

Study Protocol (Draft)
**Interventional management of hyperhidrosis: a systematic review and
value of information analysis (HTA 14/211/02)**

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1 Decision problem

1.1 Hyperhidrosis and treatment options

Hyperhidrosis is a descriptive term for uncontrollable excessive and unpredictable sweating, which occurs at rest, regardless of temperature and has a major impact on quality of life. It is caused by hyper-function of the exocrine sweat glands that are controlled by the sympathetic nervous system via postsynaptic cholinergic fibres.

Hyperhidrosis is a common condition that can be primary or secondary. Primary hyperhidrosis is excessive uncontrollable sweating without any discernible cause. It most commonly involves the axillae, palms, and soles but may also involve the face and groin or any area of the body.

Hyperhidrosis of the face can sometimes be associated with facial blushing, which further increases the anxiety and embarrassment felt by patients. Secondary hyperhidrosis has an underlying cause which may embrace endocrine disorders (e.g. hyperthyroidism), secretory tumours (e.g. pheochromocytoma), sympathetic nervous system disorders, primary neurological conditions, such as neuropathy, spinal disease or injury, or a psychiatric disorder. It is usually generalised over the entire body, i.e. not restricted to any specific areas of the body.

Excessive sweating is commonly but falsely regarded as a slightly inconvenient but non-serious condition. However, hyperhidrosis is not a minor condition: it can have a profound effect on quality of life, interfering with daily activities and work and causing anxiety and embarrassment. This condition wets, stains and ruins clothing and produces social embarrassment or functional problems arising from skin maceration and soreness. Teenagers may be referred for treatment because of an inability to do schoolwork and exams, due to the sweating ruining paperwork. Adults may find the condition affects employability; those who meet the public may be unable to shake hands or unable to remove a jacket because the shirt is stained. It may prevent individuals having relationships. Severely affected patients also may have secondary microbial infections. The unpredictable and uncontrollable nature of the condition makes it very distressing for sufferers. Its impact is captured perfectly on the Hyperhidrosis UK website,¹

“the impact of hyperhidrosis can be severe. Wetness and staining of clothes, clammy hands and sodden smelly shoes, inability to grip objects such as pens, cold and wet handshake, damage to keyboards and difficulty dealing with paper and metals, can make a miserable existence. You may constantly worry about changing clothes, freshening up, using absorbent pads or sticking with loose black or white clothes, and may avoid making friends or interacting with people at work. Patients report that they are even embarrassed to hold the hands of those they love. Loneliness, depression and decreased confidence can result.”

Hyperhidrosis is thought to affect approximately 1% of the UK population, with around 100 new patients being referred to a typical dermatology clinic each year.¹ Primary hyperhidrosis normally develops in childhood and adolescence. In a few instances it may improve with age, but usually persists for the majority of life before spontaneous resolution in the elderly. Whilst the cause of primary hyperhidrosis is unknown, it is likely that there is a genetic link, with one study reporting 65% of patients having a positive family history.²

Patients suffering from hyperhidrosis often have anxiety disorders or depression, which may exacerbate or can in some instances be the cause of their hyperhidrosis.³ Non-psychological therapy for primary focal hyperhidrosis differs depending on the site of the condition. It is important to distinguish between primary and secondary hyperhidrosis as the treatment options are different.

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Treatment for secondary hyperhidrosis should be directed towards the underlying cause rather than the hyperhidrosis itself as in primary disease.

Primary Care

Patients often delay presenting to their GP due to embarrassment and will have tried various over the counter remedies. In Primary Care it is important to explore the patient's perspective of their symptom and whether a patient does have excessive sweating: to explore not only the physical complaint but also the psychological and social effects for the patient. The generally accepted treatment pathway with the various treatment options is summarised below.

The management of hyperhidrosis has been summarised in two helpful (albeit not systematic) reviews.^{4,5} Since hyperhidrosis of all kinds can be exacerbated by stimulant-containing foods, especially caffeine and theobromine, dietary restriction of coffee, tea, cola soft drinks, and chocolate may improve mild cases of hyperhidrosis. Other lifestyle changes that can help, although not cure hyperhidrosis include avoiding clothing that can make sweating worse, such as tight fitting garments or man-made fibres, wearing clothing that absorbs sweat or disguises its appearance, or using devices such as armpit guards.⁶ Weight loss is often helpful in reducing symptoms in those with a raised BMI. The first line of treatment for primary hyperhidrosis is topical pharmacological agents.³ Most patients try a variety of topical antiperspirants and deodorants, but find no relief until they use 10% or 20% aluminium chloride applied daily; this dose of aluminium chloride has been shown to be effective in clinical trials for mild-to-moderate hyperhidrosis.⁴ It is hypothesized that the metallic antiperspirants enter the sweat gland duct and form an occlusive plug by combining with ductal keratin. Unfortunately, skin irritation is very common with these antiperspirants and often forces discontinuation of the treatment.⁵ In UK clinical practice, for axillary hyperhidrosis, a one month trial of aluminium chloride is the initial treatment. Treatment is similar for plantar hyperhidrosis except that a month's trial of 3% formaldehyde solution to be applied to the soles can be offered. Failure of these trials is followed by referral to a local dermatologist.

