National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Allergan	None	Comment noted.
	British Association for the Study of Headache	We think this is appropriate as after being granted a license on grounds of recent publication that many people have questioned about, it is important that all aspects of this treatment be appraised	Comment noted. The Committee can only make recommendations on the use of botulinum toxin type A in line with the UK marketing authorisation.
	British Pain Society	Yes. This medication is licensed, has received wide publicity and there is a demand for guidance regarding its use	Comment noted.
	The Migraine Trust	Yes absolutely	Comment noted.
Wording	Allergan	To appraise the clinical and cost effectiveness of BOTOX® (botulinum toxin type A) within its licensed indication for the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).	Comment noted. No changes to the remit required. Wording is in line with the marketing authorisation.
	British Association for the Study of Headache	Agree	Comment noted.
	British Pain Society	Yes, wording is adequate	Comment noted.

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	The Migraine Trust	Yes	Comment noted.
Timing Issues	Allergan	No timing issues to be noted.	Comment noted.
	British Association for the Study of Headache	The issue merits quick attention as there is increasing demand for this treatment by the patient group but as yet funding issue has not been identified.	Comment noted.
	British Pain Society	Should be assessed very soon. As stated above, there is a need to have clear guidance regarding the availability and use of this treatment for NHS patients.	Comment noted.
	The Migraine Trust	This technology potentially meets a significant unmet clinical need and should be assessed at the earliest opportunity.	Comment noted.
Additional comments on the draft remit	Allergan	None	Comment noted.
	British Association for the Study of Headache	No	Comment noted.
	British Pain Society	In the absence of clear guidelines, there is a risk of inequality of access for NHS patients.	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Allergan	Chronic migraine is a primary headache disorder defined by headaches on at least 15 days per month of which at least 8 days are with migraine. Chronic Migraine is therefore a separate and distinct diagnosis in a sub-population of headache patients. In the US and Europe, chronic migraine affects between 1.3 to 2.4% of the overall populations, respectively (Castillo 1999, Scher 1998, Lanteri-	Comment noted. At the scoping workshop it was acknowledged that there is a lack of consensus among clinical professionals on the definition of chronic migraine in clinical practice. It was noted that the definition of chronic

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		Minet 2003, Natoli 2010). The prevalence of chronic migraine is higher in women compared with men throughout the course of adulthood (Midgette 2009, Natoli 2010). According to Jensen and colleagues, chronic daily headache disorders such as chronic migraine are lifelong disorders and prevalence rates tend to increase until the fifth decade of life and decrease with increasing age (Jensen 2008). Observational and clinical trials have shown that 50–80% of patients with chronic migraine overuse acute medication (SIGN 2008). Furthermore, the International Headache Society (IHS) guidelines for chronic migraine trials state that due to the high prevalence of medication overuse in chronic migraine, subjects, may be included in trials for chronic migraine provided that they are stratified accordingly (Silberstein 2008). The current International Classification of Headache Disorders IIR (ICHD-IIR) from the International Headache Society (2005) excludes patients who are overusing acute medication from receiving a diagnosis of chronic migraine. However, a revision of the ICHD-IIR criteria is expected based on the proposal by experts that the inclusion of medication overuse patients should be allowed within the classification of chronic migraine to more accurately reflect the patient population seen in clinical practice (Olesen 2006). The Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies, therefore, include patients who are overusing pain medication (between 62% and 70% of patients at baseline), which were considered as representative of real-world patients, in a recent review by Schoenen (2010).	migraine from the International Headache Society is not universally accepted. The background section of the scope has been updated to reflect this. Consultees at the scoping workshop were unable to provide a sure estimate of the prevalence of chronic migraine in the UK because of the lack of consensus on its definition and its relatively recent recognition as a condition. It was estimated that approximately 1 in 1000 people may have chronic migraine. The International Headache Society does not include medication overuse in their definition for chronic migraine. Consultees acknowledged that patients who have chronic migraine due to medication overuse should be considered in an appraisal because they represent a large proportion of patients with migraine, therefore medication overuse has been incorporated into the scope as a proposed subgroup to consider if the evidence allows. It was noted during the scoping workshop that the presence or absence of

