licensed indications might have suggested. In other words clinicians are acting very responsibly in the use of this product. This is clearly discrimination against a very small patient group who will now be denied an effective and safe treatment which could revolutionise their lives. Many other countries in the Western world have approved its use. Thus the English population is being discriminated against, in comparison to most other EU countries, including Scotland. This is shameful. Trials have recently been completed on the use of omalizumab in chronic urticarial and others	Noted.

Consultee	Comment	Response
	are in progress on severe eczema, food allergy and ABPA. All are showing very promising results. On the basis of this assessment it is highly improbable that patients with complex and severe allergic disease will have any chance of receiving this therapy. Furthermore, it is unlikely that Novartis will fund any continuing research into the use of this product in the UK. Are the clinical and cost effectiveness reasonable? NO Are the provisional recommendations sound and form a good basis? NO Are there discrimination and equity-related issues? YES Either NICE recommends usage or not. As it does not recommend omalizumab usage it should state that those receiving it should cease to do so. Otherwise it is sitting on the fence. The simplistic statement that control is achieved by stepping up or down treatments according to guideline recommendations is at variance with the experience of those involved in the everyday care of asthma. Control of asthma is universally poor in adults and children with little evidence that guidelines have had a major effect on improving that control. Lung function is a poor measure of asthma control or response to therapy in children. Not all patients respond in the same way and to the same degree with any medication and clinical assessments of patients starting omalizumab have continued to demonstrate this. All the evidence in this appraisal is based on mean values and ignores those patients in whom significant benefits have been seen. Clinicians are unlikely to continue new medicines which do not work and this is especially true when the financial costs are high. NICE acknowledges that the quality of the studies was 'in general high' with little risk of bias. NICE also acknowledges effectiveness of omalizumab as well as the unpleasant and serious side-effects of prolonged high corticosteroid usage. As the recommendation stands NICE are prepared to prevent the use of the only new technology which has become available for the management of very severe asthma over the last 2 decades. It would be used in a very small number of people, and in children this number would be extremely small. The new evidence which has become available since the outcome of the 2011 recommendation is minimal and it is difficult to understand the scientific reason for the changed decision. The professionals that were allowed to comment are very small in number and exclude several with much more experience of the use of omalizumab than those actually consulted. The exclusion of those professionals recommended by RCPCH is particularly notable and suggests a pre-existing prejudice in NICE in excluding those who have opinions which would possibly conflict with the final decision. Given that the RCPCH is the recognised and respected UK institution which sets standards of	Noted. See above. The primary role of consultee organisations such as the RCPCH in a NICE Technology Appraisal is to comment on draft documents and to submit evidence to the Appraisal Committee. Consultees also have the right to appeal against the Final Appraisal Determination. The Committee do value the evidence submitted by professional