The evidence base for the use of aluminium chloride in primary care is weak: the NICE Clinical Knowledge Summary found no placebo-controlled randomised controlled trials (RCTs) and the evidence base comprised two small poor quality RCTs, an open-label trial, four small case series and expert opinion.³ However, this low-cost therapy is used mainly as a first step, helping GPs discriminate between those who do and do not require referral for more specialised care. Therefore, further research into aluminium chloride is unlikely to be warranted. Patients whose apparent primary hyperhidrosis is actually secondary to an anxiety disorder are also identified in primary care and are referred for psychological treatments rather than treatments specific to hyperhidrosis. Consequently there is little decision uncertainty in relation to the treatment of hyperhidrosis in primary care, unlike the situation in secondary care.

Dermatology

Dermatologists may prescribe any of a number of treatments: iontophoresis, botulinum toxin injections, or systemic agents such as anticholinergic (antimuscarinic) medications.^{3, 4, 7}

Iontophoresis is a process in which an electrical field drives the flow of ions in a medium and enables drug delivery through the near impenetrable barrier of the skin.⁸ The technique involves immersion of the palms of the hands or soles of the feet in a shallow tray of water through which a weak electrical current is run. Sponges soaked in water can be used to treat the axillae. It can also be used with solutions of anticholinergics although there is little evidence this offers any greater effect than

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treatment with tap water.⁵ The exact mechanism of action behind the therapeutic effect in hyperhidrosis is unknown, and efficacy has been demonstrated in only small studies.⁵

Botulinum toxin blocks neuronal acetylcholine release at the neuromuscular junction and in cholinergic autonomic neurons; blocking the postganglionic sympathetic cholinergic nerve fibres to the sweat glands.⁵ There is clinical trial evidence demonstrating the efficacy of botulinum toxin in hyperhidrosis, though this varies with specific toxin and site and is only temporary (only 3 to 6 months), and may be technique-dependent.⁹ Over the last few years, botulinum toxin injections have become an established treatment for axillary hyperhidrosis. Major drawbacks are the expense of the toxin, the discomfort associated with the injections and the need for repeated treatments.⁵

Administration of anticholinergic (antimuscarinic) agents and beta-blockers can be quite helpful in mild cases of hyperhidrosis. Oral propantheline (Pro-Banthine®) is licensed for this indication but the unlicensed drug, oral glycopyrronium bromide (Robinul®) is often used. Occasionally other anticholinergics are used such as oxybutynin and also methantheline bromide.⁴ The doses of anticholinergic medication required to truly control abnormal sweating may cause significant adverse effects, including drowsiness, dry mouth, dilated pupils, photophobia, blurred vision, acute glaucoma, impaired micturition, reduced bronchial secretions, constipation, confusion, nausea, vomiting, giddiness, tachycardia, palpitations, and arrhythmias. Thus, many patients are forced to discontinue this avenue of treatment.

Current recommendations are not underpinned by robust evidence and there are many areas of uncertainty. Importantly, the NICE Clinical Knowledge Summary on hyperhidrosis, updated in July 2013, was limited by poor quality evidence: recommendations were often based on expert opinion in the absence of trial evidence.³ In particular the relative effectiveness of treatments prescribed by a dermatologist is uncertain and further research would be required to resolve this.

Surgery

The available medical treatments for primary hyperhidrosis are of uncertain efficacy and even when effective are not curative. Thoracic sympathectomy involves interruption or ablation of the high thoracic sympathetic chain to decrease sympathetic tone to the upper extremity and/or face.⁴ Open thoracic or cervical sympathectomy is now rarely performed and the less invasive technique of endoscopic thoracic sympathectomy (ETS) is preferred.⁴ ETS is carried out under general anaesthesia through one or more small insertion incisions between the ribs. It is used for axillary, palmar, or facial hyperhidrosis. ETS can be performed at different levels of the thoracic sympathetic chain with varying efficacy and safety.¹⁰ Adverse effects of thoracic sympathectomy can be serious, such as pneumothorax or Horner's syndrome (characterised by miosis and ptosis). A common adverse effect of thoracic sympathectomy is compensatory hyperhidrosis, whereby excessive sweating occurs in other parts of the body after treatment; reported in 80% of patients in one large survey.¹¹

Lower limb sympathectomy can also be performed as an open surgical procedure under general anaesthetic but more minimally invasive procedures are now usually preferred. An alternative is endoscopic lumbar sympathectomy which is less widely available but has been proposed to produce a more reliable interruption of the sympathetic chain.¹² For lower limb hyperhidrosis chemical sympathectomy, can be performed and involves injecting the lumbar sympathetic chain with a chemical (phenol) to damage the nerve;¹³ although it is rarely performed in the UK.

NICE does specifically recommend ETS for primary hyperhidrosis of the upper limb, (NICE interventional procedure guidance 487)¹⁴ but only for those “suffering from severe and debilitating

primary hyperhidrosis that has been refractory to other treatments”. However, as for the dermatology treatment options, this recommendation for ETS was based on limited quality evidence: a non-systematic review article, non-randomised comparative studies and case series; and focussed on efficacy and safety more than quality of life.

