Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Liposuction for the treatment of chronic lymphoedema

Appraisal summary

Why did Health Technology Wales (HTW) appraise this topic?

Chronic lymphoedema affects more than 450,000 people in the UK (LWCN) and refers to the abnormal accumulation of protein-rich fluid in tissue, leading to swelling. It is caused by an impairment of the lymphatic system, which occurs either due to abnormal development or trauma. Infection, malignancy, and cancer treatment can all result in the manifestation of lymphoedema, which primarily occurs in the upper and lower extremities, leading to pain, decreased range of movement and an increase in skin infections in the affected area. Current treatment for lymphoedema is comprised of decongestive lymphatic therapy, which requires a high level of compliance from the patient to be effective.

Liposuction is a procedure which removes excess body fat using a cannula and an aspirator using negative pressure. Liposuction can be provided in conjunction with current standard practice and may be an effective treatment for the reduction or removal of excess limb volume in patients affected by lymphoedema.

HTW undertook this Evidence Appraisal Report (EAR) following the publication of the National Institute for Health and Care Excellence (NICE) Interventional Procedures Guidance (IPG) on the topic.

What evidence did HTW find?

This Evidence Appraisal Report (EAR) aimed to identify and summarise evidence that addresses the following question: 'What is the clinical and cost effectiveness of liposuction for people with chronic lymphoedema?'

HTW researchers identified a Health Technology Assessment (HTA) by the Canadian Agency for Drugs and Technologies in Health (CADTH) entitled 'Liposuction for Lymphoedema' CADTH (2022), as well as the NICE Interventional Procedures Guidance (IPG723) NICE (2022) which informed the undertaking of this appraisal. Three further studies were identified: a UK based prospective cohort study (McGee & Munnoch 2018); a 12 month follow up paper to an already included comparative cohort (Klernäs et al. 2020) and a case series evaluating incidence of skin infection before and after liposuction (Karlsson et al. 2022). Evidence was included for appraisal only if it was not covered in the CADTH review, the NICE IPG, or the reviews included therein, or if it reported data on outcomes or populations not sufficiently covered by the above.

The evidence identified reported significant improvements in the reduction of excess oedema volume, and improvements in some health-related quality of life (HRQoL) measures for participants who received liposuction for chronic lymphoedema. No major surgical complications were reported, with only small numbers of participants requiring blood transfusions. A small number of participants had skin ulcers due to garment use, and studies reporting incidence of cellulitis and erysipelas showed that the incidence appeared to reduce after liposuction.

Reduction in excess oedema volume for upper extremity lymphoedema is the most evidenced outcome in this appraisal and was evaluated in sixteen studies. Liposuction for lower extremity lymphoedema was evaluated in thirteen studies. The evidence for craniofacial lymphoedema was limited, with only two studies reporting outcomes.

It is important to note that much of the evidence is drawn from single centre case series studies, with four comparative cohort studies and one randomised controlled trial evaluating quality of life outcomes in craniofacial lymphoedema population in twenty participants also included in the assessment.

Areas of uncertainty:

- There are reported differences in liposuction techniques that may affect peri-operative outcomes and the incidence of complications or adverse events.
- Only two studies report outcomes separately for primary versus secondary lymphoedema, with the evidence suggesting there are different treatment responses between these groups.
- The clinical effectiveness evidence is comprised mostly of single centre case series, with only one randomised controlled trial and four comparative cohort studies.
- Many (16) studies included in the review included fewer than 50 participants.
- There is limited evidence available for follow-ups longer than 12 months.
- All UK studies used in this review were conducted in the same centre, with significant overlap in study sites and authors.
- The systematic review and meta-analysis by Chang et al. (2021) is of poor to moderate quality.

The health economic review identified a cost-utility analysis undertaken to determine costs and health-related quality of life (HRQoL) of power-assisted liposuction compared to conservative management in the USA. Results of the analysis showed that liposuction was expected to increase quality-adjusted life years (QALYs) by 3.7 years over a lifetime and decrease lifetime costs by $74,487 when compared to conservative management. However, the study was associated with potentially serious limitations.

As there was no directly applicable published evidence on the cost effectiveness of liposuction for chronic lymphoedema and due to the significant limitations of the included cost-utility analysis, HTW developed an economic analysis to estimate cost effectiveness compared to standard care (SC). The model showed that over a 5-year time horizon, treatment with liposuction in addition to SC is expected to increase costs by £7,577 per patient but provide an additional 0.29 QALYs compared to SC alone, resulting in an incremental cost-effectiveness ratio (ICER) value of £26,269 per QALY gained. Probabilistic sensitivity analysis showed that liposuction in addition to SC has a 35% probability of being a cost-effective treatment strategy when compared to SC alone.

What was the outcome of HTW's appraisal?

HTW is a national body working to improve quality of care in Wales. We collaborate with partners across health, social care, and industry to issue independent guidance that informs commissioning within Wales health and social care. We are supported by an Assessment Group, who ensure our work adheres to high standards of methodological and scientific rigour, and an Appraisal Panel, who consider evidence within the Welsh context and produce HTW guidance. More details on our appraisal process, the assessment group, and the appraisal panel can be found on the HTW website.

In this case, the HTW Assessment Group considered the evidence presented in this Evidence Appraisal Report (EAR056) and concluded there was sufficient evidence for the development of guidance. Please refer to the HTW website for full guidance details.

Evidence Appraisal Report (EAR056) follows below and provides full details for this topic. More comprehensive details of the HTW Guidance and HTW Appraisal Panel considerations can be found on the HTW website.

1. Purpose of the Evidence Appraisal Report

This report aims to identify and summarise evidence that addresses the following question: 'What is the clinical and cost-effectiveness of liposuction for treating chronic lymphoedema?'

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of identifying the best published evidence on the effectiveness and cost-effectiveness of health and social care technologies and models of care and support. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Context

Lymphoedema is the chronic swelling of tissue caused by an abnormal accumulation of protein-rich subcutaneous lymph fluid. Lymphoedema occurs when the lymphatic system, which would usually drain this fluid away, is disrupted – either by damage (secondary lymphoedema), or a condition affecting the development and functioning of the lymphatic system (primary lymphoedema). Approximately 450,000 people in the UK have lymphoedema (LWCN). In Wales, prevalence has increased in the last 10 years, from 2 people per 1000 in 2011 to 7.3 people per 1000 in 2023. Based on Lymphoedema Wales Clinical Network (LWCN) figures, approximately 23,000 people in Wales have lymphoedema (LWCN 2023).

Primary lymphoedema can develop at any age, but most commonly manifests during infancy. For people with primary lymphoedema, the accumulation of fluid is not attributable to another medical condition and has occurred as a result of an underdeveloped lymphatic system. Secondary lymphoedema is also referred to as 'acquired' lymphoedema and occurs as a result of damage to the lymphatic system, which can arise from infection, surgery, or trauma, and is often associated with cancer treatment.

Standard practice for the treatment of lymphoedema in Wales consists of conservative self-management and behavioural interventions, including wearing compression garments (known as controlled compression therapy/CCT), teaching health skin care habits to reduce risk of infection (particularly cellulitis and erysipelas), optimising lifestyle factors such as exercising regularly, maintaining a healthy diet, and where needed, using specialised massage techniques to manipulate the soft tissue to encourage movement of lymph fluid (manual lymphatic drainage). The intervention of interest for this appraisal, liposuction, is used for people with lymphoedema that is not responding to conservative treatment, and therefore is an adjunct intervention to standard practice.

3. Health technology

Liposuction is a possible adjunct intervention to standard practice and is a debulking procedure whereby the oedematous tissue is removed using a cannula and negative pressure (suction). This is normally followed by using a compression garment, which will be revised multiple times until the oedema reaches a steady state. However, as in standard practice, this compression garment must be worn for life.

Various liposuction techniques exist and were identified in the literature. Techniques reported include suction, vacuum, or power assisted liposuction, the use of 'dry' techniques and tourniquets in combination with tumescence to minimise blood loss. Pre-surgery mapping techniques that highlight lymphatic pathways have also been reported as a means to avoid

further damage to the lymphatic vessels during liposuction (Campisi et al. 2017). Following expert review, two primary liposuction techniques used in the NHS were identified:

- Tumescent liposuction – also known as 'local liposuction', the tumescent technique does not require patients to receive general anaesthesia. Tumescent fluid (usually comprised of lidocaine and epinephrine in a saline solution) is injected, after which the cannula is inserted, and the suction begins. Experts advised that tumescent liposuction is associated with less post-operative complications than traditional liposuction, which does not use lidocaine or epinephrine.
- The 'dry' technique – unlike traditional or tumescent liposuction, dry liposuction does not use an injection of fluid or a tourniquet and usually requires patients to receive general anaesthesia.

Experts were able to clarify that in Wales, tumescent liposuction is recommended for upper and lower limb liposuction due to a lower likelihood of post-operative complications such as pain, bruising and necrosis.

Experts were also able to provide more information about the variations in use of pre-surgery mapping techniques, and whether they constitute a major variation to clinical practice. Experts reflected that patients undergoing liposuction for lymphoedema will have previously had some imaging performed, as they tend to be complex in nature, especially patients who have undergone lymphovenous anastomosis surgery – but there was disagreement as to whether lymphoscintigraphy and/or indocyanine green (ICG) scanning are routinely offered to patients undergoing liposuction as part of standard practice.

Alternative surgical interventions, including procedures to improve symptoms through repair of the lymphatic system (e.g., vascularised lymph node transfer) are not evaluated in this EAR.

4. Health technology assessments and guidance

HTW identified existing UK and Canadian guidance relevant to this topic.

NICE (2022) Interventional Procedures Guidance (IPG723) 'Liposuction for chronic lymphoedema' recommends that there is adequate evidence for the efficacy and safety of liposuction for chronic lymphoedema. The guidance recommends that the procedure may be used with standard clinical governance arrangements providing patient selection is performed by an expert multidisciplinary team with experience in managing lymphoedema, and the procedure itself is carried out in a specialist centre by a clinician with expertise in liposuction for lymphoedema.

A CADTH (2022) health technology assessment 'Liposuction for Lymphedema' found that liposuction in combination with controlled compressive therapy (CCT) is associated with a higher reduction in excess oedema volume, compared to CCT alone. The assessment also noted an association between liposuction and improvements in health-related quality of life, but authors were unable to independently corroborate this finding. The assessment concluded the evidence available for clinical effectiveness of liposuction was uncertain, owing to a small evidence base with poor reporting and significant methodological limitations.

5. Clinical effectiveness

HTW searched for and summarised evidence on the effectiveness of liposuction for chronic lymphoedema, compared to standard models of care. The detailed criteria used to select evidence for the appraisal are outlined in Appendix 3. For details on the methodology used to identify evidence for this report, refer to Section 12.

All studies used in the CADTH HTA and NICE IPG mentioned in section 4 were included for assessment in this review, save for two primary studies which did not meet the inclusion criteria for this review. Through searching HTW were able to identify a further three studies which are included in this review (Karlsson et al. 2022, Klernäs et al. 2020, McGee & Munnoch 2018). In total, 21 primary studies, reported across 22 articles were reviewed. There was considerable overlap in the primary studies included in the systematic reviews.

One single centre RCT by Alamoudi et al. (2018) evaluated liposuction in combination with controlled compressive therapy compared to a waitlist for craniofacial lymphoedema in 20 patients. Three comparative cohort studies evaluated liposuction in combination with controlled compressive therapy, compared to controlled compressive therapy alone (Brorson et al. 1998a, Brorson & Svensson 1998b, Brorson et al. 2006) and were published by the same research team in Sweden. A further comparative cohort study evaluated liposuction and controlled compressive therapy compared to a rehabilitation programme (Klernäs et al. 2018, Klernäs et al. 2020).

Eighteen single-centre case series were included in this review, with participant numbers ranging from 8 to 146 (Agarwal et al. 1998, Boyages et al. 2015, Brake et al. 2014, Campisi et al. 2017, Chen et al. 2023, Damstra et al. 2009, Granoff et al. 2022, Granzow et al. 2014, Greene & Maclellan 2016, Hoffner et al. 2017, Hoffner et al. 2018, Karlsson et al. 2022, Lamprou et al. 2017, Lee et al. 2016, McGee & Munnoch 2018, Schaverien et al. 2012, Stewart & Munnoch 2018, Yoshida et al. 2023).

The amount of evidence and participant numbers are similar between upper and lower extremity lymphoedema, but there is a significant paucity of evidence for liposuction for use in craniofacial lymphoedema (Appendix 2). Outcomes relating to excess oedema volume are well reported for upper and lower extremity lymphoedema, with all studies reporting on this outcome. However, data for quality of life (health-related and generic) and adverse outcomes are much more limited.

For clarity, clinical evidence in this appraisal is presented separately for the three major oedema locations: upper extremity; lower extremity and craniofacial.

5.1 Clinical outcomes

Clinical outcome data are reported in Tables 1, 2 and 3.

5.1.1 Upper extremity lymphoedema

A total of sixteen studies reported outcomes for participants with upper extremity lymphoedema. Of these, six studies include both upper and lower extremity lymphoedema outcomes in their reporting, and eight report exclusively on upper extremity lymphoedema outcomes. Complete study characteristics and upper extremity lymphoedema outcomes are summarised in Table 1.

5.1.1.1 Reduction in oedema volume (%/ml)

A meta-analysis of two single centre comparative cohort studies (Brorson et al. 1998a, Brorson & Svensson 1998b) performed by Chang et al. (2021) showed a mean difference in the percentage oedema volume reduction at 12 months between liposuction plus CCT (n=25) versus CCT alone (n=23) of 63.95% (95% CI 47.29 – 78.33; p<0.0001).

A meta-analysis of two single-centre comparative cohort studies (Brorson et al. 1998a, Brorson et al. 2006) performed by Chang et al. (2021) also reported a significant (p<0.0001) difference in the reduction of oedema volume of -895ml (95% CI -1140.1 to – 650.98) between liposuction plus CCT (n=46) and CCT alone (n=23) at 12 months.

A meta-analysis of two single centre case series (Boyages et al. 2015, Campisi et al. 2017) evaluating liposuction plus controlled compressive therapy was performed by Chang et al. (2021). The meta-analysis showed a mean percentage pre and post operative reduction in oedema volume of 28.6% (95% CI 6.06 to 51.29; p=0.01).

An additional meta-analysis of five single centre case series (Brorson et al. 2006, Campisi et al. 2017, Damstra et al. 2009, Hoffner et al. 2017, Schaverien et al. 2012) evaluating liposuction plus CCT (n=207) was performed by Chang et al. (2021). The meta-analysis demonstrated a significant mean reduction of oedema volume of 1294.16ml (95% CI 460.47 to 2127.85; p<0.002) at 12 months.

A comparative cohort study by Klernäs et al. (2020) evaluated liposuction in combination with controlled compressive therapy compared to a rehabilitation program which included complex decongestive therapy, exercise, and educational components. Treatment effects for this study were grouped for patients with both upper (n=27) and lower (n=48) lymphoedema. Oedema volume decreased slightly at 6 months to 770ml (SD 1398) from 934ml (SD 1398) at baseline (p=0.05). Participants (n=57) in the liposuction group had significant decreases of oedema volume from baseline 3117ml (SD 2543) to 154ml (SD 579; p<0.001) at 12 months follow up. No between group statistical comparisons were reported. For 18 participants in the rehabilitation group, volume reduction results were not sustained at six months follow-up.

