ThemenCheck Medizin

Extract of HTA report

Advanced lymphoedema:[1]

Can non-drug interventions alleviate symptoms?

Health technology assessment commissioned by IQWiG

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IQWiG coordinated the project and conducted the literature search for the domains “Benefit assessment“ and “Health economic evaluation”.

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According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A11 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

Publisher's comment

What is the background of the HTA report?

Insured persons and other interested individuals are invited to propose topics for the assessment of medical procedures and technologies through "ThemenCheck Medizin" (Topic Check Medicine) to the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG). The assessment is done in the form of a Health Technology Assessment (HTA) report. HTA reports include an assessment of medical benefit and health economics as well as an investigation of ethical, social, legal, and organizational aspects of a technology.

In a 2-step selection procedure, which also involves the public, up to 5 new topics are selected each year from among all submitted proposals. According to the legal mandate, these topics should be of particular relevance to patients [1]. IQWiG then commissions external teams of scientists to investigate the topics in accordance with IQWiG methods, and it publishes the HTA reports.

In November 2019, IQWiG commissioned a team of scientists from the Institute for Evidence in Medicine at Freiburg University Medical Centre to investigate the selected topic "HT19-01: Advanced lymphoedema: Can non-drug interventions alleviate symptoms?" The team consisted of methodologists experienced in generating HTA reports, experts with knowledge and experience in health economic, ethical, social, legal, and organizational topics as well as a physical therapist and a clinician experienced in lymphology.

Why is the HTA report important?

Lymphoedema develops when lymphatic vessels or lymph nodes are damaged. Its primary or congenital form is distinguished from its secondary form, which develops due to another disorder. Common causes of lymphoedema include lymph node removal as part of cancer treatment, such as in breast cancer. In this case, secondary lymphoedema typically manifests in the arm, as experienced by about 17 out of 100 breast cancer patients [2].

First, the affected body part swells because lymph fluid builds up in body tissue and no longer properly drains. This can cause pain and reduced mobility. Worsening oedema increases the risk of skin infection. If the swelling persists for an extended period, the fluid may enter the deep connective tissue, which, in turn, can cause fibrosis: tissue overgrowth and hardening which is very difficult to treat.

Against this background, a member of the public asked about therapies for skin damage caused by advanced lymphoedema.

Hence, this HTA report aims to investigate the benefit of non-drug interventions compared with one another, compared to drug treatment, sham treatment, or no treatment in patients with advanced lymphoedema (stage II or above) with regard to swelling, pain, skin changes, etc.

Which questions are answered – and which are not?

The Freiburg authors found 23 studies investigating a wide range of non-drug interventions for advanced lymphoedema. Typically, they compared combinations of various interventions such as manual lymphatic drainage (MLD), compression bandaging, or exercise. None of the studies investigated complete decongestive therapy (CDT) – the current standard therapy consisting of the 5 components of MLD, compression bandaging, exercise, skin care, and training on self care – in its entirety. On surgical procedures, only 1 study was found, where the intervention group underwent vascularized lymph node transfer.

Hints of benefit regarding individual patient-relevant outcomes were derived for compression treatment, home-based programmes, vascularized lymph node transfer, and intermittent pneumatic compression.

However, a complete weighing of benefits versus harm was typically impossible because the studies did not consistently survey adverse events. In addition, the results are also limited in their adaptability to other settings. Study participants almost exclusively suffered from arm lymphoedema after breast cancer therapy. Few or no studies were found on patient populations with other indications and other lymphoedema localizations, e.g. on the legs or the head and neck area.

Because only 2 comparative cost studies were available to be included for the health economic assessment, it was impossible to determine cost effectiveness. The authors were able to estimate the expected average cost for 2 CDT components: manual lymphatic drainage with subsequent compression bandaging. They show that in arm lymphoedema after breast cancer, 1-month decongestive therapy followed by an 11-month maintenance phase costs an average of about €7700. The total cost increases by about €1600 if a home-use device for intermittent pneumatic compression is additionally rented. The statutory health insurance (SHI) covers the cost of treatment, including supplementary measures such as hot/cold therapy or exercise therapy. Unless exempted, patients must make copayments for remedies and aids, and they typically must cover the cost of further components such as skin care products.