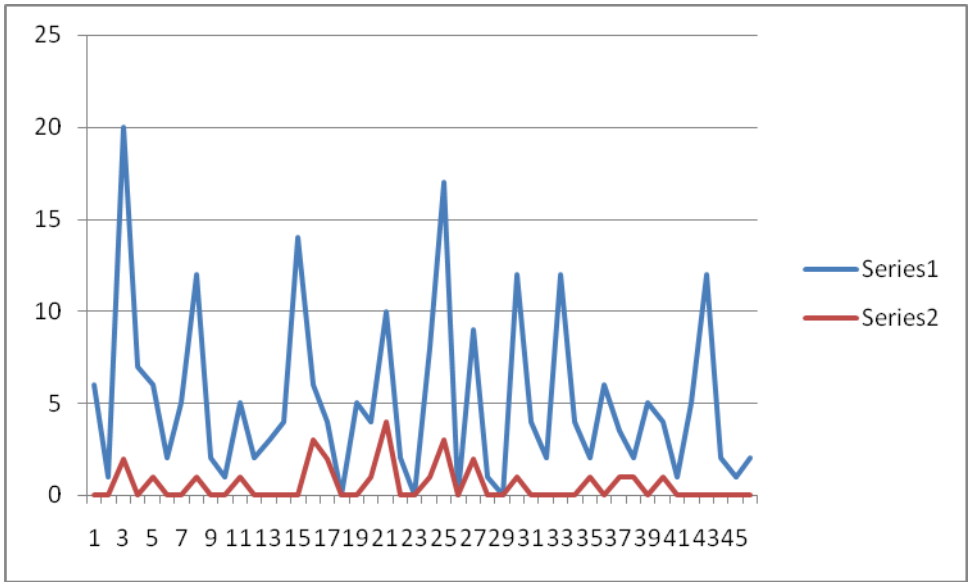
Consultee	Comment	Response
	care for the management of children's diseases we believe it is unacceptable that there was no RCPCH representative invited to participate in the Appraisal Committee decisions. We also note there was no representative from the RCP. Three patient experts were invited to participate, but there is no indication that any of them had knowledge of or suffered from very severe problematic asthma. The only other 2 selected individuals were a paediatric and an adult Allergist, both representing the British Society for Allergy and Clinical Immunology. We question whether this very small number of people is sufficient to give specific advice to a committee of 28 persons, none of whom are likely to have had any first-hand knowledge of using the technology. This specific issue was discussed at a meeting between the RCPCH and NICE some 2 or 3 years ago and no progress has been made since.	organisations and the comments made by such organisations on the draft guidance. NICE values such input. In the NICE Technology Appraisal programme decisions are taken by a standing Committee made up of professionals from a number of different fields and also lay members, not by topic experts. The Committee will look at technologies in all disease areas. NICE has four Appraisal Committees and each of these Committees has one paediatrician. Members of the Committee participate as individuals rather than as representatives of any particular body. The first time the Committee discusses a topic it is usually advised by two clinical specialists and two patient experts. These specialists are present as experts in their own right and not as representatives of an organisation. Clinical specialists are involved in the Committee discussions, but are not involved in making the decision. Although NICE asks consultee organisations such as the RCPCH to nominate clinical specialists it cannot be guaranteed that those nominated will be asked to attend this meeting. For this appraisal 16 nominations were received from a number of different consultee organisations. Those invited to the meeting were chosen by the Committee Chair who took into account factors such as what conflicts of interest those

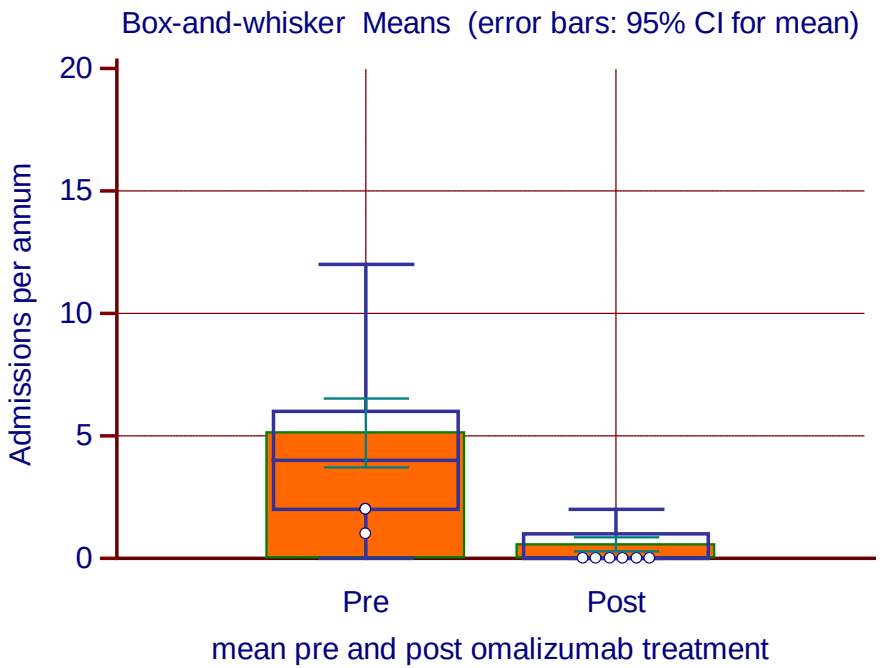
Consultee	Comment	Response
		nominated had, what geographic areas they worked in and their previous involvement with NICE. For this appraisal it was also necessary to ensure that the experts could advise the Committee on the treatment of this disease in both children and adults.
Royal College of Pathologists	It is disappointing that despite evidence of clinical effectiveness in individuals with severe asthma, particularly those on long-term oral steroids, the cost-effectiveness of omalizumab with regard to cost per QALY obtained, results in the conclusion that the drug is not a cost-effective use of NHS resources. There are concerns that evidence available does not reflect current UK practice where a small group of individuals with unstable asthma, often therapy-resistant, gain significant clinical benefit from therapy, although it is acknowledged that this experience has not been collated into published evidence and therefore remains anecdotal. **Has all of the relevant evidence been taken into account?** Relevant published evidence and appropriate modelling have been undertaken. Limitations of the available data have been highlighted in both the report and the previous Assessment Report **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Yes, given the limitations of data outlined above. **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** There are concerns over the recommendation that those currently on therapy can continue this until patient and clinician consider that treatment can be stopped, whereas following publication of these recommendations new patients with the same clinical phenotype will no longer be able access the treatment. With such unequivocal recommendations commissioning groups are highly unlikely to agree to fund treatment of severe asthma with omalizumab, even on grounds of exceptionality. This will cause clear inequality within patient groups. If final conclusions recommend that omalizumab should not be offered to patients with severe asthma, consideration should be given to the recommendation of a definite time-limit for cessation of therapy in existing patients – 12 months is suggested as evidence presented suggests declining benefit of therapy after this time.	Noted. The Committee has concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21)