A single centre case series by Granzow et al. (2014) evaluated suction-assisted liposuction for lymphoedema in 6 participants. The study demonstrated a mean percentage reduction in upper extremity oedema volume of 111% (range 98 to 120).

A single centre case series by Greene & Maclellan (2016) reported a mean reduction in oedema volume of 73% following liposuction and controlled compressive therapy at 3.1 months. It is important to note that treatment effects in this study were grouped between participants with both upper (n=6) and lower (n=9) extremity lymphoedema.

A single centre case series by Granoff et al. (2022) evaluated power-assisted liposuction for lymphoedema in 39 patients with upper and lower extremity lymphoedema. The study reported excess volume reduction of 116% for patients with upper extremity lymphoedema (n=23) at 1 year follow-up.

A single centre case series by Yoshida et al. (2023) reported an 'improvement rate' for a total of 10 participants with upper extremity lymphoedema. Authors reported an 'UEL index', calculated using five measurements from each limb, divided by BMI. An improvement rate was calculated based on the difference between UEL index (%) pre and-post op, multiplied by 100. For patients with lower extremity lymphoedema, the mean UEL index pre-surgery was 123.7% (range 103-158) reducing to 92.7% (range 76-106) at 'last observation month'. The improvement rate for upper extremity lymphoedema was reported as 24.3% (range 9.8-39.2). Treatment effects were grouped across participants, with authors claiming that the improvement rate was statistically significant (p=0.04)

A single centre case series by Chen et al. (2023) reported the average lipoaspirate volume for liposuction performed on upper extremity (n=23 limbs) lymphoedema. The average lipoaspirate volume was reported as 2035ml (± 488ml). The average reduction in volume was grouped across participants, with authors reporting a 32.2% (± 9.8) reduction in volume overall.

The two remaining single centre case series (Hoffner et al. 2018, Lee et al. 2016) have significant overlap in terms of study populations – as both were conducted at the same study site within the same recruitment period. Hoffner et al. (2017) evaluated liposuction in combination with controlled compressive therapy in participants with non-pitting upper extremity lymphoedema (n=105). The study reported a mean excess volume reduction of 117% at 5 years follow-up. Lee et al. (2016) evaluated liposuction for lymphoedema and the incidence of skin infection (erysipelas) for patients with non-pitting upper extremity lymphoedema (n=130). The study reported a mean excess volume reduction of 109% at 6 months follow-up. The authors claim results persisted to a maximum of 18 years, but data are not reported.

5.1.1.2 Disease-specific health-related quality of life

Two studies reported lymphoedema specific health-related quality of life outcome measures (Granoff et al. 2022, Klernäs et al. 2020). Both reported increases in quality of life after liposuction in combination with controlled compressive therapy.

A single-centre case series by Granoff et al. (2022) reported scores on the Lymphoedema Quality of Life (LYMQoL) measure for 39 participants with upper (n=23) and lower (n=18) extremity lymphoedema. The study reported that LYMQoL scores for patients with upper extremity lymphoedema increased from 6.5 to 8.3 (28%) at 8 months follow-up. The study reports that the most improved LYMQoL domain was the appearance sub-score (44% increase), suggesting an improvement in quality of life.

A comparative cohort study by Klernäs et al. (2020) reported scores on the Lymphoedema Quality of Life Inventory (LyQLI) for participants with both upper and lower extremity lymphoedema. Liposuction combined with controlled compressive therapy was performed across 3 centres and was compared to a rehabilitation programme in undertaken in one centre (n=75). Twenty-seven upper extremity lymphoedema patients were included in the study – 11 received the rehabilitation programme and 16 received liposuction in combination with controlled compressive therapy. In the liposuction group, LyQLI scores saw a significant reduction across all three domains: physical, psychosocial, and practical ($p<0.001$), suggesting an improvement in quality of life. Similarly, the percentage of participants in the liposuction group (n=16) who reported a score of 2 or more on any one LyQLI domain reduced – from 45% at baseline to 5% at 12 months follow-up. It is important to note that 12 months follow-up data was only available for 46 participants, and the distribution of responses from participants with either upper or lower extremity lymphoedema is unclear. In the rehabilitation programme group, participants with upper extremity lymphoedema (n=11) demonstrated significant reductions from baseline to 12 months follow-up in two domains: physical ($p=0.02$) and psychosocial ($p=0.01$) with no improvement observed in the practical domain. The percentage of participants in the rehabilitation programme group with upper extremity lymphoedema who scored 2 or more on any one LyQLI domain increased – from 21% at baseline to 28% at 12 months follow-up.

A single centre case series by Chen et al. (2023) reported outcomes for the Lymphoedema Quality of Life Measure (LYMQoL) in 41 participants with both upper and lower extremity lymphoedema. Pre- and post-operative LYMQoL scores were analysed with paired t-tests and demonstrated statistically significant improvements in appearance ($p=0.01$), function ($p=0.04$), symptoms ($p=0.01$) and authors claim a significant improvement in overall quality of life ($p=0.03$). LYMQoL scores are not reported in the study.

5.1.1.3 Generic health-related quality of life

Four studies reported generic health-related quality of life outcomes (Boyages et al. 2015, Brorson et al. 2006, Hoffner et al. 2017, Schaverien et al. 2012).

A single centre comparative cohort study by Brorson et al. (2006) evaluated liposuction in combination with controlled compressive therapy, compared to controlled compressive therapy alone in 49 participants with upper extremity lymphoedema. In the liposuction group (n=35), visual analogue scale (VAS) scores were significantly reduced at 12 months (n=35) compared to controlled compressive therapy alone (n=14) for questions related to pain (p=0.002), difficulty in activities of daily living (p=0.02), swollen arm (p=0.0001) and heavy arm (p=0.005).No significant reductions in reductions of VAS scores between groups were found for questions related to swelling of the hand, reduced mobility, fatigue, weakness, and numbness/prickling sensation or for scores on the Nottingham Health Profile and the Psychological General Well-Being Index. Hospital Anxiety and Depression scale (HADS) scores were only significantly different between groups for the anxiety sub-scale.

A single centre case series by Boyages et al. (2015) evaluated liposuction in combination with controlled compressive therapy in participants with both upper (n=15) and lower (n=6) extremity lymphoedema. Using the Patient-Specific Functional Scale (PSFS), functional impairment was assessed, and participants were asked to rate the impact of their lymphoedema on six functional and emotional domains. All patients reported improvements in the PSFS at 6 months follow-up ($p<0.01$). It is important to note that results were grouped for participants with both upper and lower extremity lymphoedema.

A single centre case series by Hoffner et al. (2017) evaluated liposuction combined with controlled compressive therapy in 60 participants with upper extremity lymphoedema, using the 36-item short-form health survey (SF-36) to assess health-related quality of life at 1, 3, 6 and 12 months follow-up. The study demonstrated improvements in physical functioning (p=<0.001), bodily pain (p=<0.001), vitality (p=<0.05), social functioning (p=<0.05) and mental component (p=<0.01) scores at 12 months follow-up.

A single centre case series by Schaverien et al. (2012) evaluated liposuction in combination with controlled compressive therapy in 12 participants with upper limb lymphoedema. Using the Hospital and Anxiety Depression Score (HADS) questionnaires, the study reported a significant reduction in anxiety scores from 9.09 to 4.60 (p=0.04) at three months follow-up. A non-significant reduction in depression scores was also reported, from 5.73 to 1.70 (p=0.05).

5.1.1.4 Adverse events

Six studies reported information about liposuction adverse events in participants with upper extremity lymphoedema.

Four studies, including 357 participants undergoing liposuction, reported that no surgical complications occurred (Brorson et al. 1998a, Brorson & Svensson 1998b, Damstra et al. 2009, Hoffner et al. 2017).

Hoffner et al. (2018) reported that in n=35 participants where the "dry" technique with a tourniquet was used, 14% (n=5) required blood transfusions following the intervention. However, when the tumescent technique with tourniquet was used in the following n=45 participants, no blood transfusions were required.

One study (Lee et al. 2016) reported incidence of erysipelas after liposuction in 130 participants with upper extremity lymphoedema. The total pre-liposuction observation years totalled 1147

years and the erysipelas incidence was 0.47 bouts per year (range 0 to 5, SD 0.8) during this time. The total post-operative observation years totalled 983 and there was a reduction in erysipelas to 0.06 bouts per year (range 0 to 3, SD 0.3), corresponding to a reduction of 87% ($p<0.001$).

Of the remaining six studies that included both participants with upper and lower extremity lymphoedema, five reported information about adverse events. Three reported no surgical complications in any participants (those with upper or lower extremity lymphoedema). Two reported complications. Granoff et al. (2022) reported three participants who had developed skin ulcers secondary to garment use but did not specify whether these participants had upper or lower extremity lymphoedema. Granoff et al. (2022) also reported an overall (across participants) reduction in incidence of cellulitis post-operatively, from 0.26 episodes per year pre-operatively (over a total of 348.5 disease years), to 0.07 episodes per year post-operatively (over a total of 27.4 post-op years). The remaining study (Greene & Maclellan 2016) reported complications but these only occurred in participants with lower extremity lymphoedema (see section 4.3.4).

5.1.2 Lower extremity lymphoedema

A total of eleven studies reported outcomes for participants with lower extremity lymphoedema. Of these, six studies included both upper and lower extremity lymphoedema outcomes in their reporting and five studies report exclusively on lower extremity lymphoedema outcomes. Lower extremity lymphoedema outcomes are summarised in Table 2.

5.1.2.1 Reduction in oedema volume (%/ml)

A comparative cohort study by Klernäs et al. (2020), detailed previously in section 5.1.1.1, evaluated liposuction in combination with controlled compressive therapy compared to a rehabilitation program which included complex decongestive therapy, exercise, and educational components. Treatment effects for this study were grouped for patients with both upper (n=27) and lower (n=48) lymphoedema. Oedema volume decreased slightly at 6 months to 770ml (SD 1398) from 934ml (SD 1398) at baseline ($p=0.05$). Participants (n=57) in the liposuction group had significant decreases of oedema volume from baseline 3117ml (SD 2543) to 154ml (SD 579; $p<0.001$) at 12 months follow up. No between group statistical comparisons were reported. For 18 participants in the rehabilitation group, volume reduction results were not sustained at six months follow-up.

A meta-analysis of two single-centre case series (Boyages et al. 2015, Campisi et al. 2017) performed by Chang et al. (2021) showed a mean reduction in oedema volume of 29.23% (95% CI 5.56 to 52.90, $p=0.02$) in participants receiving liposuction in combination with controlled compressive therapy.

A single centre case series by Granzow et al. (2014) reported reductions in oedema volume for 26 patients who had received either liposuction (n=10) or lymphovenous anastomosis / vascularised lymph node transfer (n=16) for both upper and lower extremity lymphoedema. The study reported an 86% reduction in volume at 12 months post-operatively for 4 participants who had received liposuction for lower extremity lymphoedema.

A single centre case series by McGee & Munnoch (2018) reported reductions in oedema volume for 21 participants who received liposuction in combination with controlled compressive therapy for lower extremity lymphoedema. The study reported a mean reduction of 88.9% at 12 months follow-up, with a 113% reduction reported for six participants at 5-year follow-up.

A single centre case series by Greene & Maclellan (2016) reported reductions in oedema volume for 15 patients who received liposuction in combination with controlled compressive therapy for both upper (n=6) and lower (n=9) extremity lymphoedema. Treatment effects were grouped across participants, and the study reported a mean reduction in oedema volume of 73% at 3.1 months follow-up.

Four single centre case series (Agarwal et al. 1998, Granoff et al. 2022, Karlsson et al. 2022, Stewart & Munnoch 2018) reported oedema volume reductions for a total of 219 participants with lower extremity lymphoedema. Two reported statistically significant reductions in oedema volume (Granoff et al. 2022, Karlsson et al. 2023) ($p<0.001$). Stewart & Munnoch (2018) reported mean pre-op oedema volume of 4372ml (range 229 to 15166), reducing to 1005ml (range 1987 to 5613) at 3 months in 72 participants, and 406ml (range 405 to 1497) at 9 years in five participants. Agarwal et al. (1998) reported a mean oedema reduction from pre- to post-operatively of 2287ml (range not given) in eight participants at 12 months.

A single centre case series by Yoshida et al. (2023) reported an 'improvement rate' for a total of 18 participants with lower extremity lymphoedema. Authors reported an 'LEL index', calculated using five measurements from each limb, divided by BMI. An improvement rate was calculated based on the difference between LEL index (%) pre and-post op, multiplied by 100. For patients with lower extremity lymphoedema, the mean LEL index pre-surgery was 298% (range 211-378) reducing to 248% (range 203-314) at 'last observation month'. The improvement rate for lower extremity lymphoedema was reported as 16.6% (range -0.1-27.2). Treatment effects were grouped across participants, with authors claiming that the improvement rate was statistically significant (p=0.04).

A single centre case series by Chen et al. (2023) reported the average lipoaspirate volume for liposuction performed on both lower leg (n=21 limbs) and thigh (n=13 limbs) lymphoedema. For lower leg lymphoedema, the average lipoaspirate volume was reported as 3106ml (± 824ml) and for thigh lymphoedema, the average lipoaspirate volume was reported as 5385ml (± 1246ml). The average reduction in volume was grouped across participants, with authors reporting a 32.2% (± 9.8) reduction in volume overall.

5.1.2.2 Primary and secondary lower extremity lymphoedema

Two studies reported reduction in oedema volume according to whether lymphoedema was primary or secondary in nature.

A study by Lamprou et al. (2017) reported reductions for 88 patients with lower extremity lymphoedema. For 47 participants with primary lymphoedema, median pre-operative oedema volume was 3686ml (IQR 2851 to 5121), reducing to 761ml (IQR -147 to 1554) at 24 months, with an increase in oedema volume observed between 12-24 months. For 41 participants with secondary lymphoedema, median pre-operative oedema volume was 3320ml (IQR 2533 to 4783), reducing to -38ml (IQR -1151 – 1135) at 24 months. Percentage reduction for secondary lymphoedema was higher than primary, reported at 101%, compared to 79%. Findings suggesting that liposuction may have a more sustained effect in participants with secondary lymphoedema.

A single centre case series in the UK (Stewart & Munnoch 2018) reported a higher mean percentage reduction in participants with secondary lower extremity lymphoedema at 12 months compared to those with primary lower extremity lymphoedema (95.6% [range 50 to 163.8] and 84.3% [range 31.3 to 169.9], respectively). Long term follow up data showed mean percentage reduction of 89.3% (range 74 to 111.5) in five participants with primary lymphoedema at nine years and 114%.8% (range 75.5 to 143) in four participants with secondary lymphoedema at six years.

5.1.2.3 Disease-specific HRQoL

Four studies reported lymphoedema specific HRQoL outcome measures for lower extremity lymphoedema (Chen et al. 2023, Granoff et al. 2022, Klernäs et al. 2020, McGee & Munnoch 2018). All reported increases in quality of life after liposuction in combination with controlled compressive therapy.

As previously reported, Klernäs et al. (2020) reported whole group (upper and lower lymphoedema) outcomes for the lymphoedema quality of life inventory (LyQLI) and observed significant reductions in all three domains ($p<0.001$), suggesting improved quality of life. A detailed explanation of the study is available in section 5.1.1.2.