If untreated, lymphoedema is a progressive disorder. Therefore, early diagnosis and consistent therapy are important to prevent the potential progression of disease and reduce the risk of late complications such as connective tissue fibrosis in the affected skin area. Often, treatment must be continued for years or even lifelong. Against this background, the Federal

Joint Committee decided in March 2017 to waive the existing application and approval procedure for long-term remedy needs in patients with stage II lymphoedema [3,4]. Starting from this severity level, patients are now immediately entitled to benefits without triggering additional SHI approval processes. With regard to access to services, the literature analysis revealed another aspect relevant to the ethics domain: Patients whose lymphoedema is not due to cancer or its treatment are suspected to receive poorer services because they are not included in established aftercare programmes.

In addition to physical symptoms such as swelling, pain, and mobility restrictions, lymphoedema can be associated with psychological and social burdens, thereby markedly reducing patients' quality of life. For instance, the visibility of the swelling and skin changes can result in patients feeling uncomfortable in public or even avoiding it entirely – the Freiburg authors mention this aspect as a form of self-stigmatization. In addition, decongestive exercise, skin care, and regular visits to physical therapy practices for manual lymphatic drainage and compression bandaging represent a substantial organizational burden in everyday life. According to the external authors, it is unclear whether self-management in the form of an at-home programme or intermittent pneumatic compression might afford patients some relief because these programmes, too, are time-intensive and require extensive training as well as self-discipline in independent use. Many patients therefore hope that surgery might provide relief or even cure the disease. According to the current lymphoedema guideline, "surgical therapy [...] should be considered if a patient exhibits distress or increasing secondary tissue changes despite guideline-compliant conservative therapy and treatment adherence" [5]. On the basis of the available studies, however, no conclusions can currently be drawn as to whether and how frequently surgery eliminates the need for further therapies in the long run.

What's the next step?

The HTA report reveals that there is a general need for more research. There is a particular demand for high-quality studies investigating the benefit of the individual CDT components. An additional area of focus should be surgical procedures such as lymphovenous anastomosis. Important prerequisites for comparing study results are a consistent classification of lymphoedema, the definition of a "core outcome set", and maximum possible standardization in service provision, e.g. with regard to the duration and execution of manual lymphatic drainage. To allow a comprehensive assessment, it is important to systematically record adverse events. Another field of research concerns access to services. In this context, the question should be investigated whether patients whose lymphoedema is neither due to cancer nor its treatment are in fact receiving lower quality care.

References

1. Sozialgesetzbuch (SGB) Fünftes Buch (V): Gesetzliche Krankenversicherung; (Artikel 1 des Gesetzes v. 20. Dezember 1988, BGBl. I S. 2477) [online]. 2021 [Zugriff: 18.02.2022]. URL: https://www.gesetze-im-internet.de/sgb_5/SGB_5.pdf.

2. DiSipio T, Rye S, Newman B et al. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 2013; 14(6): 500-515. https://dx.doi.org/10.1016/S1470-2045(13)70076-7.

3. Gemeinsamer Bundesausschuss. Lymphödeme ab Stadium II als Diagnosen für langfristigen Heilmittelbedarf gelistet [online]. 2017 [Zugriff: 18.02.2022]. URL: https://www.g-ba.de/presse/pressemitteilungen-meldungen/674/.

4. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Heilmittel-Richtlinie (HeilM-RL): Anpassung der ICD-Klassifikation und Delegation an den Unterausschuss Veranlasste Leistungen [online]. 2017 [Zugriff: 18.02.2022]. URL: https://www.g-ba.de/downloads/39-261-2906/2017-03-16_HeilM-RL_Anpassung-ICD-Klassifikation_BAnz.pdf.

