NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Botulinum toxin type A for the prevention of headaches in adults with chronic migraine

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
Allergan	Allergan is pleased to confirm that under separate cover all the information and analyses requests from the Committee outlined in sections 1.3, 1.4 and 1.5 of the ACD, a recent Australian survey describing patient narratives of a response to Botox®, and what it means in terms of benefits and improvement in their daily lives, and a revised economic model, were made available to NICE on 27 February 2012, in advance of the second Appraisal Committee, to afford time for Committee review. For complete transparency, these items and this Allergan response to the ACD do not contain any data marked commercial in confidence. Allergan welcomes this opportunity to comment on the ACD for Botulinum toxin type A (Botox®) for the prevention of headaches in adults with chronic migraine (CM). Allergan recognizes that the "minded no" recommendation is indicative of Committee uncertainties or lack of information. Allergan is pleased to clarify key elements of earlier responses submitted to NICE, which appear to have been overlooked or misunderstood, and importantly to correct any factual inaccuracies of the ACD. These points are outlined in order to address and remove current uncertainties. For completeness, we also attach Appendix I, which was submitted to NICE in December 2011, in relation to Allergan's factual check of the ERG Report. Allergan note that NICE accepted the statistically significant treatment response of Botox® over placebo across a broad range of measures, and accepted from clinical specialists that the response to treatments is multifaceted. The Committee noted CM was a debilitating condition significantly affecting quality of life (QOL), that Botox® was well tolerated with minimal side effects, had no issues with compliance, and that it improved QOL in CM patients.	(NB: Appendix I has been received but not reproduced) Comments noted. The Committee considered the additional information provided by the manufacturer. The additional evidence and the Committee's consideration of the additional evidence are summarised in the Final Appraisal Determination (sections 3.32 – 3.45 and 4.9 – 4.17) The Committee accepted the plausibility of using different utility values in the botulinum toxin type A and placebo arms (within the reservations expressed in section 4.13), and considered that the utility values in the economic model encompass the major health- related quality of life benefits associated with treatment with botulinum toxin type A, including duration and intensity of migraine, reduction in symptoms, need for rescue treatment, and lower dose of acute medication. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)
Allergan	**Different utilities** Allergan agree with the observation *"the Committee noted that it was plausible that patients might have a higher utility in the botulinum toxin type A arm because, as well as fewer headache days (which was already captured in the model) they may also have less severe and intense headaches"*. Allergan believe that the observation of statistically significant benefits of Botox® across a broad range of relevant primary and secondary outcome measures, achieving minimal clinically important differences for HIT-6, MSQ and QOL measures, is evidence that Botox® offers	Comments noted. Section 4.13 of the FAD includes the Committee's consideration on the use of different utilities within each health states in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost

Consultee	Comment	Response
	clinically relevant benefits in a complex multifaceted condition and an area of recognized unmet need. A variety of variables influence a chronic migraineur's QOL, in terms of their health. They include, for example, the intensity of pain, any comorbidity, the ability to operate in society, disability, access to health services, the subjective perception of general well-being, as well as general mood. While the subjective nature of headache is well known (Silberstein et al 2008 1, there is a reassuring consistency of statistically significant and clinically relevant benefit of Botox® over placebo in the PREEMPT studies. Indeed, the very strength of the Botox® evidence package is the breadth of measures demonstrating consistent and meaningful clinical benefit. This observation is reflected in the improved composite utility measure of patients on Botox® compared with patients on placebo (per same heath state). This is because CM itself is more than the total of headache days suffered per month and the response to treatment is more than simply a reduction in headache days per month. The different (improved) utility is a reflection of many other benefits (including statistically significantly lower intensity of migraine, fewer hours of migraine or headache, less use of triptans, and improved QOL) all of which are of relevance to the CM sufferer. This was evidenced by the PREEMPT data demonstrating statistically significant improvements across all these measures, and supported by narratives from CM patients who received Botox® treatment in Australia2, opinions of both UK physicians who are treating CM patients, and Botox® treated patients. Observations of different utilities are not unique. Other examples of drugs with different (improved) utilities to placebo for the same clinical measure or health state include sibutramine3 (obesity), rimonabant4 (overweight and obesity) and olanzapine5 (bipolar disorder).	effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state.
Allergan	Sibutramine Utility gains due to weight loss were derived from two sources in the sibutramine analysis. One source reported utility gains of 0.00142 per kg weight loss for placebo patients and 0.00185 per kg weight loss for sibutramine patients. Weight loss following sibutramine administration is associated with several favourable metabolic	Comment noted. Section 4.13 of the FAD includes the Committee's consideration on the use of different utilities within each health states in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was

1 Silberstein S, Tfelt-Hansen P, Dodick DW et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalagia 2008;28: 484-95
2 Data on File. Allergan Australia Report: What does treatment response mean in chronic migraine? Narratives from chronic migraine patients who have responded to BOTOX® treatment. February 2012.
3 Warren E, Brennan A, Akehurst R. Cost-effectiveness of sibutramine in the treatment of obesity. Medical Decision Making 2004; 24: 9-19
4 Rimonabant (Acomplia®) for the treatment of overweight and obese patients. Available at http://www.nice.org.uk/nicemedia/live/11738/38533/38533.pdf
5 Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007;11(39)

Consultee	Comment	Response
	effects which may influence utility associated with weight loss.	plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state.
Allergan	Rimonabant This economic analysis described utility estimation via a mapping exercise from an obesity-specific QOL measure (IWQOL-Lite). When the IWQOL-Lite scores were transformed into utilities, using the SF-6D algorithm the rimonabant group recorded higher utility scores compared to the placebo group. The authors noted that changes in weight (BMI) are considered to affects patients' QOL (utility) through both a direct effect of the weight loss, and through reduced long-term cardiovascular event rates.	Comment noted. Section 4.13 of the FAD includes the Committee's consideration on the use of different utilities within each health states in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state.
Allergan	Olanzapine This analysis reported treatment specific utility data5. Utility values applied to bipolar patients in the stable state (excluding weight gain) were 0.82 for olanzapine, 0.74 for valproate and placebo and 0.71 for lithium. The analysis also described that olanzapine led to the lowest probability of manic episodes. Given that 80% of patients suffering from an acute manic episode were assumed to be hospitalised and the utility estimate applied to hospitalised patients was markedly worse than other states, the authors considered this could account for the higher utility for patients receiving olanzapine. In summary, Botox® and the CM patient level data from PREEMPT indicate improved utility per health state for Botox® treated patients compared with placebo treated patients. Allergan believe this different (improved) utility is a reflection of the broad impact of Botox® on this multifaceted condition. Thus, headache days per month alone does not encapsulate the high morbidity and overwhelming impact of CM on the sufferer, nor does it reflect all dimensions of treatment success. The evaluation of CM is also complicated by the subjective nature of headache. Successful treatment impacts positively on patient lives, and hence overall wellbeing. This is evidenced by the improved utility capturing these benefits of	Comment noted. Section 4.13 of the FAD includes the Committee's consideration on the use of different utilities within each health states in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state.

Consultee	Comment	Response
	Botox®. This provides a perfect example of the ability of utilities to reflect these elements and the impact of treatment beyond headache days per month in one composite measure. This sentiment is widely shared by clinical specialists and patient reports of the positive impact they have derived with treatment response to Botox®.	
Allergan	**Stopping Rules** Allergan note that "*the ERG found the manufacturer's model to be reasonable for the decision problem. The ERG thought that the negative stopping rule at 24 weeks in the model was reasonable".* The revised modeling to accommodate the Committee's requested base case (including a range of negative stopping rules6, a mandated positive stopping rule of 24% based on a US abstract7 (Rothrock et al 20118), a range of other assumptions around costs, resource use and further requested model refinements) elicited an ICER of £14,999 per QALY gained. This revised base case uses different utilities for Botox® and placebo, a negative stopping rule of 30% (which was in line with UK clinical expert opinion9 and Silberstein et alError! Bookmark not defined.) and a positive stopping rule of 24%. Allergan note that the revised analyses, accommodating all Committee requirements, reinforce the clinical and cost effectiveness of Botox® in the prophylaxis of CM in patients failing 3 or more prior prophylactics in the NHS in England and Wales (the decision problem). Allergan further note that upon simulation of positive stopping rules whereby more than 24% of patients stop Botox® treatment on achieving episodic migraine (< 15 headache days per month) in the NHS, this reduces the ICER and therefore increases the cost effectiveness of Botox® further. Adopting a wider societal perspective (in which lost work time, lost family time, lost personal time, opportunities at work and lost education time) was not included in the resubmitted analyses, but would improve the cost-effectiveness further. Allergan agree with the Committee that the stopping rules strongly influence the	The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD. **Negative stopping rule.** The Committee noted from comments received during consultation that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). **Positive stopping rule.** The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine

