Supporting information to compliment the draft Greater Manchester botulinum toxin policy draft out for consulatation - October 2017

#	Indication - adults, unless indicated otherwise	Brief description AND specialties providing treatment/ patient numbers /for IFRs - see IFR tab	UK licence status, evidence, national and local guidance (where know existing)	Supporting information from clinicians/ providers (where available and relevant)	Rationale and recommendation	Criteria (mainly listed for initiation) - prior approval via BlueTeq
			Licence: BTA (B:Botox, D:Dysport, X:Xeomin), BTB (N:Neurobloc) Database searches performed on MEDLINE, PUBMED and EMBASE between June and September 2017 Where results consistent and no discussion needed, no details presented. Available on demand from anna.pracz@nhs. net.		Funding: prior approval via BlueTeq system or IFR where indicated	Continuation criteria: - frequency - min 12 weekly unless otherwise stated, - evidence of previous efficacy unless stated otherwise

A. Spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) with or without pain.

1a	Focal spasticity - upper and lower limb due to stroke	Spasticity affects about 30% of stroke patients, 60% of MS patients, and 75% of post traumatic brain or spinal cord injury. About a third will need BT. The primary aim of the treatment of spastic muscles is to maintain length and allow normal positioning of the limbs to prevent secondary soft tissue shortening. For some patients spasticity can be painful, distressing, and a potentially costly cause of disability. Secondary complications arising from spasticity include impaired movement, hygiene, self-care, poor self-esteem, body image, pain and pressure ulcers. The latter can cost over £10k over course of treatment. The mainstay of treatment of spasticity is muscle stretching, and splinting/orthotics provide a means to maintain prolonged stretching in between sessions of physiotherapy and manual handling. BT can facilitate this process by producing temporary weakness and relaxation of the targeted muscles, allowing them to be stretched more easily, thus reducing the neurogenic and biomechanical components of spasticity. However, it is important to remember that BT itself is only effective in reducing the neurogenic component of spasticity. Hence, there are two key prerequisites for the successful use of BT in management of spasticity: ● there must be a significant component of muscle overactivity ● injection must be followed by an appropriate programme of stretching and/or splinting to maximise the effects of muscle relaxation. (RCP, 2009) Other methods of treating spasticity are oral or intrathecal medications, however, their side effects can be disabling (circa 40% of patients on oral anti-spastic meds do not tolerate side effects), or surgery. Currently the BT product licenses are as follow: - Xeomin - post-stroke spasticity of the upper limb presenting with the flexed wrist and clenched first in adults. - Dysport - focal spasticity of upper limbs in adults (aetiology not specified); lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury - Botox - wrist and hand disability due to upper limb spasticity associated with stroke in adults, ankle disability due to lower limb spasticity associated with stroke in adults. Specialty: Neurorehabilitation	Licensed indication (B, D, X), see brief description column for details. Cochrane (2013) review on multidisciplinary post-stroke rehab shown low level but consistent evidence for this intervention. BT is effective in reducing spasticity by causing temporary, focal muscle weakness, lasting three to four months. Hence, it can provide a window of opportunity to maximise gains to be made during rehabilitation programmes. It can make it easier to stretch and lengthen muscles in order to prevent progression of contractures, and allow strengthening of antagonist muscles, which may improve selective movement control. BT has been shown to reduce muscle tone and improve passive function, such as for hand hygiene and reducing caregiver burden. Recommended by RCP in treatment of spasticity in adults (2009, various aetiology) , long-term neurological conditions management (2008), and NW Neurosciences Partnership guidance (2005). NOTE RCP's guidance is due for update in 2017. Evidence level 1b (RTCs).		Licensed indication, positive Cochrane review findings. Advocated by RCP (guidance adapted in NW) to treat spasticity. Recommended for use as per specified criteria.	BT can be used to treat upper and lower limb spasticity after stroke or other neurological illness including MS, CP, motor neurone disease and trauma of brain or spinal cord, where: (1) there is focal element to spasticity, and (2) spasticity is interfering with function or independence and/or is painful, and (3) treatment is conducted by suitably experienced team (e.g. neurorehabilitation team, including consultant with appropriate skills and training), and (4) treatment goals and outcome measures are agreed and documented before treatment starts. Continuation criteria (including continuation of care for patients transferred form paediatric services): (1) BT efficacy must be proved and recorded for repeated injections (2) minimum frequency between injections is 12 weeks.
1b	Focal spasticity - upper and lower limb due to MS		Off-label indication, but see brief description column. Recommended by RCP in treatment of spasticity in adults (2009, various aetiology) and NW Neurosciences Partnership guidance (2005). NB - RCP's guidance is due for update in 2017. NICE CG186, for management of MS, suggest to refer the person to specialist spasticity services, if spasticity cannot be managed with any of oral pharmacological treatments. NICE CKS suggest use BT as option for treatment of spasticity. No firm recommendation made by Cochrane (2003) due to the fact that the outcome assessment appeared to be not reliable. A literature review by Dressler, 2017, showed sufficient amount of evidence to conclude that BT can be used as a treatment modality for spasticity in MS. Evidence level 1b, and 3.		Off-label, however, BT is used to treat symptom (spasticity) occurring in neurological conditions other than stroke (MS, CP in adults, post traumatic BI and SCI). Treatment with BT allows to enhance physiotherapy with subsequent goals of improved functionality and quality of life, reduced pain, prevention of irreversible contractures and facilitated self-care and nursing. The evidence for use of BT in spasticity of upper and lower limb of various aetiology is complex but consistent and substantial and ranges from placebo controlled RTCs to retrospective case studies (level 1b to level 3). Advocated as adjunct to neurorehabilitation by national guidelines (SIGN, RCP). Recommended for use as per specified criteria.	
1c	Focal spasticity - upper and lower limb due to traumatic brain injury		Off-label indication, but see brief description column. Recommended by RCP in treatment of spasticity in adults (2009, various aetiology) and NW Neurosciences Partnership guidance (2005). NOTE RCP's guidance is due for update in 2017.SIGN guidance (2013) recommends BT can be considered to reduce tone and deformity in patients with traumatic brain surgery. This is based on few RTC which included TBI patients alongside with stroke patients (level 1b). There is consistent level 3 evidence to support those positive findings.			

1d	Focal spasticity - following other causes: - non-traumatic acquired brain injury (anoxic, infective) - cerebral palsy in adults - non traumatic spinal cord injury (cord compression, inflammatory (e.g. transverse myelitis)	These indication list examples of indications where spasticity can develop as a consequence of condition other than those where botulinum toxin is licensed. NOTE: Dysport is licensed for treatment of upper limb spasticity in adults regardless of aetiology.	Off- label indication, but see brief description column. Recommended by RCP in treatment of spasticity in adults (2009, various aetiology) and NW Neurosciences Partnership guidance (2005). NOTE RCP's guidance is due for update in 2017. There is mostly consistent evidence (level 1b and level 3 for CP patients and level 3 for SCI patients) demonstrating that BT is effective improving function, movement range, pain reduction, self –care where such problems are due to spasticity of lower and upper limb. Studies on improvement of gait were more inconclusive. Some patients with SCI were reported to benefit from combined intrathecal baclofen and BT. Most patients were given BT where oral or systematic anti-spasmodic agents were ineffective or not tolerated. Studies often reported use of BT as a part of complex rehabilitation process, where BT allowed maximising outcomes from physical therapy as well as various postural and mobility aids and appliances.	SRFT: *''... the North West Guidelines for use of Botulinum toxin in spasticity which were developed in 2005 by the North West Neurosciences Partnership. These were accepted by commissioners at the time, & it is these we have been working to.* *The restrictions [I.E. PREVIOUS DRAFT OF POLICY] suggested by the CSU will harm patients as there will be delays in treatment over weeks to months, during which time irreversible contractures will inevitably develop. Patients with painful spasticity may end up being prescribed damaging & sedating medication.* *Use of systemic anti-spasticity agents in brain injury causes sedation, lowers seizure threshold & will impact on plasticity, so impeding recovery.* *Because we have previous agreed guidance for spasticity, I would have expected professional engagement from neurorehabilitation in the development of any new guidance.''*	see above	see above
1e	Spasticity in children	NHSE commissioned - aetiology not specified - (NB Dysport, Botox is licensed in dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older).				

B. Movement disorders - incl focal dystonias, from limbs to face - (interference with joint function, mobility, communication nutritional intake) with or without pain.

2	Dystonia (upper limb - including writer's cramp)	Focal hand dystonia include task-specific writer's cramp, other occupational hand dystonia, and non-task specific hand dystonia. Therapeutic recommendations for writer's cramp include physical treatment, postural and writing re-education exercises, relaxation techniques, hypnosis, biofeedback, use of special writing devices, acupuncture and transcranial magnetic stimulation, but most of the patients do not obtain satisfactory and sustained benefit. Some patients learn to write with non-dominant hand.	Off-label indication. BTA is effective for writer's cramp and is possibly effective in other types of upper limb dystonia, but controlled dose adjustments are needed because of frequent muscle weakness (good practice point). The 'Dystonia - A guide to best practice, Dystonia Society , 2014). No other national guidelines were found. A databases search confirmed that there is evidence to support use of BT in upper limb dystonia. (level 1b for writer's cramp; level 3 for other types of upper limb dystonia). NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Off-label, however, this indication appears to have satisfactory amount and level of evidence (1b to 3). Recommended for use as per specified criteria.	BT can be used for focal hand dystonia including writer's cramp, where: (1) other methods have not been successful or were not appropriate (e.g. physiotherapy).
3	Dystonia (lower limb)	Lower leg dystonia is more complicated and there is no well-established surgical procedure to aid recovery.	Off-label indication. The evidence to support use of BT in lower leg dystonia is of small body, low quality and very small samples, and is currently insufficient to approve it's use in larger population.		Not recommended for use - off-label, and insufficient evidence.	Prior approval needed via IFR to use BT for lower limb dystonia.
4	Spasmodic torticollis (cervical dystonia)	Involuntary and often painful placement of head and repetitive contraction of muscles of the neck. Uncommon, can be very disabling and can compromise quality of life; chronic and requires long term treatment. Specialty: ENT / Neurology	Licensed indication (B, D, X and N). Meta analysis of RTCs in Cochrane review (2005) found single injection effective in treatment of cervical dystonia, and continued injections to sustain beneficial effect. Cochrane also suggest BTB can be used for patients unresponsive to BTA (2016) Evidence level 1a. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Licensed indication and sound evidence base. Recommended for use as per specified criteria.	BT can be used for cervical dystonia, where patient experiences: (1) pain and/or functional impairment that include both of the following symptoms: (a) sustained head tilt or abnormal posturing resulting in pain and/or functional impairment, and (b) recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical) Continuation criteria: (1) Maximum interval between injection is 10 weeks (Botox, Xeomin), 12 weeks (Dysport), and up to 16 weeks for Neurobloc.