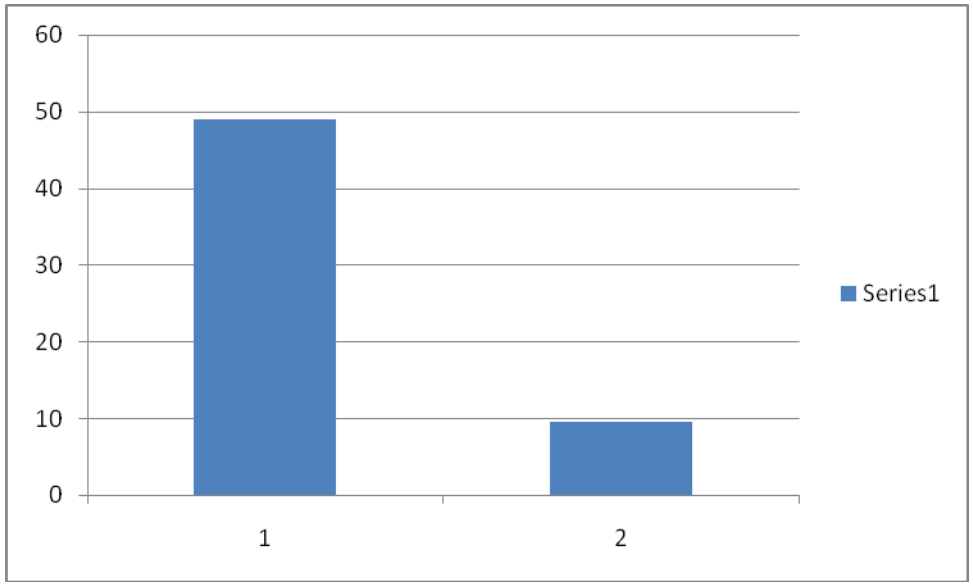
Consultee	Comment	Response
	Omalizumab is being used in an unlicensed manner for treatment of chronic urticarial and angioedema. Published small-scale studies indicate that the therapy can be effective in treatment-resistant patients. Availability of the drug for this indication, usually funded on an individual funding request basis, is likely to be adversely effected by these recommendations. **Equality Issues** None identified.	
Royal College of Physicians	The RCP has had sight of and wishes to endorse the response submitted by the British Thoracic Society (BTS) to the above ACD consultation.	Noted.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Severe and Brittle Asthma Unit Birmingham Heartlands Hospital	The severe and brittle asthma unit is one of the busiest severe asthma clinics in the country, a tertiary referral centre and has the longest experience with omalizumab treatment in UK through participation in the pivotal INNOVATE trial in 2003-2004 and others before that and subsequent treatment of large number of patients who have now been established on treatment for many years and some are exceeding 8 years. Omalizumab effectiveness was apparent to us very early on during the research phase and afterwards. It is not an overstatement to say that it has revolutionised severe asthma treatment from the nihilistic long term and high dose corticosteroids treatment which in addition to substantial side effects failed to improve lives of patients or stop hospital admissions in substantial minority. The introduction of omalizumab treatment was true breakthrough for many of our patients. We have recently conducted patients' survey on the efficacy and effect of omalizumab. We have asked patients about the frequency of admissions, if they were on maintenance oral steroids, burst courses of steroids required, if they were in employment, time off work or school and there general impression on effect of omalizumab on their lives. The results of this survey are presented below. **Omalizumab demonstrated impressive reduction in hospital admissions** The total number of admission endured by the 46 patients in the year before omalizumab treatment was	Noted. The Committee concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or