5. Gesellschaft Deutschsprachiger Lymphologen. S2k Leitlinie; Diagnostik und Therapie der Lymphödeme; AWMF Reg.-Nr. 058-001 [online]. 2017 [Zugriff: 18.02.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/058-001l_S2k_Diagnostik_und_Therapie_der_Lymphoedeme_2019-07.pdf.

HTA key statements

Research questions of the HTA report

The aims of this investigation are to

assess the benefit of treatment with non-drug interventions in comparison with one another, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema (stage II or above) with regard to patient-relevant outcomes,

determine the (intervention) costs of treatment with non-drug interventions in comparison with each other, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema,

assess the cost effectiveness of treatment with non-drug interventions in comparison with each other, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema, and

review ethical, social, legal, and organizational aspects associated with the medical intervention.

Conclusion of the HTA report

For the benefit assessment, 23 studies – 21 randomized controlled trials (RCTs) and 2 randomized cross-over studies – were found. Three RCTs were 3-arm studies. A total of 1083 patients were enrolled in the studies. A total of 19 of the 23 studies examined only women. Only 2 studies with a total of 65 participants had mixed populations and included 15 male participants, while 2 other studies with a total of 87 participants provided no data on the percentages of female versus male participants. In 20 of the 23 studies, participants suffered from breast cancer. In 1 study each, the underlying conditions were gynaecological tumours, inflammations or trauma, or were not reported. Consequently, most available data concern arm lymphoedema, while little to no data are available on lymphoedema in other locations such as the legs, trunk, or head and neck area.

Investigated experimental interventions comprised manual lymphatic drainage, compression, exercise or movement therapy, diverse components of complete decongestive therapy (CDT), Kinesio Taping, intermittent pneumatic compression, vascularized lymph node transfer, laser therapy, acupuncture, thermotherapy, and platelet-rich plasma. While none of the identified

studies investigated CDT in its entirety, studies were found which evaluated at least several CDT components or combinations of components.

In 1 study each on acupuncture and thermotherapy, patients received no co-interventions. In all other studies, patients received co-interventions – typically CDT components such as compression, exercise, or skin care – alongside the experimental or comparator intervention.

Hints of benefit regarding individual patient-relevant outcomes were derived for the comparison of compression versus placebo Kinesio Taping, home-based programmes, vascularized lymph node transfer as well as intermittent pneumatic compression versus (longer-term) manual lymphatic drainage. For the comparison of Kinesio Taping versus compression, contradictory effects were found depending on the co-intervention. For all other experimental interventions, there were no hints of benefit in comparison with the respective comparator intervention.

In 2 studies, *compression* treatment was compared with placebo Kinesio Taping in patients with breast cancer as the underlying condition. For this comparison, there was a hint of compression + co-interventions reducing swelling more effectively than placebo Kinesio Taping + co-interventions. In this case, the co-intervention consisted of intermittent pneumatic compression and manual lymphatic drainage with or without skin care. Adverse events data were unusable for the benefit assessment. Therefore, it was impossible to definitively weigh benefits versus harm.

Two studies on patients with breast cancer as the underlying condition investigated the effectiveness of a *home-based programme (self-administered [manual] lymphatic drainage, breathing exercises, exercise, and skin care or compression)* following conventional therapy. In 1 of these studies, the comparator was no home-based programme; there was a hint of the home-based programme as an add-on to the co-interventions achieving greater improvements in swelling, pain, and physical functioning than the co-intervention alone. The co-intervention consisted of manual lymphatic drainage, compression (garments), exercise, and breathing exercises. For the second study, there was a hint of pain being alleviated by the home-based programme + co-intervention when compared with standard therapy consisting of an information brochure + co-intervention. In this case, the co-intervention consisted of an arm guard. Neither study recorded adverse events, which made it impossible to definitively weigh benefits versus harm.