5	Laryngeal dystonia (spasmodic dysphonia)	Rare neurological voice disorder caused by involuntary muscle contractions in the vocal cords. There are two types: adductor (vocal cords pulled together, voice is 'strangled' and choky, most common, 80% of patients) and abductor (vocal cords pulled part, voice appears 'breathy' and quiet). Relaxation and speech therapy can be adjunct treatments. Specialty: OMFS / ENT Patient numbers: - 3-4 regular patients (SRFT) - 8 patients/month (UHSM)	Off-label indication. Cochrane (2009) reports that BT has been used for over 20 years to treat both adductor and abductor forms of the disorder, with vocal improvement noted after treatment for both. A large number of studies have attempted to document the efficacy of BT for improvement of vocal symptoms in individuals with spasmodic dysphonia. The results of the review of RTCs is that BT is safe and effective for some aspects of voice production, including perceptual measures of improvement post-injection, variability of fundamental frequency, vocal intensity and subglottal air pressure. Although small sample sizes were utilized in included and excluded studies and the observed effects were relatively inconsistent for the measurements at the post-treatment times reported, the fact remains that the overwhelming clinical evidence suggests that botulinum toxin is very effective in treating spasmodic dysphonia. (evidence level 1b=small RTC, and vast amount of evidence level 3). NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).	*UHSM: DIAGNOSIS IS MADE IN A DEDICATED VOICE CLINIC WITH THE AID OF A VOICE SURGEON AND SPECIALIST SPEECH THERAPIST. HENCE THE PROBLEM THAT THESE PTS SPENDS YRS VISITING LOTS OF DOCTORS BEFORE THE DIAGNOSIS IS MADE. BOTOX IS THE ONLY RECOGNISED TREATMENT WHICH IN ITSELF IS A DIAGNOSTIC TOOL ASWELL AS A TREATMENT. THERE ARE EXPERIMENTAL STUDIES FROM JAPAN ON SURGICAL PROCEDURES INCLUDING NEURONECTOMY AND MYOMECTOMY AND IMPLANTS BUT IT HAS NOT REACHED THE UK NOR IS THERE GUIDANCE ON THIS YET FROM NICE.*	Off-label, however, significant amount of sound evidence and recognised as effective and safe in Cochrane review. Recommended for use as per specified criteria.	BT can be used for spasmodic dysphonia, where (1) conservative measures (e.g. speech therapy) were tried and found ineffective.
6	Cricopharyngeal dysfunction	The cricopharyngeus muscle is part of the upper oesophageal sphincter mechanism. The cricopharyngeus muscle is normally contracted at rest. Upon the initiation of swallowing, the normal cricopharyngeus muscle relaxes in anticipation of the bolus and helps to form part of the pharyngeal peristaltic wave. The disorders that this muscle is subject to are: - incoordination of contractions at initiation of swallowing that can result in dysphagia, especially in the elderly population. Can affect people after stroke. - postoperative pharyngo-oesophageal spasm causing failure of tracheoesophageal speech and dysphagia. Specialty: ENT Patient numbers: 5-6 patients per each aetiology/pa (UHSM), likely to be same in other 2 head and neck centres in Mcr.	Off-label indication. Evidence level 3 supported by local clinical expertise (level 4). Evidence and findings were generally consistent in the publications found in database search. BT appears to be effective in patients with dysphagia due to cricopharyngeal hyperactivity, especially elderly and not fit for surgery. Also recommended for treatment of dysphagia and voice impairment post laryngectomy. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).	UHSM: *THESE PTS HAVE DISABLING DYSPHAGIA DUE TO A TIGHT UPPER OESOPHAGEAL SPHINCTER / CRICOPHARYNGEUS MUSCLE. FIRST LINE, SURGERY CARRIES HIGH RISKS.* *IN POST LARYNGECTOMY PTS, PTS GET A TIGHT CRICOPHARYNGEUS AS A POSSIBLE COMPLICATION AND AGAIN SAME SYMPTOMS AND TREATMENT. IST LINE FOR THESE , AS SURGERY HAS RISKS.*	Off-label, however, significant amount of sound evidence and recognised as effective and safe in Cochrane review. Recommended for use as per specified criteria.	BT can be used to treat cricopharyngeal dysfunction where: (1) surgery is inappropriate (e.g. elderly), and (2) patient has dysphagia resulting in functional impairment due to upper oesophageal spasm, or (3) functional impairment post laryngectomy inclusive of dysphagia and/or voice loss.
7	Palatal myoclonus	Palatal myoclonus is a rare cause of pulsatile tinnitus in patients presenting to the otolaryngology office. Rhythmic involuntary contractions of the palatal muscles produce the pulsatile tinnitus in these patients. Treatment of this benign but distressing condition with anxiolytics, anticonvulsants, and surgery has been largely unsuccessful. Specialty: ?Neurology Patient numbers: SRFT: 1 to 3 patients/pa	Off-label. Databases search revealed small amount of level 3 evidence to support use of BT in palatal myoclonus. The evidence appears to be consistent. Study authors raise concerns over treatment resistance due to developing of neutralising antibodies. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).	*without treatment can affect speech*	Off-label, small amount of low level evidence appears consistent and satisfactory to support BT use in this condition. Patient numbers appear to be low. Recommended for use as per specified criteria.	BT can be used for symptomatic palatal myoclonus: (1) resulting in tinnitus or other disturbing experience disabling normal functioning, and (2) where oral pharmacological intervention with anticonvulsant or anxiolytic is inappropriate or ineffective, (3) other interventions e.g. white noise have not been successful.

8	Oromandibular dystonia	Mouth, tongue or jaw dystonia characterised by forceful contractions of the face, jaw or tongue. It can cause difficulty opening or closing the mouth, often affecting chewing and speech. Jaw closing dystonia, the most common subtype of this condition, can cause trismus (lockjaw) and is frequently misdiagnosed as temporomandibular joint disorder or masseter The response of OMD to pharmacotherapy including anticholinergic agents, dopamine depleting agents, or GABA agonists is frequently unsatisfactory. Other therapies include physiotherapy, dental appliances, psychotherapy and surgery. NHS choices indicate baclofen effective in treatment of oromandibular dystonia. Specialty: ?OMFS Patient numbers: 3-4 patients (SRFT)	Off-label indication. Literature search found 2 small recent RTCs (both by Factor, 2017, level 1b) on patients with various types of OMD. The improvement in secondary measures were reported for both trials (various dystonia scores measured by unblinded injector and quality of life). However, the primary endpoint in second trial (n=18), change in blinded week 6 global dystonia score, was not significant. With clinical global improvement score, 14 were minimally or much improved, and 3 were worse. Both publications were available as abstracts only. Two literature reviews (Hallett, 2013 and Colosimo, 2011) were found and concluded that BT is probably effective, and safe in OMD (more closing than mixed and opening dystonia), but treatment can be associated with dysphagia. Four studies were included in discussions. One study (Van der Bergh, 1995, n=12) showed a marked improvement in 50% of patients including repeated injections of BT. A subsequent larger study (Jankovic, 1999, n=162) showed functional improvement (chewing, speaking) in nearly 70% of patients. Another two, small RTC studies (Jankovic, 1987, n=8 and Lee, 2010, n=12) showed improvement with decrease in bruxism. Supported by local expert knowledge (level 4). The available evidence suggests that improvement after treatment with BT in OMD appears to be lower in comparison to other dystonias. This might due to the fact that OMD appears to be an umbrella term for number of dystonias that may have different pathology and aetiology and hence response treatment in not consistent, e.g. patients with jaw-closing OMD appear to respond better to BT than patients with jaw-opening OMD. There are overall more reports of side effects, particularly dysphagia, than for other uses of BT. A few studies report systemic pharmacological interventions less effective for those patients that needed BT and so had developed more severe presentation of OMD. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).	SRFT: *''This is a complex issue and there is not much high quality evidence. I think we need to be in a position to offer BT as some people can definitely benefit and the evidence base for other treatments is poor. Need to review things on a case by case basis. I don't think there is sufficient evidence to state that BoNT is more efficacious in different types of OMD although I am familiar with the literature stating that jaw-closing dystonia is more amenable to treatment. This is mostly from retrospective or unblinded studies as most of the DBRCTs seemed to focus mostly on jaw closing dystonia. Part of this may relate to the fact that muscles injected for jaw closing are potentially easier to access without EMG guidance e.g. masseters. I would still offer treatment for jaw opening dystonia as it is potentially very disabling so even a small benefit may have a great effect on quality of life. We don't see this so often but have managed a few cases jointly (..) There are 2 small placebo-controlled studies in the literature which show some efficacy as you probably know.* *I would not describe BoNT as a "last resort" in such conditions as the evidence base for other treatments is poor. A recent case series of patients with OMD (Gonzalez-Alegre et al, Tremor and Other Hyperkinetic Movements 2014) identified little benefit from most oral drug treatments in OMD. I would definitely try oral medications in most OMD patients as sometimes it can help a little but many are poorly tolerated especially in older adults. Examples would include anticholinergics, benzodiazepines, baclofen. Dental appliances can definitely help in selected patients and I would discuss these if relevant. For the more complex patients an MDT approach with the ENT colleagues is often helpful.''*	Off-label. The evidence appears somewhat inconclusive. and comes from relatively small samples of patients with various presentations of OMD. However, there seems to be no effective alternative solution. Recommended for use as per specified criteria.	BT can be used for OMD where: (1) systemic medications ineffective or inappropriate (e.g. baclofen), and (2) patient has functional issues - pain or spasm and disfigurement, difficulties with feeding, or impaired dental care or malocclusion preventing from swallowing or impairing speech.
9	Blepharospasm	Mostly idiopathic, involuntary closure of the eyelid due to spasm of orbicularis oculi muscle. Can also be secondary (e.g. trauma) or occur in systemic conditions (e.g. MS). Specialty: OMFS/ Opht / ENT	Licensed (B, D, X). Cochrane review (2005) - no high quality RTCs but other studies suggest that BT is highly effective (90% of patients) and safe to use. Evidence level 2 and 3. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Licensed indication, and significant amount of evidence recognised as sufficient by Cochrane review. Recommended for use as per specified criteria.	BT can be used for blepharospasm: (1) associated with dystonia, and (2) there is evidence of functional and/or visual impairment.
10	Meige's syndrome	Meige's syndrome' is a type of cranial dystonia characterized by blepharospasm and oromandibular dystonia and can be associated with complex movement of lower facial muscles, mouth, jaw, tongue, pharyngeal and cervical muscles. Frequently, blepharospasm is the earliest clinical manifestation, which spreads over a period of time to involve other cranial and extra-cranial muscles. In the majority of the patients Meige's syndrome is primary or idiopathic, where the cause of spasm is not known, however secondary cases can occur following prolonged use of neuroleptics or secondary to underlying brain disorders. (Pandey, 2017)	BT considered as an alternative to drug refractory Meige's syndrome. However, it might be moderately effective in controlling lower face dystonia (medium sized retrospective clinical trials, level 31 small RTC, level 1b). Also see evidence for oromandibular dystonia and blepharospasm. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Off-label. The evidence indicates that BT is more effective in treatment of the blepharospasm component and less effective for the oromandibular dystonia. However, there is no recognised alternative for the treatment of the latter. Recommended for use as per specified criteria.	BT can be used for Meige's syndrome presenting as blepharospasm or oromandibular dystonia or both: (1) primary or secondary to brain lesion (not drug induced) (2) systemic medications ineffective or inappropriate (e.g. baclofen), and (3) patient has functional issues - pain or spasm and disfigurement, difficulties with vision, feeding, or impaired dental care or malocclusion preventing from swallowing or impairing speech.