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			medication overuse is not included in the marketing authorisation for botulinum toxin type A.
	British Association for the Study of Headache	The document refers to the burden of migraine in general but does not specify the estimate of chronic migraine in the general population. Currently the estimate is around 1.5 - 4%.	Comment noted. At the scoping workshop, the prevalence of chronic migraine in the UK was unknown, which was also complicated by the lack of consensus on its definition and its relatively recent recognition as a condition. It was estimated that approximately 1 in 1000 people may have chronic migraine.
	British Pain Society	Amitriptyline is only one of the tricyclic and tetracyclic antidepressant drugs used as migraine prophylaxis. Others include nortriptyline, imipramine, desipramine, etc.	Comment noted. Additional prophylactic agents have been added to the scope.
	The Migraine Trust	The content is appropriate.	Comment noted.
The technology/ intervention	Allergan	Botulinum toxin type A (BOTOX®, Allergan) is a protein produced by the bacterium Clostridium botulinum. Three different Botulinum toxin type A products are available in the UK of which only BOTOX® has undergone a clinical development programme and is indicated for the prophylaxis of headache in adults with chronic migraine. 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. Only appropriately trained personnel in hospital specialist centres (mainly	Comment noted. The scope gives a brief introduction to the technology of interest. Further details will be provided in the manufacturer's evidence submission. Comment noted. Consultees during the scoping workshop estimated that approximately 500

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		neurologists) will have access to BOTOX® (BOTOX® SmPC 2010). BOTOX® is administered intramuscularly in 31, fixed-site, fixed-dose, intramuscular (IM) injections (minimum dose 155 U) across seven specific head/neck muscle areas (corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal and trapezius). Depending on the location(s) of the patient's predominant pain and severity of palpable muscle tenderness, a follow-the-pain strategy, with up to 40U additional dosing (maximum dose 195 U) can be given to one or both sides in up to three muscle groups (occipitalis, temporalis, and trapezius). An outpatient appointment of 15 to 20 minutes is expected when injecting BOTOX® in adults with chronic migraine.	patients are currently receiving (privately) botulinum toxin type A for chronic migraine from approximately 10 centres in the UK.
	British Association for the Study of Headache	Correct and accurate.	Comment noted.
	British Pain Society	Yes	Comment noted.
	The Migraine Trust	Yes	Comment noted.
Population	Allergan	The population to be considered is adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine), with or without medication overuse	Comment noted. Medication overuse has been addressed in the definition of the population and proposed as a possible subgroup if evidence allows, following the scoping workshop.
	British Association for the Study of Headache	A large chunk of patients with chronic migraine overuse medication. Population based study quote figures of between 30-50% and clinic based study estimate figures of 50-80% of chronic migraine sufferers overusing medication. Chronic Migraine without medication overuse is fairly uncommon. The publication on which license was granted was challenged on the same issue as most of their patients were overusing	Comment noted. Medication overuse has been addressed in the definition of the population and proposed as a possible subgroup if evidence allows,

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		painkillers. A separation of those with or without medication overuse may be more appropriate.	following the scoping workshop.
	British Pain Society	Pregnant women and children between ages 12-18	Comment noted. The Committee can only make recommendations on the use of botulinum toxin type A in line with the UK marketing authorisation. The current marketing authorisation only includes adults; therefore the use of botulinum toxin type A for chronic migraines in children between the ages of 12-18 years cannot be appraised. The summary of product characteristics (SPC) for botulinum toxin type A states that it should not be used during pregnancy unless clearly necessary.
	National Clinical Guideline Centre	Important to distinguish population from episodic migraine People who have failed previous preventative measures are a potential subgroup	Comment noted. The remit for this appraisal only includes patients with chronic migraine as it is noted in the SPC that no efficacy has been shown to date for botulinum toxin type A in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month). The population in the scope includes adults with chronic migraine which has been

