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Botulinum toxin treatment of axillary and palmar hyperhidrosis

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VÄSTRA GÖTALANDSREGIONEN
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Botulinum toxin treatment of axillary and palmar hyperhidrosis [Botulinum toxin behandling av axillär och palmar hyperhidros]

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Summary of the Health Technology Assessment

Method and patient group

Primary hyperhidrosis is a condition of excessive sweating of unknown cause. It may severely affect the quality of life (QoL). Botulinum toxin (BTX) injections is a local treatment that can be used in patients with axillary or palmar hyperhidrosis, or compensatory hyperhidrosis following sympathectomy, if they are unresponsive to other local therapies.

Question at issue

Is injection treatment with BTX for axillary, palmar hyperhidrosis and compensatory hyperhidrosis following sympathectomy better than placebo, no treatment, or standard treatments when assessed as QoL, sweat production, duration and complications?

PICO:

P_1: Patients with primary axillary or palmar hyperhidrosis

P_2: Patients with compensatory hyperhidrosis following sympathectomy

I: BTX (A or B) injections

C: Standard treatment [topical treatment (aluminium chloride), oral anticholinergics, subcutaneous sweat gland suction curettage]
Placebo or no treatment

O: **Primary outcome variable**:
Quality of life evaluated using a validated scale e.g. Dermatology Quality of Life Index (DQLI)

Secondary outcome variables:
Measurement of sweat production using a validated scale e.g. Hyperhidrosis Disease Severity Scale (HDSS)
Duration of treatment effect
Complications (short- and long-term effects/tolerance)

Studied risks and benefits for patients of the new health technology

The systematic literature search identified eleven randomized controlled trials, one cohort study, and two case series reporting the effects of BTX injections in patients with axillary or palmar hyperhidrosis. Almost all controlled studies compared BTX with placebo, whereas only few of them compared the effects with standard treatments.

The literature search did not find any publication that reported the effects of BTX on compensatory hyperhidrosis after sympathectomy.

Axillary hyperhidrosis

Quality of life

In comparison with placebo, treatment with BTX increased the QoL-score 2-4 fold (moderate quality of evidence GRADE ⊕⊕⊕◯), and in comparison to aluminium chloride (AlCl) it increased the QoL-score 5-fold (low quality of evidence GRADE ⊕⊕◯◯)

In comparison with subcutaneous curretage BTX does not increase QoL-score (very low quality of evidence GRADE ⊕◯◯◯).

Sweat production

In comparison to placebo and AlCl, treatment with BTX reduced sweat production 3-8 times, and 2-3 times, respectively. This is of high quality of evidence (GRADE ⊕⊕⊕⊕), with regard to placebo, and of low quality of evidence (GRADE ⊕⊕◯◯), with regard to AlCl.

Duration of treatment effect

The treatment effect of BTX is about seven months, which in comparison with placebo is 2-3 times longer, whereas the effect duration is considered permanent after subcutaneous curettage. Low quality of evidence (GRADE ⊕⊕◯◯), regarding placebo, and very low quality of evidence (GRADE ⊕◯◯◯) regarding subcutaneous curettage.

Palmar hyperhidrosis

Quality of life

In comparison with placebo, treatment with BTX increased the QoL-score 8 fold. Low quality of evidence (GRADE ⊕⊕◯◯).

Sweat production

In comparison with placebo, treatment with BTX reduced sweat production twice as much. Low quality of evidence (GRADE ⊕⊕◯◯).

Duration of treatment effect

The treatment effect of BTX is about three months. No comparison has been made with placebo or standard treatment. Very low quality of evidence (GRADE ⊕◯◯◯).

Complications

Most adverse events of BTX-treatment for hyperhidrosis are mild or moderate. An increase in non-axillary sweating has been observed with an incidence of about 5% in BTX-treated patients with axillary hyperhidrosis. Mild muscle weakness, mostly transient, has been reported in about half of the patients treated for palmar hyperhidrosis.

Ethical questions

Treatment with BTX is not a curative therapy, and the duration of a single treatment is relatively short. This means repeated injections. Is it acceptable to inject the patients once to three times per year, perhaps during their whole lifespan?

Is it acceptable not to offer BTX treatment for patients with hyperhidrosis in Region Västra Götaland (VGR) when it is offered in other regions and counties of Sweden?

Economical aspects

The cost per patient per year has been estimated to 8,200 SEK. This estimation is associated with a relatively high degree of uncertainty.

Which health technology or method will be assessed?

1a **Project leader**

Kristina Maltese, MD (Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden), and Madeleine Ryndel, MD (Department of Dermatology, Skaraborg Hospital, Skövde, Sweden), were project leaders, supervised by Jan Faergemann, MD, PhD (Professor, Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden).

1b **The question was posed by:**

Carin Sandberg, MD, PhD, Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden.

Additional parties who posed the question:

The Regional Council in Dermatology and Venereology in Region Västra Götaland.

1c **Co-workers:**

Lina Hagvall, Hygiene Technician, PhD Kristina Maltese, MD, Carin Sandberg, MD, PhD; all at the Department of Dermatology, Sahlgrenska University Hospital, Göteborg, Sweden.
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1d **Other participants, from the HTA centre and external reviewers**

Christina Bergh, MD, PhD, Professor, Petteri Sjögren, DDS, PhD, Therese Svanberg, HTA-librarian; all at the HTA-centre of Region Västra Götaland, Göteborg, Sweden.
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External reviewer

Magnus Rizell, MD, PhD, Department of Transplantation and Liver Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.

1e **Are there any conflicts of interest for the proposer or any of the participants in the work group?**

No

Disease/disorder of Interest and Present Treatment

2a Disease/disorder of interest and its degree of severity

Hyperhidrosis is defined as a condition of excessive sweating in greater amounts than necessary for the thermoregulation. When hyperhidrosis is caused by an underlying disorder, such as an infection, or an endocrine, metabolic, neurologic or oncologic disease, or by medication, it is called secondary hyperhidrosis. This type of hyperhidrosis is often, but not always, generalized.

Primary hyperhidrosis, i.e. without an identified cause, is also called idiopathic hyperhidrosis. It is usually localized and bilaterally symmetrical, and is reduced during sleep (Murray *et al*., 2007). The axillae are the most common site (51%), but also the palms, the soles, and to a lesser extent the face and the groin may be affected (Strutton *et al*., 2004). It affects both men and women, and the onset is typically during puberty (Kaufmann *et al*., 2003; Lowe *et al*., 2007). It is believed that the cause of hyperhidrosis is overactivity in the sympathetic innervation of the sweat glands (Bovell *et al*., 2001). Primary hyperhidrosis may lead to physical and emotional impairments, both in social and professional settings. This may severely affect the QoL (Hamm, 2006; Swartling *et al*., 2011).

Primary hyperhidrosis is a clinical diagnosis based on patient history and signs of excessive sweating. Minor's test can be used to visualize the area of excessive sweating (Lowe *et al*., 2002; Minor *et al*., 1927). The skin is then iodinated and sprinkled with starch powder, leading the sweating areas to adopt a bright blue-black color. The sweat production can also be quantified by a gravimetric measurement. The sweat is then absorbed in a filter paper of known weight (Heckmann *et al*, 1999). A special Hyperhidrosis Disease Severity Scale (HDSS) is used to classify the degree of severity (adapted from Solish *et al*., 2005):

1. My sweating is never noticeable and never interferes with my daily activities.
2. My sweating is tolerable but sometimes interferes with my daily activities.
3. My sweating is barely tolerable and frequently interferes with my daily activities.
4. My sweating is intolerable and always interferes with my daily activities.

Compensatory hyperhidrosis can be seen in many different medical conditions. It can also occur after treatment of primary hyperhidrosis. This has been observed in a high proportion of patients treated with sympathectomy (80%) (Smidfelt and Drott, 2011), but has also been observed, to a much lesser extent, after treatment with BTX injection (5%) (Naumann *et al*., 2003).

Degree of severity

- ☐ Risk of premature death
- ☐ Risk of permanent illness or damage, or reduced quality of life
- ☑ Risk of disability and health-related quality of life

2b **Prevalence and incidence of the disease/disorder**

The prevalence and incidence of primary hyperhydrosis in the adult Swedish population is unknown. In the United States the prevalence is estimated to be about 3% (Strutton *et al*., 2004). In Region Västra Götaland (VGR) there is a clinical database of different diagnoses (Vega). The numbers of patients with one or several of the following diagnoses; Hyperhidrosis R61, Localized hyperhidrosis R61.0, Axillary hyperhidrosis R61.0A, Palmar and plantar hyperhidrosis R61.0B, Localized hyperhidrosis unspecified R61.0X and Hyperhidrosis unspecified R61.9 are presented in the table below.

Year	2005	2006	2007	2008	2009	2010
Number of patients	642	711	700	655	890	1221

2c **Present treatment of the disease/disorder in the outpatient setting/ in-patient setting.**

There are many types of treatments of hyperhidrosis. They can be divided into five major categories:

Topical agents

It is the first line of treatment of all mild forms of primary focal hyperhidrosis (Hölzle and Braun-Falco, 1984). AlCl exerts its effect by obstructing the ducts of the eccrine sweat glands. Glutaraldehyde is thought to transiently block the sweat glands (according to Murray *et al*., 2007). Topical anticholinergic drugs are mostly used in craniofacial hyperhidrosis (Hoorens and Ongenae, 2012; Seukeran and Highet, 1998).

Iontophoresis

Iontophoresis is a technique using a small electric charge to deliver a chemical through the skin. It is basically an injection without a needle. There are different types of iontoforesis available using tap water, anticholinergics, BTX-A or a dry-type (according to Hoorens and Ongenae, 2012). The exact mechanism of action is unknown, but it is believed to cause a temporary blockade of the sweat glands (Sato *et al*., 1993). This is the second line of treatment in palmar and plantar hyperhidrosis (according to Hoorens and Ongenae, 2012).

Systemic agents

Anticholinergic agents block acetylcholine transmission in the sympathetic nerves that innervate the eccrine sweat glands (according to Hoorens and Ongenae, 2012). The use of these drugs is usually limited due to intolerable side-effects (Bajaj and Langtry, 2007).

Botulinum toxin (BTX)

Botulinum toxin blocks the release of acetylcholine from peripheral cholinergic neurons (Dickson and Shevky, 1923; Simpson, 2004), and thereby reduces the sweat production in the eccrine glands (see also 5a).

Surgical treatment with excision

The sweat glands in the axillae can be destroyed by a local excision of the axillary vault by subcutaneous curettage or liposuction (Swinehart, 2000).

Surgical treatment with sympathectomy
This is a surgical method by which the innervation of the hyperhidrotic areas is surgically disrupted (Edmondson *et al*., 1992). It can give a long-term reduction in hyperhidrosis, but has potentially serious side-effects and may cause postoperative compensatory hyperhidrosis (Edmondson *et al*., 1992; Murray *et al*., 2007; Smidfelt and Drott, 2011). This method is no longer in use in Sweden.

2d **Number of patients per year who undergo current treatment regimen**
The exact number of patients who are treated annually for primary hyperhydrosis in VGR is unknown. During the first six months of 2011 approximately 40 patients were referred to Sahlgrenska University Hospital (SU), 20 patients to Södra Älvsborgs Hospital (SÄS), 20 patients to Skövde Hospital (KSS), and 20 patients to Uddevalla Hospital (NU). This would yield a total number of referrals of 200 patients per year. However, the number of patients referred to Sophiahemmet Hospital, Stockholm, could not be obtained from Sophiahemmet.