	Facial nerve disorders - (interference with joint function, mobility, communication nutritional intake) with or without pain:					
11	Hemifacial spasm	Unilateral involuntary contractions of muscles innervated by the facial nerve, ranging from isolated unilateral blinking to intense spasm of lower hemiface and neck, closed eye and progressive face weakness, can be disabling . The aetiology is usually vascular, but can be secondary to trauma. The treatment is microvascular decompression (high risk of complications) or BT injections. Some people may respond to oral pharmacological intervention (anticonvulsants, muscle relaxants). Specialty: OMFS/Opht / ENT	Licensed indication (B, D). Cochrane review (2005) found one small RTC (n=11) support the results of large, open, case-control studies showing a benefit rate between 76 and 100% and no serious safety issues. Evidence level 1b (small) and 3. NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Licensed indication, and sound evidence base, Cochrane review concluded BT effective for this indication. Recommended for use as per specified criteria.	As a treatment option for patients with hemifacial spasm, where (1) there is evidence of functional and/or visual impairment.
12	Post facial nerve palsy - hyperkinesis causing asymmetry and synkinesis	Facial nerve palsy can have different aetiology and results in weakness of the muscles of facial expression and eye closure (sagging face and voluntary eye closure may not be possible and can produce damage to cornea and conjunctiva). In partial paralysis lower face more affected, in sever cases loss of taste can occur and intolerance to high pitched voices. Can cause mild dysarthria (difficulty speaking) and difficulty with eating. 88% patients resolve spontaneously within 3 weeks (71% completely). 16% have sequelae (incl 5% severe) in form of: hemifacial spasm, gustatory lacrimation, inadequate lid closure brow ptosis, drooling. Synkinesis is often seen (e.g. blinking causes the angle of the mouth to contract), gustatory lacrimation (crocodile tears). Ophthalmologic consequences include diminished effectiveness of lacrimation, brow ptosis, entropion, epiphora, and lagophthalmos. These may lead to corneal damage from exposure keratopathy, potentially proceeding to blindness or even globe rupture. The treatment depends on symptoms which can be complex and affect various combination of facial and eye muscles, and can include physiotherapy, basic eye care, speech and language therapy.	Off-label indication. However, Botox's SPC states: *Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.* BT has been used to combat synkinesis in facial paralysis patients, and has been shown to improve patients' quality of life scores. BT can also be injected into the normal side of the face, weakening it, while simultaneously strengthening the paralyzed half, thereby improving symmetry as an adjunct to unsuccessful prior surgical therapy. Some beneficial effects were noted to persist at 6 months even after the pharmacologic effects of the toxin had run their course. (Gordin, 2015) The database search did not identify evidence to support use of BT in acute phase of facial nerve palsy. For chronic unresolved nerve palsy, the following uses of BT were investigated (only selected publications were available in full): - a- hyperkinesis of the unaffected side and further asymmetry caused by the weakened muscle tone in the affected side. BT is injected to the non-paralysed side. Evidence: 1 RTC, but comparing BTA and BTB. BT is effective in reducing asymmetry by injecting the non-paralysed, hyperkinetic side of face. This finding is supported by a number of retrospective, level 3 studies. No placebo controlled RTCs identified during evidence search. - b - synkinesis - caused by the aberrant regeneration of the nerve. BT is injected in synkinetic side. Evidence: Level 1b and consistent supporting level 3 evidence to prove that BT is effective in synkinesis. Combined intervention of BT and biofeedback (BFB) were found effective (level 3) but when BFB alone compared with BFB and BT in one RTC, no significant difference was noted (level 1b). Another RTC comparing NMRT alone and BT and NMRT (neuromuscular retraining therapy, details not specified) showed BT enhanced results of NMRT and combination therapy was better than NMRT alone. All together BT was found effective to treat synkinesis, however, the evidence was somewhat inconsistent on the place of BT in the combined therapy of synkinesis. - c - crocodile tears - BT into lacrimal gland - SEE OPHTHALMIC DISORDERS (12) - d - lagophthalmos - BT into eyelid to achieve protective eyelid ptosis - SEE OPHTHALMIC DISORDERS (13) NHS Choices lists botulinum toxin as a treatment option for dystonia (in general).		Acute phase - not approved (no evidence). Off-label use, however, evidence appears to be satisfactory to support use of BT in chronic symptoms of facial nerve palsy: - recommended for injections to hyperkinetic non-paralysed part of face to improve functionality due to asymmetry, and/or - recommended for injections in the synkinetic part of face as monotherapy or with concomitant biofeedback/physiotherapy	BT can be used for patients with chronic, unresolved facial nerve palsy resulting in asymmetry or synkinesis, where (1) there is evidence of functional impairment (e.g. communication, nutrition, pain due to disfigurement), and (2) permanent nerve damage cannot be managed by facial rehabilitation alone, and (3) where surgery not indicated or unsuccessful. Continuation: (1) patient must still show functional issues returning after pervious successful intervention with BT. BT is not commissioned solely for appearance enhancement.

C. Ophthalmic disorders

13	Crocodile tears syndrome	CTS or gustatory hyperlacrimation - uncommon condition due to aberrant regeneration of facial nerve after damage (e.g. palsy). Lacrimation occurs from one eye after eating or drinking or even smelling food; facial tic and taste loss may occur concurrently. Many patients tolerate CTS and do not require intervention. For those who not respond to or not tolerate pharmacological (anticholinergic) or surgical interventions (limited efficacy and increased morbidity), BT could be considered as alternative treatment option.	Off-label indication. Database search revealed small number of retrospective studies, that provide consistent (level 3) evidence.		Off-label, however, small amount of low level evidence appears to be satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used in patients with severe gustatory lacrimation, where: (1) symptoms cause functional problems, and (2) systemic pharmacological treatments with anticholinergic were ineffective, not tolerated or contraindicated, and (3) surgical intervention was not appropriate.
14	Prevention of corneal exposure (protective ptosis)	To protect cornea form damage resulting from difficulties with eyelid closure (lagophthalmos), which can be caused for example by facial nerve paralysis. In cases unsuitable for tarsorrhaphy (procedure is performed by partially sewing the eyelids to narrow the eye opening and prevent corneal damage). Tarsorrhaphy is usually performed after alternative measures have been tried including lenses and eye drops.	Off-label indication. Small amount of evidence level 3, but consistent results to suggest BT can be used as an alternative to conventional methods of iatrogenic temporary ptosis to achieve corneal healing in patients unsuitable for alternatives. NB there is a risk of incomplete ptosis at beginning and end of treatment and technique dependent diplopia that may persist after ptosis has resolved. Both can affect corneal healing.		Off-label, however, small amount of low level evidence appears to be satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used for induction of <u>temporary</u> protective ptosis to prevent or allow corneal healing, where: (1) eye lubrication or contact lenses are insufficient or not tolerated, and (2) patient is unsuitable for tarsorrhaphy. Discontinuation: Stop once corneal healing achieved or prevention no longer needed.
15	Dystonic brow spasm		Off-label indication. No evidence for isolated brow spasm and headache treated with Bont. Search results point towards headaches resulting from hemifacial spasm, blepharospasm, and facial nerve disorders, wrinkles and brow ptosis. Also there is no evidence on comparing intervention with Bont and analgesia. No evidence found on treatment of pain related with dystonic brow spasm.	BFT: *''where causing significant headaches from spasm, cramp of brow-creasing muscle. Patients presenting with deep forehead fold of creased skin. Treatment removes need for analgesia.''*	Not approved - off-label and no evidence found to support BT use in dystonic brow spasm	Prior approval needed via IFR to use BT for dystonic brow spasm.

16	Epiphora	Excessive eye watering caused by overproduction of tears or decreased drainage of tears due to various causes. Lacrimal outflow can be compromised by anatomical obstructions or stenoses (non-functional epiphora) or by defective lacrimal 'pump' function (functional epiphora - e.g. after facial palsy). Patients tend to experience this as a nuisance more than anything else. However, both lacrimation and epiphora can be associated with interference in vision and the surrounding skin can get very sore and excoriated from the constant wiping of tears associated with epiphora. There may also be underlying conditions that need to be addressed. Impaired drainage due to lid malposition or stenosis at various points along the nasolacrimal duct usually involves surgery.	Off-label indication. Small amount of evidence (level 3), but consistent findings. Up to 90% of patients with various aetiologies of epiphora reported at least partial improvement. Researchers compared BT to CRCP surgery and found it viable alternative for patients unsuitable for invasive procedures. (e.g. elderly or with previous localised malignancy)		Off-label, however, small amount of low level evidence appears to be satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used as an alternative to surgery for patients with epiphora who: (1) have documented functional issues, and (2) are unsuitable for surgery (e.g. elderly or previous ophthalmic malignancy).
17	Spastic entropion	An entropion occurs where an eyelid turns inwards towards the eye. This causes the eyelashes to rub against the front of the eye (the cornea). The lower eyelid is most commonly affected. If left untreated, the front of the eye (cornea) may become damaged (a corneal ulcer may develop). The cornea is vital for vision and a damaged cornea may affect eyesight. If the cause is unlikely to recover by itself, a surgery can be offered. The operation is usually successful and prevents any further damage to the front of the eye. BT can be considered as alternative to people unsuitable for surgery.	Off-label indication. Limited amount of low level evidence (3), but consistent. Most cases described in published evidence were cases of senile entropion, which if untreated can lead to vision loss due to corneal ulceration. Authors suggest alternative to surgery where condition unlikely to recover by itself or as an adjunct to incompletely successful surgery.		Off-label, however, small amount of low level evidence appears to be satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	For patients with unresolving entropion where (1) there is risk of damage to vision (e.g. corneal ulcer or ketatopathy secondary to entropion), and (2) where surgery is inappropriate or unlikely to resolve issue as a single intervention.
18	Nystagmus	Rapidly oscillating gross eye movements prevent clear vision, reduce movement or cause still eye in neurological conditions such as MS.	Off-label indication. Small amount of low quality evidence (level 3) with conflicting results. Trials were on small patient numbers (n=1 to 12). High incidence of side effects that can be potentially disabling was reported in many cases, where those effects appear to be worse than experience of nystagmus. In some studies none of the patients chose to continue with therapy. Some authors reported that oral pharmacological interventions can be tried (e.g. unlicensed gabapentin, baclofen).		Off-label, and the small amount of low level evidence appears to have conflicting findings. The side effects appear to outweigh benefits Not recommended.	