Given the reluctance of patients to undergo ETS and its apparently limited effectiveness in terms of quality of life, alternative surgical options are required. Such procedures, for which guidance has not been issued, include removal of sweat glands. Traditionally this was achieved through excision of sweat gland containing skin, such as axillary skin, but now sweat gland clearance is more often done by subcutaneous curettage by open techniques or superficial liposuction, rather than skin resection:¹⁵ the inside layer of the skin (which contains the sweat glands) is scraped (curetted) and/or suctioned under general anaesthesia to remove the sweat glands but preserve skin integrity.¹⁶⁻¹⁸ Adverse effects are not as serious as for thoracic sympathectomy, but can include wound breakdown or infection. Other emerging treatments include microwave and laser therapy.^{19,20} Whilst these less invasive procedures appear to be promising alternatives to ETS, they are only undertaken by a few dermatology surgeons in the UK, and are rarely available through the NHS.

1.2 Research aims and objectives

There is significant variation in the treatment for primary hyperhidrosis available in secondary care and current recommendations are not underpinned by robust evidence; there are many areas of uncertainty. The NICE Clinical Knowledge Summary on hyperhidrosis, updated in July 2013, was limited by poor quality evidence, with many recommendations based on expert opinion in the absence of trial evidence.³ In particular the relative effectiveness of treatment prescribed by a dermatologist is uncertain and further research (both primary studies and evidence synthesis) would be required to resolve this. Regarding the surgical treatments available, the NICE interventional procedure guidance on ETS for primary hyperhidrosis of the upper limb issued in May 2014,¹⁴ was based on limited quality evidence. Furthermore it is clear that ETS sometimes results in a deterioration in patients’ quality of life.¹⁴ Guidance on which are the best alternative surgical options is needed, but the relative effectiveness of ETS, subcutaneous curettage and targeted sweat gland removal has not been researched or reviewed comprehensively.

Given the lack of clear research evidence to guide clinical practice, new randomised controlled trials (RCTs) may be warranted. However, RCTs can be difficult to conduct and extremely expensive to run. They are also demanding of both clinicians and patients and should not be undertaken without careful consideration. The aim of this project is to establish the expected value of undertaking additional clinical studies (such as RCTs) to determine the most effective interventions for the management of refractory primary hyperhidrosis (excluding patients with social anxiety disorder) in secondary care.

The key objectives are:

- (i) to undertake an evidence synthesis by systematic review to estimate clinical effectiveness of treatments available in secondary care and inform key clinical parameters for a decision model;
- (ii) to develop a decision model to estimate cost-effectiveness; and
- (iii) using the decision model, undertake a value of information analysis.

2. Research plan

An economic model of the treatment options in secondary care for primary hyperhidrosis refractory to first line topical therapy will be developed. This model will be used to quantify the main uncertainties facing decision makers and to conduct a value of information analysis to quantify the value of undertaking further research to resolve these uncertainties. To parameterise this decision model a series of systematic reviews will be undertaken. In addition, a patient workshop/survey will be undertaken to gather information on what outcomes are important to patients.

2.1 Methods for systematic review of clinical effectiveness evidence

Three systematic reviews will be undertaken to inform the research:

- (i) the clinical effectiveness of treatments available for prescription by dermatologists;
- (ii) the clinical effectiveness of surgical treatment; and
- (iii) the quality of life outcomes.

The first two systematic reviews will be undertaken separately because the treatments offered by dermatologists and surgeons are given at different points in the treatment pathway, i.e. they apply to different patient populations and are therefore not considered comparators. The systematic reviews will be conducted according to the general principles recommended in CRD's guidance on the conduct of systematic reviews²¹ and reported according to the general principles of the PRISMA statement.²² The protocol has been written in accordance with the new PRISMA-P initiative,²³ and registered on PROSPERO, the international database of prospectively registered systematic reviews in health and social care (<http://www.crd.york.ac.uk/prospéro/>).

2.1.1 Search strategy

Comprehensive, systematic searching of the medical literature databases will be undertaken in an attempt to identify all relevant studies. Studies will be identified by searching major medical databases and trial registers.

The following databases will be searched:

- AMED (Allied and Complementary Medicine)
- British Nursing Index
- Cochrane Library (including Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), HTA Database, Methods Database)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- EMBASE
- MEDLINE
- MEDLINE In Process
- PsycInfo

In addition, information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching relevant resources including Conference Proceedings Citation Index: Science (ISI), ClinicalTrials.gov and WHO ICTRP Portal.

The search strategy will combine relevant search terms with indexed keywords (such as Medical Subject Headings, MeSH) and text terms that appear in the titles and/or abstracts of database records. Searches for the clinical effectiveness reviews of treatments for hyperhidrosis will include appropriate search terms for 'hyperhidrosis' and where appropriate will be combined with search terms for

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‘treatment’ and specific treatment types, e.g. ‘botulinum toxin’, ‘iontophoresis’, ‘sympathectomy’. For comprehensive retrieval of all potentially relevant studies, no methodological filters will be used to restrict the type of studies we search for, nor will any language or date limits be imposed. A draft search strategy is presented as an Appendix. For the review of quality of life outcomes, search terms for ‘hyperhidrosis’ will be combined with search terms for ‘quality of life’.

In addition, clinical advisors will be consulted for additional potentially relevant studies and reference lists of relevant systematic reviews will be manually searched.