2e **The normal pathway of a patient through the health care system**
Normally a patient with hyperhidrosis would initially be treated with topical agents prescribed by their general practitioner. If this treatment is ineffective he/she will be referred to a Dermatology clinic.

2f **Actual wait time in days for medical assessment /treatment**
Normally, the waiting time for a first visit to an outpatient clinic of a Dermatology clinic is less than 3 months.

Present Health Technology

3a Name/description of the health technology at issue

Botulinum toxin is a protein produced by the anaerobic bacillus *Clostridium botulinum*. It acts by blocking the release of acetylcholine from the presynaptic cholinergic fibers of the sympathetic nerves, including those that innervate eccrine sweat glands (Dickson and Shevky, 1923; Simpson, 2004). The neurotoxin exists in different types, of which type A and type B are currently used pharmacologically. The effect is reversible since the neurons form new synapses (Dressler and Bebecke, 2007).

In 1994 it was shown that BTX injections could inhibit sweating in humans (Bushara and Park, 1994). Today there is a broad spectrum of indications for BTX-A. These include blepharospasm, hemifacial spasm, focal dystonia, focal spasticity, chronic migraine, incontinence due to neurogenic detrusor overactivity, cosmetic use, and primary axillary hyperhidrosis. BTX-A is distributed as Botox®, Dysport® or Xeomin®. BTX-B is distributed as NeuroBloc®, which in Sweden currently is registered only for the indication cervical dystonia (FASS, 2012).

The indication of BTX injections for axillary or palmar hyperhidrosis is excessive sweating that has not responded to standard treatment (AlCl and/or iontophoresis) (Hoorens and Ongenae, 2012). Multiple injections are placed intradermally in the hyperhidrotic area, one to two centimetres apart. In the specific treatment of palmar hyperhidrosis a peripheral nerve blockade is commonly given prior to the injections in order to cause sufficient pain relief.

The duration of the effect on hyperhidrosis has been reported to vary from three months (Baumann *et al*., 2005) to over twelve months (Wollina *et al*., 2002), depending on the location and dose. The mean duration of the effect of 50U BTX (Botox®) on axillary hyperhidrosis is seven months (Lowe *et al*., 2007; Naumann *et al*., 2003).

3b The work group's understanding of the potential value of the health technology

Treatment with BTX has the potential to reduce excessive sweating in patients with axillary and palmar hyperhidrosis, and it has previously been offered to patients in VGR. However, due to economic reasons it was stopped in early 2011.
Since the Dermatology clinics in VGR currently are not offering local BTX therapy, the patients are often referred from a general practitioner to private hospitals or clinics. This causes emotional suffering as well as economical disadvantages for many patients. Furthermore, the patients will not initially be examined by a dermatologist, which may lead to unnecessary referrals.
If treatment with BTX was available in VGR the quality of the work-up of the patients would be improved, and external costs for VGR could be reduced.

3c **The central question for the current HTA project in one sentence**

Is injection treatment with BTX for axillary and palmar hyperhidrosis, and compensatory hyperhidrosis following sympathectomy, better than placebo, no treatment or standard treatments, when assessed as QoL, sweat production, duration and complications?

3d **PICO** *P=Patient I=Intervention C=Comparison O=Outcome*

P_1: Patients with primary axillary or palmar hyperhidrosis

P_2: Patients with compensatory hyperhidrosis following sympathectomy

I: BTX (A or B) injections

C: Standard treatment [topical treatment (AlCl), oral anticholinergics, subcutaneous sweat gland suction curettage]
Placebo or no treatment

O: **Primary outcome variable**:
QoL evaluated by a validated scale e.g. Dermatology Quality of Life Index (DQLI)

Secondary outcome variables:
Sweat production – measured by a validated scale e.g. Hyperhidrosis Disease Severity Scale (HDSS)
Duration of treatment effect
Complications (short- and long-term effects/tolerance)

Study design:
Randomized controlled trials
Cohort studies > 100 patients
Case studies > 100 patients

Limits: Publication date from 1990, English, Danish, Norwegian, Swedish

3e **Key words**

Botulinum toxin type A and B; primary, local hyperhidrosis; axillary/palmar.
Botulinumtoxin typ A och B; primär, lokal hyperhidros; axillär/palmar .

4 Search strategy, study selection and references – appendix 3 (Search strategy, Eligibility criteria, Selection process – flow diagram, References)

During October 2011, the library performed searches in PubMed, the Cochrane Library, EMBASE, PsycInfo and a number of HTA-databases. Reference lists of relevant articles were also scanned for additional references. A total of 665 articles were identified after removal of duplicates, of which the library excluded 607 abstracts. The library excluded another 15 articles after having been read in full text. 34 articles were sent to the work group for assessment. 15 of these articles are included in the report, 13 are randomized controlled trials (RCT) or cohort studies and have been critically appraised. The appraisal of articles is based on checklists from SBU regarding randomized controlled trials and cohort studies. In addition, four systematic reviews have been commented upon but not critically appraised.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 3. The literature search and exclusions of abstracts were done by two librarians (TS, ACE) in consultation with the HTA-centre and the work group.

5a Present knowledge of the health technology (Appendix 1)

The systematic literature search identified eleven RCTs (12 publications), one cohort study, and two case series. One RCT was of high quality, eight of moderate, and two of low quality. The cohort study was of low quality. Almost all controlled studies have compared BTX with placebo, whereas only few of them compared its effects with other (standard) treatments.

The literature search did not identify any publication that has reported effects of BTX on compensatory hyperhidrosis after sympathectomy.

Primary outcome variable

Quality of life

Axillary hyperhidrosis

BTX versus placebo

Four RCTs compared BTX-A with placebo, Appendix 1:1. One trial was of high and three were of moderate quality. Three trials reported improvement in QoL. This was statistically significant in two of them, but the third did not report results of inference tests. The fourth RCT found no significant improvement.

In comparison with placebo, treatment with BTX-A increases QoL-scores, two to four-fold, in patients with axillary hyperhidrosis. Moderate quality of evidence (GRADE ⊕⊕⊕○).

BTX versus aluminum chloride
One RCT of moderate quality compared BTX-A with AlCl, Appendix 1:2.
In comparison with AlCl, treatment with BTX-A increases QoL-scores five-fold in patients with axillary hyperhidrosis. Low quality of evidence (GRADE ⊕⊕○○).

BTX versus subcutaneous curettage
One cohort study of low quality compared BTX-A with subcutaneous curettage, Appendix 1:3. No significant difference in satisfaction score was demonstrated.
In comparison with subcutaneous curettage, treatment with BTX-A does not increase QoL in patients with axillary hyperhidrosis. Very low quality of evidence (GRADE ⊕○○○).

Palmar hyperhidrosis

BTX versus placebo
Two RCTs compared BTX with placebo, Appendix 1:4. One was of moderate and one was of low quality. Both reported significantly better QoL in patients treated with BTX.
In comparison with placebo, treatment with BTX-A increases QoL-score eight-fold in patients with palmar hyperhidrosis. Low quality of evidence (GRADE ⊕⊕○○).

Secondary outcome variables

Sweat production

Axillary hyperhidrosis

BTX versus placebo
Seven RCTs compared BTX-A with placebo, Appendix 1:5. One was of high, five were of moderate, and one was of low quality. All trials reported significant improvement compared to placebo. Ninety-four to 96 % were defined as responders in the 50U BTX-A group compared to 35-36 % in the placebo group.
The average change in sweat production from baseline to week four, varied from -83 to -87 % for BTX, compared to -21 % to -33% for placebo.
In comparison to placebo, treatment with BTX-A reduces sweat production three to eight times more in patients with axillary hyperhidrosis. High quality of evidence (GRADE ⊕⊕⊕⊕).

BTX versus aluminum chloride
One RCT of moderate quality compared BTX-A with AlCl, Appendix 1:6. The response rate after four weeks of treatment was significantly higher in the BTX group (92%) than in the AlCl group (33%).
In comparison with AlCl, treatment with BTX-A reduces sweat production two to three times more in patients with axillary hyperhidrosis. Low quality of evidence (GRADE ⊕⊕○○).

Palmar hyperhidrosis

BTX versus placebo
Three RCTs compared BTX with placebo, Appendix 1:7. Two of them were of moderate and one was of low quality.
In comparison to placebo, treatment with BTX injections reduces sweat production twice as much in patients with palmar hyperhidrosis. Low quality of evidence (GRADE ⊕⊕○○).

Duration of treatment effect

Axillary hyperhidrosis

BTX versus placebo
Four RCTs compared BTX-A with placebo, Appendix 1:8. Two were of moderate and two were of low quality. The average duration of the treatment effect was approximately seven months for BTX-A compared to three months for placebo.
In comparison with placebo, the treatment effect of BTX-A is about two to three times longer. Low quality of evidence (GRADE ⊕⊕○○).

BTX versus subcutaneous curettage
One cohort study of low quality compared BTX-A with subcutaneous curettage, Appendix 1:9. The average duration of the treatment effect was seven months for BTX-A. It was considered permanent after subcutaneous curettage. Very low quality of evidence (GRADE ⊕○○○).

Palmar hyperhidrosis

BTX versus placebo
One RCT compared BTX-A with placebo, and another RCT compared BTX-B with placebo, Appendix 1:10. Both were of low quality. The average effect duration was approximately three months for both BTX-A and BTX-B. The duration of the treatment effect of placebo was not reported. Very low quality of evidence (GRADE ⊕○○○).

Complications and side effects (Appendix 1:11 – 1:14)

BTX is considered to be a relatively safe and well-tolerated product. It has been in medical use since 1980 to treat a wide range of conditions, such as dystonias and other movement disorders, gastrointestinal and urological diseases, lumbal pain, headache, hyperhiydrosis, and it is also used cosmetically.

Local adverse events due to BTX injection include pain, oedema, erythema, ecchymosis, and short-term hyperaesthesia (Naumann *et al*., 2006).

Systemic adverse events are primarily nausea, fatigue, malaise, flu-like symptoms, headache and rash (Naumann *et al*., 2006). These adverse events may occur regardless of the indication. There is a dose-response relationship between the frequency and severity of systemic adverse events (Baumann *et al*., 2005; Naumann *et al*., 2006).

In 2005, Coté *et al*. reviewed all adverse events that were reported to the Food and Drug Administration (FDA) in the United States. The review included serious adverse events between 1989-2003, and non-serious adverse events from December 2001 to November 2002. The adverse events were reported both for cosmetic and therapeutic use of BTX. It was found that serious adverse events were reported 33 times more often for therapeutic use than for cosmetic use. The median dose was four times higher for the therapeutic cases than for the cosmetic cases.
Among 1,437 adverse events reported to FDA for BTX, some are associated with serious events, including 28 deaths, however with unclear causal relation to BTX. Other serious adverse effects included: dysphagia, muscle weakness, allergic reaction, flu-like syndromes, injection site trauma, arrhythmia, seizures and myocardial infarction (Coté *et al*., 2005).

Another complication is the formation of neutralizing antibodies. The incidence has previously been reported of up to 17%, but since the late 1990s it has been much lower. This is due to a new BTX formulation, which contains less proteins (Baizabal-Carvallo *et al*., 2011). Today, the incidence is about 1-5% (Naumann *et al*., 2006). The presence of neutralizing antibodies can lead to non-responsiveness. It is the main factor that determines the long-term effect and use of BTX. The risk factors to develop neutralizing antibodies include a short interval between treatment sessions, the use of booster injections, increasing doses at every session, high cumulative dose and start of treatment at an early age (Naumann *et al*., 2006).