19	Squint (strabismus) - adults and children	Strabismus (squint) is a misalignment of the eyes in which the visual axes deviate from bifoveal fixation (RCOpht, 2002). Most squints occur in young children (between 18 month and 4 years of age). It can be subdivided into esotropia (convergent or inward deviation), exotropia (divergent or outward deviation) or, less commonly, hypertropia (upward deviation), hypotropia (downward deviation) and cyclotropia (torsional deviations - inwards, incyclotorsion or out outwards, excyclotorsion.) Different types and causes and can be paediatric or acquired in adult life. Most cases are problems with muscles or nerves around the eyes. Sequelae to strabismus can include blurred vision, double vision (diplopia), impaired depth perception, and in children, amblyopia (lazy eye). If strabismus arises after the visual system matures (around the age of 8), strabismus usually results in diplopia (double vision). If it arises at an earlier age, the brain adapts by suppressing the image from the squinting eye, so that diplopia is no longer a problem, but this adaptation comes at the price of loss of stereopsis (detailed depth perception) and sometimes at the price of reduced visual acuity in one eye (amblyopia or lazy eye). (RCOphth) In another example, 6th nerve palsy causes convergent strabismus or esotropia with primary symptom as diplopia, and can be uni or bilateral. Treatment options include eye therapy, glasses, prisms, occlusion, botulinum toxin or surgery. BT acts by temporary relaxing muscles, which can help to align eyes and may lead to less blur or less double vision. It can cause ptosis which is normally self limiting. Surgery can help improve the alignment of the eyes even if a squint has been left untreated for a long time, but any vision problems may be permanent if they're not treated at a young age. Specialty: Ophthalmology; CMFT (approved by MMC, 2014), BFT	Off-label indication (in the USA, B is approved for treatment of strabismus from 12 years of age). Most evidence consists of retrospective studies, cohort studies and case series. Cochrane review, 2017, found 6 RTCs (paed and adult, and incl 6th nerve palsy, and one with hyaluronic acid). Trials were heterogenic, and all evidence of low certainly: - in children (two studies) - primary treatment and retreatment for esotropia - no difference or slightly reduce chances of recovering correct alignment of the eyes compared with surgery; - in adults - one study shown BT may decrease the chances of recovering the correct alignment of the eyes compared with surgery (for people with horizontal strabismus and without binocular vision); another study shown that combined intervention of surgery and BT can have better results than surgery alone (low quality evidence); - in 6th nerve palsy - similar or small increased chance of correct alignment of eyes compared with no treatment. Without considering the type of strabismus being treated, BT has been shown to reduce the angle of deviation by amounts comparable to surgical intervention. However, type of strabismus is important when considering the secondary outcome of binocular vision. In horizontal strabismus types without potential for binocular vision the effect of BT was found poorer than of surgery. However, BT was found to enhance surgery effect when compared with surgery alone. The review authors suggests BT can be used as option of treatment of strabismus in those types where there is potential for binocular vision, such as acute onset esotropia, sixth nerve palsy and infantile esotropia. RCOpth, 2012 suggest use of botulinum for 6th nerve palsy and infantile esotropia. *''Further treatment of any residual strabismus that persists (despite the correct glasses and following amblyopia treatment) may be indicated to improve appearance and increase the potential for binocular development. ...* **continued in next column**	**continued form previous column:** Treatment is usually surgical although there may be reasons to consider prism wear (e.g. acquired sixth nerve palsy), botulinum toxin (e. g. VI nerve palsy, infantile esotropia) and exercises (e. g. convergence insufficiency, distance esotropia and symptomatic phorias). In general there is a more profound degradation on visual acuity and binocular vision of strabismus with younger children, and so increased potential gains and risks with their management'' NICE CKS suggests BT for treatment of some childhood squints. Currently there is no GM EUR policy; only HMR have local policy that allows consideration of surgery (not BT) for children over 9 and after exhausting conservative treatment. **...continued below...**	Off-label. The evidence base is complex due to various presentations and aetiology of strabismus. Cochrane review identified RTC, which are satisfactory to conclude BT can be effective in some forms of squint. Those findings appear to be consistent with lower evidence level publications. RCOphth advocates use of BT in some forms of squint. <u>FOR DISCUSSION:</u> Should the policy include diagnostic use of BT? How many repeated injections should be allowed?	*(1) Diagnostic: Where prism adaptation test predicts post-operative diplopia, to evaluate risk of making double vision worse or demonstrate potential for binocular vision.* (2) Therapeutic: *One-off/ up to two BT injection(s) c* an be used in treatment of strabismus in children and adults, where (a) there is potential for binocular vision: strabismus in those types where there is potential for binocular vision, such as acute onset esotropia, sixth nerve palsy and infantile esotropia, and (b) conservative treatment (prisms and/or exercises) fail. (3) For medical management of cases unsuitable for surgery - e.g. where patient is not suitable for surgery (e.g. contraindication to use general anaesthesia or elderly patients). <u>Continuation criteria:</u> (1) minimum 6 months or complete resolution of previous injection effects prior to subsequent injection or surgery Note strabismus repair is considered cosmetic in adults with uncorrected congenital strabismus and no potential for binocular vision (no binocular fusion).
		...continued from above... Repeated injections: 3 of the trials discussed in Cochrane reviews reported repeated injections (outcome not discussed). In first trial 3 out of 54 participant required second injection; in second trial none of the 55 patients requested second injection; in the third trial out of 30 patients, 5 were given 2 injections, 3 were given 3 injections and one was given 4 injections to improve alignment if worse than 10DP. Cochrane review also notes recognised diagnostic use for botulinum toxin, however, this is not assessed as part of review for efficacy: ''Diagnostic uses of botulinum toxin include investigation of postoperative diplopia (double vision), to detect whether fusion (which contributes to binocular vision) is present preoperatively, to differentially diagnose between a part and complete sixth nerve palsy, to aid in the prediction of surgical results for incomitant deviations and to help in the investigation of a possible slipped muscle following surgery.''				

D. Gastrointestinal tract disorders

20	Salivary fistulas	A fistula connecting a salivary gland (mostly parotid, rarely oromandibular) and skin and causing discharge of saliva from the skin, usually caused by trauma including surgery. Can output inside mouth, nose or face, the latter two causing symptomatic discharge. Most parotid fistulae heal spontaneously within a few weeks. Conservative treatment includes dressings (long term), needle aspiration, to systemic pharmacology and radiation	Off-label indication. There is no national or local guidance. Literature search revealed a relatively small number of retrospective studies with small sample sizes (level 3, n=1-12) where BT was used as an alternative to surgical revision or to treat a fistula refractory to surgery or other interventions. Almost all interventions reported as successful with relatively long effect of BT (up to 14months symptom-free). One study authors suggest early intervention is most effective). No serious side effects were reported.		<u>FOR DISCUSSION:</u> Should BT be recommended to treat refractory and recurrent salivary fistulae?	*BT can be used for unresolving salivary fistulas, where:* *(1) discharge is severe and affects daily functioning* *(2) conservative methods have ben tried and results are not satisfactory, or* *(3) fistula is refractory to surgical revision*
21	Sialocele	A localised subcutaneous cavity containing saliva, caused by trauma (including surgery) or infection. Relatively common after parotidectomy (saliva coming from remaining parotid tissue) and self limiting. Management include repeated aspiration via needle. Rare chronic presentations may require a persistent surgical drain or BT injections.	Off-label indication. There is no national or local guidance. Literature search revealed a relatively small number of retrospective case studies on small patient numbers (level 3, n=1-4) where BT was used on recurrent or conservative treatment refractory sialocele. All cases reported as successful. No serious side effects were reported. One study used BTB.		<u>FOR DISCUSSION:</u> Should BT be recommended to treat refractory and recurrent sialoceles?	*BT can be used for unresolving sialoceles, where:* *(1) daily functioning is affected (e.g. pain, difficulties with eating, speaking),* *(2) conservative methods have ben tried and results are not satisfactory, or* *(3) fistulae refractory to surgical revision*