2.1.2 Study selection

Two researchers will independently screen all titles and abstracts obtained through the search. Full manuscripts of potentially relevant studies will be obtained wherever possible. Two researchers will independently assess the relevance of each study using pre-defined eligibility criteria. Disagreements will be resolved through discussion and, where necessary, consultation with a third reviewer. Where possible, relevant foreign language studies will be translated and included in the reviews.

The eligibility criteria for the different systematic reviews are outlined below.

Population:

Patients with primary hyperhidrosis (including adults and children). To reflect where secondary care treatments are used in current clinical practice, ideally, included trials should be of patients who have tried and failed on treatments in primary care (and for surgical treatments under the care of a dermatologist). However, such specific criteria would likely result in the exclusion of most trials and so will not be applied. Instead, the specific patient population will be a consideration for the generalisability of the trials.

Patients with hyperhidrosis secondary to other conditions, such as overactive thyroid or spinal cord injury, or social anxiety disorder, will not be eligible for inclusion.

Interventions:

(i) the clinical effectiveness of treatments available for prescription by dermatologists

Treatments for hyperhidrosis available for prescription by dermatologists.

Such interventions include topical pharmacological agents prescribed in secondary care, iontophoresis, systemic agents (e.g. glycopyrronium bromide (Robinul), atropine) and botulinum toxin injections. Studies comparing different formulations (e.g. comparing different preparations of botulinum toxin type A, such as Botox and Dysport) will not be included. NICE listed treatments for anxiety:³ clonidine, diltiazem, or benzodiazepines will also be included but only where used specifically for primary hyperhidrosis and not in patients diagnosed with, for example, social anxiety disorder.

(ii) the clinical effectiveness of surgical treatments

Surgical treatments for hyperhidrosis.

Such interventions include sympathectomy (such as thoracic, lower limb and chemical sympathectomy), and sweat gland removal using as various techniques such as curettage and liposuction. Studies comparing different surgical techniques, such as different levels of sympathectomy (e.g. comparing T2 with T2-T3 ablation in thoracic sympathectomy) will not be

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included, although studies comparing bilateral with unilateral sympathectomy will be considered in subgroup analysis if adequate data are available. In addition, studies of open sympathectomy will be excluded from the review, as less invasive methods are now generally used.

Comparators:

(i) the clinical effectiveness of treatments available for prescription by dermatologists

A different active treatment for hyperhidrosis (including surgical treatments), placebo, or no treatment.

(ii) the clinical effectiveness of surgical treatments

A different surgical treatment for hyperhidrosis, placebo, or no treatment.

Outcomes:

Any of the following:

- Disease severity (such as the Hyperhidrosis Disease Severity Score (HDSS))
- Clinical outcomes (such as sweat rate)
- Patient quality of life (such as the Hyperhidrosis Impact Questionnaire (HHIQ) and Dermatology Life Quality Index (DLQI))
- Patient preference
- Satisfaction (including treatment compliance/adherence)
- Social functioning
- Adverse events (such as compensatory sweating)
- Resource use

In addition, the duration of treatment effect will also be assessed, where longer term data are reported.

Study designs: Where a good quality, up to date, directly relevant systematic review exists, this will be included. In the absence of such a review, RCTs will be included, where available. For interventions where RCT evidence is lacking, non-randomised controlled trials will be included. In the absence of controlled trials, prospective case series (single arm trials) will be included.

(iii) quality of life measures used

Population:

Patients with primary hyperhidrosis (including adults and children).

Outcomes:

As described earlier, hyperhidrosis can have a profound effect on quality of life, interfering with daily activities and work and causing anxiety and embarrassment. The impact of hyperhidrosis for patients can only really be captured through its impact on the patient's quality of life. Quality of life outcomes can be measured using a variety of tools, disease specific, discipline specific (dermatology), general

health or utility. Scoping work would suggest that the majority of studies have utilised dermatology or disease specific measures.²⁴ These include: the dermatology life quality index (DLQI); Skindex-29; Hyperhidrosis Disease Severity Scale (HDSS); Hyperhidrosis Scale (HS) and the hyperhidrosis quality of life questionnaire (HQLQ). Other outcomes include subjective improvement, satisfaction, gravimetric assay measurements, percentage improvement (visual analogue scale), recurrence, resolution and compensatory sweating.

Study designs: Any study design is eligible for inclusion in this review.

2.1.3 Data Extraction and Quality Assessment

The quality assessment of studies will be conducted as part of the data extraction process using criteria relevant to the topic and study designs included. Data will be extracted into structured forms. The data extraction form will be developed, piloted, and refined as necessary prior to full data extraction. Data extraction and quality assessment will be conducted by one researcher and checked by a second researcher for accuracy, with any discrepancies resolved by discussion, or consultation with a third reviewer, where necessary. Authors of studies will be contacted for clarification and missing data, as necessary. The data from single studies with multiple publications will be extracted and consolidated.

Data to be extracted will include details of study methods, patient characteristics, interventions, comparators (where appropriate), all relevant outcome measures and results.

The quality of included comparative studies will be assessed using criteria appropriate to the study design, adapted from published checklists.²¹ Randomised controlled trials will be assessed using the Cochrane Risk of Bias tool which focuses on the domains shown to impact on the trial results in particular (selection, performance and detection biases and attrition).²⁵ An additional question relating to the similarity of treatment groups at baseline will be added.