Six studies on patients with breast cancer as the underlying condition compared *Kinesio Taping* versus compression; participants were allocated to 4 groups based on co-interventions. This comparison found opposing directions of effect in some cases, with statistically significant differences being found only in 2 groups. In the group with only 1 study (co-intervention of training plan), there were hints of Kinesio Taping + co-intervention

improving swelling, pain, health-related quality of life, grip strength, and the Shoulder Pain and Disability Index (SPDI) better than the co-intervention alone. However, in the other group, where co-interventions included manual lymphatic drainage and intermittent pneumatic compression, there was a hint of compression with Kinesio Taping being superior in the outcomes of swelling, mobility, and grip strength – based on the results of 3 studies and of 1 study, respectively. In the other 2 groups with 1 study each, no hint of benefit or harm was found. These opposing effects might be due to differences in the execution of the interventions, differences in co-interventions, or simply chance. For the comparison between Kinesio Taping versus no Kinesio Taping and Kinesio Taping versus placebo Kinesio Taping (+ co-interventions in each case), no hint of benefit of Kinesio Taping was found for any of the investigated patient-relevant outcomes.

The 2 studies comparing *intermittent pneumatic compression* versus manual lymphatic drainage in patients with breast cancer were analysed separately based on co-interventions. One study investigated intermittent pneumatic compression versus (longer) manual lymphatic drainage taking 30 minutes; co-interventions in both study groups were 30-minute manual lymphatic drainage, compression, exercise, and skin care. For the outcome of swelling, there was a hint of benefit. For the outcome "reduction of lymphoedema-related subjective symptoms", no differences were found, and adverse events were not investigated. Therefore, it was impossible to definitively weigh benefits versus harm. A second study, conducting a similar comparison, compared intermittent pneumatic compression versus manual lymphatic drainage using the co-interventions of compression and exercise. In this case, no hint of benefit was found for any of the investigated outcomes.

One study investigated vascularized lymph node transfer in comparison with no vascularized lymph node transfer in patients with breast cancer as the underlying condition. Both groups received the co-interventions of manual lymphatic drainage and compression for 6 months, followed by no further therapies for the subsequent 6 months. At the end of the follow-up period, there was a hint of lymph node transfer in combination with the co-interventions achieving greater improvements in swelling, pain, congestive symptoms, and limb function than the co-interventions alone. Likewise, there was a hint of adverse events (infection rates) occurring less commonly in the vascularized lymph node transfer group than in the comparator group without lymph node transfer. No studies were found on other surgical methods, such as lymphovenous anastomosis.

Due to the high risk of bias, small study sizes, study heterogeneity, e.g. regarding co-interventions, the outcome definitions as well as the uncertainty regarding the size of clinically relevant changes. Section 4.7 presents in detail the reported effects in relation to reported minimal clinically important differences.

It is unclear whether the data can be extrapolated to different patient populations because the included studies enrolled almost exclusively patients with breast cancer-related arm lymphoedema. In addition, it is unclear whether the results can be extrapolated to the general healthcare context in Germany: According to clinical experts, combined treatment with manual lymphatic drainage and compression is important to achieve an optimal effect. While this combination was found in all but 1 of the studies investigating compression or manual lymphatic drainage as an experimental or comparator intervention, the combinations of the various CDT components as well as the execution of the diverse interventions often varied markedly between studies. According to clinical experts, the provision of services, even within Germany, appears to vary greatly, in part due to marked (quality) differences. It was impossible to establish clear criteria for assessing transferability to the German healthcare context. None of the studies investigated the effectiveness of the entire CDT programme despite the fact that it represents standard therapy according to the guideline of the German Association of the Scientific Medical Societies (AWMF). Likewise, no robust data were found on adverse events, particularly on skin damage caused by lymph fluid. Generating robust evidence requires methodologically high quality RCTs as well as markedly improved reporting. Some factors affecting the risk of bias, such as blinding of outcome recorders and the implementation of the intention-to-treat (ITT) principle, are relatively easy to address, while blinding of treatment providers, in particular, can be very difficult at the least. Although this report included only randomized controlled trials, results on differences between study groups are often missing. Likely of almost equal practical importance is developing core outcome sets, reaching a consensus regarding relevant classifications of lymphoedema as well as specifying relevant subgroups based on these classifications on which systematic reporting is to be achieved. Alongside further standardization of lymphoedema classification and improved reporting, this is a prerequisite for the development of robust evidence.