22	Sialorrhea	Disease induced hypersalivation. Sialorrhea is present in up to 25-50% of patients with motor neuron disease, and in up to 80% of these individuals the symptom is poorly controlled. In Parkinson's disease it is reported at wide range (10-84%). Interventions in PD can be pharmacological or other ranging form surgical and radiotherapy to behavioural. Drugs include anticholinergics, and adrenergic blockers, and botulinum toxin injected in salivary glands. However, the mechanism of drooling in PD is unknown, and thought not to be related to oversalivation. People with PD and drooling are thought to produce less saliva. Specialty: Neurorehab Patient numbers: 0-2 per month (SRFT, saliva control), 12 inpatients plus 8 outpatient/ per month (SRFT).	Off-label indication. For drooling in motor neurone disease, there is no evidence based guidance for clinicians to make decisions with regards to the treatment options available. Antimuscarinics are used first-line but there is no evidence to inform which antimuscarinic and at what dose. Botulinum toxin is used second- or third-line although there is little evidence to guide dosing, which salivary glands to inject and which type of botulinum toxin to use. (NICE NG42, 2016) NICE guideline for PD (NG71) suggests referral to specialist service for BT , if glycopyrronium bromide is not effective, not tolerated or contraindicated (for example, in people with cognitive impairment, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment). Cochrane review (2011) for treatment of sialorrhea in people with motor neuron disease/amyotrophic lateral sclerosis, found one RTC. This was a well designed study of botulinum toxin B injected into parotid and submandibular glands of 20 patients, which showed positive results for four weeks (Jackson 2009). There was low risk of bias in the study and no significant adverse events reported. Protocol for Cochrane review to investigate use of BT (both A and B) for drooling in Parkinson's disease, 2016 reports this treatment used by clinicians. The effects last for 3-5 months. SE include dry mouth, thickening of saliva, swallowing difficulties, reduced mastication ability, diarrhoea, gait disturbance and neck pain. Further evidence search revealed sufficient amount of evidence supporting use of BT (both A and B) in disease induced sialorrhea (limited amount of small RTCs consistent with many level 3 retrospective studies). NHS Choices lists botulinum toxin as a treatment option for treatment of drooling in MND. NICE CKS for excessive salivation in PD: recommends specialist treatments which may include BT or hyoscine patches (both off-label).	SRFT *''It is also used for patients with Parkinson's Disease & Motor Neurone disease to reduce saliva production, & so reduce risk of choking.(...) Regarding saliva control, use of Botulinum toxin is in the latest MND guidelines if systemic anticholinergics fail. This is how we manage saliva control for complex tracheostomy weaning (probably only a few patients per month, & some months none). We use it for other neurological conditions which have the same effect as MND on saliva management e.g. Parkinson's disease where patients often develop neuropsychiatric complications with systemic agents. One of the problems with systemic anticholinergics such as hyoscine & glycopyrrhonium is that they make respiratory secretions viscous as well, with risk of airways obstruction & tracheostomy blockage. The Botulinum toxin companies have not pursued saliva control in their licensing so far, as it is a relatively small niche for their products. This means that it is virtually impossible to conduct research to build up the evidence base. At SRFT we inject salivary glands using ultrasound guidance, so are sure that we are hitting the spot. Personally I would never inject salivary glands blindly. Using US has increased efficacy considerably over the last few years.''* *''That is our rationale. Before we started using Botulinum toxin we could never find anyone brave enough to irradiate salivary glands, & salivary duct diversion in patients with compromised swallow just diverts saliva into the lung. Systemic anticholinergics can have significant adverse effects – confusion, impaired cognitive function, thickening respiratory secretions causing tracheostomy blockage or collapse/consolidation in the lungs due to secretion retention. I stopped using atropine many years ago after a patient developed severe bradycardia causing loss of consciousness. ''*	Off-label, however, significant amount of sound evidence and recognised as effective and safe in Cochrane review for MND. Advocated by NICE in treatment of excessive saliva of various aetiologies. Recommended for use as per specified criteria.	BT can be used for sialorrhea under following circumstances: (1) Sialorrhea is not drug induced. (2) Sialorrhea is causing functional impairment, and/ or patient is at risk of aspiration , and (3) Systemic agents have been tried and failed or were contraindicated or not tolerated (min 2 drugs). (4) BT is administered with ultrasound guidance.
23	Saliva management in patienst with tracheostomy	Saliva control in patienst with impaired swallowing due to inserted tracheostomy tube. Patient numbers: 0-2 per month (SRFT, saliva control)	No published evidence was identified for use of BT in the specific subgroup of patients with tracheostomy, however, NICE NG42 includes BT as an option to deal with 'saliva problems'. The evidence base search revealed a literature review discussing saliva management options for difficult-to-wean people with tracheostomy following acquired brain injury (Checklin 2014). This paper lists BT as on one of the treatment option, however, the author admits that there is no published evidence for this intervention. No further papers were found.	*''We use BTx to speed up tracheostomy weans, to enable use of speaking valves in patients with large volumes of oral secretions & aspiration risk, and patients with neuro-muscular disease who use NIV with the help of BTx. ''* *'' Hyper salivation treatment with BTx – which is used extremely effectively to treat refractory cases. It reduces LOS [length of stay] , prevent complication like aspiration and it facilitate weaning from trachy. ''*	<u>FOR DISCUSSION:</u> Should BT be recommended to increase speed of recovery and facilitate weaning of tracheostomy patients regardless of underlying condition?	*Suggestion to add to above following criterion:* *(5) where patients have a tracheostomy and BT can facilitate weaning?*

24	Achalasia	An oesophageal motility disorder of unknown cause, which results in increased lower sphincter tone and symptoms of difficulty in swallowing. Treatments are aimed at reducing lower sphincter tone, most often with use of botulinum toxin or endoscopic pneumatic dilatation. Surgery is also available. Specialty: Gastroenterology Patient numbers (CMFT): - 2-3 patients pa	Off-label indication. Surgery (laparoscopic Heller's myotomy) is considered first choice intervention. Pneumatic dilatation (PD) is preferred option for older and unfit patients. The rate of perforation with PD is 10% and it can be fixed by surgery. BT is considered alternative to PD, although it's use is restricted due to lower efficacy rates. Cochrane, 2014 compared BT and PD. Seven randomised controlled trials were identified for inclusion in the review, and five were suitable for meta-analysis. The results suggested that, although both interventions had similar initial response rates, the remission rates at six and 12 months were significantly greater with PD than with BT injection. PD showed greater sustained benefit for more patients; however, 10% of patients are at risk of oesophagus perforation with PD. (evidence level 1a). NHS Choices lists BT as an option for treatment of achalasia.	*''only those not fit for surgery/endoscopic dilatation. 6-12 monthly injections of BTA at each time''*	Off-label, however, evidence base appears to be satisfactory. Cochrane review recognised BT as an alternative treatment for specific patient groups. Recommended for use as per specified criteria.	BT can be used for patients with achalasia who are: (1) at high risk of aspiration, and (2) unfit for surgery and, (3) at risk from complications from pneumatic dilatation treatment (perforated oesophagus) Continuation criteria: (1) Retreatment frequency - minimum 6 months.
25	Sphincter of Oddi dysfunction (type III)	The sphincter of Oddi is a muscular valve that controls the flow of bile and pancreatic juice through ducts from the liver and pancreas into the duodenum. Sphincter of Oddi dysfunction (SOD) describes the situation when the sphincter does not relax at the appropriate time (due to scarring or spasm). The back-up of juices causes episodes of severe abdominal pain lasting between 30 mins and several hours. Often seen in women post cholecystectomy. Can lead to recurrent pancreatitis. Current treatment is sphincterotomy - relatively high risk procedure not uniformly effective (only in 50% of patients with type III SOD). Manometry used to diagnose but so not accurate as not all patients give manometric signs, and carries risk of pancreatitis. BT can be used as therapeutic trial to identify patients to go on sphincterotomy. Only for type III SOD. Specialty: Gastroenterology Patient numbers (CMFT): - 20 patients pa	Off-label indication. No national or local guidance. Database searches identified publications with evidence level 3. Those retrospective studies had small patient numbers, and were open label, but consistent results confirmed with local expertise provide sufficient evidence base to recommend this indication for BT. BT provides safer alternative to existing diagnostic method and enables clinician to exclude diagnosis and prevent unnecessary surgery if no response to BT. Only one study referred to repeated BT injection in patients who did not responded to first dose. Those patients remained symptomatic. (Macdougall, 2014, abstract only)	*2 injections 3-4 months apart and if patient is pain free - they go on to have a sphintherectomy. All pts tertiary referrals, local results suggest much lower complication rate than manometry - pancreatitis rate 3% vs. 30%. ''*	Off-label, however, the small amount of low level evidence appears to be consistent and satisfactory to support use of BT in this indication. BT was found safer alternative to existing procedure. Recommended for use as per specified criteria.	A <u>single dose</u> of BT is commissioned as a diagnostic trial instead of manometry prior to sphincterotomy only for patients with suspected type III SOD. Repeated injections are not commissioned for SOD.
26	Abdominal wall reconstruction	To relax and elongate laterally retracted abdominal wall musculature in patients with massive abdominal wall defects, hernias and loss of domain (where >20% of the peritoneal cavity resides outside of the peritoneal cavity). The technique also reduces postoperative pain and has been well described for this purpose in laparoscopic hernia repair. Specialty: Gastro surgery Patient numbers: - 10-20 patients pa (SRFT)	Off-label indication. The databases search found evidence level 1a and 3. Ultrasound guided botulinum toxin prior to abdominal wall repair is a safe and effective technique for the preoperative preparation of patients prior to laparoscopic mesh repair of complex ventral hernia. This technique allows lengthening and thinning of the contracted and retracted muscles, enabling closure of large defects. One case-control study shown less opioid analgesia and less pain reported by patients in whom botulinum was used prior to hernia surgery in comparison to patients who underwent standard procedure.	Added on request form Salford CCG as few cases at SRFT. SRFT: ''*The technique is well described by numerous authorities on massive hernia and abdominal wall repair (AWR) from Australasia (Farooq) to North America (Henniford). It helps to reduce the magnitude of surgery, increases the chances of successful AWR, and can reduce the risk of respiratory embarrassment in patients with significant loss of domain. The technique is exactly the same as that for local anaesthetic TAP blocks where the Botulinum toxin is injected under GA using USS control.* *Alternative: There are no drugs usually used for this problem.* *Criteria: We are describing a very select group of patients with abdominal wall defects >15cms, loss of domain >20% who require major abdominal surgery, separation of muscular components and mesh repair.''*	Off-label, however, the small amount of low level evidence appears to be consistent and satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used as one-off, preoperative, ultrasound guided injection in elective complex hernia patients where: (1) major abdominal surgery, separation of muscular components and mesh repair is required, and (2) abdominal wall defects are greater than 15cm, and (3) loss of domain is greater than 20%.