A single centre case series by Granoff et al. (2022) reported outcomes for the Lymphoedema Quality of Life measure (LYMQoL) in 18 participants with lower extremity lymphoedema. LYMQoL scores increased by 44%, from a pre-operative mean of 5.9 to 8.5 at 12 months follow-up. No tests of statistical significance were conducted.

A single centre case series by McGee & Munnoch (2018) reported outcomes for the lymphoedema quality of life inventory (LyQLI) for 10 participants. The mean pre-operative LyQLI score was 75.9 (range 29-111) which improved to 26.9 (range 3-51) at 12-month follow-up.

A single centre case series by Chen et al. (2023) reported outcomes for the Lymphoedema Quality of Life Measure (LYMQoL) in 41 participants with both upper and lower extremity lymphoedema. Pre- and post-operative LYMQoL scores were analysed with paired t-tests and demonstrated statistically significant improvements in appearance ($p=0.01$), function ($p=0.04$), symptoms ($p=0.01$) and authors claim a significant improvement in overall quality of life ($p=0.03$). LYMQoL scores are not reported in the study.

5.1.2.4 Generic HRQoL

A single centre case series by Boyages et al. (2015) reported outcomes for six participants on the Patient-Specific Functional Scale (PSFS), which asks participants to list three personally important activities and rate how they are impaired by lymphoedema, from 0 (not able to perform) to 10 (able). Five participants showed a significant increase in score from a mean of 7.4 (range 4-9) pre-op to 28 (range 27-29) at 6 months post op ($p<0.001$). Boyages et al. (2015) also asked participants to rate impact of lymphoedema on six functional/emotional domains that had been drawn from previous research from 0 (not at all) to 10 (extremely so). Significant decreases (reflecting improved HRQoL) were seen for domains: heaviness ($n=5$; $P=0.002$); self-consciousness ($n=5$; $P<0.001$); anxious ($n=5$; $P<0.001$); swollen ($n=5$; $P<0.001$); impact on emotions ($n=5$; $P<0.001$), but not for pain.

5.1.2.5 Adverse events

Of the five studies that evaluated liposuction only in participants with lower extremity lymphoedema, four reported adverse events.

Agarwal et al. (1998) reported that although no major complications were noted, of eight included participants, two had persistent hyperpigmentation and one developed cellulitis, which responded to conservative treatment.

Stewart & Munnoch (2018) in their case series of 69 participants, reported two participants that required post-operative blood transfusions, two with peroneal nerve palsies due to tight compression garments and three instances of skin necrosis, one of which required excision and

direct closure. Stewart & Munnoch (2018) also reported that incidence of cellulitis reduced from 21 episodes pre-operatively, to three episodes post-operatively. Skin infection (cellulitis or erysipelas) incidence was also reported in Karlsson et al. (2022) and Lamprou et al. (2017).

Karlsson et al. (2022) reported a reduction in erysipelas incidence in 124 participants, from 0.2 bouts per person per year pre-operatively to 0.07 bouts per person per year post-operatively (65% reduction; p<0.001). Lamprou et al. (2017) reported a mean of eight attacks of cellulitis per year in 41 participants with primary lymphoedema, reducing to 0.2 attacks per year after surgery (p<0.001). In 47 participants with secondary lymphoedema, from 6 attacks per year pre-operatively to 0.3 attacks per year post-operatively (p<0.001). One participant with primary lymphoedema also had a decubitus ulcer due to compression garments. Lamprou et al. (2017) also noted that a change in technique during the study reduced the need for blood transfusions. Initially a two-stage procedure was used, in which a tourniquet and liposuction of the lower leg was performed by the "dry" method, which was then followed by liposuction of the upper leg after infiltration of a tumescent solution. The technique was then modified whereby both procedures were performed simultaneously by means of tumescent infiltration of both the upper and lower leg. The authors noted that although this did not have an effect on the oedema volume difference at two years, it did reduce the need for post-operative blood transfusion (reducing mean blood transfusion from 0.75 to 0.14 units per patient; p=0.009).

Of the remaining six studies that included both participants with upper and lower extremity lymphoedema, five reported information about adverse events. Three reported no surgical complications in any participants (those with upper or lower extremity lymphoedema). Two reported complications. Granoff et al. (2022) reported one participant with lower extremity lymphoedema that required a blood transfusion. Three participants developed skin ulcers secondary to garment use, but authors did not specify whether this was in participants with upper or lower extremity lymphoedema. Granoff et al. (2022) also reported an overall (across participants) reduction in incidence of cellulitis post-operatively (see section 5.1.1.4 above). Greene & Maclellan (2016) reported that two participants (of fifteen) with severe lower extremity lymphoedema underwent blood transfusions and had localised skin loss that healed secondarily, with one participant developing a skin infection that required operative debridement.

5.1.3 Craniofacial Lymphoedema

Two studies reported outcomes for craniofacial lymphoedema (Table 3). A randomised controlled trial by Alamoudi et al. (2018) randomised 20 participants to liposuction plus CCT or to a waitlist control, reporting outcomes at 6 months. A single centre case series of nine participants (Brake et al. 2014) also reported outcomes for craniofacial lymphoedema.

5.1.3.1 Reduction in oedema volume (%/ml)

No outcome data for reduction in oedema volume were reported.

5.1.3.2 Condition-specific HRQoL

Alamoudi et al. (2018) reported outcomes for the Blepharoplasty Outcome Evaluation (MBOE) scale, a validated scale used to monitor participants" self-perception of appearance. The scale was modified for use as a survey for the submental (under the chin) region. Each question (six in total) had a graded 0 to 5-point response and a change of 2 or more points was considered

significant. After summation of the scores on the MBOE, the liposuction plus CCT group had a mean difference of 10.3 (95% CI 5.42 to 15.18) pre versus post op. The wait list group had a mean difference of -0.5 (95% CI -2.42 to 1.42). The change in scores was significantly different between groups ($p<0.0001$), suggesting an improved self-perception of appearance in the liposuction plus CCT group. Of the five individual MBOE questions, the only question that did not elicit significantly different responses between groups was 'Do you feel the current appearance of your chin limits your social and professional activities?'.

Participants in the Alamoudi et al. (2018) RCT also completed the Derriford Appearance Scale (DAS-59). This is a validated scale designed measuring psychological distress and dysfunction associated with aesthetic disfigurements and deformities. It is sub-divided into five categories (general self-consciousness of appearance; social self-consciousness of appearance; sexual and bodily self-consciousness of appearance; negative self-concept; and facial self-consciousness of appearance) across 59 questions, with a scale of 1 to 5 for each question. A change of two between baseline and follow up was deemed to be significant. After summation of the scores on the DAS-59, the liposuction plus CCT group had a mean difference of -41 (95% CI -62.92 to -19.08) pre versus post op. The wait list group had a mean difference of 10.2 (95% CI -8.28 to 28.28). The change in scores was significantly different between groups ($p=0.001$), suggesting an improvement in psychological distress and dysfunction in the liposuction plus CCT group.

Similarly, Brake et al. (2014) reported outcomes for the MBOE and DAS-59 in a nine-participant single centre case series. Brake et al. (2014) reported similar results to Alamoudi et al. (2018) with significantly improved self-perception of appearance at 6 months for all questions ($p<0.008$) apart from 'Do you feel the current appearance of your chin limits your social and professional activities?'.

Brake et al. (2014) also reported findings from objective scoring of participants' appearance pre and post op by independent head and neck oncologists. Scores ranged from 1 (normal contours, no lymphoedema) to 5 (complete loss of neck contours and severely disfiguring lymphoedema). Inter-rater reliability was 0.89 with seven participants scores reflecting improvement and 2 as having no change. Post-op scores were significantly lower than pre-op ($p=0.016$).

5.1.3.3 Generic HRQoL

No outcome data for generic HRQoL were reported.

5.1.3.4 Adverse events

A randomised controlled trial by Alamoudi et al. (2018) reported that there were no adverse events following liposuction.

Table 1 - Upper extremity lymphoedema: outcomes

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
Reduction in oedema volume (%)			
Brorson et al. (1998a) & Brorson & Svensson (1998b) in Chang et al. (2021) MA	Two single centre, matched pairs comparative cohort studies Intervention: Liposuction + CCT, n=25 Comparator: CCT alone, n=23 n=48 Stage II lymphoedema Follow-up: 12 months Country: Sweden	Mean difference in reduction in oedema volume = 63.95% (95% CI 47.29 to 78.33) P <0.0001 I^2 = 0% **Favours intervention**	Poor quality Chang et al. (2021) SR/MA: Studies incorrectly labelled in MA. Adherence to CCT not reported. To note in Brorson & Svensson (1998b) – "In patients who had surgery and a complete reduction of edema, the compression garments were removed for 1 week, 1 year post-operatively. A marked increase in the arm volume was observed, which was immediately remedied by reapplying the garments."
Boyages et al. (2015) and Campisi et al. (2017) in Chang et al. (2021) MA	Two single centre case series Intervention: Liposuction + CCT n=75 Stage II-III lymphoedema Follow-up: Campisi et al 2017 - 12 months Boyages et al 2015 – 6 months Countries: Australia and Italy	Mean reduction in oedema volume = 28.68% (95% CI 6.06 to 51.29) P=0.01 I^2 = 96%	Difference in follow up periods in studies included in the MA. Adherence to CCT not formally assessed (Boyages et al. (2015) reported "one patient had poor compression garment compliance"). Campisi et al. (2017) – all participants previously treated with lymphatic microsurgery. Campisi et al. (2017) used a pre-surgical mapping method (Fibro-Lipo-Lymph-Aspiration with a Lymph Vessel Sparing Procedure [FLLA-LVSP]) prior to liposuction
Chen et al. (2023)	Single centre retrospective case series Intervention: liposuction + CCT Upper limbs n=23 Stage II – III lymphoedema	Average reduction in oedema volume = 32.2% (± 9.8)	n of participants in each lymphoedema location is unclear, as the study reports number of limbs affected rather than participants. Treatment effect grouped for upper and lower extremity lymphoedema

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
	Follow up: 12 months Country: USA		No measure of statistical significance
Granzow et al. (2014) in Chang et al. (2021) SR	Single centre case series Intervention: Suction assisted protein lipectomy n=6 Stage II-III lymphoedema Follow up: 12 months. Country: USA	Mean reduction in oedema volume = 111% (range 98 – 120%)	Unclear whether the liposuction group were required to wear compression garments after surgery
Greene & Maclellan (2016) in IPG	Single centre case series Intervention: Suction-assisted liposuction + CCT N=15 (includes participants with upper and lower extremity lymphoedema; Upper, n=6; Lower, n=9) Lymphoedema stage NR Follow up: 3.1 months. Country: USA	Mean reduction in oedema volume: 73% (range 48% to 94%).	Treatment effect is grouped for participants with upper and lower extremity lymphoedema.
Reduction in oedema volume (ml)			
Brorson et al. (1998a) and Brorson et al. (2006) in	Two single centre comparative cohort studies (Brorson et al. (1998a) used matched pairs design)	Mean difference in oedema volume = -895.81ml (95% CI -1,140.063 to -650.98) P= <0.0001 I^2 = 0%	Poor quality Chang et al. (2021) SR/MA Adherence to CCT not reported.

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
Chang et al. (2021) MA	Intervention: Liposuction + CCT, n= 46 Comparator: CCT along, n=23 Total n=69 Stage II lymphoedema Follow up: 12 months. Country: Sweden	**Favours intervention**	
Klernäs et al. (2018) in Tang et al. (2021) and Klernäs et al. (2020)	Comparative cohort study in four centres Intervention: Liposuction + CCT (n=57) Comparator: Rehabilitation program, comprising complex decongestive therapy, exercise and educational components (n=18), Total n=75 (includes participants with upper and lower extremity lymphoedema; Upper, n=27; Lower, n=48) Lymphoedema stage NR Follow up: 6 and 12 months. Countries: Sweden, Scotland, Australia (Liposuction group); Sweden (rehabilitation group)	**Liposuction + CCT group** Pre-op mean oedema volume = 3117ml (SD 2543) Post-op (12 months) mean oedema volume = 154ml (SD 579) P<0.001 **Rehabilitation programme group** Baseline mean oedema volume = 934ml (SD 1398) 6 month mean oedema volume = 770ml (SD 1336) P=0.05	Treatment effect is grouped for participants with upper and lower extremity lymphoedema. No between group tests of statistical significance
Brorson et al. (2006), Campisi et al. (2017), Damstra et al. (2009), Hoffner et al. (2017) and Schaverien et al.	One single centre comparative cohort study (intervention group data only included) Four single centre case series Intervention: Liposuction + CCT	Mean reduction in oedema volume = 1,294.16 (95% CI 460.47 to 2,127.85) P<0.002 I^2 = 99%	Pre-op oedema volume reported for Brorson et al. (2006) is 1842ml in Chang et al. (2021) SR/MA and is 1840 in original article. HTW was not able to confirm the accuracy of the post-op volume for Brorson et al. (2006) included in the MA due to summarised reporting in the primary article.

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
(2012) in Chang et al. (2021) MA	n=207 Stage I – III lymphoedema (NR in 3 studies) Follow up: 12 months. Countries: Sweden; Italy; Netherlands; UK		Schaverien et al. (2012) reported reduction in oedema volume was stable at 5 years follow up. Schaverien et al. (2012) mean difference was reported to be 'not estimable' in Chang et al (2021) MA. Campisi et al. (2017) used a pre-surgical mapping method (Fibro-Lipo-Lymph-Aspiration with a Lymph Vessel Sparing Procedure [FLLA-LVSP]) prior to liposuction
Hoffner et al. (2018) in Chang et al. (2021) SR and NICE IPG.	Single centre case series Intervention: Liposuction + CCT n=105 Lymphoedema stage NR Follow up: 5 years. Country: Sweden	Pre-op mean oedema volume = 1573ml (SD 645) Post-op mean oedema volume (6 months) = -51ml (SD 273) P<0.001. Mean reduction in oedema volume (5 years) = 117% (range, 25–191)	There is likely significant overlap in study populations for Hoffner et al. (2018) and Lee et al. (2016) studies, which both took place at the same study site with the same recruitment period. To note – "For the majority of patients, power-assisted liposuction […] was performed to facilitate liposuction. During the period 1993–1997, the "dry technique" was used. During the period 1997–2012, a tourniquet was utilized in combination with the tumescence technique to minimize blood loss."
Granoff et al. (2022) in NICE IPG	Single centre case series Intervention: Liposuction (power assisted) + CCT n=23 Lymphoedema stage NR Follow up: 12 months. Country: USA	**Circumferential measurement:** Pre-op median oedema volume = 799ml (IQR 638 – 1,125ml) Post-op median oedema volume = 60ml (IQR -76 – 202ml) P<0.002 Median excess volume reduction 116% (n=8) **Perometry:** Pre-op median oedema volume = 1038ml (IQR 763 – 1,173ml)	CCT compliance required for inclusion in study - "Because postoperative protocol dictates 24/7 compression therapy, patients must also demonstrate adequate compliance with compression therapy at the grade they will be wearing postoperatively. Compliance that indicates readiness for surgery is at the discretion of the treating certified LE therapist."