Non-randomised trials or studies that include a comparison group will be assessed for methodological quality using criteria based on the Newcastle-Ottawa scale and those identified by the ongoing work of the Cochrane Collaboration.^{26, 27} Broadly, domains will include consideration of: selection of the groups, comparability of the groups, how the outcomes were assessed including follow-up and methods of assessment, relevant confounding factors and the potential for selective reporting.

Studies without a control group will not be formally quality-assessed however details will be presented in descriptive tables and their impact on the reliability of results will be considered.

The utility of the COSMIN check list will be explored in critically appraising studies in the review of quality of life measures.^{28, 29}

2.1.4 Data synthesis

A detailed analysis plan will be produced in the early stages of the project. In brief, the results of each of the systematic reviews will be presented separately, with separate meta-analyses (where appropriate) for treatments available for prescription by dermatologists and surgical treatments. In addition, pooling across reviews will be undertaken based on population characteristics.

In the first instance, study characteristics and quality assessment results will be presented in a series of structured tables. Results from studies will be presented graphically, in the form of forest plots, if appropriate. The clinical and statistical homogeneity of the accumulated evidence will be assessed by visual inspection of plots of the data, from the chi square test for heterogeneity and the I^2 statistic. Differences between studies will be discussed in the text, and possible reasons for heterogeneity will be explored, such as differences in the populations studied (e.g. specific conditions, comorbidities,

age, gender, etc.), the treatment given, or the way in which the outcomes were assessed. The impact of studies where the population has very different characteristics to primary hyperhidrosis patients seen in the UK, will be explored in sensitivity analyses.

Ideally, summary estimates will be derived by pooling data from prospective controlled comparative trials, calculated using established meta-analytic and evidence synthesis methods.

Where feasible, a number of pair-wise and network meta-analyses will be undertaken; network meta-analysis will be undertaken using approaches outlined by the NICE Decision Support Unit.³⁰

The results will be interpreted in the context of the quality of the individual studies. Where possible, relevant subgroups will be identified (for example, adults and children) and the results synthesised separately.

The review of patient relevant quality of life outcomes will feed into the patient workshop on this topic. All quality of life outcomes reported in the included studies will be extracted and synthesised, with the aim of identifying:

- Which outcome measures were used?
- What do they measure?
- Did they capture quality of life?

2.2 Methods of systematic review of cost-effectiveness evidence and development of decision model

2.2.1 Systematic review of published cost-effectiveness studies

A systematic review of existing economic studies will be undertaken in order to inform a de novo model-based economic evaluation. The methods will follow those of the clinical reviews with the following exceptions: (i) the inclusion criteria for study design will include cost analysis, cost-effectiveness, cost-utility and cost-benefit studies, decision model-based analyses; (ii) quality assessment will be appropriate to the study design, e.g. the Consensus on Health Economic Criteria (CHEC) list³¹ for economic evaluations and the Philips checklist³² for model-based analyses. For each included evaluation a narrative summary of methods used to model the decision problem will be conducted. Any data considered relevant to the de novo model being developed in this study will be extracted. In addition, study results will be extracted and compared to the results obtained from the de novo model.

2.2.2 Health economic modelling

A de novo decision-analytic model will be developed to allow both an estimate of the cost-effectiveness of the alternative treatment options available to patients with primary, refractory hyperhidrosis. We propose to conduct a cost-utility analysis, with results presented in terms of incremental cost per quality-adjusted life year (QALY) gained. The model will be developed in accordance with the NICE reference case (Methods for NICE technology appraisals)³³ and will capture the clinical process of the condition, characterise patients' treatment pathways and the impact of alternative therapies. The model is likely to take the form of a Markov type, state transition model. This is the most appropriate model type for this decision problem as the model can represent a clinical situation where patients change health states or experience recurrent events over a long period of time. It is anticipated that separate models will be evaluated dependent on hyperhidrosis site.

The economic model will be populated using the most appropriate data identified from the series of inter-related systematic reviews, as well as other sources required for specific information on costs,

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prevalence and incidence. Data requirements may differ dependent on hyperhidrosis site; this will depend on the model structures developed. The relative effects of interventions will be estimated in quality-adjusted-life-years (QALYs). QALYs provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources. The estimates used within the model will be based on the best available data, ideally derived using EQ-5D or SF-6D. If necessary, mapping algorithms will be used to allow us to map from disease-specific measures to utility outcomes, which will then be used to derive QALYs. Epidemiological and relative effectiveness data will be derived from the systematic reviews and meta-analyses, whilst cost data will be informed by the reviews and derived from appropriate sources such as centres currently providing the target interventions. With the help of relevant members of the expert group and a further search of the literature, we will seek information on resources required to provide each intervention. Unit costs will be taken from appropriate sources, e.g. NHS reference costs,³⁴ British National Formulary for drugs,³⁵ etc. Data on the costs of managing persistent complications of hyperhidrosis will be derived from the literature and will depend on the nature of the event.

In order to characterise the uncertainty in the data used to populate the model, both deterministic and probabilistic sensitivity analysis will be conducted. Deterministic sensitivity analyses will be carried out to test for the effect of assumptions and variability on the results. In addition, a probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty is translated into uncertainty in the overall results. Decision uncertainty in the probabilistic model will be presented using cost-effectiveness acceptability curves (CEACs), which show the probability that each intervention is cost-effective across a range of possible threshold values which NHS decision-makers attach to an additional QALY. This will highlight gaps in our knowledge and help identify priorities for future research.