Most of the adverse events that have been reported in patients treated with BTX for primary axillary hyperhidrosis are mild or moderate. An increase in the non-axillary sweating has been observed in many studies with an incidence of about 5% (Heckman *et al*., 2001; Naumann *et al*., 2003; Naumann and Lowe, 2001; Lowe *et al*., 2007; Odderson, 2002; Solish *et al*., 2005).
Muscle weakness has been reported in patients treated with BTX for palmar hyperhidrosis. The incidence varies from 28% (Schneider *et al*., 1997), to 60% (Baumann *et al.*, 2005). In the latter study a high dose of the toxin was used (5000 U BTX (Dysport®)/palm). The muscle weakness is often mild and transient with duration of two to five weeks (Schneider *et al*., 1997).

Systematic reviews

Beyond the scope of the literature search, four systematic review articles were identified, but not critically appraised (not concurrent with PICO):

Coté *et al.* (2005), conducted a systematic review on the adverse effects of BTX injections for cosmetic and therapeutic cases that were reported to FDA. It was concluded that serious adverse effects were more likely to be reported for therapeutic than for cosmetic use. However, this could be related to the complexity of treatment cases in comparison to the cosmetic cases.

Recently, Horeens and Ongenae (2011), systematically reviewed the various treatment modalities for primary focal hyperhiydrosis, and concluded that, although numerous treatment modalities for hyperhiydrosis are available, the challenge for the dermatologist is to evaluate the disease severity.

Jankovic *et al.* (2004), reviewed the effects of BTX-A, systematically, regarding patient-reported outcomes, across different disorders, by assessing the QoL or global treatment outcomes. BTX-A treatment was found to give meaningful benefits on the patients QoL.

Naumann and Jankovic (2004), evaluated the safety of BTX-A in a systematic review and meta-analysis, and stated that the evaluated BTX-A formulation has a favorable safety and tolerability, for a wide range of different therapeutic indications.

5b Outcome tables – appendix 1

5c Excluded articles – appendix 2

5d Ongoing research

A search in www.clinicaltrials.gov (2011-12-21) with the keywords:(botulinum toxin OR botulinum OR botox OR rimabotulinumtoxin OR rimabotulinum OR botulinumtoxin OR xeomin OR dysport OR myobloc) AND (hyperhidrosis OR sweating), identified 10 trials.

Five of the trials are relevant for the question at issue. Of these five trials one is still recruiting patients. It as an RCT in which BTX-A will be compared with suction curettage in patients with axillary hyperhidrosis. Another RCT has evaluated BTX-A compared with placebo, and is completed. However, there are still no results available. Three uncontrolled patient series that have evaluated safety (2 safety/efficacy) of BTX-A in axillary hyperhidrosis, are recently completed. There are still no results available.

6 Which medical societies or health authorities recommend the new health technology?

Treatment with BTX-A for axillary hyperhidrosis was approved by the Swedish Medical Products Agency (MPA) in 2003. In 2004 also the Food and Drug Administration (FDA) in USA approved BTX type A injection for axillary hyperhidrosis.

- ☐ The National Board of Health and Welfare
- ☐ Medical societies
- ☐ Other health authority

Ethical aspects

7 Ethical consequences

Treatment with BTX increases the QoL and reduces the sweat production in patients with axillary and palmar hyperhidrosis. However, it is not a curative treatment and the effect duration is relatively short. It is therefore necessary to repeat the injections one to three times per year. One may question whether it is acceptable to inject the patients once to three times a year, perhaps during their whole lifespan?

If BTX-treatment will not be reintroduced in VGR many patients most probably be referred to other clinics outside the region. This will lead to extra costs for VGR and will also result in an unequal health care.

Organisation

8a When can this new health technology be put into practice?

It is estimated that BTX treatment for axillary and palmar hyperhidrosis can be in practice at all hospitals in the VGR approximately one year after approval.

8b Is this technology used in other hospitals in Western Region of Sweden?

No. See also 3b.

8c According to the work group, will there be any consequences of the new health technology for personnel?

A reintroduction of BTX treatment would make it necessary to educate one or two nurses, and one doctor per clinic. No other consequences are expected.

8d Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

General practitioners, and other clinics, will be able to refer patients to the Dermatology clinics at the public hospitals in the VGR. This will not negatively affect other clinics or supporting functions in the region.

Economy

9a Present costs of currently used technologies

At present, patients with primary hyperhidrosis are not treated at Dermatotology clinics of the public sector in VGR. Because of this situation some patients seek care within the private sector. Currently, these patients privately pay the treatment costs. Other patients may be referred from general practitioners to the Sophiahemmet Hospital in Stockholm, which sends invoices to the Department for Administrative Affairs in VGR. A few patients have also been referred from the Dermatology clinic at Sahlgrenska University Hospital to Sophiahemmet Hospital. The costs for these patients were paid by the referring clinic.

During the period June 30, 2010 to November 6, 2011, i.e. a period of 1 year and 4 months, VGR was charged a total of 821,647 SEK for patients that had been directly referred from general practitioners to Sophiahemmet Hospital in Stockholm. One additional patient was referred from Sahlgrenska University Hospital to Sophiahemmet Hospital, because of compensatory hyperhidrosis. The total cost for these patients was 1.2 million SEK (year 2011). However, the number of patients referred from VGR to Sophiahemmet during 2011 could not be obtained from the invoice system at Sophiahemmet.
The estimated cost of BTX treatment in VGR would be 8,200 SEK per patient per year, if the treatment would be reintroduced, based on data from SÄS, VGR, from January to June 2011, including:

- Medication: 6,919 SEK (1,870 SEK (One ampoule 100E) x 3.7 [average number of ampoules per patient per year])
- Cost of doctor and nurse (time): 1,270 SEK

9b Expected costs of the new health technology?

The cost per patient and year has been estimated to be 8,200 SEK, and the number of patients in need of BTX to be at least 200 patients per year (see 2d above). This would yield a total cost of 1,640,000 SEK. However, this is probably an underestimation of the total annual cost since the general practitioner probably will refer more patients if the treatment becomes available in VGR.

9c Total change of cost

It is likely that the total cost will be reduced in VGR if BTX treatment for hyperhidrosis will be reintroduced. Thus, by not referring patients outside VGR would not need to not pay extra for rent, personnel and travels. However, if the costs in VGR would increase substantially from the calculated 8,200 SEK/patient/year, the indications could be limited to treatments with high quality of evidence for a positive effect, or for certain degrees of disease severity.

9d Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

No

9e Are there any available analyses of health economy? Cost advantages or disadvantages?

No cost effectiveness studies are available.

Unanswered Questions

10a **Important gaps in scientific knowledge?**
It is still not known whether BTX treatment has any benefical effects on compensatory hyperhidrosis after sympathectomy. The effects of BTX treatment on palmar hyperhidrosis are still not fully established. Thus, further studies are needed.

10b **Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?**
Yes. However, presently there are no detailed study protocols.

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Botulinumtoxinbehandling av axillär- och palmar hyperhidros

Frågeställning: Är injektionsbehandling med BTX för axillär- eller palmar hyperhidros, samt för kompensatorisk hyperhidros efter sympatektomi bättre än placebo, ingen behandling eller standardbehandling, mätt som livskvalitet, svett produktion, effektens varaktighet och komplikationer?

PICO (Patient, Intervention, Comparison, Outcome)

P_1:	Patienter med primär axillär eller palmar hyperhidros
P_2:	Patienter med kompensatorisk hyperhidros efter sympatektomi
I:	BTX (A eller B) injektioner
C:	Standardbehandling [topikal behandling (aluminum klorid), perorala antikolinergika, subkutan svettkörtel kyrettage], placebo eller ingen behandling.
O:	Primära utfallsmått: Livskvalitet mätt med validerad skala t.ex. Dermatology Quality of Life Index (DQLI) Sekundära utfallsmått: Mätning av svettproduktion med validated skala t.ex. Hyperhidrosis Disease Severity Scale (HDSS) Behandlingseffektens varaktighet (duration)

Resultat av HTA-processen:

Metod och målgrupp:
Primär hyperhidros är ett tillstånd av överdriven svettning av okänd orsak. Det kan allvarligt påverka livskvaliteten negativt. Botulinumtoxin (BTX) injektioner är en lokal behandling som kan användas till patienter med axillär eller palmar hyperhidros, eller kompensatorisk hyperhidros efter sympatektomi, om de inte svarar inte på andra lokala behandlingar.

Evidensläge:
Den systematiska litteratursökningen identifierade elva randomiserade kontrollerade studier, en kohortstudie, och två fallserier som rapporterade effekter av BTX injektioner hos patienter med axillär eller palmar hyperhidros. Nästan alla kontrollerade studier jämförde BTX med placebo, medan endast ett fåtal av dem jämförde effekterna mot standardbehandlingar.
Litteratursökningen kunde inte finna någon publikation som rapporterade effekter av BTX på kompensatorisk svettning efter sympatektomi.

Axillär hyperhidros

Livskvalitet
BTX behandling ökade livskvalitén 2-4 gånger mer än placebo. Måttligt starkt vetenskapligt underlag (GRADE ⊕⊕⊕◯), och i jämförelse med aluminiumklorid ökade livskvalitén 5-faldigt. Begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯). I jämförelse med subkutan kyrettage ökade inte livskvaliteten. Otillräckligt vetenskapligt underlag (GRADE ⊕◯◯◯).

Svettproduktion
BTX behandling minskade svettproduktionen 3-8 gånger mer än placebo och 2-3 gånger mer än med aluminiumklorid (AlCl), baserat på starkt vetenskapligt underlag (GRADE ⊕⊕⊕⊕), avseende placebo, och på begränsat vetenskapligt underlag (GRADE ⊕⊕◯◯), avseende AlCl.

Behandlingseffektens varaktighet (duration)
Behandlingseffekten av BTX injektioner varar i ungefär sju månader, vilket är 2-3 gånger längre i jämförelse med placebo. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).
Behandlingseffekten med subkutan kyrettage betraktas som stadigvarande. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

Palmar hyperhidros
Livskvalitet
BTX behandlingen ökade livskvalitén 8 gånger mer än placebo. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).

Svettproduktion
BTX behandling minskade svettproduktionen dubbelt så mycket som placebo. Begränsat vetenskapligt underlag (GRADE ⊕⊕○○).

Behandlingseffektens varaktighet (duration)
Behandlingseffekten av BTX varar cirka tre månader. Ingen jämförelse har gjorts med placebo eller standardbehandling. Otillräckligt vetenskapligt underlag (GRADE ⊕○○○).

Komplikationer och biverkningar:
De flesta biverkningar av BTX behandling vid hyperhidros är milda eller måttliga. En ökning av icke-axillär svettning, med en incidens på cirka 5%, har observerats hos BTX behandlade patienter med axillär hyperhidros. Mild muskelsvaghet, mestadels övergående, har rapporterats hos ungefär hälften av de patienter som behandlats för palmar hyperhidrosis.

Etiska aspekter:
Behandling med BTX är en icke-kurativ behandling, där varaktigheten av enstaka behandlingar är relativt kort. Detta innebär upprepade injektioner. Är det etiskt försvarbart att injicera patienterna, en till tre gånger per år, kanske under hela sin livstid? Är det försvarbart att inte erbjuda BTX behandling för patienter med hyperhidros i Västra Götalandsregionen (VGR) när den erbjuds i andra regioner och län i Sverige?