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
		Post-op median oedema volume = 44ml (IQR -27 – 246ml) P<0.001	
Lee et al. (2016) in NICE IPG	Single centre prospective case series Intervention: Liposuction + CCT n=130 Lymphoedema stage NR Follow up: 6 months (up to 18 years) Country: Sweden	Pre-op mean oedema volume = 1607ml (SD 707) Post-op mean oedema volume = -43ml (SD 379) P<0.001 Authors claim this was maintained up to 18 years follow up (n=1)	Low n at longer term follow up. There is likely significant overlap in study populations for Hoffner et al. (2018) and Lee et al. (2016) studies, which both took place at the same study site with the same recruitment period.
Reduction in oedema volume (UEL index)			
Yoshida et al. (2023)	Single centre case series Intervention: Liposuction + CCT n=28 (includes participants with upper and lower extremity lymphoedema; Upper n=10; Lower n=18) Lymphoedema stage: NR Follow up: 12-25 months Country: Japan	Pre-op LEL index (%) = 123.7 ± 18.8 (range 103-158) Post-op LEL index (%) = 92.7 ± 10.9 (range 76-106) P < 0.04	UEL index calculated by measurements taken from five locations on each limb divided by BMI. Circumference measurement and oedema volume (%/ml) not reported.
Disease-specific HRQoL			
Chen et al. (2023)	Single centre retrospective case series Intervention: liposuction + CCT Upper limbs n=23	**Lymphoedema Quality of Life (LYMQoL)** *LYMQoL score 0 poor QoL to 10 excellent QoL*	n of participants in each lymphoedema location is unclear, as the study reports number of limbs affected rather than participants. LymQoL scores not reported.

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
	Stage II – III lymphoedema Follow up: 12 months Country: USA	Statistically significant improvements in appearance (p = 0.01), function (p = 0.04) and symptoms (p = 0.01) Authors claim overall quality of life significantly improved (p=0.03)	
Granoff et al. (2022) in NICE IPG	Single centre case series Intervention: Liposuction (power assisted) + CCT n=23 Lymphoedema stage NR Follow up: 8 months (SD 4.5) Country: USA	**Lymphoedema Quality of Life (LYMQoL):** *LYMQOL score 0 = poor QoL to 10 excellent QoL* Pre-op mean score = 6.5 Post-op mean score= 8.3 (28% increase)	No measure of statistical significance
Klernäs et al. (2018) in Tang et al. (2021) SR and Klernäs et al. (2020)	Comparative cohort study in four centres Intervention: Liposuction + CCT (n=57) Comparator: Rehabilitation program, comprising complex decongestive therapy, exercise, and educational components (n=18), Total n=75 (includes participants with upper and lower extremity lymphoedema; Upper, n=27; Lower, n=48) Follow up: 12 months. Lymphoedema stage NR	**Lymphoedema Quality of Life Inventory (LyQLI)** *Higher score = higher impact on HRQoL* **Liposuction + CCT group** Significant (p<0.001) reduction in scores across physical, psychosocial, and practical domains (n=46 at 12 months) Baseline – n participants scoring ≥2 on at least one domain = 45% 12 months - n participants scoring ≥2 on at least one domain = 5% **Rehabilitation programme group** Significant reduction in scores across physical (p=0.024), psychosocial (p=0.012) domains, but not practical (n=18 at 12 months)	Treatment effect is grouped for participants with upper and lower extremity lymphoedema. No between group statistical comparisons Exact values only reported in figures

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
	Countries: Sweden, Scotland, Australia (Liposuction group); Sweden (rehabilitation group)	Baseline – n participants scoring ≥2 on at least one domain = 21% 12 months - n participants scoring ≥2 on at least one domain = 28%	
Generic HRQoL			
Brorson et al. (2006) in Chang et al. (2021) and Tang et al. (2021) SRs	Single centre comparative cohort study Intervention: Liposuction + CCT (n=35) Comparator: CCT alone (n=14) Total n=49 Stage II lymphoedema Follow up: 12 months. Country: Sweden	**Visual Analogue Scale (VAS)** *Scale 0 (no difficulty) to 100 (extreme difficulty)* Significantly different changes from baseline to 12 months for liposuction + CCT versus CCT alone were found for: Pain, P=0.002 Activities of daily living (difficulty), P=0.02 Swollen arm, P=0.0001 Heavy arm, P=0.005 Suggesting increased improvement in liposuction group No significant differences were found for: Swelling of hand Reduced mobility Fatigue/weakness Numbness/prickling sensation **Nottingham Health Profile** No significant differences found between groups for changes from baseline to 12 months. **Psychological General Well-Being Index:** No significant differences found between groups for changes from baseline to 12 months. **Hospital Anxiety and Depression Scale (HADS):**	

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
		7 questions with a rating scale of 0-3 for anxiety and depression subscales (total 21 indicating maximum anxiety/depression) Significantly different changes from baseline to 12 months for liposuction + CCT versus CCT alone were found for the Anxiety sub-scale only	
Boyages et al. (2015) in Chang et al. (2021) and Tang et al. (2021) SRs	Single centre case series Intervention: Liposuction + CCT n=15 Stage II – III lymphoedema Follow up: 6 months. Country: Australia	**Patient-specific functional scale (PSFS):** *PSFS scores range from '0' (not able to perform three activities at all) to '30' (able to perform three activities perfectly)* Pre-op mean: 11.1 (range 4 – 21) Post-op mean: 22.1 (range 4 - 9) N=7 included in analysis P=0.008 **Sub-domains (drawn from previous research)** *Standardised scales scores ranged from '0' (not at all) to '10' (extremely so)* Significant ***decreases*** in scores were also seen across: Pain (n=9; p=0.007) Heaviness (n=9; p<0.001) Self-consciousness (n=9; P<0.001) Swollen (n=9; P>0.001) Impact on emotions (n=9; P=0.004) NS changes in: Anxiety	PSFS not is validated for lymphoedema. It is unclear how the sub-domains drawn from previous research were measured as the cited appendix is not available.
Hoffner et al. (2017) in Chang et al.	Single centre case series	**Short-form Health Survey (SF-36)** *Higher score indicates higher QoL*	

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
(2021) and Tang et al. (2021) SRs	Intervention: Liposuction + CCT n=60 Lymphoedema stage NR Follow up: 12 months. Country: Sweden	Significant increases between pre-op and post-op were found for: Physical component score (pre-op 43, SEM 1.3; post-op 45, SEM 1.2, P=0.03) Mental component score (pre-op 49, SEM 1.3; post-op 51, SEM 1.2; P=0.01) And sub-domains: Physical functioning (pre-op 67, SEM 2.4; post-op 75, SEM 2.5; P=0.001) Bodily pain (pre-op 65, SEM 3.4; post-op 79, SEM 3.2; P=0.001) Social functioning (pre-op 83, SEM 3.2; post-op 90, SEM 2.3; P=0.01) Mental Health (pre-op 74, SEM 2.5; post-op 82, SEM 2.1; P=0.01) Vitality (pre-op 66, SEM 2.7; post-op 72, SEM 2.4; P=0.03) Non-significant changes for: Role physical Role emotion General health	
Schaverien et al. (2012) in Chang et al. (2021) and Tang et al. (2021) SRs	Single centre case series Intervention: Liposuction + CCT n= 11 Lymphoedema stage NR Follow up: 3 months Country: UK	**HADS** *7 questions with a rating scale of 0-3 for anxiety and depression subscales (total 21 indicating maximum anxiety/depression)* Anxiety Pre-op = 9.09 Post-op = 4.6 P=0.05 Depression Pre-op = 5.73	Ranges not given. VAS scale not given, although likely to be 0-100.

Evidence source(s)	Study design and population[1, 2]	Treatment effect	Comments on reliability
		Post-op = 1.7 P = NS **VAS** *Overall well-being with higher scores reflecting improved well-being* Pre-op = 64.60 Post-op = 81.20 P=NS	

[1] Follow up periods are specific to stated outcomes, not overall study follow up; [2] n participants reported are specific to population (upper extremity lymphoedema), not overall study n, except where stated; VAS = Visual Analogue Scale; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health-related quality of life; CCT = Controlled Compression Therapy; NR = Not reported; NS = Not significant at P<0.05

Table 2 - Lower extremity lymphoedema: outcomes

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
Reduction in oedema volume (%)			
Boyages et al. (2015) and Campisi et al. (2017) in Chang et al. (2021) MA	Two single centre case series Intervention: Liposuction + CCT n=88 Stage II-III lymphoedema Follow-up: 6 months (Boyages et al. 2015) 12 months (Campisi et al. 2017) Countries: Australia, Italy	Mean reduction in oedema volume = 29.23% (95% CI 5.56 to 52.90) P=0.02 I^2 = 86%	Different follow up periods in included studies. Campisi et al. (2017) – all participants previously treated with lymphatic microsurgery. Campisi et al. (2017) used a pre-op mapping method (Fibro-Lipo-Lymph-Aspiration with a Lymph Vessel Sparing Procedure [FLLA-LVSP]) prior to liposuction.
Chen et al. (2023)	Single centre retrospective case series Intervention: liposuction + CCT Lower limbs n=34 Stage II – III lymphoedema Follow up: 12 months Country: USA	Average reduction in oedema volume = 32.2% (± 9.8)	n of participants in each lymphoedema location is unclear, as the study reports number of limbs affected rather than participants. Treatment effect grouped for upper and lower extremity lymphoedema No measure of statistical significance
Granzow et al. (2014) in Chang et al. (2021) SR	Single centre case series Intervention: Suction assisted protein lipectomy n=4 Stage II-III lymphoedema Follow up: 12 months	Mean reduction in oedema volume = 86% (range 81 – 97%)	No measure of statistical significance

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
	Country: USA		
McGee & Munnoch (2018)	Single centre case series (prospectively maintained database) Intervention: Liposuction (power assisted) + CCT N=21 Stage II-III lymphoedema Follow up: 5 years Country: UK	Mean reduction in oedema volume (12 months) = 88.9% (60.9-127.50ml, SD 20.4) p=<0.001 Mean reduction (5 years; n=6) = 113.6% (SD 28.9, p=0.008)	Reduced number of participants at 5 years follow up. Same centre and recruitment time period as Stewart & Munnoch (2018). There is potential overlap in participants. Volume excess was determined using the contralateral unaffected limb as a baseline.
Greene & Maclellan (2016) in IPG	Single centre case series Intervention: Suction-assisted liposuction + CCT N=15 (includes participants with upper and lower extremity lymphoedema; Upper, n=27; Lower, n=48) Stage II-III lymphoedema Follow up: 3.1 months Country: USA	Mean reduction in oedema volume: 73% (range 48% to 94%).	Treatment effect is grouped for participants with upper and lower extremity lymphoedema.
Reduction in oedema volume (ml)			
Klernäs et al. (2018) in Tang et al. (2021) and Klernäs et al. (2020)	Comparative cohort study in four centres Intervention: Liposuction + CCT (n=57) Comparator: Rehabilitation program, comprising complex decongestive therapy,	**Liposuction + CCT group** Pre-op mean oedema volume = 3117ml (SD 2543) Post-op mean (12 months) oedema volume = 154ml (SD 579) P<0.001	Treatment effect is grouped for participants with upper and lower extremity lymphoedema. No between group statistical comparisons

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
	exercise and educational components (n=18) Total n=75 (includes participants with upper and lower extremity lymphoedema; Upper, n=27; Lower, n=48) Follow up: 6 and 12 months Stage II-III lymphoedema Countries: Sweden, Scotland, Australia (Liposuction group); Sweden (rehabilitation group)	**Rehabilitation group** Baseline mean oedema volume = 934ml (SD 1398) 6 month mean oedema volume = 770ml (SD 1336) P=0.05	
Lamprou et al. (2017) in Chang et al. (2021) SR	Case series (n study sites NR) Intervention: 'Circumferential suction-assisted lipectomy' n=88 'end stage' primary lymphoedema Follow up: 24 months Country: Netherlands	**Primary lymphoedema (n=47):** Pre-op median oedema volume = 3686ml (QR 2851 – 5121) Post-op median oedema volume = 761ml (IQR (-147 to 1554) % reduction = 79% There was an increase in oedema volume between months 12 and 24 (no statistics reported) **Secondary lymphoedema (n=41):** Pre-op median oedema volume = 3320ml (IQR 2533 – 4783) Post-op median post-op oedema volume = -38ml (IQR -1151 – 1135) % reduction = 101%	Post-op cointerventions included an exercise regimen in combination with self-managed weight control.
Agarwal et al. (1998) in Chang et al. (2021) SR	Single centre case series Intervention: Lymphosuction n=8 "Grade 2 – 5" lymphoedema Follow up: 12 months Country: India	Mean reduction in oedema volume = 2287 ml	Range not given

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
Stewart & Munnoch (2018) in NICE IPG	Single centre case series Intervention: Liposuction + CCT n=69 (72 legs) Stage II-III lymphoedema Follow up: 3 months (n=72) to 9 years (n=5) Country: UK	Pre-op mean oedema volume = 4372ml (range 229 – 15,166) Post-op mean oedema volume: 3 months (n=72) = 1005ml (range 1987 – 5613) 12 months (n=60) = 768ml (range 761 – 4952) 9 years (n=5) = 406ml (range 405 – 1497) **Primary lymphoedema:** % reduction of original oedema vol: 3 months (n=42) = 71.9% (range -1.7 – 140) 12 months (n=38) = 84.3 (range 31.3 – 169.9) 9 years (n=5) = 89.3% (range 74 – 111.5) **Secondary lymphoedema:** % reduction of original oedema vol: 3 months (n=30) = 100.8% (range 31.4 – 394) 12 months (n=22) = 95.6% (range 50 – 163.8) 6 years (n=4) = 114.8%% (range 75.5 – 143)	No test of statistical significance Reduced number of participants at follow up Same centre and recruitment time period as McGee & Munnoch (2018). Potential for overlap in participants. Ten participants were non-compliant with postoperative CCT
Granoff et al. (2022) in NICE IPG	Single centre case series Intervention: Liposuction (power assisted) + CCT n=18 Follow up: 12 months Stage of lymphoedema NR Country: USA	Circumferential measurement: Pre-op median oedema volume = 3355ml (IQR 2843 - 5428) Post-op median oedema volume = 710ml (IQR 116 – 1450ml; at 1 month, sustained at 12 months) P<0.001 Similar results obtained used perometry	
Karlsson et al. (2022)	Single centre case series Intervention: Liposuction + CCT n=124 Stage II – III lymphoedema	Pre-op median oedema volume = 3158 ml (IQR 2114–4650 ml) Post-op (1 year follow up) median oedema volume: –5 ml (IQR –430 to 568) P < 0.0001 % median reduction = 100% (IQR 83–116)	

