Aesthetic (Cosmetic) surgery and other related procedures: Evidence based framework for decision making

Procedures that NHS Leeds North Clinical Commissioning Group, NHS Leeds South and East Clinical Commissioning Groups and NHS Leeds West Clinical Commissioning Group consider are:

- medically necessary despite their aesthetic (cosmetic) aspects or
- medically unnecessary

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1 Introduction

This framework identifies procedures that Leeds Clinical Commissioning Groups (CCGs) NHS Leeds North CCG, NHS Leeds South and East CCG and NHS Leeds West CCG consider medically necessary despite their aesthetic (cosmetic) aspects as well as cosmetic procedures that Leeds CCGs consider are medically unnecessary. This Framework supports the Cosmetic Exceptions and Exclusions Panel as described in the Individual Funding Requests Policy.

2 Purpose

This Framework replaces any former Cosmetic and Aesthetic Policies used by Leeds Primary Care Trust (NHS Leeds) unless stated otherwise. It is a decision making aid for Individual Funding Requests relating to cosmetic exceptions and exclusions.

3 Scope

This document is intended as an aid to decision making. It should be used in conjunction with Leeds CCG policies on Individual Funding Requests and associated decision making frameworks.

4 Framework operation

Leeds CCGs *do not routinely commission* aesthetic (cosmetic) surgery and other related procedures that are medically unnecessary.

Providing certain criteria are met, Leeds CCGs will commission aesthetic (cosmetic) surgery and other procedures to improve the functioning of a body part or where medically necessary even if the surgery or procedure also improves or changes the appearance of a portion of the body.

Please note that, whilst this framework statement addresses many common procedures, it does not address all procedures that might be considered to be cosmetic. Leeds CCGs reserve the right not to commission other procedures considered cosmetic and not medically necessary. This framework is based on the Aetna Clinical Policy Bulletins. It is to be used in conjunction with the Individual Funding Requests (IFR) Policy for Leeds CCGs.

4.1 Endpoints

Following completion of the agreed treatment, a proportionate follow up process will lead to a final review appointment with the clinician where both patient and clinician agree that a satisfactory end point has been reached. This should be at the discretion of the individual clinician and based on agreeing reasonable and acceptable clinical and/ or cosmetic outcomes.

Once the satisfactory end point has been agreed and achieved, the patient will be discharged from the service.

Requests for treatment for unacceptable outcomes post treatment will only be considered through the Individual Funding Request route. Such requests will only be considered where a) the patient was satisfied with the outcome at the time of discharge and b) becomes dissatisfied at a later date. In these circumstances the patient is not automatically entitled to further treatment. Any further treatment will therefore be at the relevant Leeds Clinical Commissioning Group’s discretion, and will be considered on an exceptional basis in accordance with the IFR policy.

4.2 Aesthetic (cosmetic) procedures not commissioned by Leeds CCGs

The following procedures are considered cosmetic in nature and consequently are not routinely commissioned by Leeds CCGs unless there are exceptional criteria which must be approved in advcance:

- Excision of excessive skin on thigh, leg, hip, buttock, arm, forearm or hand, submental fat pad, other areas
- Fat grafting
- Suction assisted lipectomy (liposuction) for any purpose
- Correction of diastasis recti abdominis (divarication of the recti)
- Chin implants (genioplasty, mentoplasty)
- Cheek implants (malar implants).
- Cosmetic rhinoplasty
- Collagen implants
- Mastopexy (breast lift)
- Otoplasty (prominent ear correction) in adults (over 16)
- Removal of decorative tattoos
- Botulinum toxin for the following indications (Appendix K lists the indications for botulinum Toxin):
  - Wrinkles, frown lines; or
  - Aging neck; or
  - Blepharoplasty (eyelid lift)
- Poly-L-lactic acid injection (Sculptra), or calcium hydroxylapatite (Radiesse), or fat injections for HIV lipoatrophy

Providers will not be paid for any activity with regards this section of the framework which has not been approved in advance as an exception.

4.3 Aesthetic (cosmetic) procedures that are commissioned when certain criteria are met but require prior approval (appendices A-Q)

The following procedures are potentially considered medically necessary when certain criteria are met. Each request will be considered on a case by case basis. The requesting GP/clinician/patient will be required to submit documentation, demonstrating that the conditions are met in order to obtain prior approval. Failure to provide sufficient information will lead to the request being turned down. Please refer to the Individual Funding Request Policy for more information.

- **Benign Skin Lesions** eg Seborrheic keratoses, sebaceous cysts, naevi (moles) or skin tags. Removal is only considered medically necessary if criteria in appendix G or H are met.
- **Blepharoplasty**: Considered medically necessary when criteria in Appendix J are met.
- **Breast augmentation** (breast implants or pectoral implants) (for medical necessity criteria for breast reconstruction see Appendix D)
- **Breast implant removal**: Considered medically necessary when criteria in Appendix C are met.
- **Breast reduction:** Considered medically necessary when criteria in Appendix E are met
- **Dental Cosmesis** - refer to Appendix O – this is no longer a local commissioning decision.
- **Ear reconstruction** is considered medically necessary when performed to improve hearing by directing sound in the ear canal, whether the ears are absent or deformed from trauma, surgery, disease, or congenital defect.
- **Earlobe repair:** Repair of a traumatic tear is considered medically necessary (normally within 2 years of injury). Earlobe repair to close a stretched pierced hole, in the absence of trauma, is considered cosmetic.
- **Electrolysis or Laser hair removal** for abnormal hair growth is considered medically necessary when criteria in Appendix H are met.

- **Gender dysphoria interventions** See Appendix P
- **Gynaecomastia: C**onsidered medically necessary when criteria in Appendix F are met.
- **Keloids**: Treatment of keloids is considered medically necessary if they cause pain or a functional limitation.;
- **Lipomas (excision):** Considered medically necessary if tender and inhibiting the patient's ability to perform daily activities due to the lipomas' location on body parts that are subject to regular touch or pressure (via minor surgery service).
- **Male circumcision in adults:** considered necessary only when associated with an underlying condition or complication.
- **Male circumcision in children**: considered medically necessary when criteria in Appendix L are met; considered necessary for religious reasons when criteria in Appendix L are met.
- **Naevi, telangiectasia, hair associated with scarring, inflammatory or infiltrated dermatoses, port wine stains and other hemangiomas/vascular anomalies:** Considered medically necessary under certain conditions, see Appendix H.
- **Otoplasty (prominent ear correction)** considered medically necessary in children under the age of 16 where there is evidence of psychological harm or bullying at school.
- **Post massive weight loss:** Leeds CCGs will only consider funding requests for panniculectomy, breast reduction or removal of other redundant skin following significant planned weight loss (following bariatric surgery or other weight management initiatives) where criteria in appendix A are met.
- **Rhytidectomy** (including meloplasty, face lift): Considered medically necessary when there is functional impairment that cannot be corrected without surgery – evidence of a sustained period of unsuccessful non-medical treatment should be provided.
- **Scar revision:** Repair of scars that result from surgery is considered medically necessary (normally within 2 years of surgery) if they cause significant symptoms or functional impairment.
- **Septo-Rhinoplasty and Rhinoplasty**: Considered medically necessary for indications in Appendix I.
- **Skin tag removal:** Considered medically necessary when located in an area of friction with documentation of repeated (more than once) excoriation and bleeding.
- **Surgical procedures for labial hypertrophy or asymmetric labial growth** when criteria in Appendix M are met.
- **Tattoo**: Considered medically necessary when criteria in Appendix H are met, otherwise tattoo removal is a cosmetic procedure.
- **Ventral hernia:** Considered medically necessary when criteria in Appendix Q are met.

Providers will not be paid for any activity with regards the appendices in this framework which have not been approved in advance.

4.4 Implantation and attachment of prostheses

Leeds CCGs will commission prosthetic devices that temporarily or permanently replace all or part of an external body part that is lost or impaired as a result of disease, injury or congenital defect.

The following surgical implantations are commissioned even though the prosthetic device does not correct a functional deficit:

- Testicular prostheses: Considered medically necessary for replacement of congenitally absent testes, or testes lost due to disease, injury, or surgery.
- Breast reconstruction implants in specific conditions (Appendix D)
- Eye (ocular) prostheses.
- Ear (auricular) prostheses.
- Facial prostheses.
- Wigs/ hair transplant/ hair extensions. This is considered medically necessary when performed to correct permanent hair loss that is clearly caused by disease or injury or underlying mental health

problem when in conjunction with an NHS psychological treatment programme. Wigs, hair transplants or extensions to correct male pattern baldness or androgenic hair loss in women (at any age) are considered cosmetic and not routinely commissioned.

Other forms of prosthesis are considered cosmetic.

4.5 Services relevant to this framework which will be commissioned routinely and do not need prior approval or individual funding request approval.

The following services are routinely commissioned and do not need prior approval or individual funding request approval:

- Trauma and injury: acute repair and reconstruction
- Burns: acute care and reconstruction
- Reconstruction following cancer treatment
- Reconstruction following defined congenital abnormalities
- Reconstruction following female genital mutilation.

4.6 Referral Process

Refer to Individual Funding Requests Policy. Referrers must ensure that all necessary information is provided as part of the Individual Funding Request in order for the request to be considered.

4.7 Exceptional circumstances

Refer to overarching Individual Funding Request Policy.

Psychological Exceptions and Cosmetic Surgery are discussed in Appendix L.

5 Equality Impact Assessment

Appendix T documents the equality impact assessment.

6 References

The overall framework on ‘Aesthetic (cosmetic) Surgery and Other Related Procedures’ is based on the following references:

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Appendix A: Surgery Following Significant Weight Loss (panniculectomy, arm and thigh reductions, cosmetic breast procedures for males and females)

Introduction

This framework applies for all patients who achieve significant weight loss either through weight management programmes or through Bariatric Surgery.

Removal of redundant skin folds resulting from weight loss after surgery or planned weight loss is not routinely commissioned by Leeds CCGs unless the criteria outlined below are met.

Primary eligibility criteria (for any of the above procedures)

- Patient's BMI must be 30 or less for 12 months AND
- There must have been at least 25% weight loss AND
- a period of more than 2 years must have elapsed since the weight loss surgery or period of significant weight loss AND
- The patient must be a confirmed non-smoker[1.] AND
- Photographic evidence of the condition is required by the IFR panel – only photographs taken by medical photography will be accepted

Requests that do not meet these criteria will be rejected prior to panel unless there are very clear grounds for exception.

Panniculectomy

Leeds CCGs consider panniculectomy only medically necessary where, in addition to the primary eligibility criteria:

- the panniculus hangs below the level of the pubis; AND
- the medical records document that the panniculus causes chronic intertrigo (dermatitis occurring on opposed surfaces of the skin) that consistently recurs over 3 months while receiving appropriate medical therapy, or remains refractory to appropriate medical therapy over a period of 3 months.

Arm and thigh reductions and breast surgery following significant weight loss

Leeds CCGs consider arm and thigh reductions or breast surgery (in males or females) following significant weight loss medically necessary where, in addition to the primary eligibility criteria listed above:

- There is persistent and recurrent skin breakdown or ulceration which the GP has been treating for 3 months or more OR
- Intertrigo which is resistant to at least 6 months medical treatment

The above framework is based on the following references:

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[1] This applies to flap based procedures specifically and is in line with plastic surgery literature: abdominoplasty, panniculectomy, breast reduction, mastopexy.

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Appendix B: Abdominoplasty (NB excludes panniculectomy following significant weight loss)

Leeds CCGs consider abdominoplasty to be cosmetic and it is therefore not funded in the following situations:

- Panniculectomy for minimising the risk of hernia formation recurrence is considered to be experimental.
- Repair of diastasis recti, defined as a thinning out of the anterior abdominal wall fascia, is considered cosmetic since evidence suggests this does not represent a "true" hernia and is of no functional significance.

Leeds CCGs consider abdominoplasty or suction lipectomy to be cosmetic in any other situation including post pregnancy changes of the abdomen UNLESS there is substantial panniculus restricting function or causing skin ulceration.

Appendix C: Breast Implant Removal and Reinsertion

Leeds CCGs consider the removal of breast implants medically necessary for the following situations:

In patients who have undergone cosmetic augmentation mammoplasty or breast reconstruction following a medically necessary mastectomy (e.g. mastectomy for breast cancer or a prophylactic mastectomy), removal of breast implants is considered medically necessary for any of the following indications:

- Remnant breast cancer or cancer in the contralateral breast, or
- Implants complicated by recurrent infections, or
- Implants with Baker Class IV contracture associated with severe pain, or
- Implants with severe contracture that interferes with mammography, or
- Intra- or extra-capsular rupture of silicone gel-filled implants.

The Baker classification is shown below.
For patients whose breast reconstruction followed a medically necessary mastectomy (i.e., mastectomy for breast cancer or a prophylactic mastectomy), breast implant removal is also considered medically necessary for these additional indications

- Baker Class III contracture, or
- Extra-capsular rupture of saline implant if the rupture compromises the cosmetic outcome of the implant.

Removal of ruptured saline-filled breast implants is not considered medically necessary for patients who have previously undergone cosmetic breast augmentation mammoplasty.

Requests for the removal of breast implants for any of the following indications is subject to a case by case review of the exceptional circumstances:

- Breast malposition or asymmetry; or
- Baker Class II contracture; or
- Baker Class III contracture that does not follow a medically necessary mastectomy; or
- Removal of breast implant due to patient's anxiety about developing an autoimmune disease; or
- Implant removal for biopsy of breast mass that has not been proven to be cancerous; or
- Implant removal for a mastectomy or lumpectomy that cannot be performed with the implant in place.
- Silicone Implant Removal for Autoimmune Disease
- Leeds CCGs do not consider either of the following medically necessary:
- Removal of silicone implants for autoimmune disease unless the patient meets at least one of the selection criteria listed above (e.g., rupture of silicone-gel filled implant, etc.); or
- IgG testing in connection with silicone implants (the development of IgG antibodies is neither specific to silicone implants nor indicative of autoimmune disorders).
- Reinsertion of Breast Implants

Although Leeds CCGs consider the removal of breast implants medically necessary for medical indications even if the implants were originally inserted for cosmetic purposes, the CCGs normally consider the reinsertion of new breast implants to be cosmetic, and also consider mastopexy or adjustment surgery following implant removal cosmetic and hence will not be funded.

However, Leeds CCGs consider the insertion of replacement of breast implants following previous mastectomy (i.e., mastectomy for breast cancer or a prophylactic mastectomy) or for women with other significant developmental abnormalities (including Poland's syndrome) medically necessary.

Baker Classification:

Class I	Augmented breast feels soft as a normal breast.
Class II	Augmented breast is less soft and implant can be palpated, but is not visible.
Class III	Augmented breast is firm, palpable and the implant (or distortion) is visible
Class IV	Augmented breast is hard, painful, cold, tender, and distorted

Background

In 1992, the FDA advised that ruptured silicone implants should be removed since the health risks of extruded silicone are not known. At the same time, the FDA panel acknowledged that asymptomatic rupture may be present in up to 4% of women with silicone implants, but the FDA specifically did not recommend screening for asymptomatic ruptures.

Rupture of silicone implants can be subdivided into two categories - intra and extra capsular. After implantation, a reactive fibrous capsule is formed around the implant. If the extruded silicone is contained by this fibrous capsule the rupture is termed intracapsular. If the silicone gel is extruded beyond the capsule, the rupture is termed extracapsular. Extracapsular silicone can induce granulomatous reaction and can occasionally migrate to the axillary lymph nodes, producing a lymphadenopathy, which can mimic cancer. Clinically, extracapsular ruptures are often associated with a change in size and consistency of the breast. Extracapsular ruptures can usually be identified on mammography or other imaging studies. Research by the Department of Health concluded that there is no evidence of long term harm associated with the use of silicone gel implants. Nevertheless, an intracapsular rupture can evolve to an extracapsular rupture and the FDA has indicated that ruptured implants, whether intracapsular or extracapsular, should be explanted as well.

NHS Guidance has been developed following the breast implant scandal in relation to Poly Implant Prosthese (PiP).

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Appendix D: Breast Augmentation or Reconstructive Surgery

Leeds CCGs consider breast augmentation/reconstructive surgery to enhance breast size or correct breast asymmetry including changes following pregnancy and child birth are cosmetic except where:

- The patient must be a confirmed non-smoker[2] AND
- Photographic evidence of the condition is required by the IFR panel – only photographs taken by medical photography will be accepted AND
- One or both breasts must be malformed:
    - Developmental failure (eg Poland Syndrome) OR
    - Tubular breast (see http://cdn.intechopen.com/pdfs/33481/InTech-Tuberous_breast_clinical_evaluation_and_surgical_treatment.pdf accessed July 2013) type iii with severe breast constriction with minimal breast base and hypoplasia of all four quadrants OR
    - Following breast cancer to reconstruct the breast, correct for significant deformity, and to correct assymetry OR
    - Asymmetry of more than 2 cup sizes (at least an estimated 40% difference) difference where BMI is 30 or less for at least 12 months. Only the following cup sizes are recognised (see http://en.wikipedia.org/wiki/Brassiere_measurement accessed July 2013)

UK
AA
A
B
C
D
DD
E
F
FF
G
GG
H
HH
J
JJ
K

[2] This applies to flap based procedures specifically and is in line with plastic surgery literature: abdominoplasty, panniculectomy, breast reduction, mastopexy.

NOTE: Prompt repair of breast asymmetry due to trauma is exempt from the above criteria.