Modelling will conform to recommendations for best practice, including those developed for economic evaluation models.³² The economic evaluation will be carried out from a UK NHS and Personal Social Services perspective, to take into account health care costs and longer-term social care costs. Both costs and QALYs will be discounted in the base case at 3.5%.³⁶

2.3 Value of information analysis and future research priorities

In addition to assessing the relative effectiveness and cost-effectiveness of the alternative treatment options, the economic model will be used to quantify the main uncertainties facing decision-makers and to help inform decisions about the direction of future research. Within the economic component of this study, this will be explored using variants of value of information analysis.³⁷⁻⁴⁰

We will estimate the expected value of perfect information (EVPI) and expected value of removing uncertainty surrounding specific parameters or groups of parameters to identify where future research should focus on identifying more precise and reliable estimates of specific pieces of information, e.g. costs, utilities, relative effectiveness, etc. (the expected value of partial perfect information, EVPPI). EVPI and EVPPI can be interpreted as the value of eliminating an incorrect decision. The EVPI for a decision problem must exceed the cost of research to make additional investigation worthwhile. It places an upper value on conducting further research overall (EVPI) or a specific area of information (EVPPI). Sensitivity analysis will be used to explore uncertainty surrounding the estimates of EVPI and EVPPI. If relatively small values are obtained for EVPI and EVPPI (although we note that this is a judgement) then this suggests that no further research is necessary or required to obtain 'better' estimates for specific groups of parameters.

A judgement will be formed based upon the findings of the EVPI analysis as to whether it is worthwhile conducting an expected value of sampling information (EVSI) analysis. EVSI provides further information on the value of removing some of the existing uncertainty from additional research and, additionally, explicitly takes into account the cost of generating that future research to estimate the expected net benefit of sampling.

2.4 Patient workshop

Whilst the severity of hyperhidrosis can be measured in terms of the amount of sweat produced, its most significant impact is on quality of life, and therefore it is essential that this is captured in any assessment of severity and also in any measure of treatment benefit. Some attempts at capturing the impact on the patient are available in the literature, e.g. the Hyperhidrosis Disease Severity Score (HDSS), and, as described above, we propose to systematically review the available literature. However, in order to complement this and to ensure that the modelling undertaken will reflect the UK patient's perspective we propose a patient workshop to gather information on what is important to patients in terms of outcomes, both beneficial and adverse. In order to capture a wide range of opinion the workshop will be conducted as a 'virtual workshop' with the opinions of patients, dermatologists, and surgeons sought through an online survey. Patient advisors to the project will contribute to the content of the survey and in the interpretation of the data collected. The findings of this exercise will be used to guide the selection of the most appropriate outcomes for the model. They will also guide interpretation of claims of treatment effectiveness.

2.5 Dissemination and projected outputs

The projected outputs from this research project will be a full final report, two peer reviewed academic journal articles, a patient focused blog, a summary article directed at patients and a more general audience, with a targeted distribution list.

In order to disseminate the findings of our research to patients we will set up and run an internet-based blog to keep patients informed of the progress of our research, the blog will be hosted by the Hyperhidrosis Support Group web site. Also as part of a second Advisory Group meeting we will present our final results and agree with the representative of the Hyperhidrosis Support Group and our patient advisors a final dissemination plan so that the results will be made accessible to patients; probably through the Hyperhidrosis Support Group web site <http://www.hyperhidrosisuk.org>.

To disseminate the findings of our research to reviewers and health economists and health technology researchers the methodological developments in the complex evidence synthesis to be undertaken as a key part of this research will be published in appropriate peer reviewed journals such as *Medical Decision Making* or *Value in Health*.

3. The project team

The research project team is a multi-disciplinary partnership between York and Newcastle Universities, in collaboration with Harrogate and District NHS Foundation Trust, Newcastle upon Tyne Hospitals NHS Foundation Trust and Norfolk and Norwich University Hospitals NHS Foundation Trust, with advisory input from the Hyperhidrosis Support Group.

The Centre for Reviews and Dissemination (CRD) is a department of the University of York that specialises in evidence synthesis. CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of care. CRD has published over 600 systematic reviews and the Centre's methodological guidance on undertaking

systematic reviews in health care ²¹ is recommended as a source of good practice by national and international agencies. The Evidence Synthesis and Health Economics Groups within the Institute of Health & Society (IHS) Newcastle University, have extensive experience in the design and conduct of model based economic evaluations, including the use of value of information techniques. The work will build upon the existing collaborative link between CRD and IHS. The research is underpinned by robust methodological expertise and the key scientific disciplines and also involves close partnership with clinicians, as well as policy makers and practitioners from a range of health and social care settings.

3.1 Expertise in the team

The multidisciplinary team brings together expertise in systematic reviews, meta-analysis, decision modelling, and health technology assessment with relevant clinical expertise.

Dawn Craig, Principal Scientist in Evidence Synthesis, leads the Evidence Group within the Institute of Health & Society at Newcastle University. She is an experienced health economist with considerable expertise in both decision modelling and evidence synthesis. Ms Craig will lead the evidence synthesis, decision modelling and VOI analysis.