Ekonomiska aspekter:
Kostnaden per patient per år är uppskattad till 8200 SEK. Denna uppskattning är förknippad med en relativt stor osäkerhet.

Sammanfattning:
BTX förbättrar livskvalitén och minskar svettproduktionen hos patienter med primär axillär hyperhidros i jämförelse med både placebo och AlCl. Det vetenskapliga underlaget är starkare för jämförelsen mot placebo än mot AlCl. Även patienter med primär palmar hyperhidros upplever liknande förbättring av livskvalitet, och liknande minskning av svettproduktion, när BTX jämförs med placebo. Det vetenskapliga underlaget är dock inte lika starkt som vid axillär hyperhidros. Behandlingseffektens varaktighet (duration) är tre till sju månader. Patienterna behöver således upprepade injektioner, med en uppskattad årlig kostnad av 8 200 SEK per patient.

För HTA-kvalitetssäkringsgruppen
Göteborg, Sverige, 2012-02-29
Christina Bergh, Professor

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Denna HTA har genomförts på begäran av sektorsrådet, ordf. Lillmarie Persson, verksamhetschef område Medicin psykiatri, Kärnsjukhuset Skövde samt Carin Sandberg, verksamhetschef, verksamhet Hud och könssjukvård, SU/Sahlgrenska sjukhuset
Från HTA-centrum har Christina Bergh, professor (huvudansvarig) och Petteri Sjögren varit resurspersoner tillsammans med HTA-bibliotekarie Therese Svanberg och bibliotekarie AnnCatrin Ekelund. HTA-rapporten och åberopad och förtecknad litteratur har sedan granskats av Magnus Ritzell, överläkare, verksamhet Transplantation, SU/Sahlgrenska sjukhuset

Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid HTA-kvalitetssäkringsgruppens möte 2012-02-29
Projektet har pågått under perioden 2011-10-03 – 2012-02-29.

HTA-kvalitetssäkringsgruppen:

Christina Bergh Professor, överläkare	Anders Larsson Överläkare	Maria Skogby Med dr, vårdenhetschef
Thomas Franzén Bibliotekschef	Christian Rylander Med dr, överläkare	Annika Strandell Docent, överläkare
Magnus Hakeberg, Professor, övertandläkare	Ola Samuelson, Docent, överläkare	Therese Svanberg HTA-bibliotekarie
Lennart Jivegård, Docent, universitetslektor	Petteri Sjögren Med dr, tandläkare	Kjell-Arne Ung Docent, överläkare
Peter Johansson Med dr, överläkare	Henrik Sjövall Professor, överläkare	Margareta Warrén Stomberg Docent, överläkare

Statement from the Regional HTA Centre of Region Västra Götaland, Sweden

Botulinum toxin treatment of axillary and palmar hyperhidrosis

Question at issue

Is injection treatment with BTX for axillary, palmar hyperhidrosis and compensatory hyperhidrosis following sympathectomy better than placebo, no treatment, or standard treatments when assessed as QoL, sweat production, duration and complications?

PICO (Patient, Intervention, Comparison, Outcome)

P_1: Patients with primary axillary or palmar hyperhidrosis

P_2: Patients with compensatory hyperhidrosis following sympathectomy

I: BTX (A or B) injections

C: Standard treatment [topical treatment (aluminum chloride), oral anticholinergics, subcutaneous sweat gland suction curettage], placebo or no treatment

O: Primary outcome variable:
Quality of life evaluated using a validated scale e.g. Dermatology Quality of Life Index (DQLI)
Secondary outcome variables:
Measurement of sweat production using a validated scale e.g. Hyperhidrosis Disease Severity Scale (HDSS)
Duration of treatment effect

Summary of the health technology assessment

Method and patient category

Primary hyperhidrosis is a condition of excessive sweating of unknown cause. It may severely affect the quality of life (QoL). Botulinum toxin (BTX) injections is a local treatment that can be used in patients with axillary or palmar hyperhidrosis, or compensatory hyperhidrosis following sympathectomy, if they are unresponsive to other local therapies.

Level of evidence

The systematic literature search identified eleven randomized controlled trials, one cohort study, and two case series reporting the effects of BTX injections in patients with axillary or palmar hyperhidrosis. Almost all controlled studies compared BTX with placebo, whereas only few of them compared the effects with standard treatments.
The literature search did not find any publication that has reported the effects of BTX on compensatory hyperhidrosis after sympathectomy.

Axillary hyperhidrosis

Quality of life

In comparison with placebo, treatment with BTX increased the QoL-score 2-4 fold (Moderate quality of evidence GRADE ⊕⊕⊕◯), and in comparison to aluminium chloride it increased the QoL-score 5-fold (low quality of evidence GRADE ⊕⊕◯◯). In comparison with subcutaneous curettage BTX does not increase the QoL-score (very low quality of evidence GRADE ⊕◯◯◯).

Sweat production

In comparison to both placebo and aluminum chloride (AlCl), treatment with BTX reduced sweat production 3-8 times more. This is of high quality of evidence (GRADE ⊕⊕⊕⊕), with regard to placebo, and of low quality of evidence (GRADE ⊕⊕◯◯), with regard to AlCl.

Duration of treatment effect
The treatment effect of BTX is about seven months, which in comparison with placebo is 2-3 times longer. Low quality of evidence (GRADE ⊕⊕○○). The duration of the treatment effect was considered permanent after subcutaneous curettage. Very low quality of evidence (GRADE ⊕○○○).

Palmar hyperhidrosis
Quality of life
In comparison with placebo, treatment with BTX increased the QoL-score 8 fold. Low quality of evidence (GRADE ⊕⊕○○).

Sweat production
In comparison to placebo, treatment with BTX reduced sweat production twice as much. Low quality of evidence (GRADE ⊕⊕○○).

Duration of treatment effect
The treatment effect of BTX is about three months. No comparison has been made with placebo or standard treatment. Very low quality of evidence (GRADE ⊕○○○).

Complications
Most adverse events of BTX-treatment for hyperhidrosis are mild or moderate. An increase in non-axillary sweating has been observed with an incidence of about 5% in BTX-treated patients with axillary hyperhidrosis. Mild muscle weakness, mostly transient, has been reported in about half of the patients treated for palmar hyperhidrosis.

Ethical aspects
Treatment with BTX is not a curative therapy, and the duration of a single treatment is relatively short. This means repeated injections. Is it acceptable to inject the patients once to three times per year, perhaps during their whole lifespan? Is it acceptable not to offer BTX treatment for patients with hyperhidrosis in Region Västra Götaland (VGR) when it is offered in other regions and counties of Sweden?

Economical aspects
The cost per patient per year is estimated to 8,200 SEK. This estimation is associated with a relatively high degree of uncertainty.

Concluding remarks
Botulinum toxin increases quality of life and reduces sweat production in comparison to both placebo and aluminum chloride in patients with primary axillary hyperhidrosis. The quality of evidence is stronger with regard to placebo than it is with regard to aluminium chloride. Also patients with primary palmar hyperhidrosis experience an increased quality of life and a reduced sweat production of similar magnitudes when BTX treatment is compared to placebo. However, the quality of evidence is not as high as it is for axillary hyperhidrosis. The duration of the treatment effect is three to seven months. Thus, the patients will need repeated injections, to an estimated cost of 8,200 per patient per year.

On behalf of the Regional HTA-centre, Region Västra Götaland, Sweden
Göteborg, Sweden, 2012-02-29
Christina Bergh, Professor, MD.
Head of Regional HTA-centre, Region Västra Götaland, Sweden.

Appendix 1:1

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Connor 2006	USA	RCT	40	7	(20) BTX-A (Botox®) 50U+Paroxetin 25mg /day Average HHIQ[1] item score at: Baseline 1.6 Week8: 0	(20) Placebo+Paroxetin 25mg/day Average HHIQ[1] item score at: Baseline: 2.3 Week8: 0.8 p(final visit) BTX vs placebo= 0.001 p(baseline- final visit) BTX vs placebo=0.09 ns		Moderate
Lowe 2007	USA	RCT	322	70	(110) BTX-A 75U (96 after dropouts) Mean reduction in DLQI[2] score at week 4: 75U:-7.2+/-5.6 50U:-5.6+/-4.8	(108) Placebo (73 after dropouts) Mean reduction in DLQI[2] score at week 4: -1.6+/-4.5 p< 0.001 BTX vs placebo		Moderate
Naumann 2001	Multicenter Germany	RCT	320	13	(242) BTX-A (Botox®) 50U/axilla Satisfaction score* Week n mean (SD) 1 67 3.1 ± (1.1) 4 85 3.3 ± (0.9) 16 204 2.6 ± (1.6)	(78) Placebo Satisfaction score* Week n mean (SD) 1 24 0.8 ± (1.4) 4 29 0.8 ± (1.4) 16 61 0.3 ± (1.2) p<0.001 BTX vs placebo at week 1, 4 and 16.	*Global assessment of treatment satisfaction scale +4 About 100% improvement +3 About 75% improvement +2 About 50% improvement +1 About 25% improvement 0 Unchanged -1 About 25% worse -2 About 50% worse -3 About 75% worse -4 About 100% worse or greater	High

Appendix 1:1

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Naumann 2002	Germany	RCT	320	13	(242) BTX-A (Botox®) 50U/axilla Percentage of patients who report any effect of hyperhidrosis on their emotional status 16 weeks after treatment (HHIQ): 35% (53% reduction from baseline) Percentage of patients who reported feeling at least moderately limited in public places as a result of hyperhidrosis, at week 16 (HHIQ): 10% (58% reduction from baseline) Percentage of patients who reported feeling at least moderately limited as a result of their hyperhidrosis when meeting people for the first time, at week 16 (HHIQ): 8% (75% reduction from baseline)	(78) Placebo Percentage of patients who report any effect of hyperhidrosis on their emotional status 16 weeks after treatment (HHIQ): 75% (10% reduction from baseline) p<0.001 BTX vs placebo between groups Percentage of patients who reported feeling at least moderately limited in public places as a result of hyperhidrosis, at week 16 (HHIQ): 45% (23% reduction from baseline) p<0.001 BTX vs placebo Percentage of patients who reported feeling at least moderately limited as a result of their hyperhidrosis when meeting people for the first time, at week 16 (HHIQ): 48% (27% reduction from baseline) p<0.001 BTX vs placebo	Same study as Naumann 2001	High

Appendix 1:1

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
					Change in physical component summary (PCS) of the SF-12[3] from baseline to week 16: 0.9 p =0.012 within group	Change in physical component summary (PCS) of the SF-12[3] from baseline to week 16: 1.2 p= 0.221 within group	SF-12[3] The difference in change from baseline between the two treatment groups was statistically significant (p = 0.019). No statistically significant difference in change from baseline between the two groups was seen regarding mental component summary (MCS)(p = 0.247)	
Naumann 2003	Germany	RCT	207	33	(203)* BTX-A (Botox®) 50U/axilla 1-3 treatment cycles Mean satisfaction scores* at week 4: First treatment: +3.5 Second treatment:+3.4 Third treatment:+3.3	(49) Placebo No reports Mean satisfaction scores* at week 4: +1.4	*Includes the majority of patients in the placebo group who were offered BTX treatment (open label) after 16 weeks of follow up. *Measured on a 9 point scale where +4 for complete abolishment of signs and symptoms and –4 for a very marked worsening.	Moderate

1) HHIQ (Hyperhidrosis Impact Questionnaire) consists of two related modules: a 41-item module for baseline disease impact assessment and a 10-item module for follow-up longitudinal assessment and comparison with baseline. Baseline items are divided into 4 groups; disease and treatment background; direct impact on medical and non medical resource utilization; indirect impact on employment and productivity; and intangible impacts. Score 0-4: 0 =not limited, 1=somewhat, 2=moderately, 3=quiet a bit, and 4=extremely limited.