Leeds CCGs consider reconstructive breast surgery medically necessary after a mastectomy or lumpectomy that result in a significant deformity (i.e., mastectomy or lumpectomy for treatment of or prophylaxis for breast cancer and mastectomy or lumpectomy performed for chronic, severe fibrocystic breast disease, also known as cystic mastitis, unresponsive to medical therapy). Procedures include mastopexy, insertion of breast prostheses, the use of tissue expanders, or reconstruction with a transverse rectus abdominis myocutaneous (TRAM) flap, deep inferior epigastric perforator (DIEP) flap, or similar procedure. Leeds CCGs also consider associated nipple and areolar reconstruction and tattooing of the nipple area medically necessary. Reduction (or some cases augmentation) mammoplasty and related reconstructive procedures on the unaffected side for symmetry are also considered medically necessary.

Background

Breast reconstruction using autologous tissue is most commonly performed using the transverse rectus abdominis myocutaneous (TRAM) flap. This flap has been in use for 20 years and has provided excellent aesthetic results. However, a drawback of the TRAM flap is related to donor site morbidity of the abdomen. The pedicle TRAM flap frequently requires use of the entire rectus abdominis muscle, while the free TRAM flap requires use of as little as a postage-stamp size portion of the muscle. Abdominal complications resulting from a sacrifice of all or a portion of the rectus abdominis muscle include a reduction in abdominal strength (10 to 50 %), abdominal bulge (5 to 20 %), and hernia (less than 5 %).

Perforator flaps have gained increasing attention with the realization that the muscle component of the TRAM flap does not add to the quality of the reconstruction and serves only as a carrier for the blood supply to the flap. Thus, the concept of separating the flap (skin, fat, artery, and vein) from the muscle was realized as a means of minimizing the morbidity related to the abdominal wall and maintaining the aesthetic quality of the reconstruction. The deep inferior epigastric perforator (DIEP) flap was introduced in the early 1990's and is identical to the free TRAM flap except that it contains no muscle or fascia. Use of this flap has been popular in the Europe for a number of years.

Deep inferior epigastric perforator flaps tend to have less robust blood flow than is typical with a standard TRAM reconstruction, so careful patient selection is important. In patients who are non-smokers, who require no more than 70 % of the TRAM flap skin paddle to make a breast of adequate size, and who have at least 1 perforating vessel greater than 1-mm in diameter with a detectable pulse, the incidence of flap complications reportedly is similar to that seen in standard free TRAM flap reconstruction.

Superior gluteal artery perforator (SGAP) flaps may be performed on women who are not candidates for a TRAM flap or who have had a failed TRAM flap. Thin women who may not have much tissue in the lower abdominal area often have an adequate amount of tissue in the gluteal region. The inferior gluteal artery perforator (SGAP) flap shares the same indications as the superior gluteal flap, namely the inability to use the TRAM flap and an abundance of soft tissue in the gluteal region.

Poland syndrome is an extremely rare developmental disorder that is present at birth (congenital). It is characterized by absence (agenesis) or under-development (hypoplasia) of certain muscles of the chest (e.g., pectoralis major, pectoralis minor, and/or other nearby muscles), and abnormally short, webbed fingers (symbrachydactyly). Additional findings may include underdevelopment or absence of 1 nipple (including the darkened area around the nipple [areola]) and/or patchy hair growth under the arm (axilla). In females, 1 breast may also be under-developed (hypoplastic) or absent (amastia). In some cases, affected individuals may also exhibit under-developed upper ribs and/or an abnormally short arm with under-developed forearm bones (i.e., ulna and radius) on the affected side. In most cases, physical abnormalities are confined to one side of the body (unilateral). In approximately 75 % of the cases, the right side of the body is affected. The range and severity of symptoms may vary from case to case. The exact cause of Poland syndrome is not known.

Autologous fat grafting (or lipomodeling) uses the patient's own fat cells to replace volume after breast reconstruction, or to fill defects in the breast following breast-conserving surgery (NICE, 2012). It can be used on its own or as an adjunct to other reconstruction techniques. The procedure aims to restore

breast volume and contour without the morbidity of other reconstruction techniques. With the patient under general or local anesthesia, fat is harvested by aspiration with a syringe and cannula, commonly from the abdomen, outer thigh or flank. The fat is usually washed and centrifuged before being injected into the breast. Patients subsequently undergo repeat treatments (typically 2 to 4 sessions) (NICE, 2012). Autologous fat grafting may be delayed for a variable period of time after mastectomy. Most of the evidence for the use of autologous fat grafting in breast reconstruction is as a technique to repair contour defects and deformities. There is less information about the use of autologous fat grafting for complete breast reconstruction.

Guidance from the National Institute for Health and Clinical Excellence (NICE, 2012) states that current evidence on the efficacy of breast reconstruction using lipomodelling after breast cancer treatment is adequate and the evidence raises no major safety concerns. The guidance noted that there is a theoretical concern about any possible influence of the procedure on recurrence of breast cancer in the long term, although there is no evidence of this in published reports. The guidance notes that a degree of fat resorption is common in the first 6 months and there have been concerns that it may make future mammographic images more difficult to interpret.

A technology assessment on autologous fat injection for breast reconstruction prepared for the Australian and New Zealand Horizon Scanning Network (Humphreys, 2008) found that the technique has the potential to improve some contour defects; however, the results appear to be highly variable, with 2 case series finding that following autologous fat injection between 21 % and 86.5 % of patients showed substantial improvement at post-operative assessment. Patient satisfaction with the procedure was not reported. The assessment stated that longer-term follow-up is needed to determine how much of the injected fat survives and how much is eventually re-absorbed by the body. There are also important safety issues with the procedure, especially in association with the lipo-necrotic lumps that can form in the breast from the injected fat. Both case series reported this to occur in approximately 7 % of cases, and there is concern that such lumps will impede future cancer detection.

Hyakusoku et al (2009) reported several cases of complications following fat grafting to the breast. These investigators retrospectively reviewed 12 patients who had received autologous fat grafts to the breast and required breast surgery and/or reconstruction to repair the damage presenting between 2001 and 2007. All 12 patients (mean age of 39.3 years) had received fat injections to the breast for augmentation mammaplasty for cosmetic purposes. They presented with palpable indurations, 3 with pain, 1 with infection, 1 with abnormal breast discharge, and 1 with lymphadenopathy. Four cases had abnormalities on breast cancer screening. All patients underwent mammography, computed tomography, and magnetic resonance imaging to evaluate the injected fats. The authors concluded that autologous fat grafting to the breast is not a simple procedure and should be performed by well-trained and skilled surgeons. Patients should be informed that it is associated with a risk of calcification, multiple cyst formation, and indurations, and that breast cancer screens will always detect abnormalities. Patients should also be followed-up over the long-term and imaging analyses (e.g., mammography, echography, computed tomography, and magnetic resonance imaging) should be performed.

The American Society of Plastic Surgeons (ASPS) fat grafting task force (Gutowski, 2009) concluded that autologous fat grafting is a promising and clinically relevant research topic. The current fat grafting literature is limited primarily to case studies, leaving a tremendous need for high-quality clinical studies.

Mizuno and Hyakusoku (2010) stated that recent technical advances in fat grafting and the development of surgical devices such as liposuction cannulae have made fat grafting a relatively safe and effective procedure. However, guidelines issued by the ASPS in 2009 announced that fat grafting to the breast is not a strongly recommended procedure, as there are limited scientific data on the safety and efficacy of this particular type of fat transfer. Recent progress by several groups has revealed that multi-potent adult stem cells are present in human adipose tissue. This cell population, termed adipose-derived stem cells (ADSC), represents a promising approach to future cell-based therapies, such as tissue engineering and regeneration. In fact, several reports have shown that ADSC play a pivotal role in graft survival through both adipogenesis and angiogenesis. Although tissue augmentation by fat grafting does have several advantages in that it is a non-invasive procedure and results in minimal scarring, it is essential that such a procedure be supported by

evidence-based medicine and that further research is conducted to ensure that fat grafting is a safe and effective procedure.

Acellular dermal matrices are considered a standard-of-care as an adjunct to breast reconstruction. The clinical literature on acellular dermal matrix product in breast reconstruction primarily consists of single institution case series focusing on surgical technique. Much of the early literature focused on AlloDerm brand of acellular dermal matrix, since this product was first to market, but more recent literature has considered other acellular dermal matrix products. Recent literature has provided comparisons of AlloDerm to certain other acellular dermal matrix products, with the authors concluding that there is no significant difference among products (see, e.g., Ibrahim, et al., 2013; Cheng, et al., 2012). While different acellular dermal matrix products are processed differently, these appear to result in minor differences in performance in breast reconstruction.

Llewellyn-Bennett et al (2012) noted that latissimus dorsi (LD) flap procedures comprise 50 % of breast reconstructions in the United Kingdom. They are frequently complicated by seroma formation. In a randomized study, these researchers investigated the effect of fibrin sealant (Tisseel(®)) on total seroma volumes from the breast, axilla and back (donor site) after LD breast reconstruction. Secondary outcomes were specific back seroma volumes together with incidence and severity of wound complications. Consecutive women undergoing implant-assisted or extended autologous LD flap reconstruction were randomized to either standard care or application of fibrin sealant to the donor-site chest wall. All participants were blinded for the study duration but assessors were only partially blinded. Non-parametric methods were used for analysis. A total of 107 women were included (sealant = 54, control = 53). Overall, back seroma volumes were high, with no significant differences between control and sealant groups over 3 months. Fibrin sealant failed to reduce in-situ back drainage volumes in the 10 days after surgery, and did not affect the rate or volume of seromas following drain removal. The authors concluded that the findings of this randomized study, which was powered for size effect, failed to show any benefit from fibrin sealant in minimizing back seromas after LD procedures.

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Appendix E: Reduction Mammoplasty (excluding gynaecomastia)

Leeds CCGs consider breast reduction surgery cosmetic unless breast hypertrophy is causing significant pain, paraesthesias, or ulceration (see selection criteria below).

Leeds CCGs consider breast reduction surgery medically necessary for non-cosmetic indications for women aged 18 or older or for whom growth is complete when the following criteria are met, and only after trying conservative measures including specialist bra fitting prior to consideration of surgery:

Macromastia

All of the following criteria must be met:

General:

- The patient must be a confirmed non-smoker[3]. AND
- Photographic evidence of the condition is required by the IFR panel – only photographs taken by medical photography will be accepted AND
- BMI less than 30 and stable for 12 months AND
- Estimated removal of 500g of breast tissue AND
- Patient has at least one of the following:
- Chronic pain in cervical or upper thoracic spine without other acute precipitating factors.
- Chronic pain in shoulders and over trapezius muscle
- Headaches not related to other cause
- Ache with cervical stoop & associated kyphosis documented by X-rays
- Pain / discomfort / ulceration from bra straps cutting into shoulders

AND

- Pain symptoms persist as documented by the GP despite at least a 3-month trial of therapeutic measures such as:
- Supportive devices – patient has sought a professional fitting (e.g., proper bra support, wide bra straps)
- Analgesic / non-steroidal anti-inflammatory drugs (NSAIDs and or Paracetamol) interventions

Background

Reduction Mammoplasty

Reduction mammoplasty is among the most commonly performed cosmetic procedures in the UK.Reduction mammoplasty performed solely for cosmetic indications is considered not medically necessary.

Reduction mammoplasty has also been used for relief of pain in the back, neck and shoulders. Because reduction mammoplasty may be used for both medically necessary and cosmetic indications, Leeds CCGs have highlighted the above objective criteria to distinguish medically necessary reduction mammoplasty from cosmetic reduction mammoplasty.

Reduction mammoplasty has been performed to relieve back and shoulder pain on the theory that reducing breast weight will relieve this pain. For pain interventions, evidence of effectiveness from well controlled, randomised prospective clinical trials assessing effects on pain, disability, and function is limited. Well designed trials are especially important in assessing pain management interventions to isolate the contribution of the intervention from placebo effects, the effects of other concurrently

[3] This applies to flap based procedures specifically and is in line with plastic surgery literature: abdominoplasty, panniculectomy, breast reduction, mastopexy.

administered pain management interventions, and the natural history of the medical condition. Because of their inherently subjective nature, pain symptoms are especially prone to placebo effects.

In the case of reduction mammoplasty for relief of back, neck and shoulder pain, Leeds CCGs have considered this procedure medically necessary in women with excessively large breasts because it seems logical, even in the absence of firm clinical trial evidence, that this excessive weight would contribute to back and shoulder pain, and that removal of this excessive breast tissue would provide substantial pain relief, reductions in disability, and improvements in function.

The goal of medically necessary breast reduction surgery is to relieve symptoms of pain and disability. If an insufficient amount of breast tissue is removed, the surgery is less likely to be successful in relieving pain and any related symptoms from excessive breast weight (e.g., excoriations, rash). It has been argued that reduction mammoplasty may be indicated in any woman who suffers from back and shoulder pain, regardless of how small her breasts are or how little tissue is to be removed (ASPS, 2002). The suggestion is that removal of even a few hundred grams of breast tissue can result in substantial pain relief. However, this evidence comes from observational studies (Chadbourne, et al., 2001; Kerrigan, et al., 2001). These studies did not find a relationship between breast weight or amount of breast tissue removed and the likelihood of response or magnitude of relief of pain after reduction mammoplasty. It is not clear that breast weight would substantially contribute to back, neck and shoulder pain in women with normal or small breasts. Nor is it likely that removal of smaller amounts of breast tissue would offer significant relief of back, shoulder or neck pain. The lack of an expected "dose-response" relationship between the amount of breast tissue removed and the magnitude of symptomatic relief in these studies raises questions about the validity of these studies and the effectiveness of breast reduction as a method of relieving shoulder and back pain.

The studies used to support the arguments for the medical necessity of breast reduction surgery are poorly controlled and therefore subject to a substantial risk of bias in the interpretation of results. Well-designed, prospective, controlled clinical studies have not been performed to assess the effectiveness of surgical removal of modest amounts of breast tissue in reducing neck, shoulder, and back pain and related disability in women. In addition, reduction mammoplasty needs to be compared with other established methods of relieving back, neck and shoulder pain.

Consequently there is insufficient evidence to support the use of reduction mammoplasty, without regard to the size of the breasts or amount of breast tissue to be removed, as a method of relieving chronic back, neck, or shoulder pain.

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Smoking references

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APPENDIX F: Gynaecomastia Surgery

NHS Leeds will fund surgery for Gynaecomastia where the following criteria apply

Primary eligibility criteria:

- BMI must be 25 or less and stable for 12 months, unless a specific uncorrectable aetiological factor is identified such as androgen therapy for prostate cancer. However BMI should be 30 or less in these cases. AND
- the patient must be a confirmed non-smoker4. AND
- Photographic evidence of the condition is required by the IFR panel – only photographs taken by medical photography will be accepted AND
- In suspected idiopathic gynaecomastia a period of at least 12-24 months has been given to allow time for natural resolution before referral for surgery. Failure of resolution after 2-years is a reasonable time after which conservative treatment is unlikely to be associated with natural resolution and surgery can be considered.

Requests *will be rejected* prior to panel where these primary eligibility criteria are not met, unless there are very clear grounds for exception.

Other criteria considered

- Resection should be for Simon grade 2B or above (grade 2B is moderate breast enlargement with minor skin redundancy, grade 3 is gross breast enlargement with skin redundancy that simulates a pendulous female breast
- Should be for true gynaecomastia and not pseudo-gynaecomastia
- Conservative treatments have been considered, tried or have been unsuccessful
- Is causing significant patient distress through the presence of an obvious unilateral lump, abnormal appearance visible through clothing or because of pain (specifically related to the gynaecomastia) that has failed to respond to analgesia.
- Caused by a side effect of treatment of another condition such as a side effect of treatment for prostate cancer.
- The presence of unilateral gynaecomastia or marked asymmetry

Leeds CCGs will not support gynaecomastia surgery where there is evidence of on going or recurrent use of recreational drugs or anabolic steroids.

Male patients who have lost significant weight- refer to appendix A.

Background

Gynaecomastia Surgery

Gynaecomastia is common and may be asymptomatic. This disorder can lead to significant psychological stress and self-consciousness. In most cases, a thorough history and physical examination, along with limited laboratory investigations, can help to exclude breast malignancy and serious underlying endocrine or systemic disease. Careful clinical observation may be all that is required in many cases, because gynaecomastia often resolves spontaneously. Because gynecomastia is usually caused by an imbalance of androgenic and estrogenic effects on the breast, medical therapy may include antiestrogens, androgens, or aromatase inhibitors. Surgery is useful in the management of patients with long-standing symptomatic gynecomastia or when medical therapy is not successful.

[4] This applies to flap based procedures specifically and is in line with plastic surgery literature: abdominoplasty, panniculectomy, breast reduction, mastopexy.

Gynaecomastia may have an extrinsic cause in up to 39% of cases. Of the suspected idiopathic cases, some will be found to have an important aetiology, such as a testicular carcinoma. Selected endocrinological investigation is important.

Patients who are on medication that may cause gynaecomastia may not always be able to have that medication stopped. Furthermore, withdrawal of the medication may not always be associated with resolution of the gynaecomastia. There are at least 69 drugs that are known to be associatied with gynaecomastia.