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			inadequately controlled with pharmacological prophylaxis.
	The Migraine Trust	Yes	Comment noted.
Comparators	Allergan	Standard management of adults with chronic migraine without botulinum toxin type A includes numerous prophylactic pharmacological and non-pharmacological therapies, none of which are specifically licensed for the management of this condition. Based on current clinical guidelines (BASH 2010) BOTOX® should be positioned as prophylactic treatment for adults with the diagnosis of chronic migraine, who are refractory to pharmacological therapies (oral medications). Goadsby et al (Cephalalgia, 2006) have recommended that migraine patients should have failed at least four classes of the following treatments, where three should come from classes 1 to 4: 1. β-Blockers; 2. Anticonvulsants; 3. Calcium channel blockers; 4. Tricylic antidepressants; 5. Other treatments with at least one positive randomized controlled trial; 6. Non-steroidal anti-inflammatory drugs; 7. Metabolic enhancers, such as vitamin B2 or coenzyme Q10. Once these oral pharmacological therapies have been tried without success, the patients are often seen by headaches specialists in the secondary care setting and potentially considered for more invasive non-pharmacological therapies such as: greater occipital nerve block, implantation of occipital nerve or deep brain stimulators, and dihydroergotamine infusions. Due to its minimally invasive nature, clinicians recommend BOTOX® to	Comment noted. Following discussions at the scoping workshop, the comparators in the scope have been updated to specify: 'standard management without botulinum toxin type A excluding invasive procedures'. Specific pharmacological agents have not been individually listed due to the numerous options available.

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		be used as prophylactic treatment for patients with the diagnosis of chronic migraine, who are refractory to at least 4 classes of oral prophylactic medication and for whom other more invasive procedures are the next option. In this context, the main comparators to BOTOX® would be either acute medication only or combination of acute medication with procedural interventions such as greater occipital nerve block, implantation of occipital nerve, deep brain stimulators and dihydroergotamine infusions.	
	British Association for the Study of Headache	The prophylactic drugs used in migraine including tricyclic antidepressants, beta-blockers and pizotifen have been in the market for decades. They are generic and cheap to prescribe and hence it is unlikely that any data in chronic migraine prophylaxis will emerge. A comparative data with Botox is also unlikely to come out. The only prophylactic drug with robust evidence in chronic migraine is topiramate and a comparison with this agent may well be appropriate considering botox is an expensive drug	Comment noted. Following discussions at the scoping workshop, the comparators in the scope have been updated to specify: 'standard management without botulinum toxin type A excluding invasive procedures'. Specific pharmacological agents have not been individually listed due to the numerous options available. In the NICE guide to the methods of technology appraisal, comparators are considered routine or best practice in the NHS. Availability of evidence and a marketing authorisation does not, per se, dictate comparator selection.
	British Pain Society	Topiramate is the medication licensed for use as a migraine prophylaxis. This can be the main comparator.	Comment noted. In the NICE guide to the methods of technology appraisal, comparators are considered routine or best practice in the

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			NHS. Availability of evidence and a marketing authorisation does not, per se, dictate comparator selection.
	National Clinical Guideline Centre	Standard treatment for which there is evidence e.g. topiramate	Comment noted. In the NICE guide to the methods of technology appraisal, comparators are considered routine or best practice in the NHS. Availability of evidence and a marketing authorisation does not, per se, dictate comparator selection.
	The Migraine Trust	This is the most difficult question. There are a number of treatments used for patients with chronic migraine, but few of these have any evidence base in chronic migraine. This issue is compounded by the fact that most GPs and many neurologists do not recognise the chronic migraine phenotype	Comment noted. In the NICE guide to the methods of technology appraisal, comparators are considered routine or best practice in the NHS. Availability of evidence and a marketing authorisation does not, per se, dictate comparator selection.
Outcomes	Allergan	The objective of using prophylactic therapies in chronic migraine patients is to reduce the frequency of headache days. The frequency of headache days per month is the primary efficacy outcome recommended by the FDA, the expert clinical community (Silberstein 2008a) and is widely used in other chronic migraine trials (Diener 2007, Silberstein 2007). Other efficacy outcomes recommended also relate directly to the incidence of the disease and patient morbidity and includes: frequency of migraine days per month, frequency of moderate/severe headache days per month, and number of cumulative	Comment noted. Frequency of headache days and frequency of migraine days have been added to the scope following the scoping workshop. Severity of headaches has also been included to capture the extent to which a headache impacts on a patient's normal routine.