27a	Anal fissure (single dose)	Ulcer in the squamous epithelium of the anus. Typically causes pain during defecation and up to two hrs after; often related to hypertonia. Relief of the spasm has been associated with relief of pain and healing of the fissure without recurrence. The main surgical intervention is sphincterotomy, which is highly effective but carries risk of long term incontinence. Pharmacological therapies include topical GTN (licensed as 0.4%), diltiazem cream (unlicensed) and botulinum toxin. Specialty: Gastro and General surgery Patient numbers (CMFT/UHSM/SRFT): - 4 pts/6mths, expecting to do 5-10pts/pa - 4pts/2 years - 8pts/2.5 yrs - 3-4 pts/ 8months	Off-label indication. Cochrane review on non-surgical treatments for anal fissure (2012) concluded that all pharmacological therapies (including topical calcium channel blockers and BT) were found less effective than surgery. The latter, however, carries risk of long-term incontinence which has not been identified in any RTC for pharmacological treatment. NICE ESUOM14 (2013) on BT in anal fissure found 2 systematic reviews and 4 further RTCs suggesting BTA is less effective than surgery, no better or worse than topical calcium channel blocker (GTN 0.2% or ISDN) and no better than placebo or lidocaine. The authors suggest that BT could be used after unsuccessful trial of licensed 0.4% GTN ointment and before surgery. (evidence level 1b) However, there is currently no evidence to compare BT and licensed GTN formulation or after treatment failure with GTN. A further evidence search identified publications where authors dispute incontinence rates with both surgery and BT. Novel procedures like fissurectomy alone or combined with BT emerge as potential better option but evidence base is still weak (evidence level 3). BT is presented as an option for treatment of anal fissure on NHS Choices and included in the NICE CKS.	*It is rare for Botox to be used more than once in colorectal practice. There are a small minority of patients who need repeat Botox following counselling with regards to alternatives. GTN and diltiazem ointments are invariably tried (usually more than once) and sometimes not tolerated by patients; and the 'surgery' that is talked about in the evidence is highly successful but has a small but serious risk of incontinence in the short and long term (lateral sphincterotomy). I think that the evidence with regards to Botox efficacy for fissure in an has to be reviewed in the light of these important patient factors. I think that to mandate an IFR for repeat Botox in colorectal surgery after a single failed treatment is unnecessary and possibly a disservice to the patient as we only tend to use it if all medical treatments have failed and surgery is best avoided.*	Evidence base ranges from high level (RTC) to low level, however, it is inconclusive due to studies heterogeneity. BT for anal fissure can be recommended as it is a recognised clinical practice and alternative to surgical treatment carrying risk of long-term incontinence. Recommended for use as per specified criteria. <u>FOR DISCUSSION:</u> (A) - Recurrence rates reported after treatment with BT reach up to 50% after 1 year (NICE, 2013). Should this policy approve treatment with BT <u>per treatment cycle</u> (assume a min of 12 months before relapse) for patients who have recurrent anal fissure? See criterion (4). Evidence on relapsed patients treated with BT in row 23b. (B) - Maximum number of doses repeated use for anal fissure. In most cases single dose is sufficient for the anal fissure to heal, however some patients will not respond to first dose of BT. Should this policy allow second dose of BT in patients refractory to first dose of BT and opting-out surgery? See row 23b for evidence.	*A single one-off dose/ up to two doses* of BT is/are commissioned for patients meeting the following criteria: (1) The anal fissure is chronic, and (2) The following symptoms are present: (A) pain on defecation and lasting afterwards, and/or (B) bleeding, and (3) The following treatments have been tried and were unsuccessful: (A) bulk fibre supplements +/- stool softeners and adequate fluid intake (min 6-8 weeks), and (B) added 0.4% GTN ointment (BD for up to 8 weeks) +/- local anaesthetic, or (C) added 2% diltiazem cream (unlicensed, BD for 8 weeks) - maximum up to two courses if patient initially responding *(4) For recurrent anal fissure a single one-off dose/ up to two doses of BT is/are commissioned for patients in whom previous treatment with BT was effective and provided a minimum of 12 months symptom free period and patient meets criteria (1), (2) and (3).*
27b	Repeated use for anal fissure	For patients refractory to single dose of BT or those who relapsed after successful treatment with BT.	Off-label indication. There is little evidence on use of second dose of BT in patients refractory to first dose. Four articles identified in evidence review for BT in anal fissure included patients refractory to first dose of BT or those who relapsed after successful treatment with BT (one level 2b study of unknown quality, and level 3). One retrospective observational study (n=88) reported 26 patients refractory to single BT injections. Three of those patients received second dose of BT and 2 patients achieved complete response. 13 patients were reported as relapsed after successful single BT dose, 7 of those received second BT dose and 5 achieved complete response. Study authors refer to similar results reported earlier, where healing rates after second dose ranged form 60-95%, with recurrence rate of 12.5% at 6 months (Barbeiro, 2016). Another study, investigating fissurectomy combined with BT (n=102, prospective, non-randomised cohort study) reported that at 12-weeks follow up 29 patients who achieved incomplete healing, were given second dose of BT or topical treatment and subsequently all achieved complete healing (Barnes, 2015, abstract only). A retrospective cohort study (n=75) reported 42 patients with complete response and 16 of those had a recurrence. One of patients with recurrence successfully responded to second dose of BT. 20 patients were refractory and 2 of those chose to receive second dose of BT (outcome not given). Author suggests about 7% of patients who received BT will need second dose (Palominos, 2015, abstract only). A retrospective study investigating efficacy of high dose BT for anal fissure (n=80) reported that over 80% of patients, when enquired about next step of treatment, would choose further dose of BT rather than surgery. This abstract suggested some patients received three doses prior to contemplating surgical treatment, further details were unavailable. (Punch, 2013, abstract only).		See discussion point (C) above.	As above. Criteria for discussion in italics.

28	Leaking stoma (hyperactive stoma)	Hypercontractile stomas resulting in repeated pouching system failures and leaks (up to several times a day). Specialty: dermatology (SRFT) Patients numbers: 4 patients (incl 2 private)	Unlicensed indication. One level 3 publication (prospective case series, not controlled) by the consultant submitting application for policy inclusion. When BT used to reduce sweating and improve appliance adhesion in physically active patients and perimenopausal women (off- label), a paralysis of intestinal muscle was noticed in reduced peristaltic shortening of stoma. 10 patients with intestinal muscle hypercontractibility included (not large bowel stoma; only urostomy, n=7 or ileostomy patients, n=3). Treatment was found effective in 9 patients, and in one case stoma was shortened but there was no reduction in leakage). Where successful, BT allowed reduction of bag changes from several times a day to max 3 times per week. Patient QoL increased and intervention was cost effective due to less appliances used. Outcomes from this case series suggest that over a 3 month period, persons with hypercontractile ostomies may transition from spending approximately £945 on ostomy supplied (based on use of 3 pouches per day) to £126 (based on pouch changes every 2.5 days) plus the cost of £178 for 100 units of BoNT-A, representing a potential saving of £614.No side effects were noted (Lyon, 2015)		<u>FOR DISCUSSION:</u> - very little evidence Should BT for leaking urostomy bag be included in the policy?	Suggested criteria: Recurrent leaks due to shortening stoma (ileostomy or urostomy) and unresponsive to correction of size or shape of the aperture in the bag, changing the convexity of the device or using topical filler pastes.
29	Anismus (pelvic floor dyssynergia)	Anismus (or dyssynergic defecation) refers to the failure of the normal relaxation of pelvic floor muscles during attempted defecation. Anismus can occur in both children and adults, and in both men and women (although it is more common in women). Specialty: colorectal surgery Patient numbers : 2-3 patients/pa (CMFT)	Off-label. Evidence search found a systematic review (2016) , inclusive of and two RTCs (1b) but none of them placebo controlled. Treatment with BT provides alternative to surgery (better efficacy rates, but some publications report incontinence as side effect occurring in 6-13% of patients).	*CMFT: These patients present regularly in our colorectal out-patient departments and to their GP Practices with pelvic floor problems, pain, bladder and bowel symptoms. To be offered Botox treatment at CMFT they must have failed several other treatment options following our pathway. We have found 50% of these patients improve and their symptoms' go away completely. (pathway not supplied upon request). Follow up: to assess improvement and longevity of treatment. Maximum relief is seen at 4 four weeks post injections and effectiveness usually lasts for 4-6 months.*	Off-label, however, evidence identified appeared satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used for patients with anismus, where (1) conservative measures were tried and failed, including: (a) dietary and lifestyle modification, and (b) enemas and laxatives, and (c) biofeedback, and (d) surgery is inappropriate, and (2) diagnosis of prolapse was excluded.

E. Hyperhidrosis

30a	Severe primary hyperhidrosis of the axillae	Severe and intractable hyperhidrosis of the axillae resistant to conservatory treatment. Specialty: Dermatology/ Vascular or General surgery	Licensed indication (B), evidence 1b (four large RTCs, n≈1000, NICE CKS). There is a GM EUR policy, which places treatment with BT after unsuccessful trial of lifestyle interventions and topical agents, and before iontophoresis or thoracic sympathectomy (currently out for review consultation). NB: **do not** use BT for hyperhidrosis associated with social anxiety disorder (NICE). NHS Choices list BT as an option for treatment of severe hyperhidrosis. It is also included in the NICE CKS for hyperhidrosis.		Licensed indication, and sound evidence base, and a local GM EUR policy including BT in treatment of axillary hyperhidrosis. Recommended for use as per specified criteria.	BT can be used for significant and intractable excessive sweating of axillae, where (1) hyperhidrosis not associated with social anxiety disorder or secondary to other underlying cause, and (2) there is a record of unsuccessful trial of: (a) conservative measures (lifestyle factors and avoidance of triggers) and (b) aluminium based topical treatment for at least 1-2 months Continuation criteria: (1) min frequency 16 weeks