Treatments for painful or embarrassing gynaecomastia include an anti-oestrogen, such as tamoxifen (unlicensed indication), or surgery (liposuction or mammoplasty). However, although idiopathic gynecomastia is highly prevalent with hundred of millions of affected men, unfortunately, there is no proven medical therapy for this condition and the quality of the research using medications is very poor. As an example, the best publications available, for tamoxifen include only 332 individuals and of those only 10 (<3%) were studied in randomized trials.

The clinical classification of gynaecomastia, developed by Simon et al is the most commonly used classification and helps to understand the surgical correction of gynaecomastia. This classification is based on the extent of breast enlargement and the presence or absence of excess skin:

- Grade 1: minor breast enlargement with no excess skin;
- Grade 2A: moderate breast enlargement with no excess skin;
- Grade 2B: moderate breast enlargement with excess skin;
- Grade 3: marked breast enlargement with excess skin.

Patients with grades 1 and 2A gynaecomastia require no skin excision, but glandular excision alone. The breast development associated with grades 2B and 3 is so marked that excess skin must be removed. Although this classification is not applicable to the surgical management of men with breast cancer and gynaecomastia, it allows important management decisions to be made for the surgical correction of gynaecomastia.

An alternative classification, relates to the position of the nipple-areola complex: when the nipple-areola complex is above the inframammary fold (grade I and grade II gynaecomastia), complete flattening of the thorax can be achieved by means of suction or ultrasound-assisted lipectomy and skin-sparing adenectomy. When the nipple-areola complex is at the same height as, or at most 1cm below the fold (grade III gynaecomastia), skin-sparing techniques are no longer sufficient to flatten the thorax, and it becomes necessary to remove the redundant skin by means of periareolar removal of epidermis. In cases of marked ptosis, when the nipple-areola complex is more than 1cm below the fold (grade IV gynaecomastia), reduction mastoplasty becomes necessary, with upper repositioning of the nipple-areola complex; in these cases central pedicle techniques make it possible to limit scarring in the periareolar area.

Surgical excision is justified where the breast specialist has assessed the patient and recommended such an approach. Such a decision may be based on many factors. They include the rare concern that there may be an underlying male breast cancer. Cancer phobia is not uncommon in this regard. Conventional treatment of the complaint of an unresolving male breast lump remains surgical excision, and most patients may be discharged subsequently with out the need for further follow-up.

In addition, there will remain a need for this procedure in patients who have had funded treatment for morbid obesity who achieve massive weight loss where there are functional or significant psychological problems associated with such weight loss. The male breast, a body-region that symbolizes manhood and strength and often remaining as a deflated skin-envelope, is one of the most disturbing body regions, causing extreme lack of confidence in post-weight-loss patients.

Surgical excision allows evaluation of the entire tissue component such that cancerous or precancerous lesions may be identified, which although rare,continue to be reported.

The increased use of antiandrogens as monotherapy for prostate cancer is leading to an increase in the number of patients affected by gynaecomastia, and surgical excision is likely to be the most appropriate treatment where assessed as such by a breast specialist.

In cases of idiopathic gynaecomastia that do not resolve after a period of 12-24 months, acceptable resolution has been achieved with surgical excision. Surgery should only be carried out by and after review by a specialist with specific experience in this condition to recuce the potential risk of unsatisfactory surgical results.

Men under the age of 25-years should predominantly be managed conservatively as the majority of such cases resolve.

The above framework is based on the following references:

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2. Chan LK, Withey S, Butler PE. Smoking and wound healing problems in reduction mammaplasty: is the introduction of urine nicotine testing justified? Ann Plast Surg. 2006 Feb;56(2):111-5.
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Appendix G: Benign Skin Lesion Removal (also refer to Appendix H)

Leeds CCGs consider removal of seborrheic keratoses, sebaceous cysts, naevi (moles) or skin tags and warts cosmetic unless the one of the following criteria are met:

- There is documented evidence of inflammation, e.g., purulence, edema, erythema over at least 3 months not responding to conservative treatment; AND the patient has a Dermatology Life Quality Index score of over 10.
- Due to its anatomic location, the lesion has been subject to recurrent trauma; or
- The lesion restricts vision or obstructs a body orifice; or
- Lesion appears to be dysplastic or malignant (due to coloration, change in appearance or size, etc., especially in a person with dysplastic nevus syndrome, history of melanoma, or family history of melanoma);
- Biopsy suggests or is indicative of premalignancy (e.g., dysplasia) or malignancy.

The removal of warts in non immuno-compromised patients is considered cosmetic and patients should be encouraged to seek self care.

Removal of Xanthelasma is considered cosmetic.

Background

Seborrheic keratoses are non-cancerous growths of the outer layer of skin. They are usually brown, but can vary in colour from beige to black, and vary in size from a fraction of an inch to more than an inch in diameter. They have the appearance of being glued or stuck on to skin. Seborrheic keratoses are most often found on the chest or back, although, they can also be found almost anywhere on the body. These become more common with age, and most elderly patients develop one or more of these lesions. Seborrheic keratoses can get irritated by clothing rubbing against them, and their removal may be medically necessary if they itch, get irritated, or bleed easily. Although seborrheic keratoses are non-cancerous, they may be difficult to distinguish from skin cancer if they turn black. Seborrheic keratoses may be removed by cryosurgery, curettage, or electrosurgery.

Moles (naevi) can appear anywhere on the skin. They are usually brown in colour, but can be skin coloured or pink, light tan to brown, or blue-black. Moles may be flat or raised and can be various sizes and shapes. Most appear during the first 20 years of a person's life, although some may not appear until later in life. Sun exposure increases the number of moles. The majority of moles are benign. However, moles that raise suspicion of malignancy are those that change in size, shape or colour, and those that bleed, itch, or become painful. Atypical moles (dysplastic naevi) have an increased risk of developing into melanoma. Atypical moles are larger than average (greater than 6 mm) and irregular in shape. They tend to have uneven colour with dark brown centres and lighter, sometimes reddish, uneven borders or black dots at edge. The most common methods of removal include shaving and excision.

A sebaceous (keratinous) cyst is a slow-growing, benign cyst that contains follicular, keratinous, and sebaceous material. The sebaceous cyst is firm, globular, movable, and non-tender. These cysts seldom cause discomfort unless the cyst ruptures or becomes infected. Ranging in size, sebaceous cysts are usually found on the scalp, face, ears, and genitals. They are formed when the release of sebum from the sebaceous glands in the skin is blocked. Unless they become infected and painful or large, sebaceous cysts do not require medical attention or treatment, and usually go away on their own. Infected cysts can be incised and drained, or the entire cyst may be surgically removed.

A skin tag (arochordon) is a benign, soft, moveable, skin-coloured growth that hangs from the surface of the skin on a thin piece of tissue called a stalk. The prevalence of skin tags increases with age. They appear most often in skin folds of the neck, armpits, trunk, beneath the breasts or in the genital region. They are painless, but may become painful if thrombosed or if irritated. They may become irritated if they occur in an area where clothing or jewellery rubs against them. Skin tags may be removed by excision, cryosurgery, or electrosurgery.

Many people suffer from warts. Incidence figures estimated from the fourth National Morbidity Survey (1991–2) suggest that almost 2 million people in England and Wales see their GP per year about this condition, at a cost of at least £40 million per annum. Cryotherapy delivered by a doctor is an expensive option for the treatment of warts in primary care. Alternative options such as GP-prescribed SA and nurse-led cryotherapy clinics provide more cost-effective alternatives, but are still expensive compared with self-treatment.

Given the minor nature of most cutaneous warts, coupled with the fact that the majority spontaneously resolve in time a shift towards self-treatment is warranted.

The above framework is based on the following references:

1. American Academy of Dermatology (AAD). Seborrheic keratoses. Patient Information. Schaumburg, IL: AAD; 1997.
2. American Academy of Dermatology (AAD). Moles. Patient Information. Schaumburg, IL: AAD; 1987.
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Appendix H: Pulsed Dye Laser Treatment and Electrolysis (also refer to Appendix G)

NHS Leeds CCGs consider pulsed dye laser treatment medically necessary for any of the following conditions:

Laser treatable naevi (congenital and late onset) or genetically determined skin tumours at all skin sites

- in children
- in adults with a Dermatology Life Quality Index (DLQI) >10 to include:

- Vascular and lymphatic malformations and tumours
- Epidermal, melanocytic and skin appendage naevi and tumours (including hairy naevi, syringomata, trichoepitheliomata, neurofibromas)
- Connective tissue naevi and tumours
- All naevoid lesions that cause either functional problems (such as bleeding, pain, or secondary infection) and/or significant psychosocial problems due to disfigurement throughout life. Many naevi and genetically determined tumours develop in late childhood or early adult life and many will undergo changes throughout life which result in increasing disfigurement and/or functional problems.
- Lesions at all skin sites cause significant psychosocial problems due to disfigurement. Lesions are unavoidably exposed when wearing minimal clothing for common place activities such as sport and swimming and in hot weather. It is unreasonable to assume that lesions other than on the face are not visible both in adults and children. The need to wear restrictive clothing at all times to cover disfiguring lesions on non-facial sites is a significant impairment of quality of life and cause of psychosocial morbidity.

Severe telangiectasia where visible at conversational distance and causing disfigurement sufficient to score 10 or more on Dermatology Life Quality Index (DLQI) and limited to 4 treatments at each affected skin site to include:

- Telangiectasia associated with chronic inflammatory dermatoses (including rosacea, rhynophyma, lupus erythematosus, scleroderma, granuloma faciale, sarcoidosis and chronic radiation dermatitis).
- Extensive or severe telangiectasia as seen in progressive ascending arborising telangiectasia and essential telangiectasia.
- Telangiectasia associated with severe scarring as seen following large surgical wounds and burns.
- Spider angiomas in children
- Telangiectasia of all types generally will respond to four treatments to each affected site. The number of treatments offered to each skin site will therefore be restricted to four.

Abnormal hair growth or hair associated with scarring inflammatory disorders to include:

- Facial hirsutism in women affecting the face only where visible at a conversational distance and causing disfigurement sufficient to score 10 or more on Dermatology Life Quality Index (DLQI) (limited to a maximum of 2 test sessions and 3 treatment sessions to affected areas which may be by laser or electrolysis) (for women who have completed a transgender male-to-female transition, this treatment will be funded in addition to any previous facial hair treatments from NHE England, and the Leeds CCGs standard criteria and number of treatment sessions for facial hirsutism will apply)
- Hypertrichosis secondary to metabolic disorders (such as rorphyria) or drug therapy (such as ciclosporin or androgenic medications)
- Scarring folliculitis including pilonidal sinus disease where recommended by a specialist clinician

- Inflammatory or infiltrated dermatoses unresponsive to alternative therapy to include:
  - Localised severe psoriasis or eczema
  - Extensive xanthomata
  - Amyloidosis

Iatrogenic or traumatic tattoos or tattoos associated with allergic reactions to tattoo ink to include:

- Tattoos placed for radiotherapy
- Tattoos secondary to inadequate wound cleansing from abrasions, fires and explosions.

Symptomatic viral warts associated with immunodeficiency states.

*Leeds CCGs consider laser treatment for the following to be experimenta*l because of insufficient evidence in the peer-reviewed literature *and therefore will not be funded:*

- Atopic dermatitis
- Lichen sclerosus
- Morphea (scleroderma of the skin)
- Mycosis fungoides
- Onychomycosis
- Prurigo nodularis
- Vulval intraepithelial neoplasia.

Leeds CCGs consider the following to be cosmetic and therefore treatment will not be funded:

*Minor telangiectasia or minor acquired vascular lesions in adults which are asymptomatic to include***:**

- Minor forms of telangiectasia not visible at conversational distance or insufficient to score 10 or more on DLQI.
- Spider Angiomas in adults
- Cherry angiomas or Campell de Morgan spots
- Telangiectasia of legs due to or associated with varicose veins

Hair growth

- Facial hirsutism in women not visible when shaved at a conversational distance or insufficient to score 10 or more on DLQI or where the affected area has received 3 or more previous laser or Intense pulsed light (IPL) treatments.
- Hirsutism in women at non-facial sites
- Hypertrichosis unrelated to metabolic disorders or medication
- Hair growth in men not associated with scarring folliculitis

Scarring

- Scars resulting from minor surgery
- Acne scarring

Decorative tattoos

Asymptomatic viral warts or viral warts in the absence of an immunodeficiency state.

Rosacea including mild to moderate telangiectasia & rhinophyma (severe telangiectasia and severe rhinophyma may be considered an exception: Leeds CCGs may approve funding following provision of a photograph and DLQI score)

Photoaging changes to include:

- Skin wrinkling or textural changes
- Solar lentigines
- Xanthelasma

Pigmented non pathological changes including:

- Vitiligo
- Chloasma
- Melasma
- Post burns pigmentation

The above framework is based on the following references:

1. Kenton-Smith J, Tan ST. Pulsed dye laser therapy for viral warts. Br J Plast Surg. 1999;52(7):554-558.
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Appendix I: Septo-rhinoplasty and Rhinoplasty

Leeds CCGs consider septo-rhinoplasty medically necessary when any of the following clinical criteria is met:

- Septal deviation causing continuous nasal airway obstruction resulting in nasal breathing difficulty associated with a bony deviation of the nose, where an operation on the nasal septum would not be effective in restoring the nasal airway without a simultaneous operation to straighten the nasal bones.
- Asymptomatic nasal deformity that prevents access to other intranasal areas when such access is required to perform medical necessary surgical procedures (e.g., ethmoidectomy); or when done in association with cleft palate repair.

Leeds CCGs consider rhinoplasty to correct the appearance of the external nose a cosmetic surgical procedure.

Rhinoplasty may be considered medically necessary only in the following limited circumstances:

- When it is being performed to correct a nasal deformity secondary to congenital cleft lip and/or palate
- Upon individual case review, to correct chronic non-septal nasal airway obstruction from vestibular stenosis (collapsed internal valves) due to trauma, disease, or congenital defect, when all of the following criteria are met:
  - Nasal airway obstruction is causing significant symptoms (e.g., chronic rhinosinusitis, difficulty breathing), and
  - Photos demonstrate an external nasal deformity, and
  - There is an average 50 % or greater obstruction of nares (e.g., 50 % obstruction of both nares, or 75 % obstruction of one nare and 25 % obstruction of other nare, or 100 % obstruction of one nare), documented by internal inspection of the nose by an ENT surgeon, endoscopy, CT scan or other appropriate imaging modality, and
  - Obstructive symptoms persist despite conservative management for three months or greater, which includes, where appropriate, nasal steroids; and
  - Airway obstruction will not respond to septoplasty and turbinectomy alone

Documentation of these criteria should include:

- If there is an external nasal deformity, preoperative photographs showing the standard 4-way view – base of nose, anterior posterior (AP), and right and left lateral views; and
- Relevant history of accidental or surgical trauma, congenital defect, or disease (e.g., Wegener's granulomatosis, choanal atresia, nasal malignancy, abscess, septal infection with saddle deformity, or congenital deformity); and
- Documentation of duration and degree of symptoms related to nasal obstruction, such as chronic rhinosinusitis, mouth breathing, etc.; and
- Documentation of results of conservative management of symptoms

Leeds CCGs consider rhinoplasty cosmetic for all other indications.

The above framework is based on the following references:

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Appendix J: Blepharoplasty

Leeds CCGs consider Blepharoplasty is medically necessary for the following indications:

- To remove excess tissue of the upper eyelid causing functional visual impairment when photographs in straight gaze show eyelid tissue resting on or pushing down on the eye lashes (Note: Excess tissue beneath the eye rarely obstructs vision, so the lower lid blepharoplasty is rarely supported for this indication.)
- To correct prosthesis difficulties in an anophthalmia socket
- To repair defects predisposing to corneal or conjunctival irritation:
  - entropion (eyelid turned inward)
  - pseudotrichiasis (inward misdirection of eyelashes caused by entropion)
  - ectropion (eyelid turned outward)
  - corneal exposure
  - to treat periorbital sequelae of thyroid disease and nerve palsy
  - to relieve painful symptoms of blepharospasm
- Ptosis (blepharoptosis) repair for laxity of the muscles of the upper eyelid causing functional visual impairment when photographs in straight gaze show the eyelid margin across the midline or at the most 1 or 2 mm above the midline of the pupil.
- Brow ptosis repair for laxity of the forehead muscles causing functional visual impairment when photographs show the eyebrow below the supraorbital rim.

Congenital ptosis

Leeds CCGs consider surgical correction of congenital ptosis medically necessary to allow proper visual development and prevent amblyopia in infants and children with moderate to severe ptosis interfering with vision. Surgery is considered cosmetic if performed for mild ptosis that is only of cosmetic concern. Photographs must be available for review to document that the skin or upper eyelid margin obstructs a portion of the pupil.

Background

Blepharoplasty refers to surgery to remove excess skin and fatty tissue around the eyes. Blepharochalasis is a term used to refer to loose or baggy skin (dermatochalasis) above the eyes, so that a fold of skin hangs down, often concealing the tarsal margin when the eye is open. In severe cases, excess skin and fat above the eyes can sit on the upper eyelid and may obstruct the superior field of vision. Blepharochalasis may cause pseudoptosis (false ptosis), where the patient has a normal ability to elevate the eyelid, but bagging skin above the eye overhangs the eyelid margin, resembling ptosis. In some cases, excess skin around the eye may cause the eyelashes to turn in and to irritate the eye, or turn outward, resulting in exposure keratitis.