Dr Julie Jones-Diette is a Research Fellow at CRD. Dr Jones-Diette will be involved in undertaking the systematic reviews and drafting the blog and final report and subsequent publications.

Dr Alison Layton (co-PI) is a Consultant Dermatologist and Honorary Clinical Senior Lecturer at Hull York Medical School and an Affiliate of the Centre for Immunology and Infection at York University. She is Associate Medical Director for Research at Harrogate and District NHS Foundation Trust and co-Clinical Director of the NIHR Yorkshire and Humber Clinical Research Network. Dr Layton leads a busy general dermatology service and within this regularly treats patients with hyperhidrosis, with access to botulinum toxin, iontophoresis and other medically prescribed treatments. Dr Layton will co-lead the project with Dr Woolacott, providing clinical leadership and input at all stages of the project, including the protocol and final report.

Dr Nick Levell is a Consultant Dermatologist and Clinical Director of Dermatology at Norfolk and Norwich University Hospitals NHS Foundation Trust. He is also Clinical Vice President of the British Association of Dermatologists and immediate past-President of the British Society for Medical Dermatology. Dr Levell will provide input at all stages of the project, including the protocol and final report.

Eoin Moloney is a Health Economist at the Institute of Health & Society at Newcastle University. He has experience in both economic evaluation and economic modelling. Mr Moloney will contribute to the evidence synthesis, economic model and VOI analysis, drafting of the final report and subsequent publications.

Stephen Rice is a Health Economist at the Institute of Health & Society at Newcastle University. He has considerable experience in economic evaluation, economic modelling and evidence synthesis. Mr Rice will contribute to the evidence synthesis, the economic model and VOI analysis, drafting of the final report and subsequent publications.

Professor Gerard Stansby is a Consultant Vascular Surgeon with many years' experience of the surgical treatment of patients with hyperhidrosis. Professor Stansby will provide input at all stages of the project, including the protocol and final report.

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Ros Wade is a Research Fellow at CRD. She has over ten years of experience in systematic reviews and systematic review methodology. Mrs Wade will be the lead reviewer responsible for the systematic reviews and will also lead the project's dissemination activities.

Dr Nerys Woolacott (co-PI) is a Senior Research Fellow at CRD. She has been the NICE TAR project manager at CRD for 10 years and is an expert in Health Technology Assessment and evidence synthesis. She has extensive experience in leading similar projects and has a long standing research interest in the methodologies of systematic reviews and evidence syntheses. Dr Woolacott will co-lead the project with Dr Layton and will provide input at all stages of the project, including the protocol and final report. Her role will have a particular focus on the methodological aspects of the proposed work.

Kath Wright is the Information Service Manager at CRD. She has considerable experience in the design, conduct and reporting of literature searches and has supported numerous systematic reviews and health technology assessments. Ms Wright will undertake the literature searches for the systematic reviews and the associated bibliographic management.

Julie Halford, a Specialist Nurse at The Hampshire Clinic, is an advisor to our research project. She has been a nurse for 30 years and specialises in sclerotherapy and hyperhidrosis. She founded the Hyperhidrosis Support Group in 2003 and has devoted a great deal of time to running the Group and sharing her expertise. This support group is widely cited in guidelines for the management of hyperhidrosis, e.g. NICE Clinical Knowledge Summary and interventional procedure guidance and British Association of Dermatologists' guidelines. She regularly addresses groups of dermatologists and dermatology nurses to update them on the latest treatments. Ms Halford will provide advice throughout the project, including the protocol and final report.

In addition **Dr Anna Hammond**, a General Practitioner in Selby and Director of Communication Skills Teaching at Hull York Medical School, and **Professor Simon Kay**, Consultant Plastic Surgeon and Professor of Hand Surgery at Leeds Teaching Hospitals NHS Trust and Editor of the British Journal of Plastic Surgery, will provide additional clinical expert advice as necessary.

Professor Julian Higgins, Professor of Evidence Synthesis at the University of Bristol, will provide additional expert statistical advice.

3.3 Patient and public involvement (PPI)

It is our intention to recruit at least two patient advisors through the Hyperhidrosis Support Group UK, or through Dr Layton's, Dr Levell's, or Professor Stansby's clinic. We have also recruited Julie Halford, who runs the Hyperhidrosis Support Group, as a key member of our advisory team. Throughout the project we will consult Julie Halford and the patient advisors on the development of the structure of the decision model so that it captures the key elements of the condition and has face validity. We will present the results of our research to our advisors and agree a final patient focussed dissemination plan with Julie Halford and our patient advisors, so that the results are accessible to patients. In addition, we will run an internet-based Blog, hosted by the Hyperhidrosis Support Group web site, to keep patients informed of the progress of our research.

Furthermore, we will hold a virtual patient workshop to gather information on what is important to patients in terms of treatment outcomes.

4. Project timetable and milestones

The project will take place over a twelve month period. The key milestones are presented in Table 2.