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		hours of headache on headache days. In a recent review of the PREEMPT studies by Schoenen (2010), "frequency of headache episodes" was considered as an inadequate outcome measure, not clinically relevant in patients with near daily headaches who use symptomatic pain-relieving therapies. This outcome should therefore be considered as a secondary outcome. Traditionally, clinicians have accepted that clinically effective migraine prophylaxis treatments are those that provide at least a 50% reduction in headache episodes or days in at least 50% of the patients (Silberstein 2008a). Recent guidelines issued by the IHS suggest that "in [the] chronic migraine population, a >30% responder rate can be clinically meaningful" (Silberstein 2008a). Health Related Quality of Life (HRQoL) measures validated in a chronic migraine population include the Migraine Specific Questionnaire (MSQ) and the Headache Impact Test-6 item (HIT-6). Generic HRQoL measures such as the EuroQoL-5 Dimensions (ED-5D) have been used in this specific patient population. Other important outcomes relevant for prophylactic therapies which aim to reduce the number of headache days per month, are the reduction in acute headache pharmacological therapies such as triptans.	It was not considered useful to include response rate as an outcome as it is difficult to define a therapeutic success rate and the most relevant outcomes are those that impact on health-related quality of life. Health-related quality of life is included in the scope as an outcome but the specific instrument to measure it is not specified. The EQ-5D is preferred in the NICE reference case. Reduction in medication has been included in the scope as a possible outcome measure.
	British Association for the Study of Headache	Consumption of acute medication, attendance to emergency care (both primary and secondary care) may be used for cost effectiveness. Patients with chronic migraine have migrainous headaches only half of the time and capturing data on other headaches are equally important. Health related quality of life is important if it was to include lost productivity and absenteeism	Comment noted. Frequency of migraine and headache days has been included in the scope. Severity of headaches has also been included to capture the extent to which a headache impacts on a patient's normal routine.

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			Consultees highlighted during the scoping workshop that an ongoing study on the burden of headaches (which contains UK patients) is collecting data which will consider outcomes such as attendance to emergency care and lost productivity and absenteeism. This information will be available to the Committee during an appraisal. Specific costs and benefits included in the economic model are not specified in the scope. The NICE reference case includes NHS and PSS costs but not societal costs.
	British Pain Society	Yes but there are still unanswered questions: for example, how long should 3 monthly Botox injections be administered? What is the long term effect of repeated injections?	Comment noted. These issues will be addressed during the course of the appraisal.
	National Clinical Guideline Centre	Headache days is preferred outcome (In the prophylactic treatment of migraine we are also recording 50% responder rate, but the above is reported to be the most relevant outcome).	Comment noted. Frequency of headache days has been included as a possible outcome. As above, consultees at the scoping workshop did not consider response rate to be a clinically useful outcome. It has not been included in the scope.
	The Migraine Trust	Probably yes	Comment noted.

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Economic analysis	Allergan	In clinical guidelines, it is stated that gradual withdrawal should be considered after 6 to 12 months of effective prophylaxis therapy (BASH 2010, SIGN 2008). It is worth noting that these guidelines were written before the PREEMPT studies were published and therefore only considered oral prophylactics administered daily, whereas BOTOX® is administered every 12 weeks and cannot be effectively tapered in the same way as an oral prophylaxis. Clinicians with experience of managing chronic migraine patients with BOTOX® in clinical setting have recommended continuing the use of BOTOX® in patients who are benefiting from treatment for 2 years. In the PREEMPT studies, double-blind data is available until week 24 (6 months), and open-label data (for BOTOX® only) until week 56. Given the uncertainty surrounding long-term projections of chronic migraine disease progression, a time horizon of 2 years would seem appropriate.	Comment noted. These issues will be addressed during the course of the appraisal.
	British Association for the Study of Headache	It is still uncertain whether patients with chronic migraine would continue to require prophylaxis with botox injections indefinitely. Experience from other preventative treatment indicates that the vast majority of patients require a treatment between 6-18 months. If this is true with Botox than between 3-5 injections cycles would be needed and hence 18 months would be a reasonable timescale to look at	Comment noted. These issues will be addressed during the course of the appraisal.
	British Pain Society	This was not stipulated and remains unknown	Comment noted.
	The Migraine Trust	No comment at present	Comment noted.
Equality and Diversity	Allergan	No specific equality issue to be raised	Comment noted.
	British Association for the Study of	No comment	Comment noted.