Surgical removal of these overhanging skin folds may improve the function of the upper eyelid and restore peripheral vision. Blepharoplasty is also performed for cosmetic reasons to improve a sagging, tired appearance, and is the second most common aesthetic procedure performed by plastic surgeons. For coverage of this procedure, photographs in straight gaze should show sagging tissue above the eyes that is resting on or pushing down on the eyelashes.

Blepharoplasty to remove excess tissue either above or below the eyes may also be medically necessary and covered to correct prosthesis difficulties in an anophthalmia socket, to repair defects caused by trauma or tumor-ablative surgery, to correct an entropion (inward turned eyelid) or extropion (outward turned eyelid), to treat periorbital sequelae of thyroid disease and nerve palsy, and to relieve painful blepharospasm.

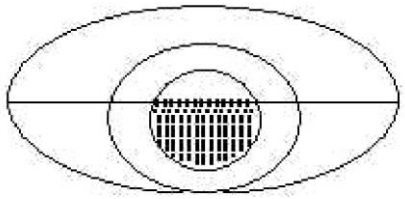
Ptosis (also called blepharoptosis) is the term for drooping of one or both upper eyelids. This may occur in varying degrees from slight drooping to complete closure of the involved eyelid. In the most severe cases, the drooping can obstruct the visual field and cause positional head changes. There are two types of ptosis, acquired and congenital. Acquired ptosis is more common. Congenital ptosis is present at birth. Ptosis may occur because the levator muscle's attachment to the lid is weakening with age. Acquired ptosis can also be caused by a number of different things, such as disease that impairs the nerves, diabetes, injury, tumours, inflammation, or aneurysms. Congenital ptosis may be caused by a problem with nerve innervation or a weak muscle. Drooping eyelids may also be the result of diseases such as myotonic dystrophy or myasthenia gravis.

The primary symptom of ptosis is a drooping eyelid. Adults will notice a loss of visual field because the upper portion of the eye is covered. Children who are born with a ptosis usually tilt their head back in an effort to see under the obstruction. Some people raise their eyebrows in order to lift the lid slightly and therefore may appear to be frowning.

Diagnosis of ptosis is usually made by observing the drooping eyelid. Ptosis is usually treated surgically. For minor drooping, a small amount of the eyelid tissue can be removed. For more pronounced ptosis the approach is to surgically shorten the levator muscle or connect the lid to the muscles of the eyebrow. Or, the aponeurosis can be reattached to the tarsal plate if it had separated. Correcting the ptosis is usually done only after determining the cause of the condition.

Ptosis (blepharoptosis) repair for laxity of the muscles of the upper eyelid causing functional visual impairment is covered when photographs in straight gaze show the eyelid margin across the midline or at the most 1 or 2 mm above the midline of the pupil (see Figure).

Figure: Diagram of upper lid margin crossing the pupil



Brow ptosis refers to sagging tissue of the eyebrows and/or forehead. In extreme cases, brow ptosis can obstruct the field of vision. Brow ptosis is caused by aging changes in the forehead muscle and skin, which leads to weakening of these tissues and sagging of the eyebrows. Brow ptosis is treated surgically with the specific operation being based on the amount and location of the brow ptosis.

Often brow ptosis coexists with eyelid ptosis and dermatochalasis; in these cases, ptosis surgery and blepharoplasty may be performed at the time of the brow ptosis surgery. The medical necessity of each surgical procedure may need to be demonstrated with separate photographs: one photograph should show the eyebrow below the supraorbital rim, a second photograph with the sagging forehead lifted up in order to see the sagging tissue above the eye resting on the eyelashes, and then a third with the sagging tissue lifted off of the eyelid in order to see the persistent lid lag (ptosis).

Visual field testing is not necessary to determine the presence of excess upper eyelid skin, upper eyelid ptosis, or brow ptosis. A patient could cause a visual field defect by lowering their lids during the test. Photographs that document eyelids crossing the pupils provide a practical indication for the need of surgery.

If visual field tests are performed, the tests should show loss of two-thirds or greater of a visual field in the upper or temporal areas documented by computerised visual field studies, with visual field restored by taping or holding up the upper lid.

The above framework is based on the following references:

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Appendix K: Botulinum Toxin

NHS Leeds CCG consider botulinum toxin botulinum toxin Type A medically necessary for the following treatments:

a. Strabismus, including gaze palsies accompanying diseases, such as:
   i. Neuromyelitis optica;
   ii. Schilder's disease.

Note: Strabismus repair is considered cosmetic in adults with uncorrected congenital strabismus and no binocular fusion.

b Blepharospasm, characterized by intermittent or sustained closure of the eyelids caused by involuntary contractions of the orbicularis oculi muscle.

c. Post-facial (7th cranial) nerve palsy synkinesis (hemifacial spasms), characterized by sudden, unilateral, synchronous contractions of muscles innervated by the facial nerve.

d. Laryngeal spasm.

e. Cervical dystonia (spasmodic torticollis) of moderate or greater severity when all of the following criteria are met:
   i. There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles); and
   ii. There is sustained head torsion and/or tilt with limited range of motion in the neck; and
   iii. The duration of the condition is greater than 6 months; and
   iv. Alternative causes of the member's symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures, or other neuromuscular disorders.

f. Focal dystonias, including:
   i. Adductor laryngeal dystonia;
   ii. Focal dystonias in corticobasilar degeneration;
   iii. Hand dystonia (i.e., organic writers cramp);
   iv. Jaw-closing oromandibular dystonia, characterized by dystonic movements involving the jaw, tongue, and lower facial muscles;
   v. Lingual dystonia;
   vi. Symptomatic torsion dystonia (but not lumbar torsion dystonia).

g. Limb spasticity, including:
   i. Equinus varus deformity in children with cerebral palsy
   ii. Hereditary spastic paraplegia;
   iii. Limb spasticity due to multiple sclerosis;
   iv. Limb spasticity due to other demyelinating diseases of the central nervous system (including adductor spasticity and pain control in children undergoing adductor-lengthening surgery as well as children with upper extremity spasticity);
   v. Spastic hemiplegia, such as due to stroke or brain injury.

h. Oesophageal achalasia, for individuals who have any of the following:
   i. Are at high risk of complications of pneumatic dilation or surgical myotomy; or
   ii. Have failed conventional therapy; or
   iii. Have failed a prior myotomy or dilation; or
   iv. Have had a previous dilation-induced perforation; or
   v. Have an epiphrenic diverticulum or hiatal hernia, both of which increase the risk of dilation-induced perforation.

i. Chronic anal fissure unresponsive to conservative therapeutic measures (e.g., nitroglycerin ointment).

j. Intractable, disabling focal primary hyperhydrosis, when all of the following are met:
   i. unresponsive or unable to tolerate pharmacotherapy prescribed for excessive sweating (e.g., anticholinergics, beta-blockers, or benzodiazepines) if sweating is episodic; and
   ii. Significant disruption of professional and/or social life has occurred because of excessive sweating; and
   iii. Topical aluminum chloride or other extra-strength antiperspirants are ineffective or result in a severe rash.

k. Ptyalism/sialorrhea (excessive secretion of saliva, drooling) that is socially debilitating and refractory to pharmacotherapy (including anticholinergics).

l. Facial myokymia and trismus associated with post-radiation myokymia.

m. Hirschsprung's disease with internal sphincter achalasia following endorectal pull-through.

n. Medically refractory upper extremity tremor that interferes with activities of daily living (ADLs). (Additional botulinum toxin injections are considered medically necessary if response to a trial of botulinum toxin enables ADLs or communication).

o Detrusor-sphincter dyssynergia after spinal cord injury.

p. Neurogenic detrusor overactivity.

Migraines – is covered by NICE guidance and also the Targetted Interventions Policy.

Leeds CCGs consider botulinum toxin Type B (rimabotuninumtoxinB) medically necessary for the treatment of any of the following conditions:

a. Individuals with cervical dystonia (spasmodic torticollis) of moderate or greater severity when the following criteria are met:

- Alternative causes of the patient's symptoms have been considered and ruled out, including chronic neuroleptic treatment, contractures; or other neuromuscular disorders ; *and*
- There is sustained head torsion and/or tilt with limited range of motion in the neck; *and*
- The duration of the condition is greater than 6 months; *and*
- There are clonic and/or tonic involuntary contractions of multiple neck muscles (e.g., sternocleidomastoid, splenius, trapezius and/or posterior cervical muscles.

b. Ptyalism/sialorrhea (excessive secretion of saliva, drooling) that is socially debilitating and refractory to pharmacotherapy (including anticholinergics).

c. Intractable, disabling focal primary hyperhydrosis, when all of the following are met:

- Patient is unresponsive or unable to tolerate pharmacotherapy prescribed for excessive sweating (e.g., anticholinergics, beta-blockers, or benzodiazepines) if sweating is episodic; and
- Significant disruption of professional and/or social life has occurred because of excessive sweating; and
- Topical aluminum chloride or other extra-strength antiperspirants are ineffective or result in a severe rash.

Leeds CCGs consider botulinum toxin (types A or type B) *experimental and investigational* for all other indications and does not routinely commission it, including for any of the following conditions:

1) Anal sphincter dysfunction; or
2) Bell's palsy; or
3) Benign prostatic hypertrophy; or
4) Biliary dyskinesia; or
5) Brachial plexus injury (also known as brachial palsy in newborns and Erb's palsy); or
6) Bruxism; or
7) Chronic constipation; or
8) Chronic low back pain; or
9) Chronic neck pain; or
10) Chronic pelvic pain; or
11) Clenched fist syndrome; or
12) Clubfoot; or
13) Complex regional pain syndrome; or
14) Congenital hypertonia; or
15) Cranial/facial pain of unknown etiology; or
16) Cricopharyngeal/oropharyngeal dysphagia; or
17) Depression; or
18) Detrusor-sphincter dyssynergia associated with multiple sclerosis; or
19) Diabetic neuropathic pain; or
20) Dyspareunia; or
21) Dsyphagia; or
22) Esophageal stricture; or
23) Fibromyositis; or
24) Focal lower limb dystonia; or
25) Gastroparesis; or
26) Graves ophthalmopathy; or
27) Gustatory sweating; or
28) Head and voice tremor; or
29) Headache (non-migraine), including cervicogenic, cluster, or tension-type or chronic daily headache; or
30) Hyper-lacrimation; or
31) Injection of the pylorus during esophago-gastrectomy; or
32) Interstitial cystitis; or
33) Irritable colon; or
34) Intra-operative relaxation of the anal sphincter during hemorrhoidectomy; or
35) Keratoconjunctivitis; or
36) Knee flexion contracture; or
37) Lateral epicondylitis (tennis elbow); or
38) Lumbar torsion dystonia; or
39) Motor tics; or
40) Myofascial pain; or
41) Obturator internus syndrome; or
42) Orofacial tardive dyskinesia; or
43) Pain from muscle trigger points; or
44) Painful cramps; or
45) Palatal myoclonus; or
46) Parotitis; or
47) Pelvic floor tension myalgia (also known as coccygodynia, diaphragma pelvis spastica, levator ani syndrome, levator spasm syndrome, spastic and pelvic floor syndrome), or
48) Phantom limb pain; or
49) Phonic tics; or
50) Piriformis syndrome; or
51) Post-hemorrhoidectomy pain; or
52) Post-herpetic neuralgia; or
53) Pudendal neuralgia; or
54) Pylorospasm; or
55) Raynaud's phenomenon/Raynaud's scleroderma; or

56) Reduction of mucin secretion; or
57) Restless legs syndrome; or
58) Schwalbe-Ziehen-Oppenheim disease; or
59) Shoulder pain; or
60) Sciatica; or
61) Scoliosis; or
62) Soto's syndrome; or
63) Spasm of the pectoralis muscle after breast reconstruction; or
64) Sphincter of Oddi dysfunction (chronic biliary pain); or
65) Stiff person syndrome; or
66) Stuttering; or
67) Temporomandibular joint disorders; or
68) Tendon contracture; or
69) Thoracic outlet syndrome; or
70) Tinnitus; or
71) Tourette's syndrome; or
72) Ulcers.

Leeds CCG consider botulinum toxin purely cosmetic for the following indications:

a. Aging neck; *or*
b. Blepharoplasty (eyelid lift); *or*
c. Wrinkles, frown lines.

Background

Local injections of botulinum toxin have been approved by the FDA for the treatment of strabismus, essential blepharospasm, and hemifacial spasm. In patients with congenital strabismus who have compromised or absent binocular vision, treatment is cosmetic as ocular realignment is not capable of restoring binocular vision.

Clinical studies indicate that botulinum toxin can also provide symptomatic relief in a variety of other conditions characterized by involuntary spasm of certain muscle groups, notably in cervical dystonia (spasmodic torticollis) and spasmodic dysphonia. Ninety percent of spasmodic torticollis patients show some improvement of pain relief, head position, and disability, and botulinum toxin is now the treatment of choice for this condition. botulinum toxin has been shown to result in normal or near normal voice in patients with adductor type (strained or strangled voice) laryngeal dystonia and to be of considerable benefit in patients with abductor type (breathy, whispery voice) laryngeal dystonia.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that while botulinum neurotoxin is probably effective for the treatment of adductor type laryngeal dystonia, there is insufficient evidence to support a conclusion of effectiveness for botulinum neurotoxin in patients with abductor type of laryngeal dystonia. The assessment also stated that while many clinicians utilize electromyographic targeting for laryngeal injections, the utility of this technique is not established in comparative trials.

Botulinum toxin has been evaluated in various spastic disorders. botulinum toxin can be used to reduce spasticity or excessive muscular contractions to relieve pain; to assist in posturing and walking; to allow better range of motion; to permit better physical therapy; and to reduce severe spasm in order to provide adequate perineal hygiene. It has been shown to improve gait patterns in patients with cerebral palsy with progressive dynamic equinovarus or equinovalgus foot deformities. Treatment of children with cerebral palsy during the early years when functional skills in walking are being developed improves the outcome and may help to avoid surgery for contracture and bony torsion. In multiple sclerosis, botulinum toxin can relieve contractions of thigh adductors that interfere with sitting, positioning, cleaning, and urethral catheterization.

Moore, et al. (2008) stated that the controlled evidence favouring botulinum toxin in the treatment for spasticity in cerebral palsy (CP) is based on short-term studies. These researchers conducted a randomized, double-blind, placebo-controlled, parallel-group study of botulinum toxin for leg

spasticity in 64 children with CP. For 2 years, the children received trial injections of up to 30 mu/kg every 3 months if clinically indicated. For the primary endpoints of Gross Motor Function Measure (GMFM) and Paediatric Evaluation of Disability Index (PEDI) scaled scores at 2 years (trough rather than peak effect), there were no differences between the mean change scores of each group. For the GMFM total score, the 95% CI of -4.81 to 1.90 excluded a 5-point difference in either direction, or a 2-point benefit with 95% confidence. There were no differences in adverse events. The authors concluded that there was no evidence of cumulative or persisting benefit from repeated botulinum toxin at the injection cycle troughs at 1 year or 2 years. The dose was not enough to change spasticity measures and thus GMFM in this heterogeneous group. Ceiling effects in GMFM and PEDI may have reduced responsiveness. This finding does not deny the value, individually, of single injection cycles or prove that repeating them is unhelpful. In this regard, botulinum toxin therapy can be viewed in the same light as other temporary measures to relieve spasticity, such as oral or intra-thecal agents: there is no evidence of continuing benefit if the treatment ceases. The study provided long-term, fully controlled adverse event data and has not revealed any long-term adverse effects.

Treatment with botulinum toxin has been shown to be safe and effective in the jaw-closing variant of oromandibular dystonia. Injections of botulinum toxin into the masseter, temporalis, and internal pterygoid muscles result in reduction in the oromandibular and lingual spasms and an improvement in chewing and speech.

Symptoms are reduced in about 70% of patients, and treatment may prevent dental complications and temporomandibular joint dysfunction. Treatment with botulinum toxin has been shown to be safe and effective for writer's cramp (local and segmental limb dystonia). This dystonia can be incapacitating and has been exceptionally resistant to treatment with oral medications. Other occupational cramps, such as musician’s cramp, respond less well to injections as they require very sophisticated neuromuscular performance.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Naumann, et al., 2008) stated that while many clinicians advocate electromyography or nerve stimulation guidance to optimize needle localization for injection, further data are needed to establish this recommendation.

Botulinum toxin has also been shown to be effective in the treatment of achalasia. Two thirds of patients with this condition respond within six months and effectiveness lasts on an average of a little over one year for an initial treatment, although shorter and longer duration have been reported. There is some question whether botulinum toxin treatments are as good as or better than conventional therapy, pneumatic dilation, or myotomy.

Botulinum toxin has been shown to be a promising alternative to sphincterotomy in patients with chronic anal fissures.

Some autonomic disorders resulting in hypersecretion of glands such as hyperhydrosis and sialism (ptyalism) respond well to botulinum toxin.

Initial reports on the use of botulinum toxin in the treatment of migraine headache are promising; however, limitations of the placebo-controlled randomized trials include the lack of a dose-response curve and the lack of a scientific explanation for the treatment effect. These initial results require further validation to confirm the effectiveness of botulinum toxin in migraine prophylaxis.