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
	Follow up: 12 months Country: Sweden		
Reduction in oedema volume (LEL index)			
Yoshida et al. (2023)	Single centre case series Intervention: Liposuction + CCT n=28 (includes participants with upper and lower extremity lymphoedema; Upper n=10; Lower n=18) Lymphoedema stage: NR Follow up: 12-25 months Country: Japan	Pre-op LEL index (%) = 298 ± 41.6 (range 211-378) Post-op LEL index (%) = 248 ± 31.6 (range 203-314) P < 0.04	LEL index calculated by measurements taken from five locations on each limb divided by BMI. Circumference measurement and oedema volume (%/ml) not reported.
Disease-specific HRQoL			
Chen et al. (2023)	Single centre retrospective case series Intervention: liposuction + CCT Lower limbs n=34 Stage II – III lymphoedema Follow up: 12 months Country: USA	**Lymphoedema Quality of Life (LYMQoL)** *LYMQoL score 0 poor QoL to 10 excellent QoL* Statistically significant improvements in appearance (p = 0.01), function (p = 0.04) and symptoms (p = 0.01) Authors claim overall quality of life significantly improved (p=0.03)	n of participants in each lymphoedema location is unclear, as the study reports number of limbs affected rather than participants. LymQoL scores not reported.
Granoff et al. (2022) in NICE IPG	Single centre retrospective case series Intervention: Liposuction (power assisted) + CCT n=18	**Lymphoedema Quality of Life (LYMQoL):** *LYMQOL score 0 = poor QoL to 10 excellent QoL* Pre-op mean score = 5.9 Post-op mean score = 8.5 (44% increase)	

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
	Stage of lymphoedema NR Follow up: 9 months Country: USA		
McGee & Munnoch (2018)	Single centre case series (Prospectively maintained database) Intervention: Liposuction (power assisted) + CCT n=10 Stage II-III lymphoedema Follow up: 12 months Country: UK	**Lymphoedema Quality of Life Inventory** *Higher score = higher impact on HRQoL* Pre-op mean score = 75.9 (range 29–111) post-op mean score =26.9 (range 3–51).	
Klernäs et al. (2018) in Tang et al. (2021) SR and Klernäs et al. (2020)	Comparative cohort study in four centres Intervention: Liposuction + CCT (n=57) Comparator: Rehabilitation program, comprising complex decongestive therapy, exercise and educational components (n=18) Total n=75 (includes participants with upper and lower extremity lymphoedema; Upper, n=27; Lower, n=48) Stage of lymphoedema NR Follow up: 12 months Countries: Sweden, Scotland, Australia (Liposuction group); Sweden (rehabilitation group)	**Lymphoedema Quality of Life Inventory (LyQLI)** *Higher score = higher impact on HRQoL* Liposuction + CCT group – Significant ($p<0.001$) reduction in scores across physical, psychosocial, and practical domains (n=46 at 12 months) Baseline – n participants scoring ≥2 on at least one domain = 45% 12 months - n participants scoring ≥2 on at least one domain = 5% Rehabilitation programme group – Significant reduction in scores across physical ($p=0.024$), psychosocial ($p=0.012$) domains, but not practical (n=18 at 12 months) Baseline – n participants scoring ≥2 on at least one domain = 21%	Treatment effect is grouped for participants with upper and lower extremity lymphoedema. No between group statistical comparisons Exact values only reported in figures

Evidence source(s)	Study design and population[1,2]	Treatment effect	Comments on reliability
		12 months - n participants scoring ≥2 on at least one domain = 28%	
Generic HRQoL			
Boyages et al. (2015) in Chang et al. (2021) and Tang et al. (2021) SRs	Single centre case series Intervention: Liposuction n=6 Stage II – III lymphoedema Follow up: 6 months Country: Australia	**Patient-specific functional scale (PSFS):** *PSFS scores range from '0' (not able to perform three activities at all) to '30' (able to perform three activities perfectly)* Pre-op mean: 7.4 (range 4 – 9) Post-op mean: 28 (range 27 - 29) N=5 included in analysis P<0.001 **Sub-domains (drawn from previous research)** *Scores ranged from '0' (not at all) to '10' (extremely so)* Significant ***decreases*** in scores were also seen in: Heaviness (n=5; P=0.002) Self-consciousness (n=5; P<0.001) Anxious (n=5; P<0.001) Swollen (n=5; P<0.001) Impact on emotions (n=5; P<0.001) NS changes in: Pain	PSFS not validated for lymphoedema. It is unclear how the sub-domains drawn from previous research were developed or measured as the cited appendix is not available.

[1] Follow up periods are specific to stated outcomes, not overall study follow up; [2] n participants reported are specific to population (upper extremity lymphoedema), not overall study n, except where stated; VAS = Visual Analogue Scale; HADS = Hospital Anxiety and Depression Scale; HRQoL = Health-related quality of life; CCT = Controlled Compression Therapy; NR = Not reported; NS = Not significant at p<0.05

Table 3 - Craniofacial lymphoedema: HRQoL outcomes

Evidence source(s)	Study design and population	Treatment effect	Comments on reliability
Alamoudi et al. (2018) in Tyker et al. (2019) and Tang et al. (2021) SR	Single centre randomised controlled trial Intervention: Liposuction (n=10) Comparator: Wait list (n=10) Total n=20 Follow up: 6 months Country: Canada	**Modified Blepharoplasty Outcome Evaluation (MBOE)** *5 question scale rating self-perception of appearance* Summation of the MBO: **Liposuction group** - Mean difference (pre/post-op) = 10.3 (95% CI 5.42–15.18) **Wait list group –** Mean difference = -0.50 (95% CI -2.42 -1.42) P<0.001 **Derriford Appearance Scale (DAS59)** Summation of the DAS-59: **Liposuction group –** Mean difference (pre/post-op) = - 41.00 (9%CI - 62.92— -19.08) **Wait list group –** Mean difference = 10.20 (95% CI -8.28—28.68) P=0.001 Number of individual questions that reached statistical significance = 21/59 **Favours intervention**	Same study site as Brake et al. (2014) – Note potential overlap in participants. No non-surgical treatment group No blinded outcome measures
Brake et al. (2014) in Tyker et al. (2019) and Tang et al. (2021) SRs	Single centre case series Intervention: Liposuction n=9 Follow up: 6 months Country: Canada	**Modified Blepharoplasty Outcome Evaluation (MBOE)** 1. How well do you like the appearance of your chin? Mean pre-op score = 1.4 Mean post-op score = 4.6 P=0 .004 2. How much do you feel your friends and loved ones like the appearance of your chin?	Blepharoplasty Outcome Evaluation scale is a facial plastic outcome measurement scale and was modified for the submental region Same study site as Alamoudi et al. (2018)– Note potential overlap in participants.

Evidence source(s)	Study design and population	Treatment effect	Comments on reliability
		Mean pre-op score = 1.9 Mean post-op score = 4.3 P=0.008 3. Do you feel the current appearance of your chin limits your social and professional activities? Mean pre-op score = 2.8 Mean post-op score = 4.6 P = NS 4. How confident are you that the appearance of your chin is the best that it can be? Mean pre-op score = 1.2 Mean post-op score = 4.6 P=0 .004 5. Would you like to surgically alter the appearance of your chin? Mean pre-op score = 3.8 Mean post-op score = 1.0 P=0.008 **Derriford Appearance Scale (DAS59)** Only P values reported **Objective scoring by two head and neck oncologists (before / after - blinded)** Interrater reliability (0.89) N=7 rated as improved N=2 rated as no change Post-op photos scored significantly lower than pre-op (P=0.016) *Scores range from 1 (normal contours, no lymphoedema) to 5 (complete loss of neck contours and severely disfiguring lymphoedema*	

5.2 Ongoing studies

HTW were unable to identify any ongoing studies that may be relevant to the effectiveness of liposuction for lymphoedema.

5.3 Certainty of the evidence

- Evidence is comprised mostly of single centre case series, with only one RCT of 20 participants with craniofacial lymphoedema and four comparative cohort studies. Thirteen of the included studies included less than 50 participants.
- The systematic review and meta-analysis reported by Chang et al. (2021) was of poor to moderate quality.
- There is limited evidence at longer term follow-up (>12 months), with reduced numbers of participants at 5 and 9 year follow ups.
- The three published studies from the UK were conducted in the same centre and there is overlap in study sites and authors across a larger proportion of the studies.
- There are reported differences in liposuction techniques (e.g., use of tourniquet and pre-surgery lymphatic pathway mapping) that may affect peri-operative outcomes/complications.
- Only two studies report outcomes separately for primary versus secondary lymphoedema and suggest potential different responses between participant groups.

6. Cost effectiveness

6.1 Economic literature review

We conducted a rapid systematic literature review to answer the following research question: What is the cost-effectiveness of liposuction for treating chronic lymphoedema when compared to standard care? Appendix 3 summarises the selection of articles for inclusion in the evidence review. The titles and abstracts of 2,271 records identified in the search for this research question were screened and three records were deemed potentially relevant economic studies. The full texts of these studies were reviewed against the inclusion/exclusion criteria and two were excluded.

One study was excluded as it was a systematic literature review (De Vrieze et al. 2020), and the other study was a rapid health technology assessment on liposuction for the treatment of fat accumulation caused by chronic lymphoedema in Norway (Kvist et al. 2021). Although this study includes a cost-utility analysis, it was not available in English, and so was excluded for the literature review. However, the economic analysis has been used to guide HTW's de novo modelling work.

The remaining included study is summarised in Table 4. The study, by Bloom et al. (2022) describes a cost-utility analysis undertaken to determine costs and health-related quality of life (HRQoL) of power-assisted liposuction compared to conservative management (compression garments and physical therapy) for the treatment of upper extremity fat-dominant lymphoedema in the USA. We assessed the study as partially applicable to a Welsh setting with potentially serious limitations.

The model utilises a decision-tree approach to estimate the lifetime costs and benefits for a hypothetical cohort of women aged 45 years undergoing the different treatment options. Successful treatment was defined as the affected limb measuring within 25% of the unaffected

limb at one year post treatment. The probability of success was obtained from a prospective institutional database; however, references have not been provided and so more detail cannot be obtained on the effectiveness data. We are therefore unable to establish whether the effectiveness data used in the model reflects the effectiveness evidence identified in this Evidence Appraisal Report.

Costs of liposuction were obtained from 2020 Medicare current procedure terminology (CPT) code 38999, whilst costs of conservative management were based on annual out-of-pocket costs projected over the course of a lifetime. There are major concerns with the calculation of these costs. The Medicare CPT code 38999 refers to any procedure in the lymphatic system, and so could encompass a broad range of procedures, and therefore may not be reflective of the true cost of liposuction. It also appears as though costs included for liposuction are procedure costs alone, whereas the costs for conservative management include lifetime costs. The inclusion of out-of-pocket costs does not reflect the NHS and Personal Social Services perspective, limiting the applicability of the study.

Utility scores were obtained using the visual analogue scale (VAS) completed by physicians who were breast tumour board members. These utilities were then converted to quality-adjusted life years (QALYs) to be used within the model. Although this provides an estimate of quality of life, physicians cannot be assumed to understand the actual impact that living with this chronic condition has on a patient's quality of life. Patients were assumed to reach a stable health utility at one year post treatment which was applied for the duration of their lifetime.

Results of the analysis demonstrated that liposuction was expected to increase QALYs by 3.7 years over a lifetime (27.05 compared to 23.34) and decrease lifetime costs by $74,487 (£51,066) ($8,753 (£6,001) compared to $83,240 (£57,067)) when compared to conservative management. Threshold analysis showed that the only instance where liposuction was not deemed cost-effective was when the probability of liposuction being a successful treatment was reduced to below 7.8%. Probabilistic sensitivity analysis showed that liposuction had a 92.7% chance of being cost-effective at a threshold of $50,000 per QALY gained.

These results should be interpreted with caution due to the major limitations associated with the study.

Table 4 – Summary of included economic studies: Bloom et al. (2022)

Study details	Study population and design	Data sources	Results	Quality assessment
Author and year: Bloom et al. (2022) **Country:** USA **Type of economic analysis:** Cost-utility analysis **Perspective:** Third-party payer **Currency:** US dollars **Price year:** 2020 **Time horizon:** Lifetime **Discounting:** NR **Potential conflict of interest:** One author was supported by the JOBST Lymphatic Research Grant awarded by the Boston Lymphatic Symposium, Inc. The other authors have no financial interest to declare.	**Population:** 45-year-old female patients with upper extremity fat-dominant lymphedema, defined by MRI imaging criteria with circumferential subcutaneous fat hypertrophy. **Intervention:** Debulking surgery via power-assisted liposuction with postoperative compression. **Comparator:** Conservative management with compression garments and physical therapy. **Study design** 1 year decision tree with lifetime costs and outcomes.	**Source of baseline and effectiveness data:** Probability of successful or unsuccessful surgery obtained from a prospective institutional database. Utility scores obtained using the VAS survey administered to breast tumour board members, which was then converted to quality-adjusted life years. Patients were estimated to reach a stable outcome at 1 year after treatment. All patients were assumed to live to age 81.1 years. **Source of resource use and cost data:** Debulking surgery costs based on 2020 Medicare current procedure terminology (CPT) code 38999. Conservative management costs based on annual out of pocket costs propagated over the course of a lifetime.	**Base case deterministic results** **Costs** Debulking surgery: $8,753 (£6,001) Conservative management: $83,240 (£57,067) Debulking surgery saves $74,487 (£51,066) **Effectiveness** Debulking surgery: 27.05 QALYs Conservative management: 23.34 QALYs Debulking surgery increases QALYs by 3.7 **ICER:** Dominates **Sensitivity analysis** Threshold analysis showed that debulking surgery remained cost-effective as long as the probability of successful surgery was greater than 7.8%. No point at which the cost of debulking surgery would mean that conservative management would become cost-effective, when costs were varied between the range from the Medicare CPT database. Utility of successful debulking surgery was the greatest variable of uncertainty in the deterministic sensitivity analysis, but conclusions of the analysis were not changed. Probabilistic sensitivity analysis showed that debulking surgery was cost-effective with a probability of 92.7%.	**Applicability** Partially applicable – correct intervention and relevant population, however a US study rather than UK. **Limitations** This study has potentially serious limitations. • We are unable to establish whether the effectiveness data used in the model is reflective of the effectiveness evidence identified in this Evidence Appraisal Report. • Utility scores provided by physicians rather than by patients. • All patients assumed to live until the age of 81.1 years of age rather than a lifetime mortality being modelled. • All effectiveness assumed to occur at 1 year with lifelong outcomes assumed to be the same for all patients. • Costs of liposuction appear to only include costs of surgery, whilst conservative management includes lifetime costs. • Cost of liposuction is assumed to be the cost of any procedure in the lymphatic system – this is unlikely to be reflective of the true cost of the intervention. • Utility of successful and unsuccessful treatment differs

Study details	Study population and design	Data sources	Results	Quality assessment
				per treatment arm with no explanation. • Lifetime outcomes extrapolated from a one-year treatment with no inclusion of adverse events or any other lifetime clinical events. • Utility assumed to remain constant from 1 year post treatment until death. • Unable to check where probabilities of successful treatment are sourced from. It is unclear if this is from a comparative study or separate sources. • No discounting of costs or benefits applied in the analysis.

Abbreviations: CPT: current procedure terminology; ICER: incremental cost-effectiveness ratio; MRI: magnetic resonance imaging; NA: not applicable; NR: not reported; QALY: quality-adjusted life year; VAS: visual analogue scale

6.2 HTW cost utility analysis

As no directly applicable published evidence on the cost effectiveness of liposuction compared to standard care for chronic lymphoedema was identified, and due to the significant limitations of the cost-utility analysis included, HTW conducted a de novo economic cost-utility analysis. The Markov model replicated the structure built for the Norwegian rapid HTA which was excluded from the economic literature review as it was not available in English. We adapted the health state modelling due to a lack of identified evidence and populated the model to reflect the UK NHS and personal social services (PSS) perspective. Costs used in the analysis were inflated to 2022 GBP (£) where necessary, and future costs and benefits were discounted at an annual rate of 3.5%. For full details of the economic analysis, please refer to Appendix 7.