2) DLQI (Dermatology Life Quality Index): a 10-item dermatology specific questionnaire that assesses Health Related Quality Of Life (RHQOL) during the previous week. Scores range from 0-30, 0 indicating no HRQOL impairment and 30 indicating the most HRQOL impairment.

3) SF-12(Medical Outcome Trust Short Form-12 Health Survey): a validated, general health-related QOL questionnaire consisting of 12 items designed to assess patients' views about their general health, physical activity, emotional health, bodily pain and social functioning. Results are reported as physical component summary (PCS) and mental component summary (MCS) scores.

4) P-HQOL (Palmar Hyperhidrosis Quality of Life): scores range from 4-15. Score 4 representing 'no interference with daily life'. Score 15 representing 'a great deal of interference with daily life'.

Appendix 1:2

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injection axillary and aluminum chloride (AlCl) in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control AlCl		
Flanagan 2008	USA	RCT	50	5	(22) BTX-A (Botox®) 50 U/axilla Mean score for degree of emotional injury due to hyperhidrosis (HHIQ) at: Baseline: 1.8 Week4: 0.2	(23) AlCl Mean score for degree of emotional injury due to hyperhidrosis (HHIQ) at: Baseline: 1.9 Week 4: 1.1 p<0.05 BTX vs AlCl at week 4		Moderate

Appendix 1:3

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injection and subcutaneous curettage in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Subcutaneous curettage		
Rompel 2001	Germany	Cohort	113	13	(23) BTX-A (14) Botox® 40-50U (9) Dysport® 200-250U General satisfaction with the procedure Very good 9 (39.1%) Good 5 (21.7%) Satisfied 2 (8.7%) Dissatisfied 7 (30.4%) No answer 0 (0.0%)	(77) (13 lost to follow-up) General satisfaction with the procedure Very good 28 (36.4%) Good 23 (29.9%) Satisfied 13 (16.9%) Dissatisfied 12 (15.6%) No answer 1 (1.3%) Not significant	Follow up 23.5 months	Low

Appendix 1:4

Outcome variable: Quality of life (QoL) after botulinum toxin (BTX) injections and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Bauman 2005	USA	RCT	20	2	(17) BTX-B (Myobloc®) 5000U/palm	(3) Placebo	Significant difference in P-HQOL scores between BTX and placebo P-HQOL, p=0.010 The results are not divided into BTX group and placebo group, which make it difficult to tabulate.	Low
Lowe 2002	USA	RCT	19	3	(16) BTX-A(Botox®) 100 U/palm At day 28, 100% of the patients were satisfied.	(16) Placebo At day 28, 12% of the patients were satisfied. p<0.0001 BTX vs placebo	The patients were their own controls; they got BTX on one side and placebo on the other.	Moderate

Appendix 1:5

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Connor 2006	USA	RCT	40	7	(20) BTX-A (Botox®) 50U+Paroxetin 25mg /day Week 8: 15 (75%) rsp	(20) Placebo + Paroxetin 25mg/day Week 8: 3 (15%) rsp p<0.001BTX vs placebo	Rsp= responders = - ≥ 2pts HDSS [1] (see below)	Moderate
Heckmann 2001	Germany	RCT	145	9	(145)BTX-A (Dysport®) 200U Mean sweat production measured gravimetrically.* Week 2 24±27mg Mean reduction in sweating 2 weeks after 200U (within group comparison) 81.4% p=0.04	(145)Placebo Mean sweat production measured gravimetrically.* Week 2 144±113mg Mean difference between the groups 111mg per minute; 95% CI (91-132) p< 0.001 BTX vs placebo	The patients were their own controls; they got BTX on one side and placebo on the other. *Measured gravimetrically, [2] (see below) 1min, rest 15 min, 25° C Sweat production at baseline 192±136mg; median 154 Open label after 2 weeks. Injection with 100U Dysport in axillae with placebo. Mean reduction in sweating 2 weeks after 100U 76.5% p=0.04 100U vs 200U Mean sweat production after 200U Week 26 67±66mg/min 100U Dysport in placebo axilla open label. Mean sweat production. Week 2 32±39 mg p<0.001 (within-group comparison) Week 24 65±64 mg	Moderate

Appendix 1:5

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Lowe 2007	USA	RCT	322	70	Measurement in HDSS (110) BTX-A 75U 49% (54/110) rsp (104) BTX-A 50U 55% (57/104) ≥2 points improvement in HDSS score from baseline 4 weeks after 1st treatment 75% in 75U & 50U 4 weeks after 2nd treatment 74% (39/53) 75U 85% (41/48) 50U Complete resolution of symptoms (HDSS= 1) 75-U 48% 50-U 42% Gravimetric measurement Mean decrease in sweat production 4 weeks after 1st treatment 75U 87% ±22% 50U 82%±33% After 2nd treatment 75U 81% ±24% 50U 87%± 12%	Measurement in HDSS (108) Placebo 6% (6/108) rsp p<0.001 BTX vs placebo -ns between 50U and 75U ≥2 points improvement in HDSS score from baseline 4 weeks after 1st treatment 25% in placebo p<0.001 75-U or 50-U vs placebo 4 weeks after 2nd treatment 26% (18/68) placebo p<0.001 75U or 50U vs placebo Complete resolution of symptoms (HDSS=1) 9% p=0.01 75-U or 50-U vs placebo Gravimetric measurement Mean decrease in sweat production 4 weeks after 1st treatment 33%±80% p<0.001 75U or 50U vs placebo After 2nd treatment 24% ±110% p<0.001 75U or 50U vs	Rsp= Responders= - ≥2 HDSS or a sustained response during the 52 weeks follow up.	Moderate

Appendix 1:5

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
					Percentage of patients with >75% reduction in sweat production 4 weeks after first treatment 75U 84% 50U 80%	placebo Percentage of patients with >75% reduction in sweat production 4 weeks after first treatment 21% p<0.001 75U or 50U vs placebo		
Naumann 2001	Multicenter Germany	RCT	320	13	(242) BTX-A Botox® 50U Rsp W eek 1: 230 (95%) Week 4: 227 (94%) Week 16: 198 (82%) Persistent treatment rsp at week 16, 77% (182/235) Mean sweat production (mg) (SD) Week 0: 215.8 ± 178.7 Week 1: 28.6 * ± 37.5 Week 4: 28.1* ± 40.5 Week 16: 53.7* ± 67.7 Sweat production (% change from baseline) (Mean) (SD) Week 1: -83.0* ± 24.1 Week 4: -83.5* ± 21.6 Week 16: -69.3* ±39.4	(78)Placebo Rsp Week 1: 25 (32%) p<0.001 Week 4: 28 (36%) p<0.001 Week 16: 16 (21%) p<0.001 p=BTX vs placebo Persistent treatment rsp at week 16, 18% (13/74) P<0.001 Mean sweat production (mg) (SD) Week 0: 235.7 ± 213.8 Week 1: 166.2 ± 178.8 Week 4: 153.0 ± 143.3 Week 16: 190.5 ± 195.6 *p<0.001 compared with placebo Sweat production (% change from baseline) (Mean) (SD) Week 1:-21.8 ± 58.7 Week 4: -20.8 ± 54.4 Week 16: -3.8 ± 93.5 *p<0.001 compared with placebo	Rsp=Responders ≥ 50% reduction from baseline in axillaries sweating measure gravimetrically. [2] See below *Includes the majority of patients in the placebo group who were offered BTX treatment (open label) after 16 weeks of follow-up.	High

Appendix 1:5

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Naumann 2003	Germany	RCT	207	33	(203)* BTX-A (Botox®) 50U/axilla % rsp Week 4, 96.1% (93.4-98.7) Week 16 79.8-89.7% Sweat production % change from baseline (within-group comparison) After 1st BTX-A treatment Week 4: -84.6±18.2 p<0.001 Week 16:-69.7±37.5 p<0.001 Sweat production (mg) After 1st BTX-A treatment Week 4: 27.4±35.2 Week 16: 59.3 ±73.0	(49) Placebo % rsp Week 4, 34.7% (21.4-48.0) Week 16, 9.1-31.7% Sweat production % change from baseline (within-group comparison) After one placebo treatment Week 4: -19.1 ±54.0 p=0.01 Week 16: 3.2±112.7 p=0.08 Sweat production (mg) After one placebo treatment Week 4: 173.0 ±157.3 Week 16: 210.0±202.4	Rsp= Responders= ≥ 50% reduction from baseline measured by gravimetric assessment. No significance test. Only descriptive data.	Moderate
Odderson 2002	USA	RCT	18	0	(12) BTX-A 50 U/axilla Average reduction in sweat after 2 weeks (within- group comparison) 91.6% (from 5.04± 4.64 to 0.42±0.30 ml/min/m2) p<0.05 within groups	(6) Placebo Temporarily experienced a mild average reduction in sweat rate, not statistically significant.	Sweating per surface area measured by filter paper	Low
Schnider 1999	Austria	RCT	13	0	(13) BTX-A (Dysport®) 200mU Objective measurement NS Mean difference in ninhydrin staining between the groups	(13) Placebo Results are presented as between groups difference.	Placebo in the other axilla on the same person NS= Ninhydrin sweat test. 3)See below	Moderate

Appendix 1:5

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
					Week 3 –34.5% (95% CI –49.7 to –19.5% Week 8 -36.9% (95%CI –50.7 to –23.1% Week 13 -28.4% (95% CI –38.9 to –18% Subjective rating, mean difference in the VAS between the groups Week 3 -56.5% (95% CI –78.8 to –34.3%) Week 8 –67.4% (95% CI –85.5 to –48.9%) Week 13 –62.5% (95% CI –79.7 to – 45.4%)	p<0.001 p<0.001 p<0.001 p<0.001	Subjective impression visual analogue scale (VAS) 0= non sweating 10= severe sweating	

[1] Hyperhidrosis Disease Severity Scale (HDSS) to classify the degree of difficulty score 1-4 (adapted from Solish *et al*., 2005):

1. My underarm sweating is never noticeable and never interferes with my daily activities.
2. My underarm sweating is tolerable but sometimes interferes with my daily activities.
3. My underarm sweating is barely tolerable and frequently interferes with my daily activities.
4. My underarm sweating is intolerable and always interferes with my daily activities.

[2] Gravimetric measurement: the sweat is absorbed in a pre-weighed filter paper during a couple of minutes and then weighted.

[3] Ninhydrin sweat test: Quantification of sweat production using digitized ninhydrin stained sheets. Ninhydrin stains aminoacids and peptides in sweat.