Although there is a randomized controlled single-center study that found benefits of botulinum toxin in the treatment of migraine, no firm conclusions can be drawn from this study because of the marginal statistical significance of the results, the lack of an expected dose-response relationship, and the lack of a valid scientific explanation for treatment effects. In a randomized double-blind, vehicle-controlled study, 123 subjects with a history of two to eight moderate-to-severe migraine attacks per month were randomized to receive single administration of placebo vehicle or botulinum toxin A 25 or 75 U, injected into multiple sites of pericranial muscles at the same visit. Study subjects were assessed at 1, 2 and 3 months. For the 25-U botulinum toxin group, reduction in migraine frequency barely reached statistical significance ($p = 0.46$) at the 3-month assessment, but did not reach statistical significance at the 1- or 2-month assessments. The 75-U botulinum toxin group had no statistically significant reduction in migraine frequency at any assessment (Silberstein, et al., 2000). A commentary on this

study (Bandolier, 2001) noted that, because of significant flaws in the design of the study by Silberstein, et al., "[t]he trial would score 2 out of a possible 5 points on a common quality scoring scale in which trials scoring 2 or less may be subject to bias." The commentary also noted the marginal statistical significance of results and the lack of an expected dose-response relationship. "The simple fact is that with one or two patients giving different responses, this would have been declared a negative trial. It does not inspire confidence, especially as this is the only randomised controlled trial for this intervention in this indication and the quality of reporting allows for the possibility of bias, as well as it being financed by the manufacturer." These results need to be replicated in a longer-term, multicenter randomized clinical study before conclusions about the effectiveness of botulinum toxin in migraine can be drawn.

A subsequent randomized controlled clinical trial found no benefit to botulinum toxin type A in preventing migraine headaches (Evers, et al., 2004). Researchers evaluated 60 migraine patients for a three-month period; participants received injections of either a high or low dose of botulinum toxin or placebo in muscles in the neck and/or forehead. During the course of the study, “migraine frequency was halved” for 30% of the participants in the botulinum toxin groups and for 25% of those in the placebo group. Researchers also found that there were “no significant differences” among the three groups regarding the number of days participants had the migraine or the amount of drugs needed to treat the headaches. The researchers concluded that their findings “did not support the hypothesis that [botulinum toxin] is [an] effective...treatment [for] migraines.” Phase III clinical trials of botulinum toxin (botulinum toxin) for FDA approval of a migraine indication are ongoing.

A study by Dodick, et al. (2005) presented a secondary analysis of data from a randomized controlled clinical trial of botulinum toxin A in the treatment of chronic daily headache, examining outcomes for a subgroup of subjects who were not receiving prophylactic medications. This was a secondary analysis of data from a study in which the overall cohort had no significant benefit from botulinum toxin (Mathew, et al., 2005). In addition, the largest study of botulinum toxin for chronic daily headache showed no overall benefit (Silberstein, et al., 2005) (see below). These inconsistent results among studies lead the American Academy of Neurology to conclude that there is insufficient evidence to support or refute a benefit of botulinum toxin for chronic daily headache (Naumann, et al., 2008).

In a phase II clinical trial (n = 702), Silberstein, et al. (2005) assessed the safety and effectiveness of three different doses of botulinum toxin as prophylactic treatment of chronic daily headache (CDH). Eligible patients were injected with botulinum toxin at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in the frequency of headache-free days at day 180 for the placebo non-responder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed in the placebo non-responder group treated with botulinum toxin at 225 U, 150 U, 75 U, or placebo, respectively ($p = 0.44$). An a priori-defined analysis of headache frequency revealed that botulinum toxin at 225 U or 150 U had significantly greater least squares mean changes from baseline than placebo at day 240 (-8.4, -8.6, and -6.4, respectively; $p = 0.03$ analysis of covariance). Only 27 of 702 patients (3.8%) withdrew from the study because of adverse events, which generally were transient and mild to moderate. These investigators concluded that although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240. The placebo response was higher than expected. botulinum toxin type A was safe and well tolerated. The authors noted that further study of botulinum toxin prophylactic treatment of CDH appears warranted. The findings of this study were in agreement with those of Mathews, et al. (2005). A review in Clinical Evidence (Silver, 2005) concluded that botulinum toxin for chronic tension-type headache was “likely to be ineffective or harmful.”

An assessment on use of botulinum toxin in pain associated with neuromuscular disorders, prepared for the Minnesota Health Technology Advisory Committee (2001), concluded that there is insufficient evidence to support the use of botulinum toxin in the treatment of migraine. A review of the literature on treatments for migraine concluded that "botulinum toxin A ha[s] recently been suggested to be effective [for treatment of migraine]; however, at present, there are insufficient rigorous and reliable controlled data on these drugs for them to be indicated for such use" (Krymchantowski, et al., 2002). A structured evidence review by the BlueCross BlueShield Association Technology Evaluation

Centre (2002) concluded “The available evidence does not permit conclusions regarding the prophylactic or abortive effect of [botulinum toxin A] or any other botulinum toxin type on chronic primary headache syndromes”, including migraine, chronic tension, and cluster headache syndromes. The BlueCross BlueShield Association Technology Evaluation Centre reevaluated the use of botulinum toxin for primary headache disorders (BCBSA, 2004) and concluded that this does not meet the TEC criteria.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann, et al., 2008) stated that botulinum neurotoxin is probably ineffective in episodic migraine and chronic tension-type headache. Also, there is currently no consistent evidence or strong evidence to allow drawing conclusions on the effectiveness of botulinum neurotoxin in chronic daily headache. The assessment also noted that the evidence for botulinum neurotoxin in gustatory sweating is suboptimal.

In a meta-analysis, Shuhendler, et al. (2009) evaluated the effectiveness of botulinum toxin type A in lowering the frequency of migraine headaches in patients with episodic migraines. A total of 1601 patients with a history of episodic migraine headaches classified as those experiencing headaches fewer than 15 times/month over a 3-month period were included in the analysis. PubMed, Google Scholar, and the Cochrane Library were searched from inception to October 2007 in order to locate randomized, double-blind, placebo-controlled trials that compared the effectiveness of peri-cranial botulinum toxin A injections with placebo in the prevention of migraines in patients with a history of episodic migraine headaches. The primary outcome of interest was change from baseline to end point in migraine frequency (number of migraines/month). A random effects model was used to combine study results, and the standardized mean difference (Cohen's d) in migraine frequency between the placebo and botulinum toxin A groups was reported. Effect sizes (d) less than 0.2 were considered small. Quality assessment was performed by using the Downs and Black scale. Eight randomized, double-blind, placebo-controlled clinical trials (1601 patients) presented a quantitative assessment of the effectiveness of botulinum toxin A versus placebo. The overall treatment effect size of botulinum toxin A over placebo for 30, 60, and 90 days after injection was d -0.06 (95 % confidence interval [CI] - 0.14 to 0.03, z = 1.33, p = 0.18), d -0.05 (95 % CI -0.14 to 0.03, z = 1.22, p = 0.22), and d -0.05 (95 % CI -0.13 to 0.04, z = 1.07, p = 0.28), respectively. Even after controlling for a high placebo effect, and after dose stratification, no significant effect of botulinum toxin A in reducing migraine frequency/month was seen over placebo. The authors concluded that botulinum toxin A for the prophylactic treatment of episodic migraine headaches was not significantly different from placebo, both from a clinical and statistical perspective.

Magalhães et al (2010) compared the effects of botulinum toxin with those of amitriptyline on the treatment of chronic daily migraines. Chronic migraine sufferers were randomized into two groups and treated with 25 or 50 mg/day of amitriptyline or 250 U of botulinum toxin. A reduction of at least 50 % in the number of pain episodes, in the intensity of pain, and in the number of drug doses for pain and reports of improvement by the patient or by the examiner were the main end points. A total of 72 subjects were enrolled in the study. A reduction of at least 50 % in the number of days of pain was recorded in 67.8 % of the patients in the botulinum toxin group and 72 % (n = 23) of the patients in the amitriptyline group (p = 0.78; RR = 0.94; CI = 0.11 to 8). The reduction in the intensity of pain, as assessed using the VAS, was 50 % in the botulinum toxin group and 55.6 % in the amitriptyline group (p = 0.79; RR = 1.11; CI = 0.32 to 3.8). The reduction in the number of pain drug doses was 77 % for the botulinum toxin group and 71 % for the amitriptyline group (p = 0.76; RR = 0.92; CI = 0.45 to 1.88). The authors concluded that botulinum toxin was as effective as amitriptyline for the prophylactic treatment of chronic daily migraines.

Aurora and colleagues (2010) evaluated the safety, effectiveness, and tolerability of botulinum toxin as headache prophylaxis in adults with chronic migraine. The Phase III REsearch Evaluating Migraine Prophylaxis Therapy 1 (PREEMPT 1) is a phase III study, with a 24-week, double-blind, parallel-group, placebo-controlled phase followed by a 32-week, open-label phase. Subjects were randomized (1:1) to injections every 12 weeks of botulinum toxin (155 U to 195 U; n = 341) or placebo (n = 338) (2 cycles). The primary end point was mean change from baseline in headache episode frequency at week 24. No significant between-group difference for botulinum toxin versus placebo was observed for the primary end point, headache episodes (-5.2 versus -5.3; p = 0.344). Large within-group decreases from baseline were observed for all efficacy variables. Significant between-group differences for botulinum toxin were observed for the secondary end points,

headache days (p = 0.006) and migraine days (p = 0.002). Botulinum toxin was safe and well-tolerated, with few treatment-related adverse events. Few subjects discontinued due to adverse events. The authors concluded that there was no between-group difference for the primary end point, headache episodes. However, significant reductions from baseline were observed for botulinum toxin for headache and migraine days, cumulative hours of headache on headache days and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling chronic migraine.

Dodick et al (2010) evaluated the efficacy, safety, and tolerability of botulinum toxin as headache prophylaxis in adults with chronic migraine. The 2 multi-centre, pivotal trials in the PREEMPT clinical program each included a 24-week randomized, double-blind phase followed by a 32-week open-label phase. Qualified patients were randomized (1:1) to botulinum toxin (155 U to 195 U) or placebo injections every 12 weeks. Study visits occurred every 4 weeks. These studies were identical in design (e.g., inclusion/exclusion criteria, randomization, visits, double-blind phase, open-label phase, safety assessments, treatment), with the only exception being the designation of the primary and secondary endpoints. Thus, the pre-defined pooling of the results was justified and performed to provide a complete overview of between-group differences in efficacy, safety, and tolerability that may not have been evident in individual studies. The primary end point for the pooled analysis was mean change from baseline in frequency of headache days at 24 weeks. Secondary end points were mean change from baseline to week 24 in frequency of migraine/probable migraine days, frequency of moderate/severe headache days, total cumulative hours of headache on headache days, frequency of headache episodes, frequency of migraine/probable migraine episodes, frequency of acute headache pain medication intakes, and the proportion of patients with severe (greater than or equal to 60) Headache Impact Test-6 score at week 24. A total of 1,384 adults were randomized to botulinum toxin (n = 688) or placebo (n = 696). Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favouring botulinum toxin over placebo at week 24 (-8.4 versus -6.6; p < 0.001) and at all other time points. Significant differences favouring botulinum toxin were also observed for all secondary efficacy variables at all time points, with the exception of frequency of acute headache pain medication intakes. Adverse events occurred in 62.4 % of botulinum toxin patients and 51.7 % of placebo patients. Most patients reported adverse events that were mild-to-moderate in severity and few discontinued (botulinum toxin, 3.8 %; placebo, 1.2 %) due to adverse events. No unexpected treatment-related adverse events were identified. The authors concluded that the pooled PREEMPT results demonstrate that botulinum toxin is an effective prophylactic treatment for chronic migraine. Botulinum toxin A resulted in significant improvements compared with placebo in multiple headache symptom measures, and significantly reduced headache-related disability and improved functioning, vitality, and overall health-related quality of life. Repeat treatments with botulinum toxin were safe and well-tolerated.

Cady (2010) stated that botulinum toxin has been studied as a migraine preventive in numerous clinical trials and in a variety of sub-populations with migraine. Overall, results from the clinical trials are mixed. However, the largest and most recent parallel studies (n = 1,330) conducted on subjects with chronic migraine achieved statistically significant efficacy on numerous end points including the primary end point of reduction of headache days. The author reviewed several clinical studies using botulinum toxin in migraine prevention and highlighted some of the inherent difficulties defining study end points and outcomes that are relevant to clinician, patients, and regulatory agencies. The author concluded that clinical trials utilizing botulinum toxin as a preventive therapy for migraine has revealed mixed results. In part this reflects the inherent difficulties in study design such as defining different sub-populations of migraine sufferers and trial end points that are meaningful to patient populations. Recent studies of subjects with chronic migraine appear to have positive results. If confirmed this would be the first preventive medication indicated specifically for chronic migraine.

In October 2010, the FDA approved botulinum toxin injection to prevent headaches in adult patients with chronic migraine (more than 14 days per month with headaches lasting 4 hours a day or longer). To treat chronic migraines, botulinum toxin is given approximately every 12 weeks as multiple injections -- a total of 31 injections into 7 specific head and neck sites for a total of 155 U per treatment session. Botulinum toxin has not been shown to work for the treatment of migraine headaches that occur 14 days or less per month, or for other forms of headache. The most common adverse reactions reported by patients being treated for chronic migraine were neck pain and headache.

Botulinum toxin has been shown to reduce muscle tone and increase range of movement in upper extremity spasticity or in spastic foot drop after stroke. However, whether this translates into functional improvement has yet to be substantiated.

The value of otulinum toxin in treating conditions other than those listed above is under investigation.b

If concomitant neuromuscular disorders, such as myasthenia gravis and certain myopathies exist, botulinum toxin may be harmful. Thus, diagnosis is crucial before undertaking botulinum toxin type A injections.

Botulinum toxin is not indicated in patients receiving aminoglycosides, which may interfere with neuromuscular transmission.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of spasticity (Simpson, et al., 2008a) recommended botulinum neurotoxin as a treatment option to reduce muscle tone and improve passive function in adults with spasticity. The assessment also recommended botulinum neurotoxin for equinus varus deformity in children with cerebral palsy, adductor spasticity and pain control in children undergoing adductor-lengthening surgery, and children with upper extremity spasticity. Furthermore, the assessment stated that there is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. It noted that further studies on injection methodology including the use of electromyographic guidance, ultrasonography, and electrical stimulation are needed to optimize treatment technique.

Both botulinum toxin A and B are neurotoxins produced by fermentation of the bacterium Clostridium botulinum. They interfere with neuromuscular transmission, temporarily paralyzing the affected muscle. Clostridium botulinum is a gram-positive, spore-forming obligate anaerobe that is widely distributed in nature and frequently found in soil, marine environments, and agricultural products. Each strain produces one of eight antigenically distinct toxins designated A through H. Human disease is caused by types A, B, E, and (rarely) F. After repeated use of high doses, antibodies can develop in some individuals, making further treatment ineffective indefinitely.
The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that the role of electromyography has not been established for cervical dystonia. It also stated that while a few patients in one Class II study suggested that botulinum neurotoxin may be effective for lower extremity dystonia, the data are inadequate to provide a recommendation A randomized controlled clinical trial (n = 16) demonstrated significant reductions in sialorrhea without compromising dysphagia in persons with Parkinson’s disease and problematic sialorrhea (Ondo, et al., 2004).

Baumann, et al. (2005) reported on the results of a pilot study of botulinum toxin for axillary hyperhidrosis. Twenty patients were randomly assigned to botulinum toxin (n = 15) or to placebo injection (n = 5). The investigators explained that this trial was initially conceived as a placebo-controlled study; however, owing to the insufficient size of the placebo group (one placebo subject failed to return for follow up and one responded to placebo injections), the placebo arm of this trial was dropped during data analysis. The investigators reported a significant difference in subject and physician assessed measures of treatment response at one month in the participants receiving botulinum toxin injections. Duration of action ranged from 2.2 to 8.1 months (mean 5.0 months).

Nelson, et al. (2005) reported on the results of botulinum toxin injections in 13 patients with axillary hyperhidrosis. The investigators reported a significant reduction in hyperhidrosis at 4-week, 8-week, and 12-week follow-up compared to baseline.

Baumann and Halem (2004) reported on a randomized controlled clinical study of botulinum toxin in palmar hyperhidrosis. Twenty persons with hyperhidrosis were randomly assigned to injection with botulinum toxin (n = 15) or placebo (n = 5). The investigators reported a significant difference in treatment response (as determined by participant assessment) between the subjects injected with botulinum toxin and placebo. The duration of cessation of palmar sweating ranged from 2.3 months to 4.9 months, with a mean duration of 3.8 months. The investigators reported, however, that 18 of 20 participants reported dry mouth/throat, 60% reported indigestion/heartburn, 60% reported muscle weakness, and 50% reported decreased grip strength. The investigators concluded that botulinum

toxin was safe and effective in treating bilateral palmar hyperhidrosis. However, the side effect profile was substantial.

A number of studies have evaluated the effectiveness of botulinum toxin in the treatment of back and neck pain, and the manufacturer is planning on pursuing FDA approval of botulinum toxin for this indication. Two small double blind studies (Foster, et al., 2000; Foster, et al., 2001) of botulinum toxin for back pain have been published, one involving 28 patients, and another involving 31 patients. However, both of these studies were small and from a single investigator, raising questions about the generalization of the findings. In addition, both of the studies were short term, with no comparisons to other treatments for back pain. Thus, there is currently insufficient scientific evidence of the effectiveness of botulinum toxin in the treatment of back pain.