A definitive health economic evaluation was impossible due to missing data. Intervention costs were estimated based on the example of arm lymphoedema after breast cancer. Estimating cost was possible only for some components of CDT, specifically for manual lymphatic drainage and compression; for a 1-month decongestive phase with a subsequent approximately 11-month maintenance phase, they equalled about €7691 annually. The cost of further CDT components (movement therapy, skin care, information, and training) are not reflected because utilization of services differs greatly between patients. The cost of the optional additional supply of a device for intermittent pneumatic compression for home use equals €1595 for about 11 months. Including intermittent pneumatic compression, the cost for 52 weeks of treatment therefore equals about €9286. The reimbursement for surgical lymph node transfer is about €3129.

However, in light of missing data, it was impossible to estimate the cost of additional long-term treatment, e.g. due to deterioration or complications as well as progression of disease.

A lack of suitable studies likewise makes it impossible to estimate the cost effectiveness of the interventions. The 2 identified cost-cost studies merely report costs for different time horizons (study on vascularized lymph node transfer) and treatment frequencies (study comparing Kinesio Taping versus compression). Specifically, the first study compared vascularized lymph node transfer + 6 months of co-interventions versus no vascularized lymph node transfer, but with co-interventions for the patient's remaining lifetime. In both study groups, co-interventions were manual lymphatic drainage and compression. The second study compared Kinesio Taping 2 x weekly versus 5 x weekly compression (bandaging), each including co-interventions. The co-interventions in both study groups were *compression (garments), manual lymphatic drainage, exercise, and skin care.* Neither study provided proof of the equivalence of the treatment options. Hence, the studies cannot be used to draw any conclusions for the present report.

The ethical and social domain identified a series of causes for long-term burden. In addition to purely health-related and financial burdens, they also cited burdens due to self-stigmatization or the feasibility of therapies in daily life, for instance. Patients report the condition to be associated with severe pain and mobility restrictions and leading to limitations in work and everyday life. Currently, patients whose lymphoedema is not due to cancer or its treatment are suspected to receive poorer care because they do not benefit from established aftercare programmes. Access to adequate therapy might be more difficult to obtain or insufficient due to cost carriers' reluctance to approve inpatient rehabilitation stays, budgetary specifications, and physicians' potential lack of awareness about said specifications. An unclear disease definition and insufficient diagnostics might present further obstacles to adequate care. The risk of lymphoedema increases with age. In view of these problems and against the background of an ageing society, a collaborative approach, where medical specialists offer support, consultation, and instruction, might be an option for facilitating adequate treatment. The new German Remedies Directive dated 21 January 2021 is likewise intended to facilitate the prescription of these therapies and might provide easier access to these therapies.

From a legal perspective, one problem area is the handling of specific treatment methods in connection with informed consent and in view of the standard of due care. Treatment providers are responsible for providing comprehensive information and treating only after obtaining valid consent. Doing so is also a prerequisite for avoiding culpability. In this context, the applicability of non-governmental guidelines and their relevance for the law are a worthy topic of discussion. Rather than constituting classic national law, these guidelines represent standards defined by certain professional or interest groups which do affect the law (e.g. with regard to negligence) – a practice which certainly warrants critical questioning.