[6] Negative stopping rules for insufficient response - Based on % reduction in headache days per month since baseline at week 24 (rather than reduction in number of health states as in original submission)

[7] This single arm observation study comprised 100 patients, the vast majority of whom were insured by Blue Cross Blue Shield. Allergan consider that the US derived data in terms of positive stopping rules is not reflective of what would happen in the NHS in England and Wales. Rather Allergan consider (based on input from clinical experts) that an NHS positive stopping rule is more likely to be that once the patient has Episodic Migraine (namely <15 headache days per 28 days) they would discontinue Botox®. In this situation, the ICER reduces further and Botox® is even more cost effective to the NHS

8 Rothrock JF, Andress-Rothrock D, Scanlon C, Weibelt S. Onabotulinumtoxina for the treatment of chronic migraine: Long-term outcome. Headache 2011;51:60

9 Allergan Data on file. Opinion obtained from UK clinical experts Advisory Board on 29 February 2012

Consultee	Comment	Response
	ICERs. Allergan understands that the practical implications of appropriate management of CM patients in clinical practice in terms of those with insufficient response and those who have derived significant response is important. Indeed, there are treatment models for the use and monitoring of Botox® in CM in the NHS in England today9. In the NHS, headache specialists prescribing Botox® routinely require refractory CM patients to use a headache diary as a clinical monitoring tool and stopping rules are defined. Three NHS models to target appropriate use of Botox® and monitor its efficacy are described next.	(that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Allergan	The North West Protocol10 Consultant neurologists in the North West are able to use Botox® according to the North West Protocol at The Walton Centre, Liverpool. Consultants or headache GPSIs diagnose CM and apply defined selection criteria to identify the small group of CM sufferers whose headache remains refractory to standard treatments and who may benefit from Botox® "since the alternatives involve frequent A&E attendances and other contacts with out-of-hours services, using unlicensed medications with a weak evidence-base (some of which are also expensive), medications with serious potential risk such as methysergide, sometimes inpatient admissions or possibly referral for nerve stimulators". These patients match the Botox® NICE decision problem. Prior to treatment with Botox® the patients must complete a 2 month headache diary documenting the number of days affected by headache, number of migraine days, GP visits, A&E visits and other hospital admissions for head pain. On the day of treatment, the Headache Impact Test (HIT-6) score is evaluated and the headache days per month evaluated. Headache diaries are continued for the duration of treatment. Three months after injection, diaries should be re-assessed and a second injection given if the patient has responded (>30% reduction in headache days). If after a further 3 months there is no significant improvement (<30% reduction in headache days), then treatment is stopped. After one year they will consider stopping treatment11.	Comments noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD. The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee recommended treatment with botulinum toxin type A in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse should be stopped in people whose condition: • is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or

[10] Dr Nicholas Silver, The Walton Centre Liverpool
[11] They await more data on recommended treatment duration

Consultee	Comment	Response
	An annual audit is planned whereby the following outcomes are monitored; i) number of patients treated, ii) number of responders (per definitions above), iii) number of non-responders, iv) of responders continuing treatment their improvement in HIT-6 and headache days compared with baseline, v) adverse events.	• has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.
Allergan	Royal United Hospital, Chronic Migraine Pathway12 This describes the care pathway of refractory CM patients once referred to secondary care. Following assessment of headache and confirmation of diagnosis, oral prophylaxis is undertaken. Where the patient fails on three treatments, Greater occipital nerve block (GON) is offered. If this is effective, GON is continued three monthly. Patients failing GON are offered Botox® injections in an outpatient setting by a trained injector. If effective, the recommended re-treatment schedule is every 12 weeks. This care pathway describes a negative stopping rule; if ineffective, Botox® is discontinued after 2 cycles. Where all other treatments have failed, Occipital Nerve Stimulation (ONS) may be a treatment option. This surgical procedure for the management of intractable headache is performed at Frenchay Hospital, Bristol or The National Hospital for Neurology and Neurosurgery, Queen's Square, London.	Comment noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD (see above). The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11).

[12] Dr Nicola Giffin, Consultant Neurologist, at the Royal United Hospital, Bath. Treatment pathway developed February 2012. Details of 'ineffective' response to trigger a negative stopping rule not defined in information currently available to Allergan

Consultee	Comment	Response
Allergan	The Chronic Migraine Pathway, Hull13 Refractory CM patients referred from centres in Yorkshire are required to complete a headache diary in order to receive Botox®. Patients are monitored based on scrutiny of diary cards and treatment response is typically assessed as one of the following; i) 50% reduction in headache days, ii) 50% reduction in migraine days, iii) 50% reduction in moderate/severe headache days to mild severity or iv) improvement in patients activity of daily living (e.g. ability to return to work). When patients achieve episodic migraine (<15 headache days per month) for three months, Botox® treatment is discontinued. Patient response to Botox® is recorded in the patient notes and in correspondence with the patients general practitioner.	Comment noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD (see above). The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).

[13] Dr Fayyaz Ahmed, Hull.

Consultee	Comment	Response
Allergan	**Botox® economic model and stopping rules in the NHS** The revised Allergan Botox model® reflects the NHS negative stopping rules reported above in a number of simulations however the positive stopping rule requested by NICE (24%; informed by a US abstract) does not reflect the three models cited above. The revised Botox® model base case reflecting NICE requirements is associated with an ICER of £14,999 per QALY gained, indicating the cost effectiveness of Botox®. A simulation employing positive stopping rules in which more responder patients (than 24%) discontinue Botox® upon achieving a state of episodic migraine (i.e. as described in the NHS models cited above) is associated with reduced ICERs14 indicating the cost effectiveness or value for money of Botox® to the NHS is further improved.	Comment noted. The Committee recognised that according to the only published longer term follow-up of patients who responded to treatment with botulinum toxin type A, only 24–25% were able to stop treatment with botulinum toxin type A and maintain a good response for at least 6 months (Rothrock et al. and Hanlon et al.) The Committee concluded that these publications provided the most plausible estimate for the likely implementation of the positive stopping rule in clinical practice in England and Wales, with 24–25% being the most appropriate figure on which to base a positive stopping rule in the economic model (FAD section 4.12).
Allergan	**Practical implications of Botox® and NICE stopping rules in the NHS** Another advantage of Botox® with its specific treatment regimen is that variation in administration of Botox® is not an issue. The injection regime is standardized for muscles and location of injection in the muscle, and the dose is fixed for each injection site. All injectors are health care professionals trained in Botox® delivery. Patient compliance is not dependent on the patient themselves as Botox® is administered by the health care professional in a routine clinic setting. Allergan appreciate that NICE and the NHS in England and Wales needs to understand the practical implications of stopping treatment and would welcome reassurance that the 'rules' of a simulation (in terms of appropriate stopping of Botox® in non-responders and in those who are responders) are plausible in clinical practice. Allergan believe that these rules are indeed implementable in today's NHS, evidenced, for example, by the ongoing North West Protocol of Botox® service in refractory CM described earlier. In the NHS, Healthcare Commissioners will want to be confident about the services they purchase and have belief the services operate according to the service specification. An audit loop would provide additional confidence to commissioners and Allergan proposes to NICE that providers should collect basic information on headache frequency to allow such review of the implementation of stopping rules.	Comments noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD. The Committee noted the consultation comments about the importance of effective stopping rules in clinical practice. Section 1.2 of the FAD states that treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition: • Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or • has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months

[14] Positive stopping rule of 50%, 75% and 100% were also simulated in the revised Botox® model. This generated ICERs as follows: 50% (ICER £12,908/QALY gained), 75% (ICER £10,967/QALY gained), 100% (ICER £9,092/QALY gained [assuming different utilities for Botox® and placebo]

Consultee	Comment	Response
	Allergan would be pleased to offer assistance in mechanisms to implement NICE stopping rules. This could complement models such as The North West Protocol by facilitating ongoing review of the Botox® service. In summary, Allergan believes that the evidence in the original submission and in the response to the ACD supports the clinical and cost effectiveness of Botox® in patients who have failed three or more prior prophylactics in the NHS. For these refractory patients treatment options are limited. These could be to retry failed treatments or consider unlicensed, exploratory, invasive, or unproven modalities that are more costly, associated with more adverse events and that are not uniformly available across the NHS. Allergan believes that the availability of Botox® provides the headache specialist (a trained provider, seeing the CM patient in an established specialist clinic setting, where the administration of Botox® would not require additional equipment) with a cost-effective, well tolerated and an important licensed addition to the treatment strategies available for this disabling condition. Comments specific to the ACD are described next.	
Allergan	**Has all the relevant evidence been taken into account?** Botox® has been extensively studied in the largest phase 3 program of CM ever undertaken (namely the PREEMPT programme) and has been proven to be effective and well tolerated in providing meaningful benefits to patients. The PREEMPT program has set a precedent in establishing substantial efficacy in the prophylaxis of headaches for this severely affected patient population with CM – a population that in the past has been systematically excluded from migraine prophylaxis treatments studies. PREEMPT takes all relevant treatment clinical effectiveness data into account and these data underpin the economic model. The International Burden of Migraine Study (IBMS) dataset15 and mapping algorithm (Gillard et al 201216), which were employed to estimate resource use and health utility of CM patients also underpinned the economic modeling and were used to inform this STA. The only other study comparing Botox® to placebo (Freitag et al 200817), was excluded from this STA because of serious concerns about its quality and relevance to the decision problem. In particular, external validity was compromised due to the small sample size (n=60) and lack of power to detect differences between treatment	Comments noted. No action is required.