According to a systematic review of the evidence for botulinum toxin for essential tremor (Ferreira & Sampaio, 2003), there is evidence of short-term reduction of tremor but no consistent improvement in disability and function. The review noted that botulinum toxin injections cause hand weakness, resulting in a "trade off" between benefits and harms. The review concluded that "RCTs [randomized controlled clinical trials] comparing botulinum A toxin-haemagglutinin complex versus placebo found short term improvement of clinical rating scales, but no consistent improvement of motor task performance or functional disability. Hand weakness, which is dose dependent and transient, is a frequent adverse effect." The American Academy of Neurology (Zesiewicz, et al,, 2005) has stated that botulinum toxin A injections for limb, head, and voice tremor associated with essential tremor may be considered in medically refractory cases. This recommendation was categorized as Level C, given the limited strength of the available evidence. The American Academy of Neurology concluded that “[t]he effect of BTX A [botulinum toxin A] on limb tremor in ET [essential tremor] is modest and is associated with dose-dependent hand weakness. BTX A may reduce head tremor and voice tremor associated with ET, but data are limited. When used to treat voice tremor, BTX A may cause breathiness, hoarseness, and swallowing difficulties.”

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson et al, 2008b) stated that botulinum neurotoxin should be considered a treatment option for essential hand tremor in those patients who fail treatment with oral agents. On the other hand, there is insufficient evidence to draw a conclusion on the use of botulinum neurotoxin in the treatment of head and voice tremor.

The evidence of botulinum toxin in the treatment of piriformis syndrome is limited to a small, controlled short-term study and a small pilot cross-over study reporting on the impact of botulinum toxin on pain, but not on disability and function (Fishman, et al., 2002; Childers, et al., 2002). In addition, the placebo-controlled study had a significant drop-out rate. The existence of piriformis syndrome as a clinical entity is controversial (NHS, 2002).

Several studies have tested the effects of pyloric injection of botulinum toxin in patients with diabetic and idiopathic gastroparesis (Parkman, et al., 2004). These studies have all been unblinded with small numbers of patients from single centers and have observed mild improvements in gastric emptying and modest reductions in symptoms for several months. Moreover, the American Gastroenterological Association (2004) has concluded that double-blind controlled studies are needed to support the efficacy of this treatment (Parkman, et al., 2004).

Bromer, et al. (2005) reviewed the use of botulinum toxin in the treatment of patients with gastroparesis. Response was defined as improvement or resolution of the patient's major symptom and/or two minor symptoms for 4 weeks. Of 115 patients treated, 63 patients met the study criteria. There were 53 women, 10 men, mean age 42 years. Most patients (56%) had idiopathic gastroparesis. Twenty-seven of 63 (43%) patients experienced a symptomatic response to treatment. By stepwise logistic regression, male gender was associated with response to treatment (OR 3.27: 95% CI[1.31, 8.13], p = 0.01). Vomiting as a major symptom was associated with a lack of response (OR 0.16: 95% CI[0.04, 0.67], p = 0.01). Despite the association of male gender with response, the mean duration of response for those patients responding, with a minimum of 3 months' follow-up was 4.9 months (+/- 2.7 months) for women and 3.5 months (+/- 0.71 months) for men (p = 0.59). The corresponding medians and inter-quartile ranges (IQR) were 5 (IQR 3 - 6) for females and 3.5 (IQR 3 - 4) for males. The authors concluded that of the patients, 43% had a response to botulinum toxin treatment that lasted a mean of approximately 5 months. Male gender

was associated with a response to this therapy; however, durability of response was unrelated to gender. Vomiting as a major symptom predicted no response. The major drawbacks of this study were: (i) it was a retrospective study, (ii) the lack of a validated symptom questionnaire or a visual analog scale before for pre- and post-injection estimation of improvement, (iii) subjects were not prescribed a standardized diet and/or medication regimen for gastroparesis following botulinum toxin injection, (iv) a high number of patients (n = 27) were lost to follow-up that may have influenced the response rate, (v) issues with experimental design -- selection bias as well as recall bias.

Ezzeddine, et al. (2002) reported their findings of pyloric injection of botulinum toxin for the treatment of diabetic gastroparesis. A total of 6 patients with diabetic gastroparesis and an abnormal solid phase gastric emptying study underwent upper endoscopy during which 100 units of botulinum toxin were injected into the pyloric sphincter. Gastric emptying studies were obtained at 48 hours and 6 weeks after injection. Patients were questioned about symptoms of gastroparesis, and a symptom score was obtained at baseline and at 2 weeks and 6 weeks after injection. There was a mean improvement in the subjective symptom score at 2 weeks of 55% (range of 14 to 80 %). This improvement was maintained at 6 weeks. There was a 52 % improvement in gastric emptying at 2 and 6 weeks. The authors concluded that pyloric injection of botulinum toxin can improve symptoms and gastric emptying in patients with diabetic gastroparesis. They stated that further evaluation of pyloric injection of botulinum toxin as a treatment for diabetic gastroparesis is warranted.

Gupta and Rao (2002) noted that well-designed, prospective, double-blinded, placebo-controlled studies are needed to establish the role of botulinum toxin in selected patients with diabetic gastroparesis.

Yeh and Triadafilopoulos (2006) reviewed injection therapies for non-bleeding disorders of the gastrointestinal tract. With regards to the use of botulinum toxin for the treatment of gastroparesis, the authors noted that data from a randomized, sham-controlled study are needed to draw firm conclusion on the utility of this treatment.

Reddymasu, et al. (2007) examined the use of endoscopic pyloric injection of botulinum toxin in the treatment of patients with post vagotomy gastroparesis (n = 11). The authors concluded that this approach appears to be safe; but randomized trials are needed.

Friedenberg and colleagues (2008) noted that observational data suggest that intra-pyloric injection of botulinum toxin reduces symptoms and accelerates gastric emptying in idiopathic and diabetic gastroparesis. These researchers examined if botulinum toxin would improve symptoms to a significantly greater extent than placebo. An additional objective was to ascertain if there is an acceleration of gastric emptying after injection. A single-institution, randomized, double-blind, placebo-controlled study was carried out. Eligible patients had a Gastroparesis Cardinal Symptom Index score greater than or equal to 27 with randomization to intra-pyloric botulinum toxin, 200 units, or saline placebo. Re-assessment of symptoms and repeat gastric emptying scan at 1-month follow-up were done. A total of 32 patients were randomized to botulinum toxin (n = 16) and placebo (n = 16). At 1-month follow-up, 37.5% randomized to botulinum toxin and 56.3% randomized to placebo achieved improvement as defined by this study. There were no identifiable clinical predictors of response. The botulinum toxin group reported improvement in gastric emptying; however, this was not superior to placebo. No serious adverse events were attributable to botulinum toxin. The authors concluded that intra-pyloric injection of botulinum toxin improves gastric emptying in patients with gastroparesis, although this benefit was not superior to placebo at 1 month. Also, in comparison to placebo, symptoms do not improve significantly by 1 month after injection. These investigators stated that they could not recommend botulinum toxin for widespread use in the treatment of delayed gastric emptying until more data are available.

Lembo and Camilleri (2003) do not recommend botulinum injection for the management of patients with chronic constipation. Furthermore, Talley (2004) stated that a novel approach for the management of chronic constipation is injection of botulinum toxin into the puborectalis muscle of patients with pelvic floor dysfunction. However, there is insufficient evidence to support the effectiveness of this approach.

Botulinum toxin is currently being studied for the management of patients with lower urinary tract dysfunctions such as detrusor-sphincter dyssynergia and detrusor overactivity. Botulinum toxin is injected into the external urethral sphincter to treat detrusor sphincter dyssynergia, while intra-detrusal injections of botulinum toxin is employed in treating detrusor overactivity and symptoms of the overactive bladder (OAB). In a single treatment, randomized, placebo-controlled study (n = 59), Schurch, et al., (2005) found that intramuscular injections of botulinum toxin into the detrusor can provide rapid, well-tolerated, clinically significant decreases in the signs and symptoms of urinary incontinence caused by neurogenic detrusor overactivity during a 24-week study period. These researchers noted that botulinum toxin is a potential candidate for the management of neurogenic urinary incontinence.

In a randomized, double-blind, placebo-controlled crossover clinical trial, Ghei and colleagues (2005) examined the safety and effectiveness of botulinum toxin for the treatment of OAB. A total of 20 patients 18 to 80 years old with detrusor overactivity unresponsive to oral anti-muscarinic agents participated in the study. They were injected with either placebo (20 ml normal saline) or botulinum toxin (5,000 IU diluted up to 20 ml) intravesically in a day case setting. After 6 weeks the treatments were crossed over without washout in line with previous findings. The primary outcome was the paired difference in change in average voided volumes. Frequency, incontinence episodes and paired differences in quality of life measured by the King's Health Questionnaire were the secondary outcome measures. Little carryover was noted in the second arm placebo and the placebo data from both arms were included in analysis. There were clinically statistically significant paired differences in the change in average voided volume, urinary frequency and episodes of incontinence between active treatment and placebo. There were similarly significant paired differences in the change in quality of life affecting 5 domains of the King's Health Questionnaire. These investigators concluded that the findings of this study provided evidence of the efficacy of rimabotuoinumtoxnB in the treatment of OAB. Autonomic side effects were observed in 4 patients. Moreover, they noted that the short duration of action will presumably limit the use to patients who have experienced tachyphylaxis with botulinum toxin.

In an editorial that accompanied the study by Ghei, et al., Chancellor (2005) stated that “one undesirable feature of the study was that the hypothesis was tested on a mixed population of patients (patients with mixed etiologies of detrusor overactivity, 3 neurogenic and 17 nonneurogenic with detrusor overactivity). This limits the generalizability of the findings. The authors made a strong argument why a crossover design was appropriate and their data were valid. However, since almost all studies have shown that botulinum toxin A has a duration of efficacy of approximately 6 months, most experts in the field would still question the merit of a crossover at 6 weeks as not all the patients returned to pre-injection clinical and urodynamic values done at 6 weeks. Most experts would submit that a washout period after the crossover may have been appropriate. Since there are limited experiences with BTX-B in the bladder, assessment of duration of response would be valuable”. Chancellor was surprised how short the duration of effectiveness attained by botulinum toxin was. Moreover, it is unclear how useful botulinum toxin will be in urology since there are suggestions that botulinum toxin has a more systemic effect that botulinum toxin.

In a multi-center, randomized, placebo-controlled trial (n = 86), Gallien, et al., (2005) assessed the safety and effectiveness of botulinum toxin in the treatment of detrusor sphincter dyssynergia in patients with multiple sclerosis (MS). Individuals with chronic urinary retention were included if they had post-voiding residual urine volume between 100 and 500 ml. They received a single transperineal injection of either botulinum toxin (100 U) or placebo in the sphincter and also 5 mg slow release alfuzosin twice daily over 4 months. Main endpoint was post-voiding residual urine volume assessed 1 month after injection. Follow-up duration was 4 months. The study was stopped after the 4th analysis (placebo = 41, botulinum toxin = 45). At inclusion, there was no significant difference between groups whichever variable was considered. Mean (standard deviation) post-voiding residual urine volume was 217 (96) and 220 (99) ml in placebo and botulinum toxin groups, respectively. One month later, post-voiding residual urine volume was 206 (145) and 186 (158) ml (p = 0.45) in placebo and botulinum toxin groups, respectively. However, compared to placebo, botulinum toxin significantly increased voiding volume (+54%, p = 0.02) and reduced pre-micturition (-29%, p = 0.02) and maximal (-21 %, p = 0.02) detrusor pressures. Other secondary urodynamic endpoints and tolerance were similar in the two groups. These investigators concluded that in MS patients with detrusor sphincter dyssynergia, a single injection of botulinum toxin (100 U) does not decrease post-voiding residual urine volume. Also, De Laet and Wyndaele (2005) noted that

generalized side effects after botulinum toxin injection for voiding disorders are rare but they can be very disabling for patients with spinal cord injury. Although no long-term side effects are reported so far, urologists should be aware that these effects of botulinum toxin injections are unknown.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann, et al., 2008) reported that botulinum neurotoxin is safe and effective for the treatment of neurogenic detrusor overactivity in adults. On the other hand, data on the use of botulinum neurotoxin for detrusor-sphincter dyssynergia (DSD) are conflicting. Botulinum neurotoxin is probably safe and effective for the treatment of DSD in patients with spinal cord injury and should be considered for use in these patients. However, it does not provide significant benefit for the treatment of DSD in patients with multiple sclerosis.

Other than detrusor-sphincter dyssynergia after spinal cord injury, the role of botulinum toxin in the treatment of lower urinary tract dysfunctions has yet to be established. Sahai, et al., (2005) stated that application of botulinum toxin in the lower urinary tract has produced promising results in treating lower urinary tract dysfunction, which needs further evaluation with randomized, placebo-controlled trials. This is in agreement with the observations of Schurch and Corcos (2005) as well as Grise, et al., (2005). Schurch and Corcos noted that botulinum toxin appears to be a reasonable alternative to surgery in the management of intractable OAB in children. However, studies of the delivery method, site of injection, dose and long-term follow-up are needed to confirm the good safety profile/clinical benefit of this new, minimally invasive approach. In a review on the use and mechanism of botulinum toxin in the treatment of OAB, Grise and colleagues stated that further studies remain necessary regarding the dosage of botulinum toxin, selection of patients, combination with anti-cholinergic treatment, as well as effects of repeated injections.

Chuang, et al. (2003) stated that botulinum toxin type A treatment inhibits afferent-nerve-mediated bladder contraction. This analgesic effect may expand the application of botulinum toxin type A in the localized genitourinary tract pain syndrome, such as interstitial cystitis and prostatodynia. The authors concluded that application of botulinum toxin type A is a promising treatment for lower urinary tract dysfunction with profound basic and clinical implications. Chancellor and Yoshimura (2004) noted that among the potentially effective new treatment modalities for interstitial cystitis currently under investigation are suplatast tosilate, resiniferatoxin, botulinum toxin, and gene therapy to modulate the pain response.

Kuo (2005) evaluated the clinical effectiveness of sub-urothelial injection of BTX-A in patients with chronic interstitial cystitis (n = 10). Eight women and 2 men with chronic interstitial cystitis who had failed conventional treatments were enrolled in this study. In 5 patients, 100 units of BTX-A was injected sub-urothelially into 20 sites, and an additional 100 units was injected into the trigone in the other 5 patients. Therapeutic outcome including functional bladder capacity, number of daily urinations, bladder pain, and urodynamic changes were compared between baseline and 3 months after treatment. In 2 patients bladder pain and urinary frequency were improved 3 months after treatment. Mild difficulty in urination was reported by 7 patients. Functional bladder capacity recorded in a voiding diary was significantly increased (155 +/26.3 versus. 77 +/- 27.1 ml, $p < 0.001$), and the frequency of daily urinations (18 +/- 7.7 versus. 24.2 +/- 10.3, $p = 0.025$) and the pain score (2.4 +/- 1.6 versus. 3.2 +/- 1.1, $p = 0.003$) were mildly but significantly reduced after treatment. Only the cystometric capacity improved significantly (287 +/- 115 versus. 210 +/- 63.8 ml, $p = 0.05$) in urodynamic results. Trigonal injection had no therapeutic effect on symptom or urodynamic improvement. No adverse effect was reported. The author concluded that the clinical result of sub-urothelial BTX-A injection was disappointing. None of the patients was symptom-free and only a limited improvement in bladder capacity and pain score was achieved in 2 patients.
Toft and Nording (2006) reviewed the recently published literature on intravesical therapy strategies in painful bladder syndrome/interstitial cystitis. Bladder irrigation with different agents has been used during years in an attempt to treat painful bladder syndrome/interstitial cystitis. The 'traditional' agent for glycosaminoglycan substitution is hyaluronic acid. Often used are heparin and dimethyl sulfoxide, the actions of which are not quite clear but supposedly on an anti-inflammatory basis. Other agents for intravesical treatment are Bacillus Calmette-Guerin vaccine and BTX, and some recent studies have pointed to resiniferatoxin and RDP58. The authors concluded that painful bladder syndrome/interstitial cystitis persists as a challenging syndrome in urology. Intravesical instillation therapy has basically not change during the last few years, although some studies have disconfirmed some regimens. Intensive research may hopefully result in more effective treatments in the future.

Shah, et al. (2005) described the development of a flexion contracture in a patient with Parkinson's disease after total knee arthroplasty. This contracture was successfully treated with manipulation under anesthesia and injections of BTX- A into the hamstring and gastrocnemius muscles, in conjunction with a static progressive extension orthosis and rigorous physical therapy. This was a case study; and the clinical benefit of BTX, if any, is confounded by the multiple therapies used in this patient.

In a prospective, double-blinded study, Stidham, et al. (2005) assessed the potential benefit BTX-A in the treatment of tinnitus. A total of 30 patients with tinnitus were randomly placed into 1 of 2 treatment arms. Patients either received BTX-A (20 to 50 units) or saline injection at the first treatment, and the opposite treatment 4 months later. Prospective data including tinnitus matching test, tinnitus handicap inventory (THI), tinnitus rating scale (TRS), and patient questionnaires were obtained over a 4-month period after each injection. Twenty-six patients completed both injections and follow-up and were included in data analysis. After BTX-A, subjective tinnitus changes included 7 patients improved, 3 worsened, and 16 unchanged. Following placebo, 2 patients were improved, 7 worsened, and 17 unchanged. Comparison of the treatment and placebo groups was statistically significant ($p < 0.005$) when including better, worse, and same effects. A significant decrease in THI scores between pretreatment and 4 month post-BTX-A injection ($p = 0.0422$) was recorded. None of the other comparisons of pre-treatment to 1 month, or pre-treatment to 4 months were significantly different. This study found improvement in THI scores and patient subjective results after BTX- A injection compared with placebo, suggesting a possible benefit of BTX- A in tinnitus management. The authors noted that larger studies need to be completed to further evaluate potential benefits of BTX- A in treatment of this difficult problem.