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Table 2: 12 month timetable from 1 December 2015 to 30 November 2016

Task	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
<i>Systematic reviews</i>												
Protocol development	■											
Literature searches	■	■										
Screening and study selection		■	■	■								
Data extraction, quality assessment, checking			■	■	■	■	■					
Synthesis (network meta-analysis)						■	■	■				
<i>Workshop on patient perspective and outcomes</i>							■	■	■			
<i>Value of information analysis</i>												
Literature searches	■	■										
Screening and study selection		■	■	■								
Data extraction, quality assessment, checking			■	■	■	■	■					
Model development			■	■	■	■	■	■	■			
Model results								■	■	■	■	
Value of information analysis – EVPI								■	■	■	■	
Value of information analysis – EVSI								■	■	■	■	
<i>Report</i>												
Report writing									■	■	■	■
Preparation of journal articles									■	■	■	■
Other dissemination activities									■	■	■	■

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Appendix

The following draft search strategy to identify relevant studies was devised for MEDLINE (Ovid interface). This strategy will be further developed as necessary and converted to run appropriately on other databases.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Draft Search Strategy:

-
- 1 exp Hyperhidrosis/ (3160)
 - 2 hyperhidrosis.ti,ab. (2734)
 - 3 hyperhydrosis.ti,ab. (181)
 - 4 (excess\$ adj2 sweat\$.ti,ab. (527)
 - 5 (primary HH or secondary HH).ti,ab. (10)
 - 6 1 or 2 or 3 or 4 or 5 (4432)

 - 7 antiperspirants/ or deodorants/ (442)
 - 8 Aluminum Compounds/ (4285)
 - 9 (aluminum adj2 (chloride or hydrochloride)).ti,ab. (772)
 - 10 (aluminium adj2 (chloride or hydrochloride)).ti,ab. (356)
 - 11 (antiperspirant\$ or deodorant\$.ti,ab. (581)
 - 12 driclor.ti,ab. (1)
 - 13 anhydrol forte.ti,ab. (0)
 - 14 7 or 8 or 9 or 10 or 11 or 12 or 13 (5752)
 - 15 6 and 14 (173)

 - 16 Iontophoresis/ (6925)
 - 17 (iontophoresis or iontophorese).ti,ab. (3956)
 - 18 16 or 17 (8455)
 - 19 6 and 18 (201)

 - 20 exp Botulinum Toxins/ (13421)
 - 21 botulinum toxin\$.ti,ab. (10519)
 - 22 botox.ti,ab. (1495)
 - 23 20 or 21 or 22 (16170)
 - 24 6 and 23 (643)

 - 25 exp Cholinergic Antagonists/ or exp Muscarinic Antagonists/ (75926)
 - 26 Quaternary Ammonium Compounds/ (22365)
 - 27 Glycopyrrolate/ (762)
 - 28 glycopyrronium bromide.ti,ab. (66)
 - 29 robinul.ti,ab. (17)
 - 30 glycopyrrolate.ti,ab. (797)
 - 31 propantheline.ti,ab. (382)
 - 32 anticholinergic\$.ti,ab. (10389)
 - 33 pro-banthine.ti,ab. (31)
 - 34 oxybutynin.ti,ab. (1147)
 - 35 methantheline.ti,ab. (58)
 - 36 vagantin.ti,ab. (3)
 - 37 methantheliniumbromide.ti,ab. (2)
 - 38 atropine.ti,ab. (26970)
 - 39 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (115995)

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- 40 6 and 39 (229)

- 41 Sympathectomy/ (8174)
- 42 sympathectom\$.ti,ab. (6633)
- 43 sympathicotomy.ti,ab. (120)
- 44 sympathotomy.ti,ab. (25)
- 45 (sympathetic adj2 (ablation or surgery or block\$ or excision\$)).ti,ab. (2523)
- 46 endoscopic thoracic sympathectom\$.ti,ab. (165)
- 47 ETS.ti,ab. (9140)
- 48 41 or 42 or 43 or 44 or 45 or 46 or 47 (22486)

- 49 6 and 48 (1156)
- 50 Curettage/ (3788)
- 51 curettage.ti,ab. (9432)
- 52 curretage.ti,ab. (89)
- 53 50 or 51 or 52 (11497)
- 54 6 and 53 (70)

- 55 Lasers/ (33283)
- 56 laser\$.ti,ab. (204821)
- 57 55 or 56 (210086)
- 58 6 and 57 (69)

- 59 Microwaves/ (14049)
- 60 microwave\$.ti,ab. (24662)
- 61 59 or 60 (27278)
- 62 6 and 61 (15)

- 63 Ultrasonic therapy/ (8581)
- 64 ultrasound.ti,ab. (175480)
- 65 63 or 64 (179752)
- 66 6 and 65 (33)

- 67 Lipectomy/ (3569)
- 68 (lipectom\$ or liposuction).ti,ab. (3370)
- 69 67 or 68 (4790)
- 70 6 and 68 (54)

- 71 miraDry.ti,ab. (0)
- 72 bilateral axillae aspiration.ti,ab. (0)
- 73 shelley\$ procedure\$.ti,ab. (1)
- 74 ((remove\$ or removal or removing) adj2 sweat gland\$).ti,ab. (12)
- 75 6 and 74 (9)

- 76 Clonidine/ (13022)
- 77 Diltiazem/ (6059)
- 78 Benzodiazepines/ (19583)
- 79 76 or 77 or 78 (38536)
- 80 6 and 79 (27)

- 81 15 or 19 or 24 or 40 or 49 or 54 or 58 or 62 or 66 or 70 or 71 or 72 or 73 or 75 or 80 (2158)