15 Blumenfeld, A., Varon, S., Wilcox TK, Buse DC, Kawata AK, Manack A, Goadsby PJ, & Lipton RB 2011. Disability, HRQoL and resource use among chronic and episodic migraineurs: Results from the International Burden of Migraine Study (IBMS). Cephalalgia, 31, (3) 301-315 available from: http://cep.sagepub.com/content/early/2010/08/26/0333102410381145
16 Gillard P, Devine B, Varon S et al. Mapping from Disease-Specific Measures to Health-State Utility Values in Individuals with Migraine. Value in Health 2012. doi:10.1016/j.jval.2011.12.007
17 Freitag, F.G., Diamond, S., Diamond, M., & Urban, G. 2008. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache, 48, (2) 201-209

Consultee	Comment	Response
	groups. Approximately 30% of patients discontinued after being allocated to treatment and therefore only 60% of patients had complete data for the final analysis at week 16. Most patients who discontinued did not receive allocated intervention after randomisation due to medication overuse during the baseline period (patients with medication overuse were explicitly excluded from the study). In addition, the NICE decision problem could not be addressed because the study did not report details of prior oral prophylactic medication use in the study subjects. For these reasons, Allergan agree that all the relevant evidence has been taken into account to inform this STA.	
Allergan	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The Allergan response document, Australian patient survey data and revised economic model submitted to NICE on 27 February 2012, describing additional analyses and explanation around various clinical and cost-effectiveness assumptions, have addressed Committee questions in the ACD. In addition, Allergan wishes to draw the Committee attention to Appendix I of this document, describing blinding in the PREEMPT studies and to correct a number of factual inaccuracies about Botox® and the evidence.	(NB: Appendix I has been received but not reproduced) Comments noted. The Committee considered the additional evidence submitted by the manufacturer along with consultation comments from other consultees. Areas of factual inaccuracy in the ACD have been addressed - see responses below.
Allergan	Statement 2.1: "Botulinum toxin type A (Botox, Allergan) is a purified neurotoxin complex which produces seven neurotoxins that are structurally similar but immunologically distinct. It has neuromuscular transmitter blocking effects". <u>Response: This statement needs to be corrected as follows</u> "Botulinum toxin type A (Botox, Allergan) is a purified neurotoxin complex and is one of the seven serotypes (A–G) of botulinum neurotoxins derived from the bacteria Clostridium botulinum. Botulinum toxin type A blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies".	Comment noted. Section 2.1 of the FAD is intended to provide a brief description of the technology, and its UK marketing authorisation, including the recommended indication, dose, and treatment schedule. Section 2.1 of the FAD has been amended for clarity. The technology is now described as 'Botulinum toxin type A (Botox, Allergan) is a purified neurotoxin complex, which is derived from the *bacterium Clostridium* botulinum. It has neuromuscular transmitter blocking effects.'
Allergan	Statement 2.2: "The summary of product characteristics lists the following adverse reactions that may be associated with botulinum toxin type A treatment: blepharospasm, cervical	Comment noted. Section 2.2 of the FAD has been amended in accordance with the list of adverse reactions noted in the summary of product characteristic. Section 2.2 of the FAD now states

Consultee	Comment	Response
	dystonia, paediatric cerebral palsy, primary hyperhidrosis of the axillae and focal spasticity of the upper limb associated with stroke" Response: This statements needs to be corrected to state: "The summary of product characteristics lists the following adverse reaction rates that may be associated with botulinum toxin type A treatment. Based on controlled clinical trial data patients would be expected to experience an adverse reaction after treatment with Botox at the rates of 35% of patients treated for for blepharospasm, 28% of patients treated for cervical dystonia, 17% of patients treated for paediatric cerebral palsy and 11% of patients treated for primary hyperhidrosis of the axillae. Sixteen percent of participants in clinical trials treated with Botox for focal spasticity of the upper limb associated with stroke and 23% with glabellar lines experienced an adverse reaction. In clinical trials for chronic migraine, the adverse reaction incidence was 26% with the first treatment and declined to 11% with a second treatment".	that 'the adverse reactions that may be associated with botulinum toxin type A treatment: headache, migraine, facial paresis, eyelid ptosis, rash, neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness, and injection site pain. It states that 'in general, adverse reactions occur within the first few days following injection and while generally transient, may have a duration of several months or, in rare cases, longer'. For full details of adverse reactions and contraindications, see the summary of product characteristics'.
Allergan	Statement 3.2 (last sentence) "The third was a small trial (n=60) that was not described". Response: This sentence should be corrected to state: "The third was a small trial (n=60) that was excluded from further discussion because of concerns regarding its quality and relevance to the decision problem".	Comment noted. Section 3.2 of the FAD has been amended to reflect that the third was a small trial (n = 60) that was excluded from further discussion because of concerns regarding its quality and relevance to the decision problem.
Allergan	Statement 3.5 (last sentence) "In PREEMPT 1, most differences between groups were statistically non-significant, except for mean headache episodes and mean migraine episodes which were higher in the botulinum toxin type A group compared with the placebo group, and the number of cumulative headache hours which were lower in the botulinum toxin type A group compared with placebo group." Response: This sentence should be corrected to state: "In PREEMPT 1, most differences between groups were statistically non-significant, except for mean headache episodes and mean migraine episodes, which were **lower** in the botulinum toxin type A group compared with the placebo group, and the number of cumulative headache hours, which were **higher** in the botulinum toxin type A group compared with the placebo group."	Comment noted. Section 3.5 of the FAD has been amended to reflect that most differences between groups were statistically non-significant, except for mean headache episodes and mean migraine episodes, which were **lower** in the botulinum toxin type A group compared with the placebo group, and the number of cumulative headache hours, which were **higher** in the botulinum toxin type A group compared with the placebo group.

Consultee	Comment	Response
Allergan	Statement 3.6 "There was no difference in the intake of acute pain medication between the arms in both studies." <u>Response: This sentence should be corrected to state:</u> "There was no difference in the intake of acute pain medication intake between the arms in both studies, although a statistically significant difference favoring Botox was seen for triptan use". The evidence that Botox® treated patients were using significantly fewer triptans than placebo treated patients suggests that headaches that were still occurring were perhaps less intense, as most patients reserve triptan use for their worst headaches. Indeed, this is substantiated by the fact that Botox® treated patients had significantly fewer moderate/severe headache days compared to placebo treated patients.	Comment noted. Section 3.6 of the FAD has been amended to reflect that 'there was no difference in the intake of acute pain medication between the arms in both studies, although there was statistically significant lower triptan use in the botulinum toxin type A arm.
Allergan	Statement 3.14. "Utility was assumed to differ for each health state in this model and also between treatments within the same health sate, the latter being justified on the grounds that treatment with botulinum toxin type A was shown to affect the severity and intensity of headaches, as well as the number of headache days" <u>Response: This statements needs to be corrected as follows:</u> "Utility was different for each health state in this model and also between treatments within the same health sate, the latter being justified on the grounds that treatment with botulinum toxin type A was shown to affect the severity and intensity of headaches, as well as the number of headache days" Utilities derived from patient data in PREEMPT revealed differences between the health states that underpin the economic model. Allergan believe this observation is a reflection of the broad range of patient relevant benefits which when experienced together, even if of themselves each may be small, manifest in an overall higher utility for patients receiving Botox® compared to placebo per health state when this is defined according to number of headache days. As noted earlier, there are other examples in NICE HTA submissions of improved utilities of drugs compared with placebo (or standard of care) per same health state or measure, in the management of obesity and bipolar disorder. These observations	Comment noted. Section 3.14 of the FAD has been amended to reflect that the difference in utility for each health state in this model and also between treatments within the same health state for each state was justified on the grounds that treatment with botulinum toxin type A was shown to affect a broad range of relevant outcomes, such as the severity and intensity of headaches, as well as the number of headache days.