In a randomized, double-blind, placebo-controlled study (n = 60), Wong, et al. (2005) examined if an injection of BTX is more effective than placebo for reducing pain in adults with lateral epicondylitis (tennis elbow). The primary outcome was change in subjective pain as measured by a 100-mm visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain ever) at 4 weeks and 12 weeks. All patients completed posttreatment follow-up. Mean VAS scores for the BTX group at baseline and at 4 weeks were 65.5 mm and 25.3 mm, respectively; respective scores for the placebo group were 66.2 mm and 50.5 mm (between-group difference of changes, 24.4 mm [95% CI, 13.0 to 35.8 mm]; $p < 0.001$). At week 12, mean VAS scores were 23.5 mm for the BTX group and 43.5 mm for the placebo group (between-group difference of changes, 19.3 mm [CI, 5.6 to 32.9 mm]; $p = 0.006$). Grip strength was not statistically significantly different between groups at any time. Mild paresis of the fingers occurred in 4 patients in the BTX group at 4 weeks. One patient's symptoms persisted until week 12, whereas none of the patients receiving placebo had the same complaint. At 4 weeks, 10 patients in the BTX group and 6 patients in the placebo group experienced weak finger extension on the same side as the injection site. The study was small, and most subjects were women. The blinding protocol may have been ineffective because the 4 participants who experienced paresis of the fingers could have correctly assumed that they received an active treatment. The authors concluded that BTX injection may improve pain over a 3-month period in some patients with lateral epicondylitis, but injections may be associated with digit paresis and weakness of finger extension. This positive finding is in contrast to that of Hayton et al (2005) who performed a double-blind, randomized, controlled, pilot trial comparing injections of BTX- A with those of a placebo (normal saline solution) in the treatment of chronic tennis elbow. A total of 40 patients with a history of chronic tennis elbow for which all conservative treatment measures, including steroid injection, had failed were randomized into two groups: (i) half the patients received 50 units of BTX- A, and (ii) the remainder received normal saline solution. The intramuscular injections were performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. The two solutions used for the injections were identical in appearance and temperature. The results of a quality-of-life assessment with the Short Form-12 (SF-12), the pain score on a VAS, and the grip strength measured with a validated Jamar dynamometer were recorded before and 3 months after the injection. Three months following the injections, there was no significant difference between the two groups with regard to grip strength, pain, or quality of life. The authors reported that with the numbers studied, they failed to find a significant difference between the two groups. Therefore, they concluded that there is no evidence of a benefit from BTX injection in the treatment of chronic tennis elbow.

Monnier, et al. (2006) stated that musculoskeletal pain in patients with rheumatic disorders is among the emerging indications for BTX therapy. Preliminary data have been obtained in patients with cervical or thoracolumbar myofascial pain syndrome, chronic low back pain, piriformis muscle

syndrome, tennis elbow, and stiff person syndrome. At present, the effects of BTX and its use for pain relief remain controversial. Carefully designed prospective studies are needed to ascertain the safety and effectiveness of BTX in pain disorders. In a double-blind, randomized, placebo-controlled, parallel clinical trial, Qerama, et al. (2006) studied the effect of BTX-A on pain from muscle trigger points and on EMG activity at rest and during voluntary contraction. Thirty patients with trigger points in the infra-spinatus muscles received either 50 units/0.25 mL of BTX-A or 0.25 mL of isotonic saline. Baseline measures were determined during a run-in period of 1 week. Outcome measures including local and referred spontaneous pain, pain detection and tolerance thresholds to mechanical pressure, and shoulder movement were assessed at 3 and 28 days after injection. The interference pattern of the EMG during maximal voluntary effort of infra-spinatus muscle was recorded and a standardized search for spontaneous electrical motor endplate activity at the trigger points was performed before and 28 days after BTX-A or saline injection. Botulinum injection reduced motor endplate activity and the interference pattern of EMG significantly but had no effect on either pain (spontaneous or referred) or pain thresholds compared with isotonic saline. The authors concluded that their findings do not support a specific anti-nociceptive and analgesic effect of BTX-A.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain (Naumann et al, 2008) found that botulinum neurotoxin is possibly effective for the treatment of chronic predominantly unilateral low back pain. This was based on a single Class II study. The authors stated that the evaluation and treatment of low back pain (LBP) is complicated by its diverse potential causes. In most clinical settings, it is difficult to diagnose the precise origin of pain. This creates challenges in study design, especially in the selection of homogeneous subject populations. The assessment also noted that there is insufficient evidence to support the effectiveness of botulinum neurotoxin in hyper-lacrimation.

In a review of the evidence for non-surgical interventional therapies for LBP for the American Pain Society, Chou and colleagues (2009) concluded that there is insufficient (poor) evidence from randomized controlled trials (conflicting trials, sparse and lower quality data, or no randomized trials) to reliably evaluate botulinum toxin injection.

The findings from Qerama, et al. (2006) are in agreement with that of Ojala, et al. (2006) who, in a double-blind, randomized, controlled cross-over study (n = 31) found that there was no difference between the effect of small doses of BTX-A and those of physiological saline in the treatment of myofascial pain syndrome as well as that of Ferrante, et al. (2005) who, in randomized, double-blind, placebo-controlled study (n = 132) reported that injection of BTX-A directly into trigger points did not improve cervico-thoracic myofascial pain.

In a controlled placebo pilot study with a 6-month follow-up period, Guarda-Nardini and associates (2008) examined the effectiveness BTX in treating myofascial pain in bruxers. A total of 20 patients (10 males, 10 females; age range of 25 to 45 years) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles were randomly assigned to either a treatment group (10 subjects treated with BTX injections- BTX-A) or a control group (10 subjects treated with saline placebo injections). A number of objective and subjective clinical parameters (pain at rest and during chewing; mastication efficiency; maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements; functional limitation during usual jaw movements; subjective efficacy of the treatment; tolerance of the treatment) were assessed at baseline time and at 1 week, 1 month, and 6 months follow-up appointments. Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest; pain during chewing) clinical outcome variables were higher in the BTX-treated group than in the placebo-treated subjects. Patients treated with BTX-A had a higher subjective improvement in their perception of treatment efficacy than the placebo subjects. Differences were not significant in some cases due to the small sample size. Results from the present study supported the efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger samples.

In a double-blind, randomized, placebo- controlled trial (n = 60), Abbott, et al. (2006) examined if BTX-A is more effective than placebo at reducing pain and pelvic floor pressure in women with chronic pelvic pain and pelvic floor muscle spasm. Subjects had chronic pelvic pain of more than 2 years duration and evidence of pelvic floor muscle spasm. Thirty women had 80 units of BTX-A injected into the pelvic floor muscles, and 30 women received saline. Dysmenorrhea, dyspareunia, dyschezia, and

non-menstrual pelvic pain were assessed by VAS at baseline and then monthly for 6 months. Pelvic floor pressures were measured by vaginal manometry. There was significant change from baseline in the BTX- A group for dyspareunia (VAS score 66 versus 12; chi2 = 25.78, p < 0.001) and non-menstrual pelvic pain (VAS score 51 versus 22; chi2 = 16.98, p = 0.009). In the placebo group only dyspareunia was significantly reduced from baseline (64 versus 27; chi2 = 2.98, p = 0.043). There was a significant reduction in pelvic floor pressure (centimeters of water) in the BTX- A group from baseline (49 versus 32; chi2 = 39.53, p < 0.001), with the placebo group also having lower pelvic floor muscle pressures (44 versus 39; chi2 = 19.85, p = 0.003). The authors concluded that objective reduction of pelvic floor spasm reduces some types of pelvic pain. Injection of BTX- A reduces pressure in the pelvic floor muscles more than placebo; it may be a useful agent in women with pelvic floor muscle spasm and chronic pelvic pain who do not respond to conservative physical therapy. There were no significant inter-group differences reported in this study between BTX-A and placebo for pain scores. These investigators noted that more research in this area is essential to further define this tool in the treatment of chronic pelvic pain.

Awaard (1999) reported that the combination of baclofen/botulinum toxin type A are very effective, safe, and reliable in the treatment of tics/Tourette's syndrome. It is worthwhile considering this treatment approach in patients with tics/Tourette's syndrome in order to reduce or avoid the side effects of other medications. Moreover, the author concluded that further studies are needed.

Marras, et al. (2001) discussed the use of botulinum toxin for simple motor tics (n = 18). The authors concluded that botulinum toxin reduced treated tic frequency and the urge associated with the treated tic. Despite these changes, patients did not report an overall benefit from the treatment.

The American Academy of Neurology's assessment on the use of botulinum neurotoxin in the treatment of movement disorders (Simpson, et al., 2008b) stated that botulinum neurotoxin is possibly effective for the treatment of motor tics (based on one Class II study). On the other hand, there is insufficient data to ascertain the effectiveness of botulinum neurotoxin in patients with phonic tics.

Botulinum toxin is the only known treatment for painful dystonia accompanying rare corticobasilar degeneration (CBD). Dystonia, often accompanied by painful rigidity and fixed contractures, is one of the most disabling features of CBD. Vanek and Janovic (2001) found that dystonia is a common manifestation of CBD; of 66 patients with CBD, 39 (59.0%) had dystonia. The investigators noted that there is no effective treatment for this relentless disorder, except for temporary relief of dystonia and pain, with local botulinum toxin injections.

Botulinum toxin has also been studied for its use in treating brachial plexus injury and restless leg syndrome. However, there is currently insufficient evidence to support it use for these indications.

Heise, et al. (2005) reported their preliminary experience with the use of BTX-A for the treatment of biceps-triceps muscle co-contraction. A total of 8 children were treated with 2 to 3 U/Kg of BTX injected in the triceps (4 patients) and biceps (4 patients) muscle, divided in 2 or 3 sites. All patients submitted to triceps injections showed a long-lasting improvement of active elbow flexion and none required new injections, after a follow-up of 3 to 18 months. Three of the patients submitted to biceps injections showed some improvement of elbow extension, but none developed anti-gravitational strength for elbow extension and the effect lasted only 3 to 5 months. One patient showed no response to triceps injections. The authors stated that their findings suggested that BTX can be useful in some children that have persistent disability secondary to obstetrical brachial plexopathy.

DeMatteo, et al. (2006) noted that following obstetrical brachial plexus injury, infants are unable to learn specific patterns of movement due to the disruption of neural pathways. Even with successful re-innervation (spontaneously or post-surgical reconstruction), function can be suboptimal due to over-activity in antagonist muscles preventing movement of re-innervated muscles. Botulinum toxin type A was used to temporarily weaken antagonistic muscles early in the re-innervation process following brachial plexus injury, with the aim of facilitating functional improvement. These researchers reported a case series of 8 children (5 females, 3 males; mean age of 12.5 months [SD 6.43]; range of 5 to 22 months) with significant muscle imbalances but evidence of re-innervation who were given BTX-A injections into the triceps, pectoralis major, and/or latissimus dorsi muscles. After a single injection, all parents reported improvement in function. Active Movement Scale total score changed

significantly between pre BTX-A and 1 month (p = 0.014), and 4 months (p = 0.022) post BTX-A injection. The authors proposed that BTX-A facilitated motor learning through improved voluntary relaxation of antagonist muscles while allowing increased activity in re-innervated muscles.

Price, et al. (2007) retrospectively reviewed 26 patients who underwent reconstruction of the shoulder for a medial rotation contracture after birth injury of the brachial plexus. Of these, 13 patients with a mean age of 5.8 years (2.8 to 12.9) received an injection of BTX-A into the pectoralis major as a surgical adjunct. They were matched with 13 patients with a mean age of 4.0 years (1.9 to 7.2) who underwent an identical operation before the introduction of BTX therapy to these investigators' unit. Pre-operatively, there was no significant difference (p = 0.093) in the modified Gilbert shoulder scores for the 2 groups. Post-operatively, patients who received the BTX had significantly better Gilbert shoulder scores (p = 0.012) at a mean follow-up of 3 years (1.5 to 9.8). It appears that BTX-A produces benefits which are sustained beyond the period for which the toxin is recognised to be active. The authors suggested that by temporarily weakening some of the power of medial rotation, afferent signals to the brain are reduced and cortical recruitment for the injured nerves is improve.

In a double-blind, placebo-controlled, pilot trial (n = 6), Nahab and colleagues (2008) examined the effects of botulinum toxin A in the treatment of patients with restless legs syndrome (RLS). Patients, aged 18 or older, had a diagnosis of primary RLS based on International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria,1 had a minimum score of 11 (at least moderate severity) on the IRLSSG rating scale (IRLS), and were stable on medications for greater than 6 weeks prior to enrollment. Patient assessment included a medical history, neurological examination, and baseline ratings. Eligible patients were evaluated by a second investigator who documented symptom location. A standard set of muscles were selected as potential targets: quadriceps femoris (QF), tibialis anterior (TA), gastrocnemius (GCS), and soleus (SOL). After baseline ratings, patients were randomized to receive BTX-A or saline. The maximum dose was 90 mU per leg, distributed in the following sites (number of injections): QF-40mU (4); TA-20mU (2); GCS-20mU (2); SOL-10mU (1). At week 12, patients received the alternate compound with continued monitoring.

These researchers used the IRLS and the Clinical Global Improvement scale (CGI) to assess efficacy. To monitor adverse effects (AEs), patients were asked to rate from 0 (no symptoms) to 10 (severe symptoms) the presence of weakness, pain, swelling, and redness based on the preceding 2 weeks. Ratings were completed at baseline (weeks 0 and 12), and 2 and 4 weeks post-injections. The primary outcome measure was mean change in IRLS from baseline at 4 weeks post-injection. Secondary outcomes included mean IRLS change from baseline at 2 weeks post-injection, mean CGI scores at weeks 2 and 4, and reported AEs. A power analysis using standard treatment and placebo response rates reported for pramipexole was performed. These investigators estimated a mean difference from baseline between placebo and BTX-A of 10 points ± 3 (SD) on the IRLS. They therefore required a sample size of 3 patients per group (power = 0.80, a = 0.05).

A total of 7 patients were screened, with 1 excluded due to leukocytosis on laboratory testing. All remaining patients completed the study. Five patients were on stable doses of a dopamine agonist, and 1 patient was on a stable dose of clonazepam. No patient had received prior BTX treatment. Group demographics were as follows: 57.7 ± 8.8 years of age, equal male-female ratio, 33.5 ± 14.4 years disease duration, and an IRLS score of 27 ± 4.8. All patients received the maximum BTX dose of 90 mU/leg with the exception of 1 patient who had no symptoms in the proximal legs and did not receive injections into his QF. At week 2, placebo-treated patients noted a 5.0 ± 5.1 point improvement on the IRLS versus a 1.0 ± 3.5 point improvement in the BTX-arm (p = 0.06). At week 4, placebo-treated patients maintained only a 2.7 ± 5.9 point improvement from baseline, whereas BTX-treated patients showed a 5.0 ± 6.0 point improvement (p = 0.24). The CGI showed similar findings for the BTX-arm with scores of 4.3 ± 0.8 at week 2 (p = 0.01) and 3.7 ± 1.4 at week 4 (p = 0.74), compared to placebo-arm scores of 2.8 ± 1.2 at week 2 and 3.8 ± 1.7 at week 4. These researchers compared baseline scores at week 0 and week 12 to assess for any carry-over effect in the BTX-arm and found no differences (p = 0.55). Reported AEs were similar between groups, with mean placebo AE scores of 1.5 ± 2.5 at baseline, 3.2 ± 5.4 at week 2, and 5 ± 7.4 at week 4, while BTX-A scores were 1.8 ± 3.3 at baseline, 6.3 ± 7.1 at week 2, and 4.5 ± 5.6 at week 4. Two patients reported mild weakness following both placebo and BTX-A injections. This study showed no significant improvement in IRLS and CGI at week 4 for BTX-A. A statistically significant benefit was noted on the CGI secondary endpoint for the placebo group at week 2. Adverse events were similar between the groups. Any

future studies should be powered to account for the significant placebo response while exploring higher doses without unmasking controls.

Slotema and colleagues (2008) stated that orofacial tardive dyskinesia (OTD) is difficult to treat and botulinium toxin A (BTA) may be an option. In a single-blind (raters were blind) study (n = 12, duration 33 weeks), OTD was treated with BTA in 3 consecutive sessions with increasing dosages. The severity was measured with the Abnormal Involuntary Movement Scale (AIMS). Overall, there was a non-significant reduction in the severity of OTD (p = 0.15). However, in patients with no change in their anti-psychotic medication (n = 8) the reduction was significant (p = 0.035). After the study, 50% of the patients preferred to continue the treatment with BTA. The authors concluded that BTA was well-tolerated and showed a nonsignificant improvement for OTD. They stated that a larger double-blind study is warranted.