Nominating organisation	Comment	Response
	240.6 admissions (mean per patients per annum of 5.2 and range between 0-20). Omalizumab treatment results in remarkable reduction in total admissions to 26.6 (mean per patients per annum of 0.57 and range between 0-4). Total admissions saved in these 46 patients were 214 admissions annually (Figure 1).  Figure 1: Admissions during the year before (blue) and after (red) omalizumab treatment in 46 patients treated at severe and brittle asthma unit, Birmingham Heartlands.	frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21) The Committee acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.21)

Nominating organisation	Comment	Response
	 Figure 2: mean number of hospital admissions per annum in the 12 months before omalizumab compared an annualised admission rate after omalizumab. Assuming that on average any admission would cost NHS £1,500 in this group of patients with severe asthma, this would translate into savings of £321,000 year. This would compare to an average cost of omalizumab of 8,000 per annum per individual or £368,000 in 46 patients. **Patients treated with omalizumab experienced substantial reduction in oral steroids requirement** In keeping with several national and international studies omalizumab treatment resulted in marked steroids sparing effect. We have quantified this in 46 patients and found an averaged daily dose of 48.9mg of prednisolone in the year before omalizumab (range 0-60mg/day), reducing to 9.6mg/day (range 0-20mg/day) and for total cumulative dose for cohort reducing from 1150mg/day to 224.5mg/day. In addition	Noted. See above.

Nominating organisation	Comment	Response
	22 patients (48%) were weaned off OCS completely.  ***Figure 3: reduction in mean prednisolone daily dose (mg) from pre (1), to post (2) omalizumab treatment.*** In our patients omalizumab reduced corticosteroids exposure by more than 80% with 48% of patients weaned off corticosteroids completely. This reduction in corticosteroids exposure carries important long-term benefit to these patients in the form of reduction of various corticosteroids induced side effects that include cataract, osteoporosis, ischemic heart disease, diabetes, hypertension etc. **Improving patients working or school attendances** Semi quantitative data was available from 32 patients. All 15 unemployed pre omalizumab were not working at most recent review. However in the 17 patients employed or in full time education pre therapy, total days lost reduced from 1,218 to 699 with treatment, a per patient per annum saving of 31 days in the population who were working or 16.2 days average over the total population.	Noted. See above.