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	Headache		
	British Pain Society	See comments below	Comment noted.
	The Migraine Trust	Greater recognition of chronic migraine as a significant clinical problem will help eliminate discrimination (particularly workplace related) to which many migraine sufferers are exposed. The widespread use of this technology may aid this	Comment noted.
Innovation	Allergan	BOTOX® should be consider as an innovative technology for patients with the diagnosis of chronic migraine, who are refractory to oral medication, as more invasive procedural interventions such as greater occipital nerve block, implantation of occipital nerve, deep brain stimulators and dihydroergotamine infusions would be the next option. The main objective of using prophylactic therapies in chronic migraine patients is to help these patients reduce the frequency of headache days, therefore allowing chronic migraine patients to significantly improve their health-related quality of life, reduce their work absenteeism and improve their effectiveness at work. Unfortunately, the ability of chronic migraine patients to reduce their work absenteeism even though is a significant and substantial outcome for these patients which is unlikely to be included in a QALY calculation.	Comment noted. The innovative nature of botulinum toxin type A will be considered by the Committee during the course of the appraisal.
	British Association for the Study of Headache	We consider this treatment to be innovative and a welcome development for Chronic Migraine sufferers. Chronic Migraine is the most disabling of all migraine disorders. However, this is true that not every chronic migraine patient will be suitable for this treatment. Although there is no published evidence in the literature for betablockers, pizotifen and tricyclic antidepressants in chronic migraine, it does not mean that such agents are of no use. Hence only those patients with chronic migraine who have not responded to the first line agents should be considered for such treatment. It is also fair to say that non-responders of two cycles of treatment should not receive further treatments and that one would expect that a great proportion of patients would only require 3-5	Comment noted. The innovative nature of botulinum toxin type A will be considered by the Committee during the course of the appraisal.

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		treatments to bring remission. Medication overuse need to be addressed at the same time.	
	British Pain Society	Yes and data from the combined studies will clarify this: Dodick DW, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the doubleblind, randomized, placebo-controlled phases of the PREEMPT clinical trial programme. Headache 2010	Comment noted.
	The Migraine Trust	Yes. As mentioned above there very few treatments for chronic migraine with any evidence base. The usual approach is to use tricyclic antidepressants or anitconvulsants, all of which have significant tolerability and side effects issues, and which - with the exception of topiramate and sodium valproate - have no evidence to back up their use. Patients with chronic migraine are significantly disabled by their condition, and even if this technology is only available in specialist headache centres, it has the potential to make major improvements in some - but not all - cases.	Comment noted. The innovative nature of botulinum toxin type A will be considered by the Committee during the course of the appraisal In the NICE guide to the methods of technology appraisal, comparators are considered routine or best practice in the NHS. Availability of evidence and a marketing authorisation does not, per se, dictate comparator selection.
Other considerations	Allergan	No additional issues applicable.	Comment noted.
	British Association for the Study of Headache	No comment.	Comment noted.
	British Pain Society	What is the level of expertise necessary for clinicians to diagnose, administer and manage these patients?	Comment noted
	The Migraine Trust	No comment at present.	Comment noted.