Consultee	Comment	Response
	likely reflect added drug benefits, such as improved mood or QOL, over and above trial clinical endpoints.	
Allergan	Statement 3.22 "The ERG pointed out that in previous botulinum toxin type A trials, 70% of patients receiving botulinum toxin type A correctly guessed what they had received, because of changes in muscle tone such as reduced wrinkling of the forehead. The ERG further explained that because unblinding is an important factor in controlled trials of preventive treatment of chronic migraines, the International Headache Society guidelines recommend that subjects and investigators should be questioned at the end of trials about whether they thought the subject was assigned to the active or placebo group during the trial. This was not done in the PREEMPT trials". Response: This statements needs to be corrected as follows: "The ERG pointed out that in a previous Phase II botulinum toxin type A trial **involving a placebo run-in**, 70% of patients receiving botulinum toxin type A correctly guessed the treatment they had received. No data were collected as to the reason for the treatment guess. Mean improvements from baseline were observed; therefore it is unknown if the treatment guesses were influenced by clinical improvement of their headaches or whether there was an effect on the muscle tone of the forehead. The ERG further explained that because unblinding is an important factor in controlled trials of preventive treatment of chronic migraine, the International Headache Society guidelines recommend that subjects and investigators should be questioned at the end of trials about whether they thought the subject was assigned to the active or placebo group during the trial. This was not done in the Phase III PREEMPT trials **since the PREEMPT studies predated this IHS recommendation".** Allergan note that the ERG did acknowledge there were differences between the Phase II Botox® trials and Phase III Botox® trials (see Issue 4 - ERG comments on Allergan response to ERG report) and hence were surprised to read statement 3.22 in the ACD. **Of note** Allergan wish to reiterate that: • Reduced muscle tone was NOT reported in these studies as a reason for correctly guessing their treatment. • There was one report of reduced wrinkles but this was in a patient receiving	Comments noted. Section 3 of the FAD reflects the ERG critique of the manufacturer's submission. No changes required.

Consultee	Comment	Response
	placebo in the PREEMPT trials. • Further, the conduct of the PREEMPT programme (from January 2006 through July 2008) predates the publication of IHS guidelines in 2008 recommending that CM patients be questioned at the end of the RCT on their opinion as to which treatment they had received, hence this was not a feature of the PREEMPT trial design.	
Allergan	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Allergan believe that the provisional recommendations, namely a 'minded not to recommend' Botox® for the prevention of headaches in adults with CM, are not sound or a suitable basis for guidance to the NHS. Allergan responses to the ACD reaffirm the cost effectiveness of Botox® in the NHS. Importantly, not allowing the small group of CM sufferers who have failed 3 prior prophylactics the opportunity to benefit from Botox®, within an NHS infrastructure easily able to accommodate it, leaves highly disabled patients with limited, less attractive treatment options. Patients may have no prophylactic medication (i.e. acute rescue medication only) or could be referred for greater occipital nerve block (GON) with local anaesthetic with or without corticosteroids. Alternatively, also in a specialist setting, patients could be prescribed unlicensed medications (e.g. methysergide, with long-term side effects and a need for renal and liver function monitoring). The use of occipital nerve stimulation (ONS) is new, exploratory, costly and available in selected tertiary centres only. These options remain unproven and would be expensive to deliver equitably in the NHS. Headache specialists prescribing Botox® require patients to use a headache diary as a routine clinical monitoring tool in the NHS, as described earlier in the three CM Botox models9 and in which stopping rules are defined. We hope the Allergan offer to assist in mechanisms to help to implement the practicalities surrounding appropriate and recommended Botox® stopping rules will make it significantly easier to manage optimal Botox® use in practice in the NHS. For example, Allergan assistance to develop a contemporaneous diary capturing ongoing patient outcomes could facilitate daily capture of relevant outcomes and stopping rules information for use in an audit loop with healthcare providers.	Comments noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).

Consultee	Comment	Response
Allergan	**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?** CM is primarily a disorder of middle aged women; females are 2.5 to 6.5 times more likely to suffer from the disorder than males (Scher et al, 199818; Castillo et al, 199919; Lanteri-Minet et al, 200320; Natoli et al, 200921). Moreover, such highly disabled CM patients have been systematically excluded from other registration studies evaluating migraine prophylaxis as well as migraine acute treatments (Rapoport, 200822; Silberstein et al, 200423; Brandes et al, 200424). This STA describes the value of Botox®, a treatment which has uniquely been studied in an underserved and under-diagnosed population of sufferers.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17). An equality impact assessment for this appraisal will be published on the NICE website.
Allergan	**Are there any equality related issues that need special consideration and are not covered in the appraisal consultation document?** A number of headache physicians are already providing Botox® in the private sector to patients who are self-funding and those that are approved by the Exceptional Treatment Panels of the PCT. If recommended by NICE, Botox® will be available for use within existing headache centres with existing infrastructure. In the event it is not approved, Botox® will be available only to CM patients able to self-fund.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17). An equality impact assessment for this appraisal will be published on the NICE website.

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Consultee	Comment	Response
Association of British Neurologists	There appears to be a minor erroneous reference to “adverse reactions” in section 2.2 about the technology. The ABN suspects this should read “licensed indications” not adverse reactions”.	Comment noted. Section 2.2 of the FAD has been amended in accordance with the Summary of Product Characteristics. Section 2.2 of the FAD now states that ‘the adverse reactions that may be associated with botulinum toxin type A treatment: headache, migraine, facial paresis, eyelid ptosis, rash, neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness, and injection site pain. It states that ‘in general, adverse reactions occur within the first few days following injection and while generally transient, may have a duration of several months or, in rare cases longer. For full details of adverse reactions and contraindications, see the summary of product characteristics.’
Association of British Neurologists	Question 1: Has all the relevant evidence been taken in to account? The ABN Pain Section agrees that the main clinical trial evidence for Botulinum toxin type A in chronic migraine has been evaluated i.e. PREMPT 1 and 2 trial programme sponsored by Allergan. We are not aware of other placebo controlled data although are aware of recently published comparator trials compared to Topiramate. The ABN notes that the NICE appraisal committee recognised that chronic migraine is a debilitating condition seriously affecting quality of life. The ABN is keen to ensure that all evidence based treatments are appropriately available to appropriate patients and their doctors, given the current reliance on open label consensus therapies for this disorder. The ABN headache and pain section noted that the following areas of evidence were not potentially taken into account	Comments noted. See responses below.

Consultee	Comment	Response
Association of British Neurologists	Issue 1. The relative clinical effectiveness and cost effectiveness of advocated alternatives: Although the appraisal consultation document suggests expert consensus treatment with 3 prior agents prior to receipt of Botulinum toxin type A the fact that there is poor quality clinical trial evidence, let alone cost effectiveness evidence, for most alternative oral drug therapies advocated for the treatment of chronic migraine appears does not appear to have been considered by the appraisal document. The only other drug with an evidence base from a positive double-blind randomised trial is Topiramate. This data is based on 2 small studies (total patient population = 387). The treatment dropout rate due to tolerability and significant side effects, let alone recurrent NHS services usage due to tolerability issues, is not insignificant with this treatment. (Data available from studies of Topiramate). None of the other agents suggested have adequate methodically sound clinical trial evidence for the treatment of chronic migraine and any prior consensus is based on open label studies often with heterogeneous population, shorter follow-up and less robust assessment criteria than the PREMPT studies.	Comments noted. The Committee were aware of consultation comments from the clinical community on the lack of evidence in form of randomised controlled trials for other active treatment for chronic migraine. The Committee considered the clinical trial evidence in light of the views of the patient experts and clinical specialists. The Committee noted the improvements in quality of life for patients whose condition responded to botulinum toxin type A. The Committee concluded that botulinum toxin type A was clinically effective in people with chronic migraine whose condition had not responded to three prior preventive (sections 4.4 and 4.5 of the FAD).
Association of British Neurologists	Issue 2. Evidence for differential effects within the studied chronic migraine trial population to better assess cost effectiveness relating to outcome: The ABN agrees that although the “absolute mean effectiveness” of Botulinum toxin type A versus placebo for a population of sufferers may not be very large but for specific patients the benefit in reducing migraine related impairment may be much greater. • It would have been useful to see the relative % frequency reduction in both headache assessment parameters in addition to quality of life data between both treatment/placebo groups e.g. splitting the data into 10% responder groups e.g. 20%, 30%, 40%, 50% etc. so as to help calculate cost effectiveness or alternatively into 25%, 50% & 75% responder groups? The Appraisal committee state in their consultation documents that they are not aware of any relevant differential effectiveness subgroups but the ABN was unable to find data in the released documentation relating to point 2 outlined above. In summary, in contrast to advocated alternative therapies in chronic migraine Botulinum toxin type A appears to show some evidence of benefit in contrast to lack of evidence for other drugs advocated for treatment of this disorder. This is potentially an important consideration if one seeks evidence based rather than simply consensus based clinical care	Comments noted. The Committee considered the additional evidence supplied by the manufacturer during consultation, including the impact of different negative stopping rules on the cost effectiveness of botulnium toxin type A treatment. The Committee concluded that: a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). It also concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Association of	Question 2: Are the summaries of clinical and cost effectiveness reasonable	Comments noted. The Committee were aware of