The model tracks a cohort of female patients with complex chronic lymphoedema of the upper limb over a five-year time horizon. Clinical evidence shows a significant reduction in oedema volume at 12-months following liposuction compared to standard care, with one identified study reporting sustained benefits up to five years post-surgery.

The model operates a monthly cycle length and patients are subject to a cyclic probability of death in line with general mortality. The following two treatment strategies were included:

1. Liposuction in addition to standard care (SC)
2. Standard care (decongestive lymphoedema treatment (DLT) including compression therapy).

Costs in the model include those related to initial treatment and annual follow up costs for patients. Upfront treatment costs of liposuction include assessment, surgery and an initial follow up appointment. Costs for liposuction have been sourced from an NHS treatment appraisal decision summary from 2022 (NTAG 2022). Treatment costs in the control arm account for complex lymphoedema patients requiring intensive DLT. Costs for the SC arm have been sourced from the National Lymphoedema Partnership (NLP 2019). Follow up costs in both treatment arms include appointments and compression garments. Costs applied in the model are provided in Table 5.

Table 5 - Costs applied in model.

	Liposuction in addition to SC	SC alone
Initial assessment costs	£0	£198
Treatment	£11,578	£4,035
Follow up – initial 12 months	£344	£397
Follow up – subsequent years	£344	£265
Abbreviations: SC: standard care		

Utilities within the model have been applied as per the Norwegian rapid HTA. Within their analysis, quality of life data was sourced from Hoffner et al. (2017), where data were collected using the Short Form 36 (SF-36) at 1-, 3-, 6- and 12-months post-surgery. These values were converted to EuroQol 5 dimensions (EQ-5D) and applied within their health economic analysis. Within our analysis we have assumed that after the initial 12-month period, quality of life in people who received liposuction tapers linearly over a one-year period to the general population quality of life. Patients within the liposuction arm are assumed to have a quality of life in line with the general population for the remainder of the modelled time horizon. Patients within the

SC arm are assumed to have the pre-surgery utility value for the duration of the modelled time horizon.

Mortality for the general population is derived using published life tables for Wales (Office for National Statistics 2021).

The results of the base case analysis are presented in Table 6. The results show that treating patients with liposuction in addition to SC is expected to increase healthcare costs by £7,577 per patient over a five-year time horizon and provide an additional 0.29 QALYs compared to SC alone. This translates to an incremental cost-effectiveness ratio of £26,269 per QALY. Results from probabilistic sensitivity analysis show that liposuction in addition to SC has a 35% probability of being a cost-effective treatment strategy when compared to SC alone.

Table 6 - Base case results

	Liposuction in addition to SC	Standard care	Incremental
Total QALYs	3.68	3.39	0.29
Total costs	£13,152	£5,575	£7,577
ICER			**£26,269 per QALY**
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SC: standard care			

Deterministic sensitivity analysis showed that reducing the utility of SC, reducing patients' baseline age and reducing the cost of liposuction could all translate to liposuction in addition to SC becoming a cost-effective treatment strategy compared to SC alone.

A threshold analysis on the cost of liposuction showed that when costs are less than £4,000, liposuction in addition to SC is expected to be a dominant treatment strategy, meaning that it costs less than SC alone while providing greater quality of life to patients. When costs range from between £4,000 and £9,700 liposuction is expected to be cost-effective compared to SC alone, and above this, liposuction is no longer a cost-effective treatment strategy.

7. Organisational considerations

As part of HTW's appraisal process, experts were contacted to give comment on organisational considerations. Their comments are summarised below.

7.1 Training and Cost

Experts agreed that effective implementation of liposuction for lymphoedema would require appropriate training across all healthcare professionals involved. Experts advised that specific training would be needed for the following groups:

- Surgeons: Experts identified that two surgeons are already trained to perform liposuction for lymphoedema in NHS Wales. New staff would require training in liposuction techniques, and it is recommended by experts that this training is updated regularly – two centres in Scotland and Sweden were identified as appropriate centres of knowledge in this area.

- Theatre and ward staff: Experts identified that staff in the theatre and on the ward would need specific training in limb measurement, post-operative compression bandaging and garment fitting as this is currently outside of standard practice.
- Therapy Staff: Experts identified that therapy staff are likely well placed to need minimal training as they have the required skills to support the service under standard practice. One expert did identify the importance of staff time in the clinical pathway.
- Local Lymphoedema service HCPs: One expert identified that the local lymphoedema service HCP would need updating on the long-term care and support requirements for people who have received liposuction for lymphoedema.

One expert identified the need to consider all therapies required to support the patient throughout the clinical pathway, along with cost considerations for controlled compressive therapy following the procedure, as this is not costed in current service provision. One expert identified the need for purchasing a new liposuction device.

7.2 Clinical pathways

All experts who contributed to the appraisal commented on the need for a clear eligibility criterion that patients must meet in order to be offered liposuction. One expert in particular commented that these criteria should be informed by the stage and type of lymphoedema, the person's mental health and expectations, as well as expected tolerance of post-surgical compressive therapy and existing comorbidities.

Experts also identified the need for a clear distinction between the care that is to be delivered in the hospital setting, and the care that can be provided in an outpatient setting. An agreed period between the transfer of care from secondary to primary care was suggested as an example.

Overall experts agreed that there should be clear protocols and standard operating procedures regarding the transfer and responsibility of care for people who have received liposuction for lymphoedema.

7.3 Location of lymphoedema

Experts were able to provide valuable information on the proportions of people presenting with each type of lymphoedema in clinical settings in Wales.

Much of the clinical and economic evidence included in this assessment were related to studies of upper extremity lymphoedema – with much less data available for lower and craniofacial lymphoedema. Experts were able to advise that the majority of lymphoedema cases in Wales are presenting with lower limb lymphoedema, with approximately 15-30% of the caseload comprised of upper limb cases. When asked about this discrepancy, experts advised that a higher proportion of complex upper limb cases may be eligible for liposuction than complex lower limb cases, as lower limb cases are more likely to have comorbidities that would affect the likelihood of successful surgery such as obesity and severe skin changes.

One expert commented that it may be difficult to generalise findings to craniofacial lymphoedema due to differences in outcomes and the criteria for surgery. Experts also commented that liposuction is not currently offered for craniofacial lymphoedema in Wales – partially due to a lack of cases significant enough to consider liposuction.

8. Patient, carer, and family considerations:

As part of their 2022 guidance on liposuction for lymphoedema, NICE consulted Lymphoedema UK and conducted a survey of their patient network. Ten patients who had received liposuction for lymphoedema responded to the NICE survey. Permission has been received from Lymphoedema UK to report the results of the NICE survey in this appraisal.

8.1 NICE survey of Lymphoedema UK patients

8.1.1 Impacts of living with lymphedema:

Patients advised that lymphedema had a substantial impact on their daily lives, often inhibiting their ability to walk about. They describe the condition as 'embarrassing' and 'distressing' and that it impacts every aspect of their lives. Leg heaviness, skin feeling hot, and pain prevented patients from being 'on their feet' for long periods, keeping them from being able to 'pop to the shops' as they would soon need to return home to rest having become 'tired from carrying around the extra weight'. One patient advised their left leg was 'double the size' of their right and this prevented them from bending, kneeling and had an impact of their hips, ankles, and knees, even to the point where their bone density had increased to cope with the extra weight. In addition to walking, taking steps to traverse stairs, onto a bus, up inclines etc was extremely difficult and tyring for patients, as well as manoeuvring in small spaces (i.e., walking the aisles of theatres or cinemas, taking a seat at restaurants and on planes) and performing basic tasks like cleaning. Patients also experienced back pain that required them to have physiotherapy. Lymphedema meant that for a lot of patients, they had trouble working and socialising.

One patient described how at one point, they needed to have emergency surgeries. They noted how information on how to manage their lymphedema during this time was very limited and that healthcare professionals had 'no interested in my lymphedema'.

Swelling and increased leg size due to lymphedema can have a hugely negative impact on patient's wellbeing, preventing them from being able to wear shoes, boots and trousers. One patient described how they would need to make their own clothes. Wearing the compression garments limited their mobility as well as causing irritation if they got too hot/wet, as well as putting extra pressure on their upper limbs. Patients advised that they often experienced people pointing and staring at them in public, expressing negative comments, which could lead to feelings of depression.

8.1.2 Experiences of the treatment:

Patients described paying privately for this procedure, having to travel abroad for it and having it refused to them on the NHS.

Of the ten respondents, only one patient reported that their symptoms reoccurred after they had the procedure. Additionally, only one patient reported having side-effects in the form of a 'burn' sustained from wearing the pressure garment after surgery. They advised that this burn left a permanent scar that intermittently causes pain.

Patients describe varying recovery processes post-surgery. Patients spent between 3 and 5 days in hospital before being discharged. Patients described how bruises and scars took some time to heal, as well as slowly recovering their walking. One patient described being 'out walking and riding my horse' within a week of surgery. Most described a recovery process of up to 6 weeks, but some experienced ongoing swelling and required physiotherapy for up to 6 months. One

patient described how they continue to need to preform daily massages and while their leg size has reduced considerably, they still need to wear full leg compression stockings daily. Additionally, one patient experienced nerve end tingling that lasted a few weeks.

8.1.3 Positive impacts of the treatment

Patients describe how the procedure has made a 'huge difference' to their lives and 'immensely' improved things, describing it as 'life-saving'. Greatly reduced leg size, with patients reporting up to 2 litres or 8kg of excess fluid being removed, has allowed them to achieve things they previously could not, such as walking, taking part in sports and travel, and enjoying life as their condition is now so much more manageable. Patients advised that they are 'far more mobile' following the procedure than they were before, allowing them to be more active and engage in more activities for longer periods, including daily activities such as gardening, housework and shopping.

Patients also describe how the procedure has given them more confidence and as a result, they have more choice in the clothing they can wear. They describe their self-esteem as being 'restored' and one patient stated 'I now feel human as opposed to previously a freak'. State of mind and emotional health of patients greatly improved. Family and friends often comment on 'how much happier' they are as a result and altogether are 'delighted' with the results. One patient also noted how their partner and their families lives also improved following her procedure, as it made life easier for them as well as for her.

Patients advise that they would 'highly recommend' this procedure being made available more widely.

8.1.4 Negative impacts of the treatment

Four of the ten respondents reported experiencing no negative impacts from the procedure. Five advised that their only negative experiences were in the recovery period from the procedure when they were required to wear the support garments, but that they considered this 'well worth it' as they were 'so happy with the outcome'. One patient reported experiencing some ongoing swelling in their foot that requires them to wear compression stockings.

8.1.5 Importance of patient choice

Patients advised that this procedure is 'worthwhile' and should be offered or at least explained to patients who can then make decisions based on their own values and priorities. While post-surgery recovery is difficult, patients view this as completely worthwhile when considering what they are gaining in the long-term.

9. Conclusions

This evidence review summarised published evidence on the clinical and cost effectiveness of liposuction for chronic lymphoedema. This review has also summarised available evidence for patient, carer, and family considerations for the intervention.

The literature search identified two pieces of guidance, one RCT and four comparative cohort studies. Individual studies from the systematic reviews included in the two identified pieces of guidance have also been included in this review. A summary of these systematic reviews, including study characteristics is available in Appendix 6. The evidence included in this review suggests that liposuction for chronic lymphoedema may be effective in reducing excess oedema volume and improving quality of life for patients with upper and lower extremity lymphoedema. Outcomes for craniofacial lymphoedema remain mixed or unavailable.

Remaining uncertainties primarily relate to the evidence base. As mentioned throughout this review, much of the available evidence is limited to case series with small participant numbers. In many cases there is also overlap in the population, author or centre conducting the study. There is also uncertainty relating to the long-term effectiveness of liposuction for chronic lymphoedema post 12 months follow-up, with participant numbers declining in the studies with longer follow up.

Cost-effectiveness studies suggest that although treatment with liposuction in addition to SC is expected to increase QALYs in people with chronic lymphoedema of the upper limb, it is unlikely to be considered a cost-effective treatment option compared to standard care alone.

Experts raised some organisational considerations, including the training necessary for the intervention and associated costs, and the need for a clearly defined clinical pathway in order for the intervention to be implemented effectively.

10. Contributors

The HTW staff and contract researchers involved in writing this report were:

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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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Appendix 1 – Evidence review methods

We searched for evidence that could be used to answer the review question: 'What is the clinical and cost-effectiveness of liposuction for treating chronic lymphoedema?'

The criteria used to select evidence for the appraisal are outlined in Appendix 3. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

The systematic search followed HTW's standard rapid review methodology. A search was undertaken of Medline, Embase, Cumulated Index to Nursing and Allied Health Literature (CINAHL), KSR Evidence, Cochrane Library, Scopus and the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database. Additionally, searches were conducted of key websites and clinical trials registries. The searches were restricted to English language with no date limits. The searches were conducted in July 2023, with an update search of the key databases and citation tracking conducted in December 2023. Appendix 4 gives details of the search strategy used for Medline. Search strategies for other databases are available on request.

Appendix 5 summarises the selection of articles for inclusion in the review.