Appendix 1:6

Outcome variable: Sweat production after botulinum toxin (BTX) injection and aluminium chloride (AlCl) in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control AlCl		
Flanagan 2008	USA	RCT	50	5	(22) BTX-A (Botox®) 50U Week 4, (24 subjects) 91.7% rsp* Mean change in HDSS from baseline -2.42 ±0.65 Mean HDSS score at week 4: 1.21±0.41 Week 8, (22 subjects) 90.0% rsp Mean change in HDSS from baseline -2.32± 0.78 Week 12 77.3% responders Mean change in HDSS from baseline -2.23±0.92	(23) 20% AlCl Week 4, (24 subjects) 33.3% rsp p<0.001 Mean change in HDSS from baseline -1.33 ±1.13→ see comments p<0.0001 BTX vs AlCl Mean HDSS score at week 4: 2.38± 1.06 p<0.0001 BTX vs AlCl Week 8, (6 subjects) 83% responders Mean change in HDSS from baseline -2.83±0.41 p<0.001 BTX vs AlCl	*Rsp= Responders = - ≥2 pts HDSS Hyperhidrosis severity scale 17 patients in the AlCl group were non-responders or did not tolerate the treatment. Among the 7 subjects responding to and tolerating AlCl therapy at week 4, there was no significant difference in HDSS scores when compared with the BTX-A responders. 17 subjects (71%) did not tolerate AlCl, not responders-start with BTX-A Week 4 after BTX 16 (94.1%) treatment rsp to BTX-A Mean change in HDSS -2.83±0.41 Week 12, 7 subjects with AlCl 100% responders Mean change in HDSS -2.86±0.38 Mean HDSS score 1.14± 0.38 not significantly different from the BTX-A Week 12 crossover group 16 subjects Mean change in HDSS from baseline to week 12 -2.56±0.63 The difference in treatment response between the groups at week 12 was not significant.	Moderate

Appendix 1:7

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Baumann 2005	USA	RCT	20	3	(15) BTX-B (Myobloc®) 5000U/palm	(5) Placebo Significant difference in P-HI scores between Myobloc and placebo at day 30 p=0.002 BTX vs placebo	P-HI=Palmar hyperhidrosis improvement. Lowest score 2 (great improvement in palmar hyperhidrosis), highest 8 (worsening hyperhidrosis) No difference between the groups with starch iodine test p=0.056 Mixed blinded and unblinded patients	Low
Lowe 2002	USA	RCT	19	3	(16) BTX-A(Botox®) 100 U Gravimetric measurement (mg/5min) Day 0 290 Day 7 160 Day 14 120 Day 28 100 Patients' assessment on clinical severity Day 0 VAS 8.5 Day 7 VAS 6* Day 14 VAS 4.5* Day 28 VAS 4*	(16) Placebo Gravimetric measurement (mg/5min) Day 0 300 Day 7 270 Day 14 240 Day 28 210* *p=0.0027 BTX vs placebo Patients' assessment on clinical severity Day 0 VAS 8.5 Day 7 VAS 7.5 Day 14 VAS 7 Day 28 VAS 7 *p= 0.0062 BTX vs placebo for change from baseline.	The patients were their own controls; they got BTX on one side and placebo on the other. Gravimetric=Sweat production is determined over 5 minutes by absorption onto a filter paper. VAS= Visual analogue scale 0= non sweating 10= severe sweating Figure 4 incorrect. No placebo at day 7 and 28. Different values of p in text 0.008 and under the figure 0.088	Moderate

Appendix 1:7

Outcome variable: Sweat production after botulinum toxin (BTX) injection and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Schnider 1997	Austria	RCT	11	0	(11) BTX-A (Dysport®) 120 mouse U Mean reduction in sweat production NST[1] Week 3 26% (95% CI 13%-39%) p<0.001 within group Week 8 26% (95% CI 11%-42%) p=0.002 within group Week 13 31% (95% CI 20%-42%) p<0.001 within group Subjective mean improvement in sweat production measured by VAS* Week 3 38%(95% CI17%-59%) p=0.002 Week 8 40% (95% CI 18%-63%) p=0.002 Week 13 38% (95% CI 16-61% p=0.002	(11) Placebo Mean changes in sweat production were not statistically significant and varied from 0.2% to 1.2% No statistically significant subjective improvement was found at any of the time points in the placebo group	Within-group comparison. The patients were their own controls; they got BTX on one side and placebo on the other. *Subjective impression visual analogue scale (VAS)	Moderate

[1] NST= Ninhydrin sweat test: Quantification of sweat production using digitized ninhydrin stained sheets. Ninhydrin stains aminoacids and peptides in sweat.

Appendix 1:8

Outcome variable: Effect duration after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Lowe 2007	USA	RCT	322	70	(214) BTX-A (110)75U/axilla (104)50U/axilla Mean duration after 1st treatment BTX-A 75U 197 days BTX-A 50U 205 days Mean duration after 2nd treatment BTX-A75U 182 days BTX-A 50U 159 days*.	(108) Placebo Mean duration after 1st treatment Placebo 96 days p<0.001 Mean duration after 2nd treatment Placebo 62 days p<0.001	*The duration of effect after 2nd treatment may have been underestimate, because follow-up was truncated in subjects who still had a response when the study was completed 22% of the BTX-A-treated subjects did not return to an HDSS score of 3 or 4 at 52 weeks after their first treatment.	Moderate
Naumann 2003	Germany	RCT	207	33	(203)*BTX-A (Botox®) 50U/ axilla A prolonged duration of effects was seen following each BTX-A treatment. The overall mean duration: 30.6 weeks (range 15.4-51.3) between 2 consecutive treatments.*	(49) Placebo No data given	*Includes the majority of patients in the placebo group who were offered BTX treatment (open label) after 16 weeks of follow up) *This calculation only applies to subjects who received at least 2 BTX-A treatments. 28% of the subjects who completed the 16- months study period did not receive additional treatments. They were treated with a new injection when they requested it, provided that sweat production in each axilla was at least 50% of the baseline valued and that at least 16 weeks had to elapse between the treatments.	Moderate

Appendix 1:8

Outcome variable: Effect duration after botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Odderson 2002	USA	RCT	18	0	(12) BTX-A 50 U/axilla At day 100, all but two patients had sweat productions levels that were approximately 70% below baseline.	(6) Placebo During the 5-month study The placebo group temporarily experienced a mild reduction in sweat rate (not statistically significant).		Low
Schnider 1999	Austria	RCT	13	0	(13) BTX-A (Dysport®) 200mU They have not measured duration specifically but subjective rating revealed a beneficial effect lasting for the entire observation period (13 weeks) in all patients at the BTX treated site.	(13) Placebo No data given	The patients were their own controls; they got BTX on one side and placebo on the other.	Low

Appendix 1:9

Outcome variable: Effect duration after botulinum toxin (BTX) injection and subcutaneous curettage in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Subcutaneous curettage		
Rompel 2001	Germany	Cohort	113	13	(23) BTX-A (14) Botox® 40-50U (9) Dysport® 200-250U	(77) (13 lost to follow- up)	Follow up 23.5 months	Low
					Mean duration of antiperspirant effect: 7.6 months (median 7) No difference between Botox and Dysport. Two cases of especially long duration 14 an 18 months.	Stated as 'permanent efficacy', but not reported in detail.	*Score ranging from 1 (no axillary secretion) to 6 (maximum axillary secretion)	
					Subjective score of axillary sweating at rest was reduced to: 48.5% after 6 months 68.8% at the end of follow up (median 16.1 months)	Subjective score of axillary sweating at rest was reduced to: 40% after 6 months 45.7 % at the end of follow up (median 28.2 months)		
					The overall subjective score* was reduced to: 52.8% after 6 months 68.6% at the end of the follow up (median 23.5 months) Compared with the initial score (100%)	The overall subjective score* was reduced to: 48.2% after 6 months 56.9% at the end of the follow up (median 23.5 months) Compared with the initial score (100%)	*Overall subjective score= (sweating at rest, physical stress, heat, psychic stress, hot spices)	

Appendix 1:10

Outcome variable: Effect duration after botulinum toxin (BTX) injection and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Baumann 2005	USA	RCT	20	3	(17) BTX-B (Myobloc®) 5000U/palm Mean time until return of baseline levels of sweating 113 days (3.8 months) ranging from 69-147 (2.3-4.9 months) Median time of sweating cessations: (106 days 3.5 months)	(3) Placebo No reports		Low
Schnider 1997	Austria	RCT	11	0	(11) BTX-A (Dysport®) 120 mouseU 8 patients' beneficial effect, lasting for the entire observation period (13 weeks).	(11) Placebo 2 patients, with excellent response at the treated site, also experienced substantial relief on the placebo treated palm.	The patients were their own controls, they got BTX on one side and placebo on the other. Subjective rating They have not measured duration specifically.	Low

Appendix 1:11

Outcome variable: Complications and side effects of botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Connor 2006	USA	RCT	40	7	(20) BTX-A (Botox®) 50U+Paroxetin 25mg /day 6 (30% insomnia 3 (15%) drowsiness 2 (10%) nausea 3 (15%) dry mouth and headache	(20) Placebo+Paroxetin 25mg/day 3 (15%) insomnia 4 (20%) drowsiness 4 (20%) nausea 3 (15%) dry mouth and headache 3 (15%) increased sweating	No serious or unexpected side effects occurred from BTX-A or placebo group	
Goldman 2000	Brazil	Case study	243		BTX-A (Botox®) 30-50U or (Dysport®) 90-150U 18(45%) slight decrease in muscle strength, spontaneous improvement within 2 weeks.	No control group	2 patients had previously done sympathectomy	
Heckmann 2001	Germany	RCT	145	9 after 14 weeks	(145) BTX-A (Dysport®) 200U 4 (4/145=2.8%) headache 2 (2/145=1.4%) muscle soreness of the shoulder girdle 1 (1/145=0.7%) increased facial sweating 1 (1/145=0.7%) axillary itching	(145) Placebo	The patients were their own controls; they got BTX on one side and placebo on the other. During the first 14 weeks of follow-up, no major adverse events were associated with treatment with BTX.	
Lowe 2007	USA	RCT	322	70	(110) BTX-A 75U (96 after dropouts) Injection site pain: 9% (75U) 12% (50U) Injection site bleeding: 6% (75U)	(108) Placebo (73 after dropouts) Injection site pain: 8 % Injection site bleeding: 3%	There was no significant between-group differences in the incidence of any treatment related adverse event and no serious treatment-related adverse event were reported during the 52 weeks follow up. The mean duration of injection-site pain was 2.4 days with a maximum duration	

Appendix 1:11
Outcome variable: Complications and side effects of botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
					5 % (50U) Non-axillary sweating: 6% (75U), 10% (50U)	Non-axillary bleeding: 4%	of 10 days.	
Naumann 2001	Multicenter Germany	RCT	320	13	(242) BTX-A (Botox®) 50U/axilla 14/242 (6%) common cold Treatment related adverse events were reported by 27 (11%) patients 11 patients (5%) compensatory hyperhidrosis.*	(78) Placebo 10/78 (13%) common cold p 0.049 BTX vs placebo Treatment related adverse events were reported by 4 (5%) patients ns. BTX vs placebo none compensatory hyperhidrosis	Adverse events were similar between treatment groups in type, incidence, and severity. Most adverse events in both groups were mild or moderate. The only significant difference between the groups was in the incidence of infection, predominantly common cold *All eleven were responders, and non axillary sweating were reported at various body sites (4 forehead, 3 palmar, 2 facial, 1 hands, 1 feet, 1 back, 1 chest, 1 trunk, 1 groin, 1 unspecified), with five patients reporting sweating at two sites	
Naumann 2003	Germany	RCT	207	33	(203)* BTX-A (Botox®) 50U/axilla 1-3 treatment cycles The most common treatment related adverse event was increase in non axillary sweating: 9/207(4.3%)	(49) No reports	*Includes the majority of patients in the placebo group who were offered BTX treatment (open label) after 16 weeks of follow up. No increase in the number of AEs with additional treatment cycles. Of the 49.3% (102/207) who reported at least one adverse event, 13.5% (28/207) reported events that were considered treatment related The most common adverse event was infection (predominantly common cold), followed by flu syndrome and a perceived increase in non-axillary sweating (which occurred at several sites including the forehead hand, face, feet,	