Consultee	Comment	Response
British Neurologists	interpretations of the evidence? The ABN agrees that there is an absence of data on the use of the positive stopping rule. The ABN suggests that this is also the case for many other therapies used in clinical practice. The ABN suggests that if the appraisal were positive that its approval might be subject to an on-going condition that a positive stopping rule be audited to facilitate future assessment. The ABN notes the comment from the appraisal recommendation that the PREMPT studies had a limited follow-up duration of 1 year. The ABN accepts this is potentially an important point but also wishes to point out that the PREMPT studies are the highest quality and longest ever follow-up studies performed in this condition. The study was performed according to the universally accepted International Headache society trial standards at the time of study inception so although the uncertainties may be valid, the reason for adopting these standards seem reasonable in the absence of retrospective knowledge. The ABN would like to highlight areas of potentially missed NHS utility costs for the current care pathway that bear strong consideration in any health economic model over and above comparator potential approval of Botulinum toxin type A for chronic migraine. Chronic migraine patients more often need secondary care outpatient consultations and its associated consultation related tariff costs for the following reasons: • Lack of widespread GP familiarity with how to diagnose and treat chronic daily headache disorders. • Frequent work or daily activity related impairment resulting from chronic migraine and associated symptoms • The prescription of non-licensed, non-evidenced based drug therapies suggested to primary care physicians for this disorder who are unprepared or unfamiliar with using these drugs. • The lack of adherence to advocated oral medications due to tolerability issues and thus frequent repeat consultation and/or wasted prescription costs Chronic migraine patients treated with oral medications have “unseen” and difficult to calculate iatrogenic morbidity costs: • Obesity as a side effect of consensus suggested therapies eg tricyclic antidepressants, beta-blockers • Psychiatric morbidity, oral and depot contraceptive drug interaction and teratogenicity for Topiramate therapy The ABN notes and welcomes a review of the model used to assess cost effectiveness and utility costs and looks forward to seeing if it is any better than the	consultation comments from the clinical community on the lack of evidence in form of randomised controlled trials for other active treatments for chronic migraine. The Committee noted the considerable uncertainties in the original economic model submitted by the manufacturer and considered whether each of these had been addressed in the revised economic model. The Committee noted that the revised model included their preferred assumptions and inputs and concluded that because the most plausible presented ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD sections, 4.9 and 4.16).

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	one originally proposed. The ABN would additionally highlight previous comments (see question 1 above) in relation to evidence interpretation.	
Association of British Neurologists	Question 3: Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The ABN is keen to ensure cost effective use of evidence based therapies. The ABN notes that Botulinum toxin type A has received a license in the UK, Europe and USA based on its differential efficacy over placebo. The ABN is disappointed that NICE "are not minded to recommend" Botulinum toxin type A for the treatment of appropriately assessed and diagnosed patients with chronic migraine as it will: 1. Deprive sufferers of a new potentially effective and well tolerated therapy (especially compared with currently advocated oral evidenced based therapies). 2. Unintentionally lead to the withdrawal of already NHS initiated and commissioned therapies in some areas and/or if these already PCT approved treatment pathways continue, produce a situation of difficult to challenge problematic inequality to chronic migraine Botulinum toxin type A treatment provision.	Comment noted. The Committee considered the additional evidence supplied by the manufacturer during consultation, including the impact of different negative stopping rules on the cost effectiveness of botulnium toxin type A treatment. The Committee concluded botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).
Association of British Neurologists	Question 4: 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? Migraine affects the female adult population 3 times as more males and has its highest incidence in the teenage years and early twenties and its highest prevalence between the ages of 30-50 years. Chronic Migraine is more prevalent in females. Whilst it is noted that any recommendation is not targeted to discriminate against women the decision will have a 3 times greater effect on women when compared with men eg a negative recommendation would indirectly increasing their risk of exposure to drugs with teratogenicity and/or contraceptive drug interaction. A positive decision does not take away this risk buts allows an informed discussion to occur to avoid unnecessary clinical risk.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).

Consultee	Comment	Response
Association of British Neurologists	Question 5: Are there any equality related issues that need special consideration and are not covered in the appraisal consultation document? See comments discussed in Question 4 above.	Comment noted. See response to question 4 above. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
British Association for the Study of Headache (BASH)	Question a) Has all of the relevant evidence been taken into account? BASH agrees that the main trial evidence (PREMPT 1 and 2) has been evaluated. The NICE committee recognised CM as a debilitating condition that affects quality of life. BASH would like to highlight the fact that there is lack of data on both clinical and cost-effectiveness of the other preventative treatments. BASH feels that more emphasis has been given to the economic aspect of treatment and less on the clinical needs of a group of patients suffering from the most disabling form of headache refractory to currently available treatments. Botulinum Toxin type A (Botox) has a place in the treatment of patients who have failed to respond to at least three first line treatments namely tricyclic antidepressants, beta-blockers and the anti-convulsant Topiramate. In the absence of Botulinum Toxin type A (Botox) the available options include oral medications i.e. Sodium Valproate, Methysergide or invasive treatments i.e. Greater Occipital Nerve Block (GON), Occipital Nerve Stimulator (ONS). The oral medications have unpleasant and intolerable side effects and Methysergide has to be prescribed and monitored in the secondary/tertiary care requiring frequent consultations. GON injection is associated with local side effects and is effective in only 30% for a very short period for which the evidence is not robust; moreover ONS is extremely expensive and require referral to the National Hospital for Nervous Diseases, London. BASH acknowledges the fact that reduction in headache days (the primary end point) in the Botox arm was modest in the clinical trials and there was a large placebo response (PREEMPT). However, measuring a meaningful response is more than a simple count of the headache days. In clinical practice patients may experience improvement in the duration or intensity of migraine or a reduction in associated symptoms such as nausea, vomiting, sensitivity to light sound, a better quality of life and the ability to return to work or other activities of daily living. BASH would like to highlight the fact that Botulinum Toxin type A showed a 50% reduction in headache days in 47% of patients compared to 37% for Topiramate; the drug with best available evidence in CM. BASH would like the committee to consider	Comment noted. The Committee were aware of consultation comments from the clinical community on the lack of evidence in form of randomised controlled trials for other active treatments for chronic migraine. The Committee heard from the clinical specialists at the first committee meeting that it is important for people first presenting with chronic migraine to try a range of oral preventive treatment options before considering treatment with botulinum toxin type A. The Committee were also mindful that scope specified that the population should include adults with chronic migraine whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies, and whose medication overuse has been appropriately managed. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.17).

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	the comparative data for placebo and the active group for 25%, 50% and 75% response rate. BASH acknowledges the fact that a robust response criterion has to be agreed if the treatment is to be recommended by NICE on the National Health Service (NHS) currently faced with a challenge of using resources appropriately	
British Association for the Study of Headache (BASH)	Question b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Patients with CM are more likely to visit their primary care physician than those with episodic migraine. More patients with CM are referred and re-referred to specialist care (secondary or tertiary) and are less likely to be discharged back to primary care unless a treatment is able to achieve remission. Irrespective of the treatment offered by the specialist, all patients require a consultation for at least 30 minutes. Treatment with Botulinum Toxin is simple and takes 10-15 minutes in addition to a standard consultation. The treatment is delivered in the out-patient setting and once trained can be given by a registrar or specialist headache nurse. The follow ups can be conducted via telephone with patients mailing (or emailing) their diaries beforehand. Patients only need to re-attend the clinic for repeat treatment. BASH feels the treatment can be delivered in the NHS through existing resources except the cost of the drug. BASH is aware of the financial constraint faced by the NHS and is fully supportive of the fact that treatment be restricted to those who benefit most from it. BASH also acknowledges the fact that a more objective and strict criteria would have to be in place for the start and stoppage of treatment to minimise waste. BASH recommends that treatment be restricted to those who have failed to respond to adequate trial of three prophylactic medications; the diagnosis of CM is made by physician with special interest and training in headache disorder and the treatment delivered by those trained in the technique; medication overuse must be addressed appropriately and all patients must maintain a headache diary to monitor the response and need for further treatment. A responder must be defined as one with at least 30% reduction in headache days and those who fail to respond to two treatment cycles should not receive any further treatment (Negative stopping rule). The treatment is repeated to those still fulfilling the criteria for CM but has shown a 30% reduction in headache days. Those with episodic migraine (14 days or less) should not receive further treatment unless they have a relapse (15 or more headache days with 8 or more migraine days for at least three months) (Positive stopping rule). BASH would like to highlight the fact that there is absence of data regards to stopping rules for any preventive treatment in migraine. BASH feels that headache physicians should be able to ensure they use	Comments noted. The Committee's discussions on administration of botulinum toxin type A are summarised in section 4.4 of the FAD. The Committee heard from clinical specialists that an initial consultation typically lasts between 45 minutes and 1 hour and includes administration of botulinum toxin type A, which can take between 15 and 30 minutes depending on the experience of the person administering the injection. After treatment patients are asked to keep a headache diary. Routine follow-up appointments are either a telephone consultation with a consultant or headache specialist nurse, or a 30 minute clinic appointment with the consultant. Sections 4.11and 4.12 of the FAD include the Committee's consideration on the use of stopping rules. The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It

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	the health resources appropriately and limit the treatment to those benefiting most from it.	therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
British Association for the Study of Headache (BASH)	Question c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Botox is the only licensed treatment available for prophylaxis of headache associated with CM. The only other drug with class I evidence is Topiramate which has its limitations of poor tolerability, cognitive and teratogenic side effects. This is important as a large number of CM sufferers are females of child-bearing potential. Botox is often their last hope to continue to live normally and be able to return to work. BASH is disappointed with the draft recommendation of the committee and feels strongly that the decision must be carefully considered.	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).
British Association for the Study of Headache (BASH)	Question d) 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? CM is more common in females at a young age. This is the most productive period of their life both from family and work point of view.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).