Appendix 2 – Number of studies evaluating liposuction for upper, lower and craniofacial lymphoedema and included participants

Primary studies - first author (year), (n=21)	Lymphoedema location, n patients included in study		
	Upper extremity	Lower extremity	Craniofacial
Agarwal et al. (1998)	No	Yes, n=8	No
Alamoudi et al. (2018)	No	No	Yes, n=20
Boyages et al. (2015)	Yes, n=15	Yes, n=6	No
Brake et al. (2014)	No	No	Yes, n=9
Brorson et al. (2006)	Yes, n=49	No	No
Brorson et al. (1998a)	Yes, n=20	No	No
Brorson & Svensson (1998b)	Yes, n=28	No	No
Campisi et al. (2017)	Yes, n=63	Yes, n=82	No
Chen et al. (2023)	Yes, n= NR	Yes, n= NR	No
Damstra et al. (2009)	Yes, n=37	No	No
Granoff et al. (2022)	Yes, n=23	Yes, n=18	No
Granzow et al. (2014)	Yes, n=6	Yes, n=4	No
Greene & Maclellan (2016)	Yes, n=6	Yes, n=9	No
Hoffner et al. (2017)	Yes, n=60	No	No
Hoffner et al. (2018)	Yes, n=105	No	No
Karlsson et al. (2022)	No	Yes, n=124	No
Klernäs et al. (2018) and (2020)	Yes, n=27	Yes, n=48	No
Lamprou et al. (2017)	No	Yes, n=88	No
Lee et al. (2016)	Yes, n=130	No	No
McGee & Munnoch (2018)	No	Yes, n=90	No
Schaverien et al. (2012)	Yes, n=12	No	No
Stewart & Munnoch (2018)	No	Yes, n=69	No
Yoshida et al. (2023)	Yes, n=10	Yes, n=18	No
Total studies (Total n participants)	**16 (n=614)**	**13 (n=598)**	**2 (n=29)**

Appendix 3 – Inclusion and exclusion criteria for evidence included in the review

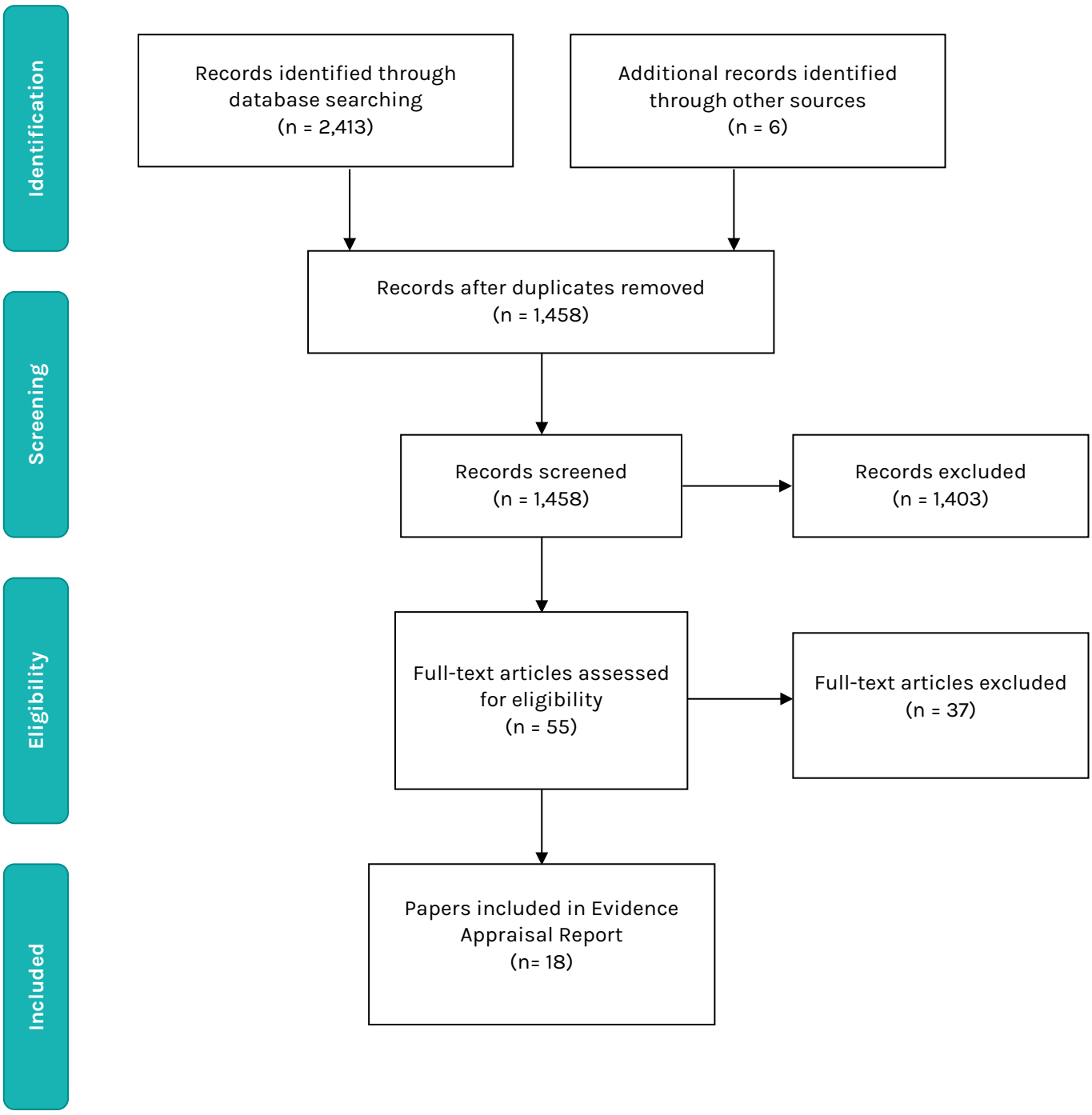
	Inclusion criteria	Exclusion criteria
Population	Adults with chronic lymphoedema, either primary or secondary	
Intervention	Liposuction (+/- standard practice)	
Comparison/ Comparators	Standard practice, including: • Decongestive lymphatic therapy (DLT) e.g., compression bandages, skin care, exercise, specialist massage • Lymphaticovenular anastomosis (LVA)	Lipolysis (e.g., cryolipolysis, laser-lipolysis or deoxycholic acid injections) Any other alternative decongestive therapy (e.g., therapeutic taping, deep oscillation therapy). Any other surgical intervention for chronic lymphoedema (e.g., vascularised lymph node transfer)
Outcome measures	Reduction in excess extremity volume, incidence of adverse outcomes, any change in quality of life, economic outcomes especially where they relate to cost and use of resources.	
Study design	We will prioritise the following study types, in the order listed: • Systematic reviews of randomised controlled trials. • Randomised controlled trials. • Non-randomised comparative trials. • Single-arm (no control group) trials that report any relevant outcome. We will only include evidence from "lower priority" sources where this is not reported by a "higher priority" source. This could be because higher priority evidence: • Does not cover all relevant populations. • Does not compare the technology of interest to all relevant comparators. • Does not cover all outcomes of interest. • Reports over short-term follow up periods, and longer follow up data is required to facilitate decision making. Where relevant and well-conducted systematic reviews exist, we will use these by: • Reporting or adapting their reported outcome measures where these are fully relevant to the scope of our review, and appropriate synthesis methods have been used. • Using these reviews as a source of potentially relevant studies where the review cannot be used as a source of outcome data. We will prioritise systematic reviews in terms of the sources of evidence they include, using the order described above.	
Search limits	No date limits apply.	
Language limits	English language only.	

	Inclusion criteria	Exclusion criteria
Publication Status	We will include evidence from studies that are published in full. We will only include evidence from conference abstracts if there are critical gaps in the fully published evidence. We will include details of any ongoing trials that have a planned completion or reporting date within 24 months of the date searches are carried out. We will only include trials of a design that is likely to add to the existing evidence in terms of certainty; for example, if we report evidence from randomised controlled trials in the EAR, we will only report details of ongoing trials if they also use a randomised design.	

Appendix 4 – Medline strategy

Ovid MEDLINE(R) ALL 1946 to December 01, 2023		
Lymphoedema		
1	exp Lymphedema/	14287
2	Lymphocele/	1094
3	(lymph?ed?em* or lymphooedem* or lymph?edm* or lymph?edenopath* or lymphaedenitis* or lymphoc?el*).tw,kf.	14752
4	(lymph* adj3 (edema* or oedema*)).tw,kf.	1454
5	(milroy* adj2 (diseas* or syndrome*)).tw,kf.	189
6	Nonne-Milroy-Meige*.tw,kf.	22
7	or/1-6	21746
Liposuction		
8	Lipectomy/	4098
9	(lipectom* or dermolipectom* or lipoplast* or lipo-plast* or liposuction* or lipo-suction* or vibroliposuction* or vibro-liposuction).tw,kf.	5001
10	(lipoaspirat* or lipo-aspirat* or (lipo* adj3 aspirat*)).tw,kf.	1074
11	(fat* adj3 (suction* or excision* or remov* or aspirat*)).tw,kf.	3253
12	Surgery, Plastic/	28380
13	((plastic or cosmetic or esthetic) adj3 surger*).tw,kf.	27440
14	or/8-13	53493
Set combinations		
15	7 and 14	413
16	exp Animals/ not Humans/	5175557
17	15 not 16	411
18	limit 17 to english language	344

Appendix 5 – Flow diagram outlining selection of relevant effectiveness evidence



Appendix 6 – Included systematic reviews: design and characteristics

Review	Design, search period	Eligibility criteria	Study & participant characteristics	Outcomes	Comments
Chang et al. (2021) **Country:** USA and Canada	Systematic review and meta-analysis of non-randomised cohort studies and case series **Number of included studies relevant to this appraisal:** 12 (total in SR = 67) **Search period:** Up to September 20, 2019	Adults with secondary lymphoedema. **Total number of participants:** 584	**Case series, n=9** Interventions: Liposuction alone: 2 studies Liposuction + CCT: 7 studies **Non-randomised cohort studies, n=3** Interventions: Liposuction + CCT, n=3 studies	**Outcomes:** Volume reduction (ml / %), Limb circumference (cm), Patient reported outcomes (e.g., quality of life; anxiety; depression, BMI), Complications (e.g. incidence of cellulitis), continued need for compression or lymphoedema therapy. **Follow up:** 6 months to 5 years	Meta-analyses had high heterogeneity with no indication as to whether sensitivity analysis had been conducted.
Tang et al. (2021) **Country:** Australia	Systematic review of RCTs and non-randomised trials. **Number of included studies relevant to this appraisal:** 7 (total in SR = 25) **Search period:** Up to 30 November 2020	Adults with primary or secondary lymphoedema. **Number of participants:** 239	**Case series, n=4** Liposuction alone: 1 study Liposuction + CCT: 3 studies **Comparative cohort, n=2** Comparators: CCT: 1 Rehabilitation programme: 1 **Randomised Controlled Trial** Comparator: Wait list	**Outcomes:** Disease specific health-related quality of life (HRQoL), generic HRQoL, patient satisfaction **Follow up:** 6 months to 5 years	Eligible comparators were not appropriately defined – individual comparators that may have been relevant were not discussed, nor was any detail given about specific comparators searched for, if any. Numerical data from individual studies is not reported, with findings presented narratively.
Tyker et al. (2019) **Country:** USA	Systematic review of RCTs, non-randomised trials, case series and case reports. **Number of included studies relevant to this appraisal:** 2 (total in SR = 27) **Search period:** Up to September 2018	Adults with secondary craniofacial lymphoedema. **Number of participants:** 29	**Case series, n=1** **Randomised Controlled Trial** Comparator: Wait list treatment: 1	**Outcomes:** Patient satisfaction, improvement in lymphoedema, patient reported outcomes (improvement in appearance; distress reduction), objective observer score **Follow up:** 6 months	

Abbreviations: CCT = Controlled Compression Therapy

Appendix 7 – HTW cost utility analysis

1. Background and objective

A de novo economic analysis was developed to estimate the cost effectiveness of liposuction in addition to SC for treating patients with complex chronic lymphoedema, compared to SC alone.

The basic structure of the economic analysis followed that of a cost-utility analysis developed by the Norwegian Institute of Public Health for a rapid health technology assessment of liposuction for the treatment of chronic lymphoedema (Kvist et al. 2021). The model was adapted to reflect the UK NHS and Personal Social services (PSS) perspective and captured both costs and benefits of both interventions over a time horizon of five years.

2. Methods

2.1 Model approach

A Markov model was developed using Microsoft Excel to comprise five-year predictions of mortality and quality of life to evaluate the cost effectiveness of treatment strategies for chronic lymphoedema of the upper limb. The following two strategies were included:

1. Liposuction in addition to SC.
   Patients receiving liposuction are assumed to receive this in the first modelled cycle. Following liposuction, patients will need to remain using compression bandages for the remainder of their lifetime.

2. SC alone.
   Standard care for lymphoedema in Wales consists of decongestive lymphoedema treatment (DLT) including compression therapy.

All patients in the model are assumed to have complex chronic lymphoedema of the upper limb. The model operates a monthly cycle length, and patients are at risk of general mortality each cycle (See section 3.2). The analysis took the perspective of the Welsh NHS and PSS. Future costs and benefits were discounted at a rate of 3.5%.

3. Clinical data

3.1 Baseline characteristics

The cohort is entirely female and is initiated with an average age of 64 years, which reflects the population in Hoffner et al. (2017). This study followed a cohort of 60 women following liposuction surgery for upper limb lymphoedema. The gender distribution of the model was not varied in sensitivity analyses due to the identified evidence being primarily in female patients.

3.2 Mortality

Mortality for the general population is derived using published life tables for Wales for 2017-19 (Office for National Statistics 2021).

3.3 Costs

The costs considered in the analysis reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS and PSS were included. Where possible, all costs were estimated in 2022 prices. Where costs were reported in a different cost year, they were inflated to 2022 prices using data from the Personal Social Services Research Unit (PSSRU) (Jones et al. 2022).

Costs in the model include those related to initial treatment and annual follow up costs for patients. Upfront costs of liposuction include assessment, surgery and an initial follow up appointment. Costs for liposuction have been sourced from an NHS treatment appraisal decision summary from 2020 (NTAG 2022). Treatment costs in the control arm account for complex lymphoedema patients requiring intensive DLT. Costs for the SC arm have been sourced from the National Lymphoedema Partnership (NLP 2019). Follow up costs in both treatment arms include appointments and compression garments. Costs applied in the model are provided in Table A1.

Costs are input as annual values and are converted to monthly costs within the model to be applied per cycle.

Table A1 - Treatment costs applied in the model

	Liposuction in addition to SC		SC alone	
	Mean	SE	Mean	SE
Initial assessment costs	£0	£0*	£198	£19.84*
Treatment	£11,578	£1,157.83*	£4,035	£403.48*
Follow up – initial 12 months	£344	£34.42*	£397	£39.69*
Follow up – subsequent years	£344	£34.42*	£265	£26.46*

SC: standard care; SE: standard error
* Standard error assumed 10% of the mean. Sampled from a gamma distribution.

4. Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality-adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state.

Utilities within the model have been applied as per the Norwegian rapid HTA (Kvist et al. 2021). Quality of life data has been derived from a study by Hoffner et al. (2017) where data were collected on a cohort of 60 female patients undergoing liposuction following lymphoedema onset by breast cancer treatment. Patients were evaluated using the Short Form 36 (SF-36) at 1-, 3-, 6- and 12-months post-surgery. These values were converted to EuroQol 5 dimensions (EQ-5D) for use in the Norwegian model and have been applied as such in our health economic analysis. Utility values are provided in Table A2.

Post-surgery values have been applied to patients receiving liposuction in addition to SC. After the initial 12-month period, it is assumed that the quality of life for a patient who has undergone liposuction will taper over a one-year period to align to the general population quality of life. They are assumed to have a quality of life in line with the general population for the remainder of the modelled time horizon. Patients in the SC arm are assumed to have the pre-surgery quality of life for the duration of the modelled time horizon, unless the general population quality of life is lower than that of the pre-surgery utility value, in which case this will be applied instead.

General population utility values have been sourced from the NICE Decision Support Unit (Hernández Alava et al. 2022).

Table A2 - Utility values

	Utility value	Alpha	Beta
Pre-surgery	0.742	44.54	15.46
1 month following liposuction	0.766	45.98	14.02
3 month following liposuction	0.833	49.96	10.04
6 month following liposuction	0.833	49.96	10.04
12 month following liposuction	0.838	50.28	9.72
Alpha and beta values calculated from a cohort size of 60 patients. Sampled from a beta distribution.			

5. Results

5.1 Base case results

The base case health economic results are provided in Table A3. Over a five-year time horizon, results show that treating an upper limb complex chronic lymphoedema patient with liposuction in addition to SC is expected to increase healthcare costs by £7,577 and increase QALYs by 0.29 years, when compared to SC alone. This translates to an ICER of £26,269 per QALY, which is above the commonly accepted cost-effectiveness threshold of £20,000 per QALY.

Table A3 - Base case per-patient results

	Liposuction in addition to SC	SC	Incremental
Total QALYs	3.68	3.39	0.29
Total costs	£13,152	£5,575	£7,577
ICER (cost/QALY)			£26,269
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SC: standard care			

5.2 Scenario analysis

Two scenario analyses were conducted to assess the impact of key assumptions in the model. Table A4 provides the results of the scenario analyses. Neither scenario resulted in liposuction becoming a cost-effective strategy.