30b	Severe primary palmar hyperhidrosis	Severe and intractable focal hyperhidrosis of the hands (palms).	Off-label indication. NICE CKS recommend oral anticholinergics (including licensed propantheline, off-label oxybutynin) as an option for people in whom conservative measures and topical Al based treatment were not efficient in controlling excessive sweating. Other treatments that may be considered include topical therapies (including topical glycopyrronium), iontophoresis, botulinum toxin injections, other systemic therapies (including clonidine, diltiazem, benzodiazepines) and surgery.The CKS informs that BT can also be helpful for palmar, plantar, and craniofacial hyperhidrosis but the procedure may be more difficult and painful particularly when injected to feet and hands. NHS Choices also list BT as an option for treatment of severe hyperhidrosis affecting hands, feet and face. The British Association of Dermatologists adds that '' Botulinum toxin is not commonly used in the palms and soles because it can cause temporary weakness of hand and foot muscles and is painful''. The International Hyperhydriosis Society (2012) recommends: - for primary craniofacial hyperhidrosis: topical aluminum based product as first line, BT as second line, and systemic medication as third line. - for primary palmar hyperhidrosis: 1st line: topical antiperspirant (Al and Zn salts) or iontophoresis (+/- anticholinergic in water); 2nd line: BT, then systemic medications , then ETS surgery as last resort - for primary plantar hyperhidrosis - as above, without EST as last step. The Canadian guidelines (2007) have similar recommendations, which are additionally graded depending on severity of symptoms. The evidence base is strongest for the application to hands and ncludes two small quasi-RTCs (level 2) with positive findings, which are consistent with substantial amount of level 3 evidence. There is substantially less published evidence for plantar hyperhidrosis, however, it is consistent level 3 evidence. Similarly there is lack of RTC for craniofacial presentation, but the level 3 evidence is consistent. A limitation to administration of BT may be temporary muscular paresis (particularly hands, forehead). Injections to hands and feet are painful. Patients are typically injected 2-3 times per year. NB EUR policy on hyperhidrosis allows use of BT in the axillae only; however, this policy is currently under review.		Off-label indication, however, this is a recognised treatment modality for plantar hyperhidrosis resistant to conservatory treatment and topical antiperspirants. The evidence is of moderate to low quality but appears consistent. Recommended for use as per specified criteria. <u>FOR DISCUSSION:</u> Should oral anticholinergic be added as a treatment step before using BT?	BT can be used for significant and intractable excessive sweating of the palmar area: (1) hyperhidrosis not associated with social anxiety disorder or secondary to other underlying cause, and (2) there is a record of unsuccessful trial of: (a) conservative measures (lifestyle factors and avoidance of triggers) and (b) aluminium based topical treatment for at least 1-2 months or iontophoresis *(c) treatment with systemic anticholinergic (preferably oxybutynin, off-label) was ineffective or not appropriate*
30c	Severe primary plantar hyperhidrosis	Severe and intractable focal hyperhidrosis of the feet.			Off-label indication, however, this is a recognised treatment modality for plantar hyperhidrosis resistant to conservatory treatment and topical antiperspirants. The evidence is of low quality but appears consistent. Recommended for use as per specified criteria. <u>FOR DISCUSSION:</u> <u>Should oral anticholinergic be added as a treatment step before using BT?</u>	BT can be used for significant and intractable excessive sweating of the plantar area: (1) hyperhidrosis not associated with social anxiety disorder or secondary to other underlying cause, and (2) there is a record of unsuccessful trial of: (a) conservative measures (lifestyle factors and avoidance of triggers) and (b) aluminium based topical treatment for at least 1-2 months or iontophoresis *(c) treatment with systemic anticholinergic (preferably oxybutynin, off-label) was ineffective or not appropriate*
30d	Severe primary craniofacial hyperhidrosis	Severe and intractable focal hyperhidrosis of the face (often frontal) and / or scalp.			Off-label indication, however, this is a recognised treatment modality for plantar hyperhidrosis resistant to conservatory treatment and topical antiperspirants. The evidence is of low quality but appears consistent. Recommended for use as per specified criteria. <u>FOR DISCUSSION:</u> Should oral anticholinergic be added as a treatment step before using BT?	BT can be used for significant and intractable excessive sweating of craniofacial area: (1) hyperhidrosis not associated with social anxiety disorder or secondary to other underlying cause, and (2) there is a record of unsuccessful trial of: (a) conservative measures (lifestyle factors and avoidance of triggers) and (b) aluminium based topical treatment for at least 1-2 months *(c) treatment with systemic anticholinergic (preferably oxybutynin, off-label) was ineffective or not appropriate*
30e	Severe generalised sweating	Diffuse sweating affecting head, chest, back and occasionally other body parts – axillae, hands and feet. It is often a symptomatic presentation of underlying condition from infection, endocrine dysfunction to neurological or psychological disorders and side effect of drugs or drug withdrawal. Treatment is casual, and application of BT might be problematic due to widespread presentation However, focal frontal or cranial hyperhidrosis can be treated with BT (Derssler, 2012)	Off-label indication. Evidence search did not identify relevant publications. The International Hyperhidrosis Society recommends that when symptoms persist during or after the underlying condition has been treated and/or mediation adjusted, a consideration can be give to using systemic treatment (bearing in mind interactions, or contraindications). In the rare case where no underlying cause is found treatment to most involved areas can be used as per recommendation for each focal hyperhydriosis presentation.		Not recommended - off-labela nd no evidence identified to support use of BT in diffuse sweating.	Prior approval needed via IFR to use BT for generalised hyperhidrosis (including use of focal area in diffuse sweating).

31	Frey's syndrome	Facial hyperhidrosis (gustatory sweating) secondary to parotidectomy. Rare, symptoms include sweating, flushing, warming over the preauricular and temporal areas following gustatory stimulus. Often in patients who have undergone parotidectomy, submandibular gland surgery, radical neck dissection, infection and traumatic injury in the parotid region and is caused by aberrant regrowth of facial autonomic nerve fibres. Interventions include topical application of anticholinergics and antiperspirants, and intradermal injection of BT. Specialty: ENT/ OMFS Patient numbers: - 1-3 patients pa (SRFT)	Off-label indication. Cochrane review (2014) found no RTC and reported that retrieved studies were of poor quality. A further databases search found large body of low level (3) but consistent evidence. One RTC was found, however, only abstract was available in English. BT is discussed as treatment option within NICE CKS on hyperhidrosis (including craniofacial area). The International Hyperhidrosis Society recommends conservative measures as initial intervention (triggers avoidance), then BT or topical aluminium based products as first line treatment and systemic medication as third line .		Off-label, and Cochrane evidence did not identify high quality evidence. However, substantial amount of low quality evidence appeared satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used for significant and intractable excessive sweating of craniofacial area in Frey's syndrome where: (1) there is a record of unsuccessful trial, history of intolerance or contraindication to: (a) conservative measures (lifestyle factors and avoidance of triggers), and (b) topical aluminium based treatment

F. Oromandibular disorders

32	Temporomandibular joint disorders	Temporomandibular disorders (TMD) are disorders that affect the joint between the temporal bone on the side of the head and the mandibular (jaw) bone of the face, and the associated muscles. Pain is the defining feature of TMD and the primary reason for seeking care. TMD may also involve joint noises or restricted jaw function or both (Cochrane, 2010). Aetiology can be myofacial (pain from hyperfunctioning muscles of mastication leading to chronic myositis) or arthrogenic (intracapsular pathology with pain at level of joint itself). Treatment: nonpharmacological (trigger avoidance, adjusting diet, physio, warm compresses, splints for patients with bruxism), conservative pharmacotherapy (analgesics, anti inflammatory, muscle relaxants, TCAs) and surgery. Specialty: ENT/ OFMS? Patient numbers: SRFT: 6pts/pa	Off-label indication. Cochrane for pain management in TMD did not include botulinum toxin (2010). Literature search revealed a review inclusive of one RCT (level 1b) and consistent lower quality evidence (level 3). BT injections are included in the NICE CKS for TMD management as option of treatment by specialist and can be considered alongside intra articular hyaluronate or steroids or various surgical procedures for people with significant functional impairment of the temporomandibular joint (TMJ), and/or an intra-articular disorder such as anterior disc displacement or degenerative joint disease.	*early cons: TMJ which causes myofacial spasm and severe pain. May use for severe pain where amitriptyline or other no drug related treatments have failed e.g. physio and splints or failed surgery .One injection every 6 months. Used less commonly now for this indication but may be treated for localised spasm/pain affecting one or two muscles. Would not be used now for diffuse spasms.*	Off-label, however, evidence identified appeared satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used for people with TMD, where (1) symptoms result in functional issues (e.g. spasm and pain, limited mouth opening), and (2) the spasm is localised (not diffuse), and (3) other measures were tried and not helped: (a) non-pharmacological (physiotherapy, orthodontic interventions - bite adjustments or teeth splits where relevant), and (b) pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and (c) surgery not appropriate.
33	Masseteric hypertrophy	Benign swelling near the angle of mandible, may be associated with pain and cause functional issues (e.g. limited mouth opening or spasm). It has been suggested that hypertrophied muscles of jaw can lead to increased pressure in temporomandibular joint (TMJ) and cause severe pain and mimic temporomandibular disorder (TMD). Interventions vary from pharmacotherapy (analgesia, muscle relaxants, antidepressants), nonpharmacological (e.g. dental interventions), BT to surgical reduction. Note that BT is also advocated for cosmetic sculpting of the face including injections in the masseter muscle. Specialty: ENT/ OFMS? Patient numbers: 2-3, may be 1-2 post surgery (SRFT).	Off-label indication. Cochrane review 2013 did not find any RTC and was inconclusive, however authors suggest that BT might be superior to surgery. Further evidence search for literature only yielded single case reports (level 3). The findings are consistent with those in the review and with local expert knowledge (level 4).	*Treated where there is limited mouth opening and /or pain – may be a complication of surgery.*	Off-label, and Cochrane evidence did not identify high quality evidence. However, substantial amount of low quality evidence appeared satisfactory to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used for masseter hypertrophy, where: (1) symptoms result in pain, spasm or other functional issues (e.g. limited mouth opening or severe facial disfigurement), and (2) other measures were tried and not helped: (a) non-pharmacological (physiotherapy, orthodontic interventions - bite adjustments or teeth splits where relevant), and (b) pharmacological interventions (analgesics, anti-inflammatories, muscle relaxants), and (c) surgery is not appropriate.

G. Pain syndromes

34	Refractory trigeminal neuralgia	First line of treatment of TGN is oral pharmacotherapy with carbamazepine. 50% of patients are long term responders. Other anticonvulsants may be tried as alternative treatment (gabapentin, pregabalin, topiramate), as well as baclofen. Alternatives encompass a number of surgical procedures that also carry risks. Specialty: Neurology Patient numbers 3 (SRFT)	Off-label indication. Sound evidence - two systematic reviews identified (one with 1 small RTC, second with 2 small RTCs), followed by 2 more RTCs and a prospective study (level 1b), results consistent with available evidence level 3 (retrospective studies) and 4 (local expert knowledge). BT effective in at least 50% of pain resolution in patients with TGN refractory to oral pharmacological treatment (or treatment inappropriate) and where surgery deemed inappropriate (e.g. complex procedure or elderly patients).	*Trigeminal neuralgia is another important off-label indication. The data so far, notwithstanding publication bias, looks good and 2 of the 3 patients I've injected have improved (waiting to find out if the 3rd has).*	Off-label, however, evidence identified (high level studies consistent with large amount of low level evidence) appeared to support use of BT in this indication. Recommended for use as per specified criteria.	BT can be used in patients with documented TGN: (1) refractory to oral pharmacotherapy, where at least 3 oral medications tried and unsuccessful, not tolerated or contraindicated (carbamazepine, and second anticonvulsant and baclofen), and (2) where surgery inappropriate.