Consultee	Comment	Response
British Association for the Study of Headache (BASH)	Question e) Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document? Currently the treatment is mainly delivered in the private sector and only those who can afford the treatment are able to receive it. The treatment is commissioned by some Primary Care Trusts in line with the licensed recommendation. The other Primary Care Trust is considering individuals on the basis of exceptionality and has rejected the vast majority of applications through individual funding requests. If the treatment is not recommended on the NHS than it will only be received in the private sector by those who have the ability to pay for it. This is discriminatory as the medication is licensed.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
British Pain Society	There is too much uncertainty about this treatment for widespread use within the NHS at present. It may be better to negotiate a risk sharing scheme with the company: drug cost for all those who fail to respond (satisfy the negative stopping rule) should be paid for by the company. For those who fulfil the positive stopping rule (change from chronic to episodic migraine) but refuse to stop having injections, the company should also pay for their drugs. This will also help us to see in a prospective manner how many is in each category. If we set up such an observational study, we may not be able to calculate ICER but if data is collected and compared to each patient's historical course of illness, it will provide better information and answer some of the uncertainties raised. The cost-effectiveness of this treatment can also be gauged: not only in direct medical costs but also other things such as loss of productivity, etc. Whatever other health utility measures that we need can be built into this study so that the appropriate data is collected. The HTA committee may just say no to this treatment but make a research recommendation that can be beneficial to the NHS and also get more information to help other health economies to decide on utility of this treatment. This way, Botox can be used in a controlled manner with centres set up all over the country and patients will benefit as well. Some of these sites could be joint collaborations between Neurology and Pain services pooling their expertise. It will also ensure that the appropriate levels of expertise are defined, the use of Botox can be audited and a lot more information about utility of this treatment can collected.	Comment noted. The Committee noted the considerable uncertainties in the original economic model submitted by the manufacturer and considered whether each of these had been addressed in the revised economic model. The Committee noted that the revised model included their preferred assumptions and inputs and concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD sections, 4.9and 4.16). Section 1.2 of the FAD states that treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition: • Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or • has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

Consultee	Comment	Response
Primary Care Neurology Society	The Primary Care Neurology Society is disappointed at the initial indication from NICE of the minded no position for what is the only licenced intervention in migraine. Migraine, as recognised by the WHO continues to be extremely debilitating condition which has a significant detrimental impact on a person's quality of life. New treatment options are clearly needed. We are concerned that the appraisal currently fails to recognise the full extent of the quality of life burden associated with migraine because simply looking at a reduction in headache days as a negative stopping rule does not reflect clinical practice. It could be argued that a reduction in migraine days would be more accurate. But either way, a person's quality of life can be significantly improved simply by a reduction in severity and duration of migraine as well as a need for rescue medication. These quality of life changes along with the positive effects on symptoms such as light sensitivity, nausea, and dizziness, could all be missed by focusing on a reduction in headache days. If the appraisal is only to focus on percentage reduction of headache days we feel that a tipping point less than 50%, e.g. 25-30% would be better.	Comment noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4.12 of the FAD. The Committee noted from comments received during consultation that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). Section 1.2 of the FAD states that treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition: • Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or • has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.
Migraine Action	The World Health Organisation ranks migraine as the 19th most disabling disease. Women are three times as likely as men to suffer from migraines, which are also linked to depression and anxiety, of which the cost to the NHS and the economy runs into billions of pounds per year. This condition can greatly affect all aspects of life - family, work, and social life. Migraine Action is extremely concerned that should, what is the only licensed Chronic Migraine treatment, Botulinum Toxin, not be made available to patients, an opportunity would be lost to reduce further patient suffering. Key findings of recent online survey of 97 patients with Chronic Migraine:	Comment noted. The Committee considered the impact of chronic migraine on the everyday life of people with the condition. It heard from the patient experts that chronic migraine is accompanied by severe pain, which impacts greatly on people's quality of life, affecting their ability to work and participate in social activities. The patient experts also noted that people with chronic migraine often experience anxiety and depression related to their condition. The Committee considered chronic

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	13.4% of participants had tried Botox to manage their chronic migraine. Interestingly 48.5% would like to try Botox to manage their chronic migraine suggesting lack of control from current treatment but as yet could not access the new option. Of those who had tried Botox, over 60% found the treatment beneficial or very beneficial. The initial survey results have now led us to undertake a further "drilled down "survey with the following questions in an attempt to further discuss some of the issues raised in the preliminary recommendations. This survey can be found by visiting our website at www.migraine.org.uk However we do have a number of observations to make which have been raised by some members over the last couple of weeks in response to the media activity. Concentrating on the change in number of days of headache doesn't fully tell us how a patient has actually responds to treatment. It doesn't reflect "reality and relevance of transforming lives". For instance we have members real life experiences recorded who tell us that their "end point" was the improvement in their overall quality of life even though some days the headaches were still there. However the severity, length of headache and associated symptoms had improved to such an extent that these patients were not bedridden or unable to interact socially with their family and friends, or for some, do the school run for the first time in weeks and months. Change in non headache symptoms may be key. We have patients whose dizziness was so much reduced that even on their" break through headache" days they were still able to travel on public transport and continue to work. This suggests that their QUALY had been improved and this is not recorded in the studies. We understand that any treatment needs to be cost effective. However what our members wish addressed is the need to demonstrate there was enough effect on the QUALY to justify carrying on treatment. Additionally, if successfully managed and then migraines were to return- how would they as patients be handled? What would be the procedure to reenter the programme or would they be excluded until they had exhausted once again all other treatments and their migraines had worsened to a point where they reached the expected criteria. In our opinion this is discriminatory practice.	migraine to be a debilitating condition which significantly affects health-related quality of life. (FAD Section 4.2). The Committee accepted the plausibility of using different utility values in the botulinum toxin type A and placebo arms, and considered that the utility values in the economic model encompass the major health- related quality of life benefits associated with treatment with botulinum toxin type A, including duration and intensity of migraine, reduction in symptoms, need for rescue treatment, and lower dose of acute medication. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16) The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD. The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It

Consultee	Comment	Response
		therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Migraine in Primary Care Advisors	This organisation is disappointed to read that the committee is minded not to recommend botulinum A for the prevention of headaches in adults with chronic migraine. We understand the need to demonstrate cost effectiveness and that the committee have already requested additional information from Allergan, both with regard the presented data and proposed delivery model. Might we respectfully remind the committee that chronic migraine is reported by WHO to be one of the top 20 conditions for lifetime disability and that Botox is the only licensed intervention available to clinicians at this time. Unlicensed agents have low efficacy and high tolerability and are often not acceptable to patients. Clinicians recognise that disability and quality of life are not only improved by less headache days. Reduced severity and duration of headache as well as reduced comordid symptoms can be equally important. Reduction in the need preventative medications and changing to simpler analgesic rescue and using less doses might be the key parameter for some sufferers. It is our view that a more global view of a patient's health status is required both in clinical practice but also in your appraisal process. An area where this is particularly relevant is the stopping rule that at present suggests stopping if less than 50% reduction in headache days are reported. It is our opinion that clinically significant benefit is seen well before a 50% reduction and that a broader outcome than headache days would be optimal.	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).The Committee noted that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive

Consultee	Comment	Response
		months is the most clinically relevant (FAD section 4.12).
Migraine Trust	Question a) Has all of the relevant evidence been taken into account? The Migraine Trust takes the view that not enough weight has been given to the benefits that patients experience when being treated by Botulinum Toxin A (Botox). Patients who have benefitted have already failed to respond to at least 3 other treatments and the options left to them are less desirable, with often intolerable side effects and indeed more expensive. The disabling nature of Chronic Migraine means that any reduction in the severity of symptoms can make an enormous difference to the patient's ability to function and to their general quality of life. Botox may help return a patient's migraines to the episodic state where other treatments become available to them and are therefore able to avoid the devastating impact that CM has on family relationships, ability to work and quality of life.	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16). The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Migraine Trust	Question b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? NICE has looked at the cost of an episode of treatment with Botox in the NHS but has not, in our view, given enough emphasis to the fact that patients with CM have repeated referrals to the NHS due to the nature of their condition. There seems to be an assumption that no treatment means no cost but there is a cost in that patients who are not getting relief will take up more time within the NHS. The cost of treatment would reduce with specialist headache nurses administering the treatment. The Migraine Trust organised a training day for specialist headache nurses on treating CM with Botox and I can say from personal experience that they are well placed to fulfill this role. Research has shown that people with CM move back to episodic migraine in the	Comment noted. The Committee noted that the revised model included their preferred assumptions and inputs. See FAD sections 4.9 to 4.15 on the Committee discussions on the revised model. Following consideration of whether the uncertainties had been addressed in the revised economic model, the Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis

Consultee	Comment	Response
	same proportions as those who move into it which suggests that patients would not be likely to need continuous treatment with Botox to treat CM. (Bigal M E, Lipton E; 'The chronification of headache' Headache January 2008 pp7-15	therapies and whose condition is appropriately managed for medication overuse. See FAD section 4.16. Comment noted. Sections 4.11 and 4,12 of the FAD include the Committee's consideration on the use of stopping rules. .The Committee noted from comments received during consultation that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee also noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Migraine Trust	Question c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The Migraine Trust is disappointed that NICE was not able to recommend Botox. This is the last hope for a number of people and the only licensed treatment available. The only other preventative with evidence is Topiramate which as an anti epileptic drug has obvious limitations for a patient population which is predominantly young and female.	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic

Consultee	Comment	Response
		migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16). Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
Migraine Trust	Question d) 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? CH is common in younger women so there needs to be due consideration to this group. Migraine, although not specifically mentioned by name, can be classed as a disability when the patient with the condition meets the criteria of disability in The Equality Act 2010	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
Migraine Trust	Question e) Are there any equality-related issues that need special consideration and are not covered in the ACD. As above in d). If people with CM are forced to go privately, then women are doubly disadvantage by earning on average less than 15% than men.	Comment noted. The Committee's discussions on whether NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
Royal College of Nursing	Question 1) Has the relevant evidence has been taken into account? The evidence considered seems comprehensive.	Comment noted. No action required.
Royal College of Nursing	Question 2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We would ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by patients with headaches associated with chronic migraine. The preliminary views on resource impact and	Comment noted. Section 3 of the FAD is intended to provide a summary of the evidence provided by the manufacturer and the ERG critique. The Committee's discussion of current practice is summarised in Section 4.3 of the FAD. The

Consultee	Comment	Response
	implications should be in line with established standard clinical practice.	Committee was aware that the manufacturer had focused on a population of adults with chronic migraine whose condition has failed to respond to at least three prior pharmacological prophylaxis therapies, and whose medication overuse has been appropriately managed in a sensitivity analysis and that its main submission compared botulinum toxin type A with placebo in people whose condition has failed to respond to at least one prior preventive medication. The Committee noted comments from the clinical specialists that people first presenting with chronic migraine will be prescribed a range of oral preventive medication options before treatment with botulinum toxin type A is considered. It concluded that it was only relevant for the Committee and the NHS to consider the clinical and cost effectiveness of botulinum toxin type A in people whose chronic migraine has failed to respond to at least three prior preventive medications. (Section 4.8 of the FAD).
Royal College of Nursing	Question 3) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? The RCN notes that Appraisal Committee has recommended that NICE requests further information on the clinical and cost effectiveness of botulinum toxin type A from the manufacturer, as described in 1.3 to 1.5 of the ACD. We also note that the recommendation that this information should be made available for the next Appraisal Committee meeting. The RCN looks forward to receiving the Committee's view following consideration of this information.	Comment noted. No action required.
Royal College of Nursing	Question 4) 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? None that we are aware of at this stage.	Comment noted. No action required.
Royal College of Nursing	Question 5) Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document? We are not aware of any specific issue at this stage. We would however, ask that	Comment noted. An equality impact assessment for this appraisal will be published on the NICE website. The Committee's discussions on whether

Consultee	Comment	Response
	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.	NICE's duties under the equalities legislation required it to alter or add to its recommendations in any way is summarised in Section 4.17 of the FAD. Because the recommendations do not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups (FAD section 4.17).
Royal College of Physicians	The RCP is pleased to endorse the response submitted by the ABN on the above consultation.	Comment noted. See responses to the Association of British Neurologists comments above.

Comments received from commentators

Commentator	Comment	Response
Medicines and Healthcare products Regulatory Agency	Page 5, paragraph 2.1: Please check this description. Section 5.1 of the summary of product characteristics states: The active constituent in BOTOX is a protein complex derived from Clostridium botulinum. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin. *Clostridium botulinum* toxin type A neurotoxin complex blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals. Page 5, paragraph 2.1: The conditions listed (blepharospasm, cervical dystonia, etc) are in fact **indications** for botulinum toxin type A, *not* adverse reactions. Also, we suggest that the wording of therapeutic indications should closely match that in the summary of product characteristics. For example, the summary of product characteristics states 'dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients' rather than just 'paediatric cerebral palsy'.	Comment noted. Section 2.2 of the FAD has been amended in accordance with the summary of product characteristics. Section 2.2 of the FAD now states that 'the adverse reactions that may be associated with botulinum toxin type A treatment: headache, migraine, facial paresis, eyelid ptosis, rash, neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness, and injection site pain. It states that 'in general, adverse reactions occur within the first few days following injection and while generally are transient, may have a duration of several months or, in rare cases, longer. For full details of adverse reactions and contraindications, see the summary of product characteristics'.

The following consultees/commentators indicated that they had no comments on the ACD

The Department of Health

Comments received from members of the public

Role*	Section	Comment	Response
Patient 1	1	As a patient suffering with chronic migraine, who has benefitted from three treatments of Botox injections, I consider that the Appraisal Committee should without doubt recommend botulinum toxin type A for the prevention of headaches in adults with chronic migraine. My response to the injections has been 'life changing'. Â Prior to the injections, I was suffering with typically 26-30 days of totally debilitating pain per month. This was reduced by more than 50% following the second administration of Botox. Â I have not been part of a trial of Botox but have been given this treatment by my consultant neurologist after having tried numerous other prophylactic drugs (and many alternative therapies) to no effect over a 20-year period. Â According to my consultant neurologist, not only has the frequency of my severe headache days reduced but my background headache severity has improved as assessed using the HIT6 score i.e. 66 to 64. There has also been a halving of my Hospital Depression score and reduction in my Hospital Anxiety score. He feels that this is largely related to the reduction in headache related impairment leading to resolution of reactive anxiety/depressive symptoms.	Comment noted. The Committee carefully considered the comments received from members of the public in response to the Assessment Report. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)
Patient 1	2	I have experienced several significant benefits, the major one being the reduction of the frequency and severity of the pain - a reduction from almost constant pain to just a few days of pain a month. There has also been a lifting of the horrible cloud of depression which accompanies the pain and for the first time in many years, a return of a clear mind, enabling me to get on with my life and my work. The Botox injections help dramatically with all aspects of the condition including the head pain, depression, irritability, exhaustion, clumsiness, speech difficulties and cognitive impairment. Unlike some of the other medicines which I have used for my chronic migraine (e.g. Amitryptyline, Propranalol), I have suffered no side effects from treatment with Botox.	Comment noted. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)

* 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.