The first scenario looked at the utility in the liposuction in addition to SC arm. Under base case assumptions the utility at 12 months is tapered to the general population by month 24 and patients within this arm are assumed to have the utility of the general population applied for the remainder of the modelled time horizon. However, expert opinion noted that this may be an optimistic assumption as patients will still be required to wear compression bandages for the remainder of their lifetime, which is known to be associated with a decrease in quality of life. As such, the first scenario tested the impact of tapering to the control arm utility by month 24 and being subject to this utility value for the remainder of the modelled time horizon. This is likely to be a conservative assumption as clinical literature suggests sustained benefits of liposuction up to five years post-surgery. The results of this analysis showed fewer incremental QALYs and thus a much higher ICER, just over £60,000.

The second scenario analysis examined the impact of using the same annual follow up costs between treatment arms. Costs for the treatment arms have been sourced from different locations and it is likely that these costs could be similar, if not the same. Using equal follow up costs in both arms had a minor impact on incremental costs which resulted in a marginally lower ICER of approximately £25,000, which would still not be classed as cost-effective.

Table A4 - Scenario analysis results

	Incremental costs	Incremental QALYs	ICER (cost/QALY)
Treatment utility tends to control by month 24	£7,577	0.12	£60,710
Same annual follow up costs between treatment arms	£7,345	0.29	£25,464
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year			

5.3 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses (DSA) were conducted, whereby an input parameter is changed, the model is re-run, and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. For all inputs in the model, mean values were varied by 20% above and below the mean value for the analysis, with the exception of time horizon and discounting. The time horizon was tested for one year and three years, and the discount rate applied to both costs and benefits was tested at 0% and 6%.

The impact of the analysis on the ICER are presented in Figure 1. Most of the results do not translate to cost-effective ICERs, however there are a few cases where changes in the input values resulted in cost-effectiveness.

The utility of the SC arm had the biggest impact on modelled results. Increasing the annual utility to 0.891 resulted in an ICER of over £200,000. This is due to minimal differences in quality of life between the treatment arms, as those receiving liposuction are only receiving a quality-of-life benefit over SC for two years. Conversely, reducing the annual utility of the SC arm to 0.594 results in liposuction in addition to SC becoming a cost-effective treatment option, with an ICER of £7,936 per QALY, due to an additional 0.95 QALYs compared to SC alone.

Time horizon had the second largest impact on the ICER. Reducing the time horizon increased the ICER as the majority of costs are incurred in the initial year of treatment, and so modelling treatment for a longer time made little difference to incremental costs. However, over a shorter time horizon, there is less time to accumulate quality-of-life benefits and so there are fewer incremental QALYs between treatment arms when a shorter time horizon is used.

Increasing age to 76.8 resulted in an ICER value of £61,271. In this scenario, patients treated with liposuction are no longer receiving a quality-of-life benefit after two years post-surgery compared to SC alone patients, as general population utilities are used for both treatment arms. However, reducing the baseline age to 51.2 translates to a cost-effective result, with an ICER of £16,833 per QALY. This is due to a much larger quality-of-life benefit being seen in patients treated with liposuction due to the age-dependent utility being higher at a younger age.

Reducing the cost of liposuction produced cost-effective results due to a smaller incremental cost between the treatment arms and increasing the utility 12 months post liposuction translates to cost-effectiveness due to higher incremental QALYs between treatment arms.

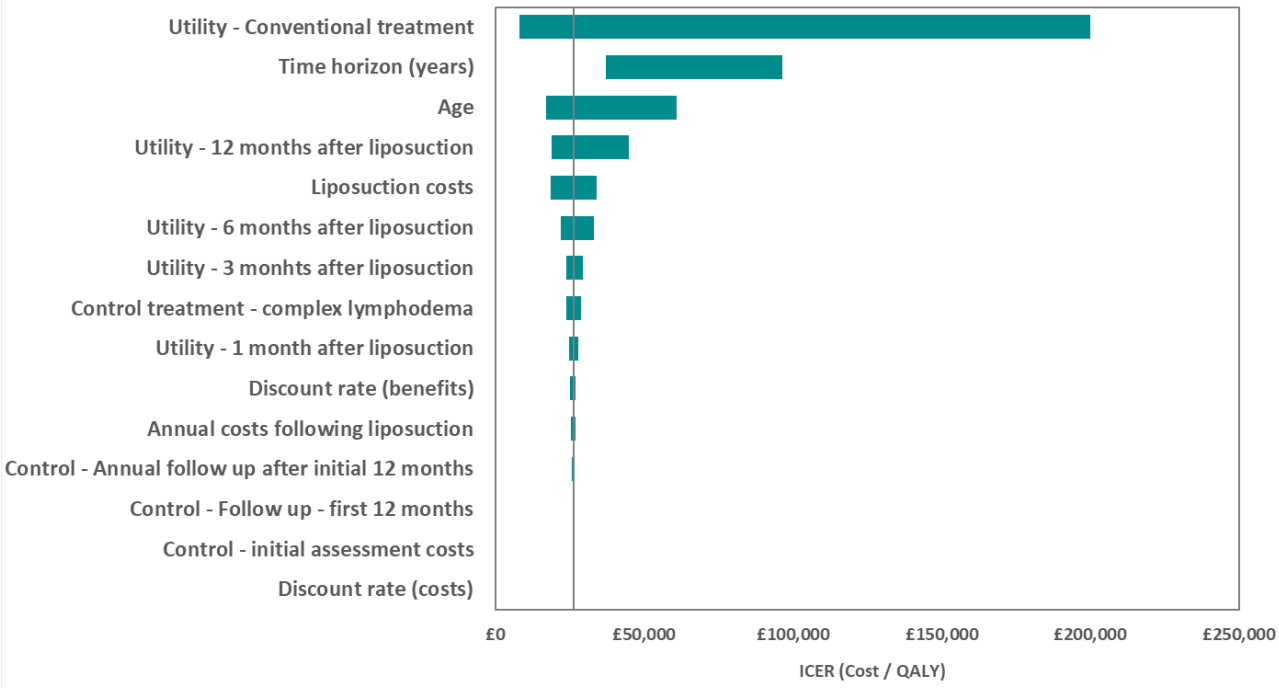


Figure 1 – Deterministic Sensitivity Analysis results

5.4 Threshold analysis

As the modelled costs of liposuction are based on uncertain estimates, a threshold analysis has been conducted to assess the cost at which liposuction in addition to SC would be considered a cost-effective treatment strategy. As data from the NHS (2023) suggests that liposuction costs range between £3,000 and £8,000, costs from £3,000 and above have been tested in the threshold analysis. Whilst these costs are lower than the base case cost used in the model, it should be noted that these values are likely to be for surgery alone, and not include assessment and initial follow-up costs.

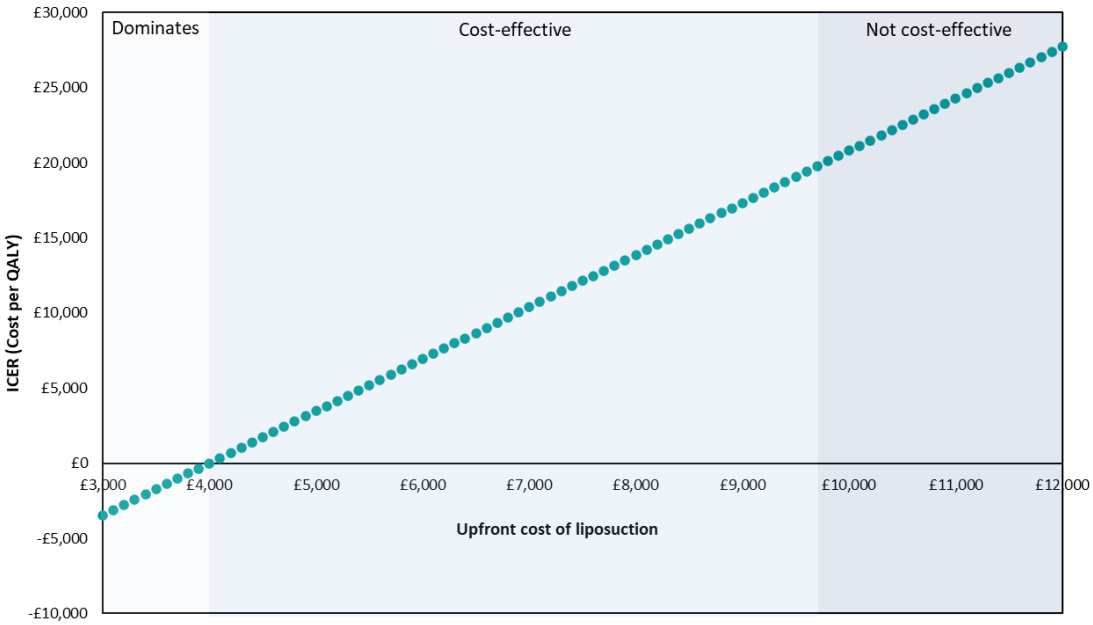


Figure 2 – Threshold analysis

When liposuction costs between £3,000 and £4,000, it is expected to be a dominant treatment strategy, meaning that it costs less than SC alone while providing greater quality of life to patients. When costs are between £4,000 and £9,700 liposuction is expected to be cost-effective compared to SC alone, and above this, liposuction is no longer a cost-effective treatment strategy.

5.5 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are presented using ICER scatterplots and cost-effectiveness acceptability curves (CEACs). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC shows the probability of liposuction in addition to SC being considered cost effective at various cost-effectiveness thresholds.

Table A5 presents the health economic results from the PSA. Under this analysis, liposuction in addition to SC is not expected to be cost-effective at a cost-effectiveness threshold of £20,000.

Table A5 - Probabilistic sensitivity analysis: health economic results

	Liposuction in addition to SC	SC	Incremental
Total QALYs	3.68	3.38	0.31
Total costs	£13,158	£5,575	£7,584
ICER (cost/QALY)			£24,632
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SC: standard care			

Figure 3 shows the ICER scatterplot for the PSA. Whilst 97% of the points reside in the more effective side of the graph, the high incremental costs between the treatment arms means that in the majority of cases, liposuction in addition to SC is not a cost-effective treatment option.

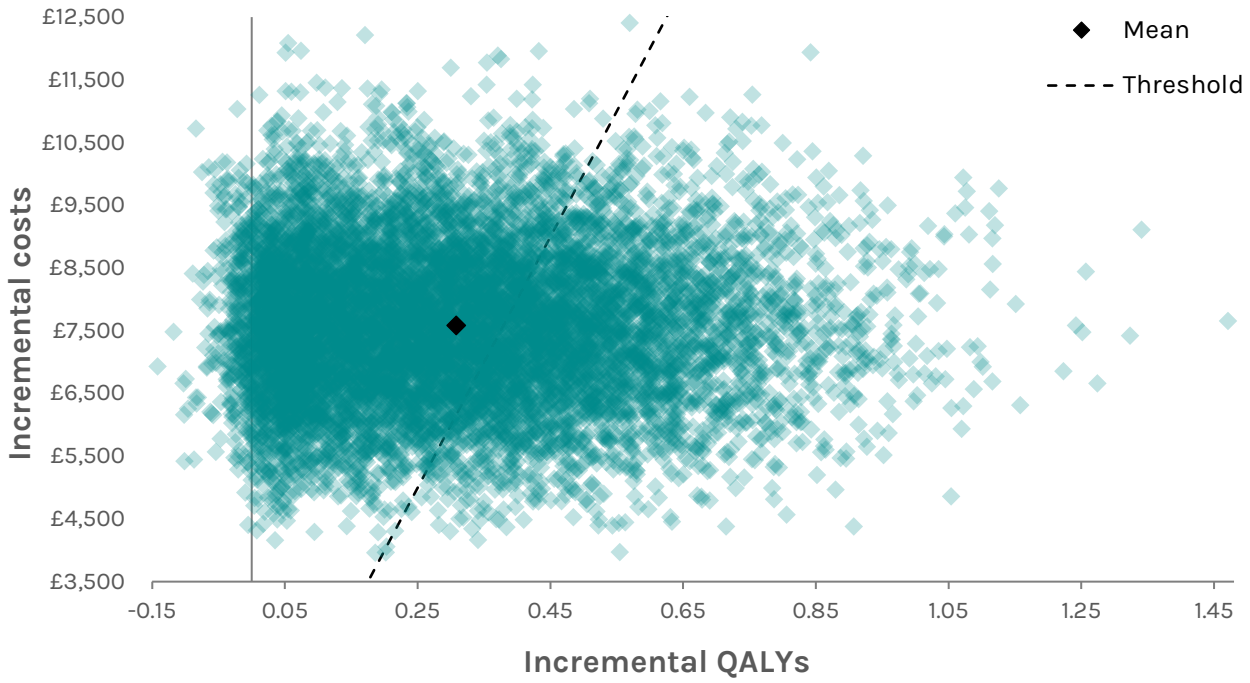


Figure 3 – Cost-effectiveness plane from the PSA

Figure 4 presents the probability of liposuction in addition to SC being considered cost-effective at various cost-effectiveness thresholds. At a threshold of £20,000 per QALY, there is a 35% probability that the strategy would be cost-effective, rising to 54% as the threshold reaches £30,000.

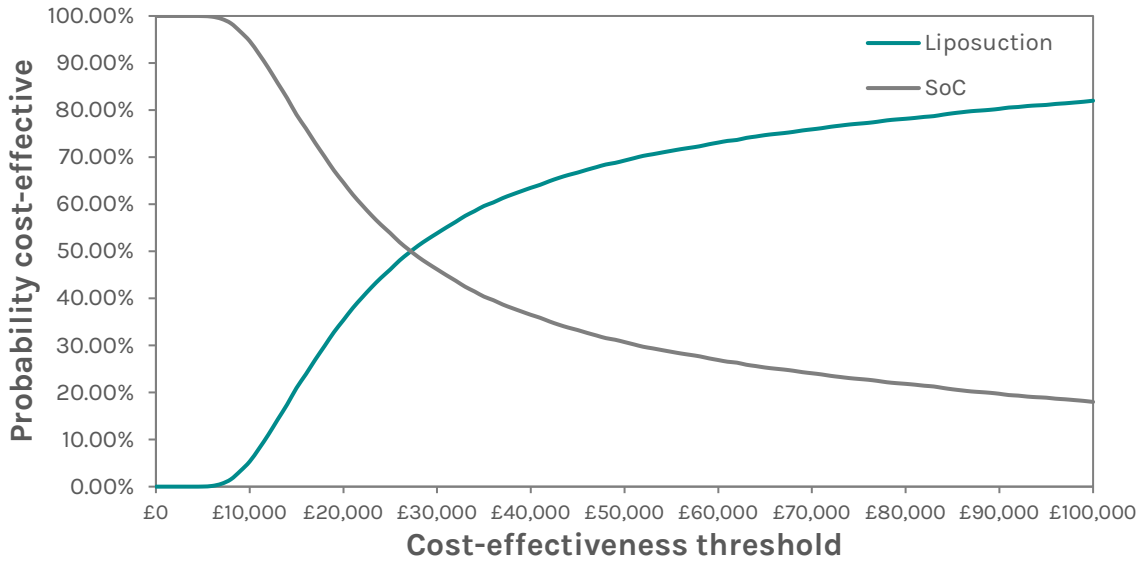


Figure 4 – Cost-effectiveness acceptability curve