Appendix 1:11

Outcome variable: Complications and side effects of botulinum toxin (BTX) injection and placebo in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
							back, chest, trunk, and groin) Eleven reported serious adverse events, but none was considered to be related to the study. One possible seroconversion for neutralizing antibodies to BTX-A.	
Odderson 2002	USA	RCT	18	0	(12) BTX-A 50 U/axilla	(6) Placebo	During the study only 1 of 18 patients reported an adverse event (localized, mild compensatory hyperhidrosis between the thighs). It is unclear whether this subject was in BTX- or placebo group	
Schnider 1999	Austria	RCT	13	0	(13) BTX-A (Dysport®) 200 mouse U/axilla	(13) Placebo	The patients were their own controls; they got BTX on one side and placebo on the other. 2 patients: transient minor pruritus at the toxin-treated axilla and at both axillae, respectively for one week 2 patients: mild constipation and increased palmar sweating, lasting one week.	
Solish 2005	Canada	Case study	146	17	BTX A (Botox®)50U/axilla 1 patient: 'Light – headed'. 2 patients: injection-site pain. 3 patients: compensatory sweating (front of head, chest and neck, palms and feet). 2 patients: tenderness or pain on touching of the axillae	No control patients	Treatment-related adverse events were observed in 5.5% (8/146) of patients. All adverse events were mild and had a probable or definite relationship to the study treatment.	

Appendix 1:12

Outcome variable: Side effects of botulinum toxin (BTX) injection axillary and aluminum chloride (AlCl) in patients axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control AlCl		
Flanagan 2008	USA	RCT	50	5	(22) BTX-A (Botox®) 50 U/axilla 12% adverse events e.g. mild redness and tenderness at injection sites One subject with flu-like illness lasting 3 days after the injection.	(23) AlCl 92% adverse events e.g. skin irritation, redness, itching	60 adverse events in 37 subjects were reported. Of these, 31 events were related to study treatments, with the majority (68.3%) of adverse events occurring in the AlCl group (p>0.0001) No serious adverse events were reported during the study in either group.	

Appendix 1:13

Outcome variable: Side effects of botulinum toxin (BTX) injection and subcutaneous curettage in patients with axillary hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Subcutaneous curettage		
Rompel 2001	Germany	Cohort	113	13	(23) BTX-A (14) Botox® 40-50U (9) Dysport® 200-250U No adverse events except from minimal superficial hematoma with spontaneous resolution in a few days.	(90) Complete follow-up* in 77 2 (2.2%) wound infection 12 (13.3%) bleeding/haematoma 2 (2.2%) partial epidermal necrosis	*Follow-up 23.5 months	

Appendix 1:14

Outcome variable: Side effects of botulinum toxin (BTX) injections and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
Bauman 2005	USA	RCT	20	2	(15) BTX-B (Myobloc®) 5000U/palm 83 adverse events (79.8% of total events) were determined to be definitely related to the study: Number of Event events Decreased grip strength 12 Muscle weakness 12 Dry eyes events 7 Dry mouth/throat 19 Instances of excessively dry hands 13 Indigestion or heartburn 17 Other events 3 Most of these events were transient resolving within 2 months after injection 13 adverse events(12.5%) were rated as possibly related Number of Event events Acne 3 Excessively dry hands 1 Indigestion 1 Flu-like symptoms 1 Other events 7	(5) Placebo	Injection with Myoblock did not hurt more than injection with placebo. No significant differences in grip strength (dynamometer measurements).	
Lowe 2002	USA	RCT	19	3	(16) BTX-A (Botox®) 100 U/palm	(16) Placebo	The patients were their own controls; they got BTX on one side and placebo on the other. No significant difference in grip strength between the palm receiving BTX-A or placebo at any point during the study (dynamometer measurement). One patient reported minor thumb and finger weakness which resolved within 2	

Appendix 1:14

Outcome variable: Side effects of botulinum toxin (BTX) injections and placebo in patients with palmar hyperhidrosis

Author, year	Country	Study design	Number of patients n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention BTX	Control Placebo		
							weeks. Unclear if BTX and/or placebo side. 3 patients reported adverse events related to the study during the 28-day follow up. One with tingling and numbness the hand receiving BTX. One with weakness in the hand receiving placebo, one with pain in both hands.	
Schneider 1997	Austria	RCT	11	0	(11) BTX-A (Dysport®) 120 mouse U/palm 3 (3/11=27.3%) transient minor muscle weakness lasting 2-5 weeks. 3 (3/11=27.3%) more painful injections at the BTX treated hands compared to placebo.	(11) Placebo	The patients were their own controls; they got BTX on one side and placebo on the other. 1 (1/11=9.1%) minor haematoma, not clear if BTX or placebo hand	

Appendix 2

Study (author, publication year)	Reason for exclusion
Baizabal-Carvallo JF, 2011	Review of side-effects.
Crowner BE, 2010	Review and three cases of adverse events.
Davarian S, 2008	Intervention not concurrent with PICO.
Glogau RG, 2007	Intervention not concurrent with PICO.
Heckmann M, 1999	Case series <100 cases.
Ito K, 2011	Comparison not concurrent with PICO.
James R, 2005	Case-study without reported complications.
Kavanagh GM, 2006	Intervention not concurrent with PICO.
Naumann M, 2006	Review of safety.
Naumann M, 2008	Review of already included articles.
Naver H, 2000	Cohort with<100 patients.
Shams K, 2011	Cochrane protocol that is not completed.
Weber A, 2005	Group of patient not concurrent with PICO, n< 100.
Yamashita N, 2008	Not adequate study-design, no RCT, few patients.
Zachrisson T, 2008	Comparison and outcome not concurrent with PICO.

Appendix 3, Search strategy, study selection and references

Question(s) at issue:

Is injection treatment with BTX for axillary and palmar hyperhidrosis, and compensatory hyperhidrosis following sympathectomy, better than placebo, no treatment or standard treatments, when assessed as QoL, sweat production, duration and complications?

PICO *P=Patient I=Intervention C=Comparison O=Outcome*

P_1: Patients with primary axillary or palmar hyperhidrosis

P_2: Patients with compensatory hyperhidrosis following sympathectomy

I: BTX (A or B) injections

C: Standard treatment [topical treatment (AlCl), oral anticholinergics, subcutaneous sweat gland suction curettage]
Placebo or no treatment

O: **Primary outcome variable**:

QoL evaluated by a validated scale e.g. Dermatology Quality of Life Index (DQLI)

Secondary outcomes variables:
Sweat production – measured by a validated scale e.g. Hyperhidrosis Disease Severity Scale (HDSS)
Duration of treatment effect
Complications (short- and long-term effects/tolerance)

Study design:
Randomized controlled trials
Cohort studies > 100
Case studies > 100

Limits: Publication date from 1990, articles published in English, Danish, Norwegian, or Swedish

Search strategies

PubMed 2011-10-18

botulinum toxin OR botulinum OR botox OR rimabotulinumtoxin OR rimabotulinum OR botulinumtoxin OR xeomin OR dysport OR myobloc
AND
hyperhidrosis OR sweating

NOT publication type Editorial OR Letter OR Comment OR case reports

Limits: Publication date 1990, English, Danish, Norwegian, Swedish

326 results

EMBASE 2011-10-18

exp. hyperhidrosis OR exp. sweating OR (hyperhidrosis OR sweating) ti,ab
AND
(botulinum toxin OR botulinum OR botox OR rimabotulinumtoxin OR rimabotulinum OR botulinumtoxin OR xeomin OR dysport OR myobloc).ti,ab OR exp. botulinum toxin OR exp. botulinum toxin a OR exp. botulinum toxin b OR exp. botulinum toxin e OR exp. botulinum toxin f

Limit: Publication Date from 1990 to 2011/10/18, English, Danish, Norwegian, Swedish, Human, (article OR note OR report OR review)

548 results

PsycInfo 2011-10-18

exp. Sweating OR (hyperhidrosis or sweating).ab,ti
AND
(botulinum toxin OR botulinum OR botox OR rimabotulinumtoxin OR rimabotulinum OR botulinumtoxin OR xeomin OR dysport OR myobloc).ab,ti.OR
exp. botulinum toxin

Limit: Publication Date from 1990 to 2011/10/18, English, Danish, Norwegian, Swedish

13 results

The Cochrane Library 2011-10-18

botulinum toxin OR botulinum OR botox OR rimabotulinumtoxin OR rimabotulinum OR botulinumtoxin OR xeomin OR dysport OR myobloc in Title, Abstract or Keywords
AND
hyperhidrosis OR sweating in Title, Abstract

Cochrane reviews: 1
Other reviews: 0

Technology Assessments: 2
Economic evaluations: 1
Clinical trials: 62

HTA-databases: SBU, Kunnskapssenteret, Sundhedsstyrelsen

Nothing relevant to the question at issue was found

Reference lists

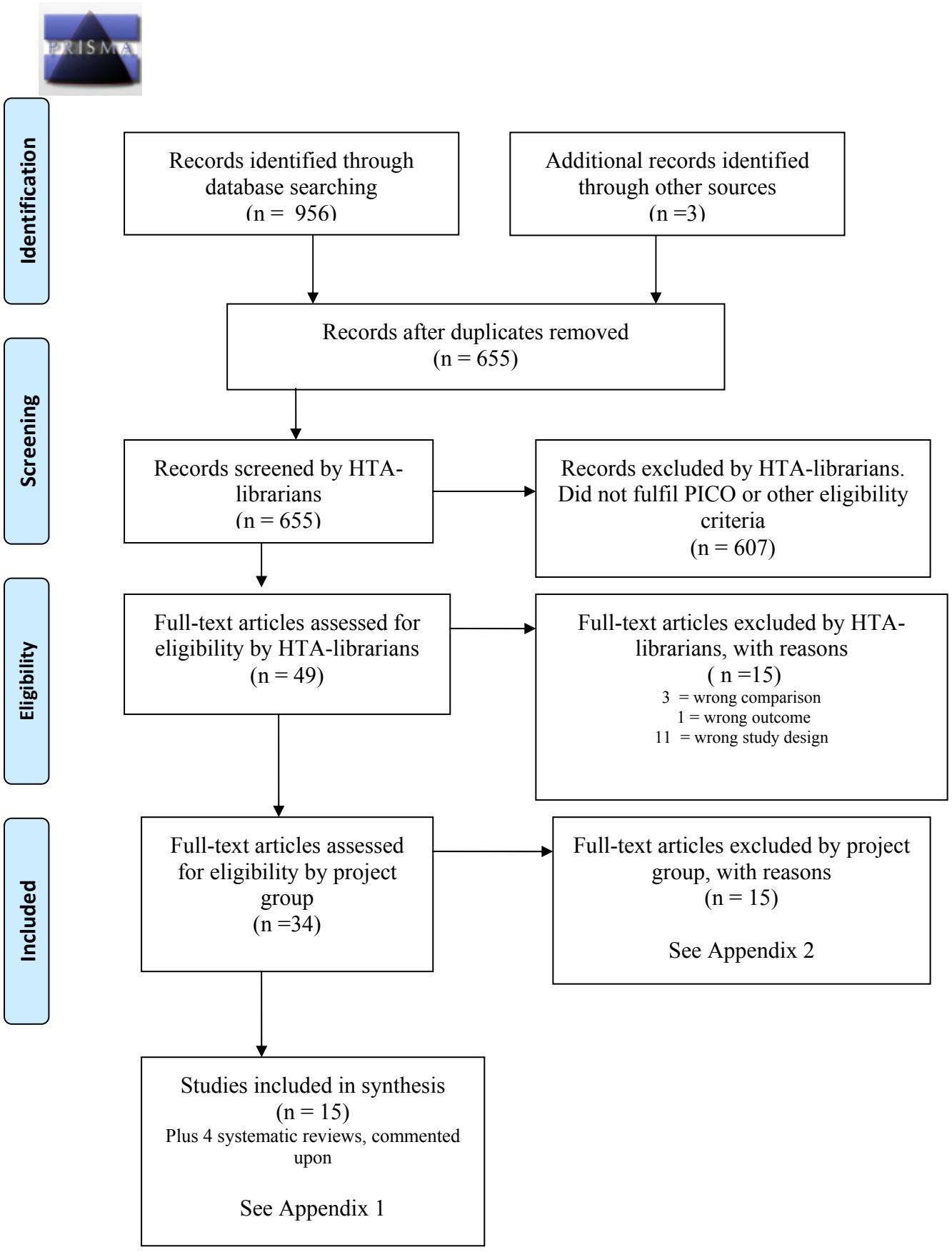
A comprehensive review of reference lists brought