Park and Paraiso (2009) stated that refractory dyspareunia presents a challenging therapeutic dilemma. These researchers presented the case of a woman with defecatory dysfunction and dyspareunia presented with stage 2 prolapse. She underwent laparoscopic and vaginal pelvic floor reconstruction with excision of endometriosis. The patient experienced increased dyspareunia and de novo vaginismus post-operatively that were refractory to trigger point injections, physical therapy, and medical and surgical management. She underwent botulinum toxin type A (BoNT/A) injections into her levator ani muscles, which allowed her to have sexual intercourse again after 2 years of apareunia with no recurrence of pain for 12 months. The authors concluded that injecting botulinum toxin into the levator ani muscles shows promise for postoperative patients who develop vaginismus and do not respond to conservative therapy.

Yuan, et al. (2009) noted that diabetic neuropathy is a common complication in diabetes, with patients typically experiencing diverse sensory symptoms including dysesthesias in the feet and usually accompanied by sleep disturbance. There is still no comprehensive understanding of the underlying biologic processes responsible for diabetic neuropathic pain. Thus, the current symptomatic therapy remains unsatisfactory. Recent experimental evidence suggested that BoNT/A may not only inhibit the release of acetylcholine at the neuromuscular junctions, but also modulate afferent sensory fiber firing, thereby relieving neuropathic pain. These investigators performed a double-blind cross-over trial of intradermal BoNT/A for diabetic neuropathic pain in 18 patients. They found significant reduction in VAS of pain by 0.83 +/- 1.11 at 1 week, 2.22 +/- 2.24 at 4 weeks, 2.33 +/- 2.56 at 8 weeks, and 2.53 +/- 2.48 at 12 weeks after injection in the BoNT/A group, as compared to the respective findings for a placebo group of 0.39 +/- 1.18, -0.11 +/- 2.04, 0.42 +/- 1.62, and 0.53 +/- 1.57 at the same time-points ($p < 0.05$). Within the BoNT/A group, 44.4% of subjects experienced a reduction of VAS greater than or equal to 3 within 3 months after injection, whereas there was no similar response in the placebo group. At the 4-week post-injection stage, improvement in sleep quality was measured using the Chinese version of the Pittsburgh Sleep Quality Index. The authors concluded that the findings of this pilot study showed that botulinum toxin type A significantly reduced diabetic neuropathic pain and transiently improved sleep quality. They stated that further large-scaled study is warranted. In an editorial that accompanied the afore-mentioned study, Apfel (2009) stated that larger, carefully designed, multi-center, clinical trials with longer periods of observation are needed to ascertain the clinical value of botulinum toxin for neuropathic pain. The author also noted that it will be essential in future studies to examine the effectiveness and tolerability of multiple dosing.

Fregene et al (2009) performed a retrospective chart review on the use of botulinum toxin type A (BTX-A) for the treatment of digital ischemia in patients with Raynaud's phenomenon. All patients presented with a diagnosis of Raynaud's phenomenon with worsening pain, discoloration, or non-healing wound of the hand. Patients received BTX-A injections into the peri-neurovascular tissue of the wrist or the distal palm, or along the digit. Outcomes measured included pain rating, digit color and appearance, transcutaneous oxygen saturation, and healing of chronic ulcers. A total of 26 patients were treated, with a total of 55 treatment encounters. Patients were observed for an average of 18 months. Statistically significant improvements were noted for pain score and digit transcutaneous oxygen saturation measurements after treatment ($p < 0.05$). These investigators found smokers and women were more likely to have improved coloration and appearance after injections. Complications included localized injection-related pain and transient intrinsic muscle weakness. The authors concluded that BTX-A significantly improves pain and improves healing in Raynaud's patients with few complications. Botulinum toxin type A was found to be a safe and useful

treatment option for vasospastic digital ischemia. Moreover, the authors stated that none of the studied demographic data was a significant predictor of improved response to BTX-A. They noted that further investigation is underway to determine the risk factors that respond best to peri-vascular BTX-A therapy.

Neumeister and colleagues (2009) performed a retrospective study focused on patient outcomes on 19 patients diagnosed with Raynaud's phenomenon. Patients suffered from chronic ischemic hand pain. All patients had vascular studies to rule out occlusive disease. Fifty to 100 units of botulinum toxin were injected into the palm around each involved neurovascular bundle. Pre-injection and post-injection laser Doppler scanning was performed on most patients to measure blood flow. Sixteen of 19 patients (84 %) reported pain reduction at rest. Thirteen patients reported immediate relief; 3 reported more gradual pain reduction over 1 to 2 months. Three patients had no or minimal pain relief. Tissue perfusion results demonstrated a marked change in blood flow (-48.15 % to 425 %) to the digits. All patients with chronic finger ulcers healed within 60 days. Most patients (n = 12 [63 %]) remained pain-free (13 to 59 months) with a single-injection schedule. Four patients (21 %) required repeated injections because of recurrent pain. The authors concluded that vascular function is abnormal in patients with Raynaud's phenomenon. Although its mechanism is unknown, botulinum toxin yielded a distinct improvement in perfusion and reduction in pain in patients failing conservative management. They stated that continued research may lead to more specific and reliable treatment for Raynaud's patients.
The drawbacks of this study include (i) this was a non-controlled case series without a placebo group, (ii) various confounding factors may be important in the findings, including ambient room temperature, patient core temperature, time of year injected, and (iii) small sample size, broad inclusion criteria, as well as lack of a subjective or objective pain scale. The authors stated that randomized, controlled, prospective studies are needed to address these issues and to define the true benefits of botulinum toxin injections in patients with ischemic digits.

The above framework is based on the following references:

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Appendix L: Male circumcision in children

Leeds CCGs will fund male circumcision in children when medically necessary only in accordance with the Statement from the British Association of Paediatric Surgeons, The Royal College of Nursing, The Royal College of Paediatrics and Child Health, The Royal College of Surgeons of England and The Royal College of Anaesthetists (2001).

Indications for male circumcision in children according to this statement are as follows:

- The one absolute indication for circumcision is scarring of the opening of the foreskin making it non-retractable (pathological phimosis). This is unusual before 5 years of age.
- Recurrent, troublesome episodes of infection beneath the foreskin (balanoposthitis) are an occasional indication for circumcision.
- Occasionally specialist paediatric surgeons or urologists may need to perform a circumcision for some rare conditions.

A further indication is pain on passing urine in young children because of the build up of pressure under the skin due to the tiny orifice (phimosis).

Leeds CCGs will also fund circumcision for male babies under the age of 12 weeks for religious reasons in accordance with the Leeds Circumcision Service or other locally commissioned service.

The above framework is based on the following references:

1. Paediatric Forum, Children's Surgery – A First Class Service, May 2000
2. American Academy of Paediatrics, Circumcision Policy Statement, Paediatrics Volume 103, 3,
3. March 1999
4. Guidance for Doctors Who Are Asked to Circumcise Male Children, GMC, Sept 1997
5. Circumcision of Male Infants – Guidance for Doctors, BMA, Sept 1996
6. Australian College of Paediatrics, Position Statement on Circumcision, Newsletter June 1996
7. Williams N, Kapila L; Complications of Circumcision. Review, British Journal of Surgery 80 (10): 1231-6, October 1993.
8. Rickwood AMK, Walker J; Is Phimosis Overdiagnosed in Boys and Are Too Many Circumcisions Performed in Consequence? Annals of the Royal College of Surgeons of England, Vol 71 No 5, 275-277, 1989.
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10. British Medical Association. The Law and Ethics of Male Circumcision. Guidance for Doctors. 2006.
11. British Association of Paediatric Surgeons, Royal College of Nursing, Royal College of Paediatrics and Child Health, Royal College of Surgeons of England and Royal College of Anaesthetists. Statement on male circumcision. London: Royal College of Surgeons of England, March 2001.

Appendix M: Labial Reduction and Cosmetic Vaginal Procedures

NHS Leeds CCGs regard surgery for labial reduction as cosmetic.

Many requests for labial reduction are motivated by unrealistic expectations of the appearance of the vulva. Potential referrers and their patients are reminded that the normal vulva includes a wide spectrum of shape and size (referrers are requested to see reference below[5]). Prominent labia minora and/or projection of the labia minora beyond the labia majora are normal variants and not an indication for surgery, even if visible through tight-fitting clothing.

In the case of congenital/pathological abnormalities of the external genitalia, Leeds CCGs consider treatment medically necessary only where the American College of Obstetricians and Gynecologists Committee Opinion on cosmetic vaginal procedures indicate it is medically necessary.

Medical indications for surgical procedures for labial hypertrophy or asymmetric labial growth include:

- congenital conditions; or
- chronic irritation (with documented evidence of ulceration/severe excoriation over several months that has failed to respond to conservative treatment); or
- excess androgenic hormones

Note: Treatment for female genital mutilation is not considered cosmetic and does not require prior approval.

The above framework is based on the following references:

1. ACOG Committee Opinion. Vaginal “rejuvenation” and cosmetic vaginal procedures. Obstet & Gynecol 2007.110(3) pp. 737-738.
2. Requests for cosmetic genitoplasty: how should healthcare providers respond? Lioa LM, Creighton S. BMJ 2007;334:1090

[5] Potential referrers and patients are encouraged to view Jamie McCartney’s exhibition of anatomical moulds (“Changing female body image through art”) at www.greatwallofvagina.co.uk for a demonstration of the wide variety of normal appearances.

Appendix N: Psychological Exceptions

Cosmetic procedures are popular and sought after and the limited data available suggests that the majority of patients can expect good psychosocial adjustment in the short to medium term.

Honigman et al reviewed 37 studies suggesting that poor psychosocial adjustment prior to the procedure is probably the best indicator of a poor psychosocial outcome after the procedure.

There is no literature on what might constitute a psychological exception to warrant NHS funding of cosmetic medical and surgical procedures.

A psychological exception might suggest an unusual case, a more deserving set of circumstances, or an appearance feature which causes pain or other functional impairment which contributes to distress.

The CCGs understand that the most psychologically distressed patients requesting cosmetic procedures often have very complex emotional problems. They often focus their distress upon an appearance feature which is to the lay observer within the normal range. They may have features that would suggest a poor psychosocial outcome after the procedure

Psychological exceptions are determined on a case by case basis taking into account the particular context of the individual and his/her life. Exceptions tend to have proportionate and reasonable concerns about an appearance feature which is to a lay observer abnormal or outside the normal range.

Individuals who function very poorly, have unrealistic expectations of the effect of the procedure on their life or who seem desperate to change features which are within the normal range are unlikely to qualify.

Occasionally it may be necessary to decline a request for surgery that might normally be funded, where the patent's psychological profile predicts a poor outcome from surgery (e.g. revision of visible scars in the context of ongoing self-harm).

Inability to establish a relationship, or failure of an established relationship, are not normally grounds for a psychological exception.

Note on psychological treatment for body dysmorphic disorders

Access to psychological treatment for body dysmorphic disorder is through an initial assessment through the local Increasing Access to Psychological Therapies (IAPT) service. Treatment at steps 1-4 will be offered as required from this initial assessment including onward referral to step 4 if required (through the Single Point of Access to LYPFT (Psychological Therapy Service) which offers treatment for body dysmorphic disorder).

The above framework is based on the following reference:

Honigman RJ, Phillips KA, Castle DJ. A Review of Psychosocial Outcomes for Patients Seeking Cosmetic Surgery Plast Reconstr Surg. 2004; 113: 1229-1237.

Appendix O: Cosmetic Dental Care

This is no longer CCG responsibility. Referrals should be made to NHS England as the commissioner.

Appendix P: Additional procedures following Gender Dysphoria treatment funded by NHS England

1. Breast Augmentation

Patients who have been treated for gender dysphoria funded by NHS England will only be funded for breast augmentation in line with the recommendations in the national Gender Dysphoria policy[6] ie following 18 months of failed hormone treatment

2. Facial Feminisation Surgery and lipoplasty/ body contouring

Leeds CCGs do not normally fund facial feminisation surgery and lipoplasty/ body contouring. Any exceptional requests should be supported by 2 NHS medical clinicians from specialist Gender Dysphoria services to state that treatment is essential to the success of the gender transition rather than for solely cosmetic purposes.

3. Facial or other bodily hair removal

3 locally NHS funded (CCG) treatments of electrolysis or laser will be considered medically necessary for the face only as per appendix H.

[6] http://www.england.nhs.uk/resources/spec-comm-resources/npc-crg/group-c/c05/ (policy to be added October 2013)

Appendix Q: Repair of true incisional or ventral hernias

Leeds CCGs consider repair of a true incisional or ventral hernia to be medically necessary. Photographic evidence of the condition is required by the IFR panel – only photographs taken by medical photography will be accepted.

In order to distinguish a ventral hernia repair from a purely cosmetic abdominoplasty, NHS Leeds requires documentation of the size of the hernia, whether the ventral hernia is reducible, whether the hernia is accompanied by pain or other symptoms, the extent of diastasis (separation) of rectus abdominus muscles, whether there is a defect (as opposed to mere thinning) of the abdominal fascia, and GP notes indicating of the presence and size of the fascial defect.

Appendix R: Version Control Sheet

Version	Date	Author	Status	Comment
Draft 1	4/7/13	J D Fear	Draft	Updated for Leeds CCGs
Draft 2	17/713	J D Fear	Draft	Updated for Leeds CCGs
Draft 3	9/9/13	Fiona Day	Draft	Addition of cover sheet. Helen Lewis clarifications.
Draft 4	12/19/13	Fiona Day	Draft	Addition of 'in conjunction with NHS psychological therapy' in 4.4 relating to wigs. Addition of electrolysis to appendix F and Facial hirsutism in women visible when shaved (limited to a maximum of 2 test sessions and 3 treatment sessions to affected areas which may be by laser or electrolysis)
Draft 5	15.10.13	Fiona Day	Draft	Amended following meeting with Plastic Surgeons. Also addition of gender dysphoria x-reference with NHS England agreed by medical directors on 25.9.13.
Draft 6	18.11.13	Fiona Day	Draft	Final changes from plastic surgeons regarding appendices a-f; addition of new appendix on hernias. Addition of pigmented nonpathological changes. Remove itch in skin lesions. Include 2 test for laser/electrolysis hair removal. Addition of 'additional to NHS E' hair removal for GD patients. Addition of smoking references.Amends to wording in 4.2 and 4.3, 4.4, Addition of comments regarding female genital mutilation. Alterations to criteria for labiaplasty. Addition of treatment end point in 4.1. Changes to wording of psychological exception and addition of note on treatment for body dysmorphic disorders.
Draft 7	29.11.13	Fiona Day	Draft	Addition of pilonidal sinus treatment using laser and reference. Clarification of wording re payment of providers; addition of dissemination plan.

Appendix S: Plan for Dissemination of Framework Documents

To be completed and attached to any document which guides practice when submitted to the appropriate committee for consideration and approval.

Title of Framework:	Cosmetic exceptions and exclusions		
Date finalised:	29.11.13	**Dissemination lead:**	CCG x3 Medical Directors
Previous framework already being used?	**Yes**	**Print name and contact details**	
If yes, in what format and where?	Electronic and paper		
Proposed action to retrieve out-of-date copies of the document:	Official launch of new policies in Feb 2014, with request to delete any previous versions.		
To be disseminated to: **General Public**	This has been shared with: All 3 CCG intranet & extranets LTHT Intranet & Extranets Leeds Health Pathways 3rd sector via Voluntary Action Leeds bulletins and website and Healthy Lives Leeds LLMC Leeds GPs at Target events (one in each CCG) Links to this document on the relevant section of each CCG website will be sent to: All 3 CCG intranet & extranets; LTHT, LCH and LYPFT Intranet & Extranets; Leeds Health Pathways; 3rd sector via Voluntary Action Leeds bulletins and website and Healthy Lives Leeds; LLMC; Healthwatch; LCC scrutiny; LCC Lead Member for Health and Wellbeing; LCC Director of Public Health; CCG Patient assurance groups; PALS. LWCCG will hold the master copies.	**Paper or Electronic** **Electronic**	**Comments**

Clinicians	Links to the final versions will be circulated to all Practice Managers and local provider Medical Directors plus relevant Clinical Directors in LTH, LYPFT, LCH, independent providers. Specific clinicians where relevant eg cosmetics, plastics, dermatology, breast. Also to be discussed at primary care TARGET or similar events.	Electronic	
Panel Members	Final versions will be circulated to Panel Members	Electronic	

Acknowledgement: University Hospitals of Leicester NHS Trust.

Appendix T: Equality Impact Assessment

To ensure the Individual Funding Requests Policy and associated decision making frameworks for the Clinical Commissioning Groups in Leeds reflects due process for identifying the effect, or likely effect, of the policy on people with Equality Act protected characteristics – age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex, sexual orientation - and that the policy demonstrates due regard to reducing health inequalities, addressing discrimination and maximising opportunities to promote equality the following steps have been taken.

The update to the policy results from the iterative refresh process, and the requirement to make changes to care as indicated by an evolving evidence-base. This means that access is broadened as more treatments and interventions become available without the need for an IFR. There is no change to the underlying principles of the policy. In order for an IFR to be approved according to the core principles for managing Individual Funding Requests, it must be demonstrated that the patient's case is exceptional.

The following consultation and engagement activities have been undertaken. The evidence-based policy has been circulated to all GPs and secondary care consultants for comment, and has been made available on the internet to the public, along with Plain English patient information leaflets. The core principles for managing Individual Funding Requests in Leeds have been made available online for twelve weeks and disseminated through Patient Advisory Groups and Patient Reference Groups along with a cascade through the Community and Voluntary Service network. Feedback from all these sources has been collected by the Clinical Commissioning Groups. There is also an open and transparent approach to the processes of the decision making panel with an established mechanism for appeals.