35	Prophylaxis of headaches with chronic migraine	Migraine headache prophylaxis. Specialty: Neurology Patient numbers (SRFT): - 40pts/week and on increase. Jan log from migraine clinic shows 350pts.	Licensed indication (B), and has an positive NICE TA260. Level of evidence 1b (RTCs identified in Cochrane review protocol, 2015). A systematic review (Jankovic, 2012), level 1a) shown efficacy in pooled analysis. Also as option in the GMMMG/NM headache management guide (based on NICE CG150). Also included in the BASH guideline for headache. NHS Choices lists botulinum toxin as a treatment option for migraine. NICE CKS for migraine includes use of BT.	*SRFT: Note initiation criterion (4) based on the GMMMG/NM headache management guide/NICE CG150. Can be modified to alternative suggested by SRFT as follows: Tried three (3) of the following (unless contraindicated) and continued each for 3 months at maximum tolerated target dose without significant benefit (unless inappropriate, as judged by the clinician):* *i. Amitriptyline or nortriptyline: 100mg o.n. or highest tolerated below that* *ii. A Betablocker: Propranolol MR 240mg a day or max tolerated below that; or Metoprolol 200mg per day or max tolerated below that* *iii. Topiramate: highest tolerated dose up to 100mg b.d.* *iv. Sodium Valproate: highest tolerated dose up to 1000mg b.d.* *v. Lisinopril up to 20mg o.d. or candesartan up to 32mg o.d.* *vi. Venlafaxine MR up to 225mg o.d.* *vii. Flunarizine (unlicensed) 10mg o.n.*	Licensed indication and positive NICETA 260. Recommended for use as per specified criteria. <u>FOR DISCUSSION</u>: Should criterion (4) more specific? See column with supporting information from clinician.	BT can be used for chronic migraine, where: (1) patient experiences headaches on at least 15 days per month of which at least 8 are with migraine. (2) medication overuse headache has been ruled out (<10 days per month of opiate or triptan use, <15 days/month of other analgesics) or previous withdrawal of analgesics/triptans for 3 months had no effect). (3) other causative disorders have been ruled out. (4) a record of prior three pharmacological preventative interventions, but NOT pizotifen, at maximal doses (propranolol, topiramate, amitriptyline, gabapentin), used for at least 3 months each (give start date, stop date & reason for discontinuation). Continuation criteria: (1) Percentage of reduction (min 30%) in headache days per month after initial 2 treatment cycles, measured over min month. Calculated as no of headaches over consecutive 3 months per day/month. Discontinuation: (1) chronic migraine changes to episodic (less than 15 days/month in 3 consecutive months, or (2) treatment not effective (max 2 cycles)
36	Medication overuse headache	To induce headache remission in patients overusing analgesia and allow them taper off painkillers. Specialty: Neurology	Off-label indication. Not recommended in the GMMMG/NM headache management guide. The guideline recommends stopping medication for 3 months as treatment for both triptan induced and analgesic induced headaches. NICE CKS, 2012: withdraw analgesia and wait for pain to resolve. The prophylaxis of underlying primary headache disorder will dictate drug choice. Ideally overused medication should be withdrawn and prophylaxis started 1-2 months after. <u>Occasionally, for a person who is unable to otherwise withdraw from the overused medication, prophylactic treatment may be considered in addition to withdrawal.</u> CKS expert reviewers agree that on occasion it can be useful to start prophylaxis earlier in a person who otherwise may not withdraw. BT is not discussed as an option. BASH guidelines (2010), do not discuss use of BT for MOH. An RTC was found during database search comparing BT and placebo in MOH(Sandrini, 2011, n=68). No significant differences were found in frequency of headache days for the 28-day period ending with week 12, a significant reduction was recorded in secondary end point, mean acute pain drug consumption in patients given BT (level 1b). No other relevant studies were identified.	SRFT: With respect to analgesic overuse as an off-license indication, many believe this may help; indeed the PREEMPT studies included many patients with overuse. However NICE stipulate they should not be treated. I think it would be a useful tool to induce a temporary reduction in headache to facilitate analgesic withdrawal, maybe limiting treatment for that indication for 2 courses irrespective of benefit. There is no proven reliable way of getting people to stop their medication overuse - it's somewhat opinion driven.	Not recommended - off-label and insufficient evidence.	Treatment of MOH with BT requires prior approval via IFR.
37	Post-craniotomy pain	delayed onset pain after craniotomy	Off-label indication. Very little evidence base (2 case series, n=7) In first report all patients had hypertrophy of temporalis muscle, potentially aberrant facial nerve regeneration), all patients responded well to BT. Second report available as abstract only.		Not recommended - off- lable and insufficient evidence.	Treatment of post-craniotomy pain with BT requires prior approval via IFR.

H. Bladder dysfunctions

38a	Overactive bladder with symptoms of urinary incontinence, urgency and frequency	Overactive bladder (OAB) syndrome is characterised by urgency, often with frequency and nocturia and sometimes leakage (urge incontinence). It is often but not always associated with detrusor muscle overactivity. It can be idiopathic or neurogenic. OAB is the second most common cause of female urinary incontinence (stress incontinence is the most common). OAB may be associated with Parkinson's disease, spinal cord injury, diabetic neuropathy, multiple sclerosis, dementia or stroke; however, most cases have no specific cause. OAB treatment range from behavioural and lifestyle changes to pharmacological - antimuscarinics (poorly tolerated), mirabegron, and invasive options and intravesical inj of botulinum toxin. Specialty: Urology Patient numbers: BFT - about 100 pts/pa	Licensed indication (B). Cochrane review (2011) found BT effective and safe in treatment of OAB regardless of aetiology (neurogenic or idiopathic). Since then, NICE included BT in CG for treatment of incontinence in women (CG171), LUTS in men (CG97) and in incontinence due to neurological disease (CG148). Product license was granted more recently and was based on two large RTC for each indication (OAB and incontinence due to neurogenic detrusor overactivity). *Cochrane review notes that the duration of effect of botulinum toxin type A may range from three to twelve months. The effect of botulinum toxin type B seems to be limited to less than ten weeks. This may give botulinum toxin type B a role in test-dosing of patients, limiting the duration of adverse effects.* BT is included in as option in treatment of bladder disorders on NHS Choices and NICE CKS. NICE does not recommend use of BT B to women with proven detrusor overactivity.	*Comments from BFT: In our Urology department, I use Botulinum toxin for neurogenic and idiopathic bladder overactivity and urge incontinence. As you have said, it has been approved by NICE for women with detrusor overactivity and urge leakage (CG 171) and also for patients with neurogenic bladders (CG 148). There are a handful of men with severe intractable detrusor overactivity who also get Botulinum toxin inj to their bladders.*	Licensed indications, advocated by NICE clinical guidelines, and found safe and effective by Cochrane review. Recommended for use as per specified criteria.	BT can be used intravesically in patients with OAB, who: (1) received and not responded to a trial of conservative management including: (A) lifestyle interventions (adequate fluid intake, reduced caffeine intake, weight management) (B) appropriate behavioural management programme (e.g.. bladder training lasting at least 6 weeks) (C) for patients with mixed urinary incontinence pelvic floor muscle training lasting at least 3 month, and (2) have urodynamic confirmed detrusor over activity (3) received and not responded to drug trials of (unless contra-indicated or not tolerated): (A) at least 3 antimuscarinics drugs tried for 2 months each (B) in post-menopausal women with vaginal atrophy intra-vaginal oestrogen for 3 months (4) are willing and able to self-catheterise, and (5) the clinical suitability was determined by MDT on basis of symptoms severity (patient completed bladder diary over at least 3 days) Continuation criteria: (1) assessed at 3 months and (2) showing a 50% or greater improvement in continence episodes or urgency episodes per day
38b	Neurogenic detrusor overactivity with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis				Licensed indications, advocated by NICE clinical guidelines, and found safe and effective by Cochrane review. Recommended for use as per specified criteria.	
	Note NHSE commissioned where BT used intravesically in spinal cord injury, and patient is treated under recognised MS specialist centre with specialist nurse support. Follow NHSE process for funding approval.					
38c	Bypassing catheter in patients with MS	Leakage around the catheter is another problem associated with indwelling catheters. This can happen as a result of bladder spasms or during opening bowels, one of the causes can be blocked catheter (NHS Choices, urinary catheterisation). In case of bladder spasm of detrusor instability antimuscarinics can be considered (NHS Lothian, Catheter problem solving guide, 2015) Specialty: Urology	Off-label indication. Only one publication identified during database search (matching that supplied by clinician). Small retrospective case series (n=3), all patients had end-stage MS, and indwelling catheter for over 3 years, catheterised to try address urethral incontinence. The urodynamic assessment was not performed due to patients disability. 2 patients were found continent for 40 weeks, on died at 27 weeks (BT was deemed effective prior to death). No mention of trial of antimuscarinics prior to BT (evidence level 3, low quality and small patient numbers).	*...and also for catheter bypassing. Successful treatment with intradetrusor Botulinum toxin for urethral urinary leakage (catheter bypassing) in patients with end-staged multiple sclerosis and indwelling suprapubic catheters.*	Not recommended - insufficient evidence	Prior approval needed via IFR to use BT for catheter bypassing.

I. Skin

39	Scar softening and modification	It is impossible to predict if the scar resulting from surgery will be disabling in any way.	Off-label .The British Association of Aesthetic Plastic Surgeons does not recommend BT for the treatment of any kind of scars (including active). For severe hypertrophic scars and keloids the BAAPS recommend topical treatment with pressure, silicone and steroids. There is a GM EUR policy on surgical scar revision, which only allows interventions in case where the scar is causing demonstrable functional problem, which has been present for a minimum of 18 months post injury/surgery. Evidence base search revealed a number of literature reviews and studies investigating use of BT in various circumstances ranging from preventative intervention by injecting wound surrounding muscles to intralesional administration to mature keloid scars. The studies were heterogenic, the sample sizes small and the outcomes chiefly patient reported (perception of wound healing). One study evaluating intralesional use of BT in keloid scars (n=4) did not find any improvement in objective measurement. Two RTC reported injections within a week of surgery (post-thyroidectomy scar and facial wound) as successful, but outcome measures were subjective (patient reported). None of the studies identified functional issues due to scarring; the results were discussed in terms of appearance rather than improving function. Authors' conclusions suggesting BT could be regarded as a novelty treatment for scars were often based on findings of in-vitro, tissue model investigations and animal studies, explaining mode of action of BT rather than objective measures from human high level quality studies. One RTC comparing BT to steroid injections found standard therapy with steroids better than BT at 6 months. One RTc found BT not better than placebo in treatment of acne scars.		Not recommended - insufficient evidence	Prior approval needed via IFR to use BT for scar prevention, modification and softening.