3 results

Eligibility criteria

Randomized Controlled Trials, Cohort studies > 100, Case studies > 100, publication date from 1990, articles published in English, Danish, Norwegian, or Swedish

Selection process – flow diagram



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Summary of Findings: Botulinumtoxin (BTX) injections in patients with axillary and palmar hyperhidrosis

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Level of evidence GRADE
Quality of life axillary BTX vs placebo										
4	RCT [1]	Serious limitations (-1)	No important inconsistency	No uncertainty	No important imprecision	Unlikely	Not relevant	BTX 2-4 times better than placebo		Moderate ⊕⊕⊕○
Quality of life axillary BTX vs AlCl										
1	RCT	Serious limitations (-1)	No important inconsistency	No uncertainty	Imprecision (-1)	Unlikely	Not relevant	BTX 5 times better than placebo		Low ⊕⊕○○
Quality of life axillary BTX vs curettage										
1	Cohort	Serious limitations (-1)	No inconsistency	No important uncertainty	Imprecision (-1)	Unlikely	Not relevant	Not significant		Very low ⊕○○○
Quality of life palmar BTX vs placebo										
2	RCT	Serious limitations (-1)	No important inconsistency	No uncertainty	Imprecision (-1)	Unlikely	Not relevant	BTX 8 times better than placebo (one study)		Low ⊕⊕○○

Summary of Findings: Botulinumtoxin (BTX) injections in patients with axillary and palmar hyperhidrosis

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Level of evidence GRADE
Sweat production axillary BTX vs placebo										
7	RCT	No limitations	No inconsistency	No uncertainty	No imprecision	Unlikely	Not relevant	BTX 3-8 times larger reduction and response than placebo		High ⊕⊕⊕⊕
Sweat production axillary BTX vs AlCl										
1	RCT	Serious limitations (-1)	No inconsistency	No uncertainty	Imprecision (-1)	Unlikely	Not relevant	BTX 2-3 times larger reduction and response than placebo		Low ⊕⊕○○
Sweat production palmar BTX vs placebo										
3	RCT	Serious limitations (-1)	No inconsistency	No uncertainty	Imprecision (-1)	Unlikely	Not relevant	BTX 1-2 times larger reduction and response than placebo		Low ⊕⊕○○

Summary of Findings: Botulinumtoxin (BTX) injections in patients with axillary and palmar hyperhidrosis

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect	Level of evidence GRADE
Duration axillary BTX vs placebo										
4	RCT	Serious limitations (-1)	No inconsistency	No uncertainty	Imprecision (-1)	Unlikely	Not relevant	BTX 2-3 times longer duration than placebo		Low ⊕⊕○○
Duration axillary BTX vs curettage										
1	Cohort	Serious limitations (-1)	No inconsistency	Indirectness (-1)	No imprecision	Unlikely	Not relevant	Not stated [2]		Very low ⊕○○○
Duration palmar BTX vs placebo										
2	RCT	Serious limitations (-1)	No inconsistency	Indirectness (-1)	Serious imprecision (-2)	Unlikely	Not relevant	Not stated [3]		Very low ⊕○○○

[1] Five RCT publications (two describing the same trial).

[2] Data on the effect duration for the subcutaneous curettage group was not reported (Rompei and Scholz, 2001).

[3] Data on the effect duration for the placebo group was not reported (Baumann *et al*., 2005, Schnider *et al*., 1997).

Abbreviation list

AE=Adverse event.

AlCl=Aluminum Chloride.

BTX=Botulinum toxin.

DLQI=Dermatology Life Quality Index. A 10-item dermatology specific questionnaire that assesses Health Related Quality Of Life (HRQOL) during the previous week. Scores range from 0-30: 0 indicating no HRQOL impairment and 30 indicating the most HRQOL impairment.

FDA=Food and Drug Administration.

HDSS=Hyperhidrosis Disease Severity Scale.

HHIQ=Hyperhidrosis Impact Questionnaire consists of two related modules. A 41-item module for baseline disease impact assessment, and a 10-item module for follow-up, longitudinal assessment, and comparison with baseline. Baseline items are divided into four groups: disease and treatment background; direct impact on medical and non-medical resource utilization; indirect impact on employment and productivity; and intangible impacts. Score 0-4: 0 =not limited; 1=somewhat; 2=moderately; 3=quite a bit; 4=extremely limited.

KSS=Skövde Hospital.

NU=Uddevalla Hospital.

P-HQOL=Palmar Hyperhidrosis Quality of Life. Scores range from 4-15. Score 4 representing ‘no interference with daily life’. Score 15 representing ‘a great deal of interference with daily life’.

QoL= Quality of Life.

SF12=(Medical Outcome Trust Short Form-12 Health Survey). A validated, general health-related QoL questionnaire consisting of 12 items designed to assess patients’ views about their general health, physical activity, emotional health, bodily pain and social functioning. Results are reported as physical component summary (PCS) and mental component summary (MCS) scores.

SU=Sahlgrenska University Hospital.

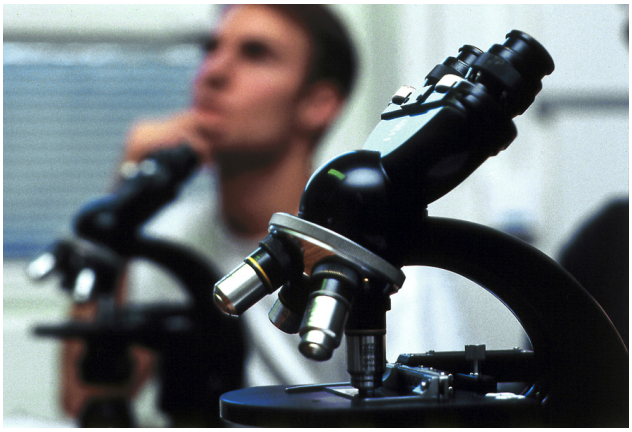
SÄS=Södra Älvsborgs Hospital.

VAS=Visual Analogue Scale.

VGR= Västra Götaland Region.

Region Västra Götaland, HTA-centre

Health Technology Assessment
Regional activity-based HTA



HTA

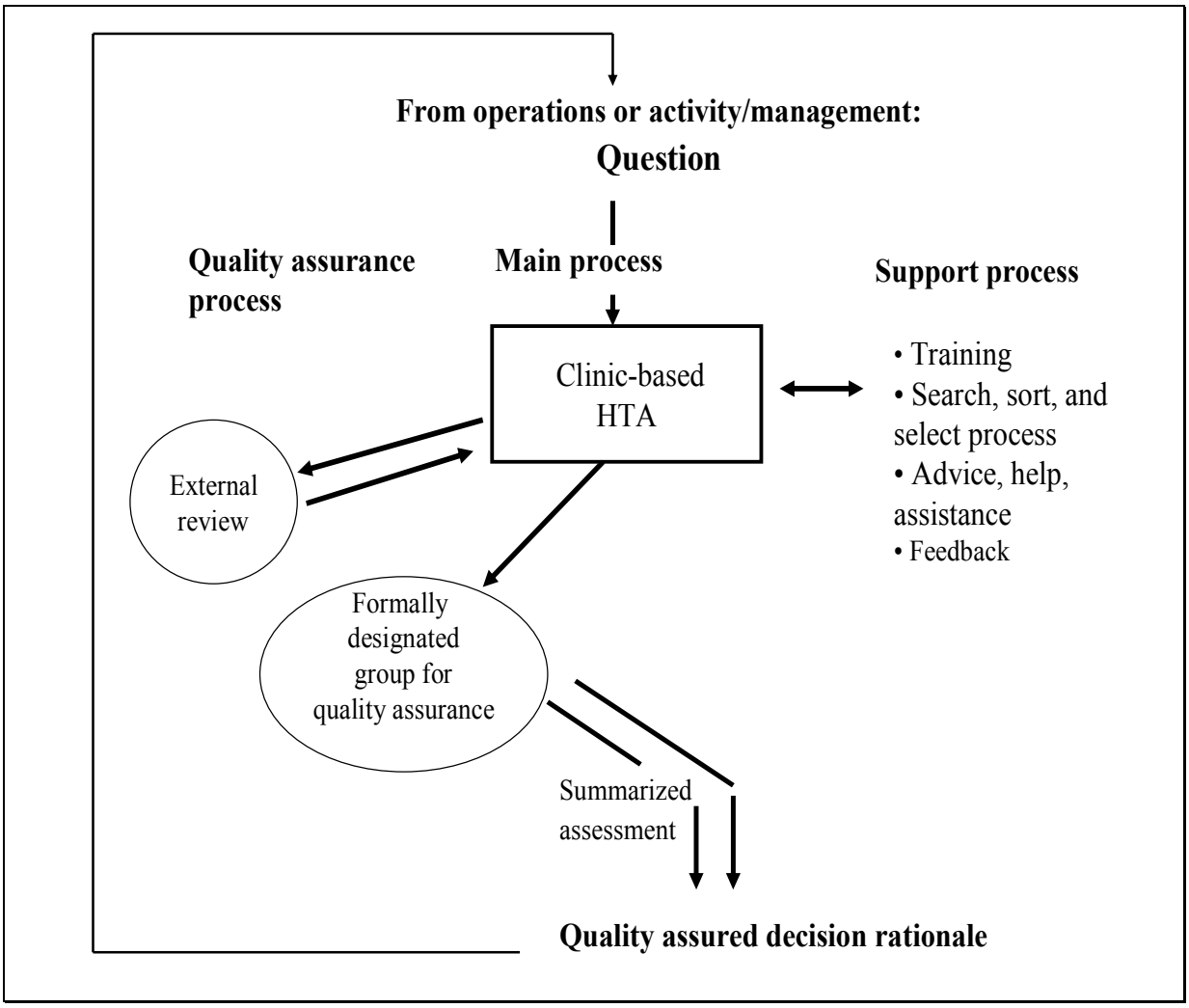
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centre


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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