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Questions for consultation	Allergan	The population to be considered are adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine), with or without medication overuse. BOTOX® is a prophylactic treatment for patients with the diagnosis of chronic migraine, who are refractory to at least 4 classes of oral prophylactic medication and for whom other more invasive procedures are the next option. These patients are typically managed in a secondary care centre. The efficacy outcomes to be considered are as follows: • frequency of headache days per month; • frequency of migraine days per month; • frequency of moderate / severe headache days per month; • number of cumulative hours of headache on headache days, responder rate of at least 50% reduction in headache days; • HRQoL measures such as the Migraine Specific Questionnaire (MSQ) and the Headache Impact Test-6 item (HIT-6) and the EuroQoL-5 Dimensions (ED-5D); • reduction in acute headache pharmacological therapies such as triptans. Other types of outcomes to consider are the Incremental Cost Effectiveness Ratio (ICER), for BOTOX® compared to standard of care expressed as • Cost per Quality Adjusted Life Year (QALY) gained; • Cost per headache-day avoided.	See previous comments about the population and the outcomes. The proposed population is in line with the marketing authorisation. The NICE reference case includes NHS and PSS costs but not societal costs

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		A cost-effectiveness analysis in this population would need to also consider a societal perspective as productivity costs represent more than 70% of the total costs of chronic migraine. During a cross-sectional, web-based, observational survey (International Burden of Migraine Study- IBMS), 8,726 episodic and chronic migraine individuals recruited across 9 countries including the UK (Blumenfeld 2011) completed the EQ-5D questionnaire, to determine the range of utility values for patients with different frequency of headache days per month. The results of this study demonstrate the impact that a high number of headache days have on chronic migraine patient's quality of life and the importance of providing them with an effective and well-tolerated treatment to help these patients to return to the lowest possible episodic stage. In a pooled analysis of the PREEMPT studies at week 24 (after 2 BOTOX® injection cycles), the proportion of chronic migraine patients treated with BOTOX® who had previously failed on oral prophylaxis for each the above categories of headache days per month were: • 1 to 3 headache days per month: 12.6%; • 4 to 9 headache days per month: 25.2%; • 10 to 14 headache days per month: 20.5%; • 15 to 19 headache days per month: 15.0%; • 20 to 23 headache days per month: 7.1%; • +24 headache days per month: 8.3%; • Discontinued form treatment: 11.2%. When treated with BOTOX®, more than 58% of the chronic migraine	

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		patients from the PREEMPT studies were experiencing “episodic” frequency of headache days per month, therefore providing patients with significant improvements in their HRQoL at 24 weeks (after 2 BOTOX® injection cycles).	
	British Association for the Study of Headache	None	Comment noted.
	British Pain Society	None	Comment noted.
	The Migraine Trust	No comment at present	Comment noted.
Additional comments on the draft scope.	Allergan	None	Comment noted
	British Association for the Study of Headache	None	Comment noted.
	British Pain Society	There is uncertainty about the long term use of this technology. In the medical literature, there are many studies that have reported no benefit in the use of Botox for preventing migraine. It is also unclear whether similar brands of botulinum toxin, e.g. Dysport which is cheaper have the same beneficial effect. One possibility is to consider using this technology as part of a “risk sharing” scheme similar to the use of interferons and copolymer for multiple sclerosis patients. Strict guidelines can be set on the use of this technology. The appropriate level of expertise of clinicians administering and managing patients can be defined. The selection criteria for choosing patients who may benefit from this treatment can also be set. Prospective data can then be collected to try and answer some of the questions	Comment noted. Botulinum toxin type A is the only botulinum toxin with a UK marketing authorisation for chronic migraine so this will be considered as a single technology appraisal.

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		regarding this treatment. A link between efficacy and funding will also be established.	
	National Clinical Guideline Centre	NB The title of our clinical guideline in development was changed due to stakeholder comments with NICE and DH approval to remove 'new onset'. New title: Diagnosis and management of headaches in young people and adults'.	Comment noted. The scope has been amended to reflect this change.
	The Migraine Trust	None at present	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Healthcare Improvement Scotland (formerly NHS Quality Improvement Scotland)
MHRA
Public Health Wales NHS Trust
Royal College of Nursing
Welsh Government