Nominating organisation	Comment	Response
	What did omalizumab treatment mean to patients (patients perspectives) Omalizumab treatment is frequently described by patients as life changing experience (gave me my life back). The following are extracts of patients 'general comments about omalizumab. *Transformed my life. Enabled to contribute to society where wouldn't have been able to previously* *"Wouldn't be here if wasn't for Xolair"* *life changing drug* *daily life is much improved, QOL vastly improved, flare ups but still to work through it* *improved asthma QoL* *She feels she now has a life and is able to get out and about* *life changing* *Xolair has allowed him to start exercising again, improved his quality of life* *Has improved her quality of life* *has improved his life* *Changed her life, could not walk up the stairs but now can* *Has reduced her hospital admissions, has helped her mobility and she feels better than before* *'life changing' he believes that he would not be alive today without Xolair.* *Has improved her quality of life, is able to exercise and has lost weight* *Has improved her quality of life, is able to exercise and has lost weight* *Has improved her life* *Her asthma is now more manageable then before Xolair and less variable* *Makes asthma more manageable* *Believes it is the only treatment to have made a difference for her* *Now-feels so much better, has transformed his life. Able to walk and lost weight* *It has made a big difference to her life, went 10 months without an admission* *her employment was terminated due to sickness level due to her asthma* *has felt that* *" Gave me my life back* *Was taking high doses of oral steroids and was previously on a Bricanyl pump and other asthma*	

Nominating organisation	Comment	Response
	medication which has now been stopped since Xolair. *Was a head teacher and enjoyed her professional role but due to her asthma had to give up her role when she was 48. she feels that it has turned her life around and revolutionised her life* **Summary** Omalizumab is a breakthrough treatment and is the only proven treatment to significantly reduced steroids and admissions in the long term in severe allergic asthma. We had witnessed an extremely positive experience in which we observed the lives of our patients' have transformed in a way that did not seem possible. The treatment provided hope for many patients, has saved admissions and reduced exposures to steroids and improved our patients' quality of life. NICE decision on omalizumab is of pivotal importance to current and future welfare of these patients. Not recommending omalizumab is a major mistake and will set back a tremendous progress has been achieved over last decade. We strongly request the extension of NICE recommendation of omalizumab in severe allergic asthma as per NICE 2007 report.	Noted. See above.

Comments received from commentators

Commentator	Comment	Response
Health 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? Yes 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? Yes 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? There is a definite unmet need for patients with severe persistent allergic asthma despite currently available treatment options .I still have some concerns about the overall main recommendation in severe persistent allergic asthma, because there is no such thing as an average patient, and there are clearly individual responders where there may be marked benefits which can be identified from an initial 4 month trial, using pragmatic metrics such as ACQ, AQLQ and steroid sparing .	Noted.

Commentator	Comment	Response
	Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No 7. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment None 1. 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? The review seems very comprehensive and thorough 2 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? I concur with the Assessment Group's conclusion that the mortality rates for acute asthma used by the manufacturer are too high (sections 4.2.2, 4.2.15). The notion that mortality for patients >45 is 2.478% per exacerbation is not born out clinically. If this were the case we would be seeing large numbers of asthma deaths in admitted patients, this is simply not the case, I cannot remember the last time I saw an asthma death in an admitted patient. 3. 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? This is dependent on the Appraisal Committee's judgement as to the cost per QALY that is acceptable to the NHS. As the health economic analysis is highly specialised and somewhat difficult to follow (it might as well have been written in hieroglyphics) I really can't comment on the validity of the recommendations. 4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?	

Commentator	Comment	Response
	The pathways and treatment options are applicable to Scotland, having worked both sides of the border there are minimal differences in asthma or asthma care between England and Scotland Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. I suspect that all of the patients in Scotland who will benefit from Omalizumab are currently prescribed the medication. This would continue based on the provisional recommendation. However, if applied the recommendation would prevent the use of Omalizumab in the patients who develop severe asthma in the future, this would impact children first. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. Presumably this depends on the cost per QALY deemed acceptable to NHS Scotland/SMC, I do not know this. In the first instance the guidance should be valid in Scotland Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment Nothing to add.	