Role*	Section	Comment	Response
Patient 1	3	Botox is the only treatment which has enabled me to live a normal life for the first time in twenty years. If this treatment is not made available on the NHS, I am not sure how I would be able to carry on. I have had to borrow the money to pay for the treatment on a private basis up to now from my elderly parents who are unable to continue to support this indefinitely. I would be suffering in utter misery just wanting to 'chop my head off'. If this treatment were available on the NHS, it would mean that I would be able to have the injections as required, leaving me without pain and able to get on with my life, do my work, be a proper father to my three children and generally make a contribution to society. The total cost of the treatment to the NHS would work out at £29.12 per week (based on your figures). To me this is a small price to pay to be able to live my life. I will be able to contribute many times this sum per week by being able to get on with my work, earn money and pay income tax instead of drawing Statutory Sick Pay and other benefits e.g. Child Tax Credit.	Comment noted. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)
Patient 1	4	The effect of the migraines drastically reduces my ability to get on with my work (and life in general). As I am self employed, this reduces my income significantly and reduces my ability to pay for the Botox injections privately. The cost to the NHS would be significantly outweighed by my increase in productivity and quality of life. For example I would not need to claim periods of Statutory Sick Pay, as I have had to do prior to the Botox treatment, and my earnings would be greater such that I would be paying more income tax and therefore making a worthwhile contribution to the UK economy rather than being a burden. I understand your necessity to consider all aspects of the introduction of such a treatment through the NHS but your whole document is based on a very theoretical approach. Hopefully my comments outlined above will bring some real evidence of the effectiveness of Botox in the prophylactic treatment of chronic migraine in adults from someone who has experienced this first hand!	Comment noted. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)

Role*	Section	Comment	Response
Health Professional (NHS and private sector)	1	I am a consultant neurologist and run a quarternary clinic in the UK for refractory and severe headache disorders. The neurology units in the North West UK agreed a protocol with commissioners regarding use of Botox and commissioners agreed to fund Botox in such cases. Despite this, I am aware that as a neurology Trust serving more than 3 million patients, we have actually considered and/or moved to treat patients with Botox in less than 10 cases as of this date. This includes many patients seen for some years in one of very few specific "refractory" headache clinics. As such, I believe that it is appropriate use of resources to treat the small number of patients who have nothing else to offer, who have fully eliminated all medication and caffeine overuse, who have maintained excellent lifestyle re fluids/food/sleep, where we have eliminated and treated comorbid sleep disorder first and they have failed a minimum of at least 3 reasonable trials of preventative drug. This is as per the North West protocol. I state this, as I believe it is possible to prescribe and treat just those patients who have nothing else to offer and have very severe disability and distress.	Comment noted. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16)
Health Professional (NHS and private sector)	2	This treatment is a relatively safe one when comparede with other migraine preventatives. Just this week I have seen a patient with neutropenia from an anticonvulsant (prolonged admission after number of GP visits before diagnosed), a patient with heart block on calcium anatagonist, and a patient who has come off topiramate (only drug out of more than 9 preventatives to have worked) where she developed severe renal calculi on topiramate. I often see such problems and many of the drugs we use are extremely toxic, causing both severe morbidity (as above) or severe side effects (eg 1/4 of those on topirmaate for migraien develop severe cognitive disturbance, mood disorder, or suicidal ideation. In comparison, Botox has an excellent safety profile. In addition, with the North West Botox protocol, it is cost effective (patients do not get triptans etc to any degree)	Comment noted. The Committee's consideration of the adverse reactions to treatment with botulinum toxin type A is summarised in the FAD (section 4.7). The Committee noted the adverse reactions reported in the trials with botulinum toxin type A (see section 3.8). It heard from the patient experts that there is often pain around an injection site lasting a few days after treatment with botulinum toxin type A. However, people would be willing to tolerate the adverse reactions with botulinum toxin type A treatment to reduce the frequency or severity of their chronic migraine. The Committee concluded that botulinum toxin type A is generally well tolerated; a conclusion supported by the patient experts and clinical specialists (section 4.7 of the FAD).
Health Professional (NHS and	3	1. patients for botox should be those who have by definition failed other treatments. 2. they are very disabled. 3. if the North West protocol or similar is adopted, the process would select those most in need (a very	Comment noted. The Committee's considerations on the use of stopping rules are summarised in Sections 4.11 and 4,12 of the FAD. The

Role*	Section	Comment	Response
private sector)		very small number of all migraineurs) in the most difficult state, they would receiveonly 2 sessions and then be evaluated by established disability/impact scales and diary, and would only continue if 30% response at 6 months. If good response, they would receive Rx for 1 year only, then have 6-8 month assessment period with possibility of further Rx year thereafter. 4. Costs would need to be offset against cost of GP visits/A+E visits (often admitted as ? subarachnoid haemorrhage - to CT and LP etc to DGH), against costs of other acute treatment (triptans, painkillers, antiemetics) and against other preventatives (cost of Rx and dealing with severe side effects. Data from open label studies shows response of 2/3 reduction in headache days, with redued severity as average response. We should only continue to treat those that respond. If you want, I can send North West Protocol as agreed with commissioners in N West UK if is agreement from commissioners/Walton	Committee's recommended negative and positive stopping rules are summarised in Section 1.2 of the FAD. **Negative stopping rule.** The Committee noted from comments received during consultation that there was agreement between the manufacturer and the clinical community that a 50% response rate is considered to be too high, and that a 30% response rate recommended by the British Association for the Study of Headache is used in clinical practice. The Committee concluded that a 30% response rate (that is, a 30% reduction in the number of headache days per month after two cycles of treatment) was the most clinically relevant and reasonable negative stopping rule on which to base its decision (FAD section 4.11). The Committee's most plausible ICER presented included a negative stopping rules based on, a 30% reduction in the number of headache days per month after two cycles of treatment. (See FAD sections 4.15 and 4.16). **Positive stopping rule.** The Committee noted that the marketing authorisation for botulinum toxin type A does not include use in people with episodic migraine. It therefore concluded that a positive stopping rule in which patients stop treatment if their condition has changed to episodic migraine (that is, fewer than 15 headache days per month) for three consecutive months is the most clinically relevant (FAD section 4.12).
Health Professional (NHS and private sector)	4	Allergan is conducting further studies and I am principal investigator in one. We have a catch 22 situation. NICE wants more information. The provisional report has led to Commissioners temporarily halting North West Protocol and our Trust treating new patients. The Allergan study does not pay for Botox. Hence I cant add new patients to study that will	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible

Role*	Section	Comment	Response
		increase knowledge on Botox. I have already made comments regarding evidence. In the N West UK, we have a protocol that allows us only to continue in those with clearly documented efficacy. In clinical practice, we always utilise a placebo response (friend of the physician, foe of the researcher!). In clinical practice we do not have an alternative (we can not "give" placebo as it is unique to a trial setting. The patients treated under an agreed protocol such as we use only continue if proven benefit and only start treatment after many leayers of other treatment (a. strict elimination of acute attack drugs and caffeine & exemplary lifestyle, b. failed Rx on 3 (often than3) preventative trials each 4 months @ max tolerated dose,c. Rx sleep disorder. Placebo response likley would have been seen before if "respond" to botox.	ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).
Health Professional (NHS and private sector)	5	We have established a protocol in the North West UK that should be evaluated as a pilot in the UK (in my opinion) to determine if utility of Botox will provide effective treatment for low cost, maximising selection, retention and further evaluation criteria for patients to only continue to use Botox where proven long term benefit, stopped after reasonable treatment period and not maintained where poor response. And only given where failed number of other first line treatments, most likely where we have nothing else to offer this highly disabled group (WHO rank migraine as one of top 4 most disabling conditions, equal alongside dementia, psychosis and quadriplegia) - these patients usually have no alternative at this late stage of treatnment and nowhere else to turn - often young, lose jobs, families break up (I see this regularly in this group). Yet, Botox has proven benefit in some patients vs placebo. Guidance from NICE needs to take this into account	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16). Section 1.2 of the FAD states that treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition: • Is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) or • has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months.

Role*	Section	Comment	Response
Patient 2	2	How much does it cost for an person to stay in hospital for 5 days and recieve intravenous D.H.E. which dosnt work very well but is offered because everything else has been tried?	Comment noted. The Committee considered the additional information supplied by the manufacturer and comments received during consultation on the Appraisal Consultation Document. The Committee concluded that that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse (FAD section 4.16).
Patient 2	4	I am sorry but I didnt really understand all of the report, but I would like to say I am a 48 yr old woman with chronic migraine who cannot hold down a job because of it. I have had progressivly worsening migraines since age 12 and have taken many medicines for the condition, both preventitives and pain relief, non of which have been effective. Approx a year ago I was given injections of Botox and had a wonderful 4 months of reduced migraines and deminished pain. Now I am back to dreadful pain almost everyday, constantly battling the desire to take frequent pain relief.Please, please make Botox available for those of us who need it. Thank you.	Comment noted. The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16).

Role*	Section	Comment	Response
Health Professional (NHS)	1	Stopping rules: there can be made to work in a robust and auditable manner using patient-held headache diaries, copied for the medical record. In clinic, no diary means no Botox treatment. Differential utilities: counting headache days captures useful information but does not tell the whole story. Many patients I have treated with prophylaxis, including Botox, advise that headache may have diminished duration or impact fewer associated symptoms e.g. vomiting or enhanced acute treatment response: taking, compared with not taking prophylaxis.	Comment noted. Section 4.13 of the FAD includes the Committee's consideration on the use of different utilities within each health states in each arm. The Committee concluded that although using different utility values within each health state in the botulinum toxin type A and the placebo arm was plausible and better than applying the same utility values within each health state to calculate the most appropriate ICER for considering cost effectiveness, there was still considerable uncertainty around the degree to which differential utilities existed within each health state (FAD section 4.13). The Committee concluded that because the most plausible ICER presented was less than £20,000 per QALY gained, botulinum toxin type A could be considered an appropriate use of NHS resources for the prevention of headaches in adults with chronic migraine that has not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. (FAD section 4.16).