Comments received from members of the public

Role*	Section	Comment	Response
General Public	1	I work in the field of asthma and have met many people with the condition. Therefore I have seen, met and spoken to many people who have benefitted from taking Xolair. I appreciate that you have to have guidelines and policies around costs/effectiveness but I can't believe that you are unable to see that when this treatment works for people it not only stops them from being ill, it makes them well. This keeps them out of hospital (in the first instance) but it also means they can come off steroids which have a HUGE impact on their life. I know of one amazing woman who at 16 had no hope to be quite honest. She was house bound, wheelchair bound, and had really bad mental health issues (not to mention issues with her adrenal glands) due to having to take high doses of steroids. It is so hard to put a cost on the impact this has on someone at that age. Because of xolair she is now married, working and has lost weight - living like a 'normal' 23 year old. That alone is worth £millions. It breaks my heart that others may not be able to benefit. I think this is the wrong decision - please reconsider.	Noted. The Committee concluded that, with the patient access scheme submitted after consultation on the ACD, omalizumab as an add-on to optimised standard therapy is a cost-effective use of NHS resources for treating severe persistent confirmed allergic IgE-mediated asthma in people aged 6 years and over who need continuous or frequent oral corticosteroid treatment (defined as 4 or more courses in the previous year) and should be recommended as an option for treatment in this population. (See FAD paragraph 4.4.21) The Committee acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.2.21)

Summary of comments received from members of the public

Theme	Response
All comments received disagreed with the ACD recommendation stressing that omalizumab is an “invaluable tool” that enables clinicians to help patients control severe asthma symptoms	Noted. The Committee concluded that omalizumab as an add-on to optimised standard care is more clinically effective in treating severe persistent allergic asthma than optimised standard care alone. (See FAD 4.4.6)
Clinicians follow the current guidelines. Omalizumab used only on small percentage of patients, but with positive outcomes	Noted. The Committee is aware that only people with the most severe persistent allergic asthma despite optimised treatment should be offered omalizumab. (See FAD 4.4.3.)

* When comments are submitted via the Institute’s web site, individuals are asked to identify their role by choosing from a list as follows: ‘patent’, ‘carer’, ‘general public’, ‘health professional (within NHS)’, ‘health professional (private sector)’, ‘healthcare industry (pharmaceutical)’, ‘healthcare industry’(other)’, ‘local government professional’ or, if none of these categories apply, ‘other’ with a separate box to enter a description.

Theme	Response
Omalizumab has a life changing effect in some people with severe asthma	Noted. The Committee heard from patient experts and clinical specialists, and again from comments received during consultation, that omalizumab resulted in life-changing improvements in reducing the number of asthma-related clinically significant exacerbations. The Committee has concluded that omalizumab as an add-on to optimised standard care is more clinically effective in treating severe persistent allergic asthma than optimised standard care alone. (See FAD 4.4.6)
Marked improvement in lung function, reduction in exacerbation number and severity and reduction in hospitalisation with omalizumab	Noted. The Committee was presented with evidence that omalizumab treatment resulted in small increases in lung function in adults as measured by percentage of predicted FEV1 but that no FEV1 data were collected in the children's trials. (See FAD 4.4.6)
Sparing of oral corticosteroids effect under-valued e.g. frequency and severity of chest infections, osteoporosis, fractures, diabetes	Noted. The Committee has acknowledged the uncaptured benefits of reducing dependence on oral corticosteroids and was persuaded that these uncaptured benefits were sufficient to justify accepting an ICER of £23,200 per QALY gained. (See FAD 4.4.21) .
Other benefits of omalizumab including reduction in hayfever symptoms not taken into account	Noted.
Without omalizumab, hospitalisations will increase. It is more cost effective to use omalizumab to a small proportion of patients than to utilise hospital resources.	Noted.
Omalizumab is too expensive and manufacturer should lower the price	Noted. The manufacturer agreed a patient access scheme with the Department of Health, in which the manufacturer offers a discount on the list price of omalizumab to the NHS. (See FAD 4.2.34)
There are ethical implications of stopping omalizumab treatment of asthma for people who are already receiving it.	Noted.
Asthma not a "self-inflicted" disease. Compare with other diseases such as smoking related illnesses, obesity, etc.	Noted.