With regard to the interventions examined herein, it should be noted, firstly, that from a legal perspective, surgical measures represent a treatment alternative if the conservative treatment approach does not achieve sufficient improvement after at least 6 months of therapy. Improvement is insufficient if the patient's suffering is not alleviated by the conservative therapy, an increase in secondary tissue changes is recorded, or the therapy presents an excessive burden for the patient. In these cases, patients should be informed about surgical alternatives even if conservative treatment is to be preferred. The legal provisions regarding medically indicated procedures, i.e. the corresponding provisions of the German Civil Code, become applicable in this case, with specific consequences including regarding liability. Secondly, it should be noted that in 2017, the Federal Joint Committee (G-BA) decided to list the diagnosis of lymphoedema stage II or above for long-term remedy needs to thereby facilitate patients' long-term care for the disease. No such decision has been taken for surgical measures.

Relevant organizational aspects of these often-lifelong therapies include the setting in which they are to be carried out as well as the need for interdisciplinary collaboration. Most therapies are administered in an outpatient or inpatient setting, e.g. during rehabilitation, and therefore require patients to travel to a therapist for each session. Some interventions, particularly self-manual lymphatic drainage, compression, other CDT components, and possibly also intermittent pneumatic compression, may also be carried out at home by trained persons. However, because self-administration is time-intensive and requires self-discipline, it remains unclear whether, in view of the chronic nature of the condition, this represents relief for patients.

Seen from the social domain, the assessment of the various therapies must take into account that physical therapies are apparently well accepted, with evidence showing that Kinesio Taping is better accepted than compression. However, acceptance might depend on patients' individual experiences. In the ethical domain, the discussion involves patients potentially preferring surgical procedures over symptomatic therapy due to the former's potential curative effect. Currently, no data on this topic are available, and the existing evidence regarding patient preferences is based on the conclusions from a small number of studies. While the diagnosis of lymphoedema stage II or above has been listed for long-term remedy needs, no corresponding decision has been taken for surgical measures. From a legal perspective, therefore, surgical measures represent the state of medical science as per professional standard based, among others, on AWMF guidelines, only after 6-month therapy with the conservative treatment approach has failed to achieve adequate improvement. From an organizational perspective, curative surgical therapy is less human resource-intensive than lifelong physical therapy. Based on the available studies, however, it is not possible to determine whether and to what extent patients in fact need no further therapies postoperatively. The required professional qualifications differ markedly, so that bottlenecks

would probably occur if surgical therapy were found to be associated with substantial added benefit and patients preferred it over other therapies. Currently, however, robust evidence on benefit and harm is missing for all interventions, including the entire CDT programme; therefore, this essential information cannot be taken into account when determining preferences.

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List of abbreviations

Abbreviation	Meaning
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies)
BMI	body mass index
CES-D	Center for Epidemiological Studies–Depression
CDT	complete decongestive therapy
DASH	Disabilities of the Arm, Shoulder, and Hand
DRG	diagnosis-related group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	5-level EQ-5D version
EUnetHTA	European Network for Health Technology Assessment
FACT-B	The Functional Assessment of Cancer Therapy – Breast
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	health technology assessment
ICD	International Classification of Diseases
IPC	intermittent pneumatic compression
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ISL	International Society of Lymphology
LD	lymphatic drainage
LSIDS-A	Lymphedema Symptom Intensity and Distress Survey – Arm
LYMQOL	Lymphoedema Quality of Life
MCID	minimal clinically important difference
MDC	minimal detectable change
MLD	manual lymphatic drainage
NRS	numerical rating scale
POMS-SF	Short Form of the Profile of Mood Scales
PRP	platelet-rich plasma
QLQ-C30	Quality of Life Questionnaire-Cancer 30
RCT	randomized controlled trial
SF-36.m	36-Item Short Form Survey mental component
SF-36.p	36-Item Short Form Survey physical component
SGB	Sozialgesetzbuch (Social Code Book)

Abbreviation	Meaning
SHI	statutory health insurance
SPADI	Shoulder Pain and Disability Index
ULL-27	Upper Limb Lymphoedema 27
VAS	visual analogue scale
VLNT	vascularized lymph node transfer

HTA overview

1 Background

1.1 Health policy background and commission

According to § 139b (5) of Social Code Book V, Statutory Health Insurance, statutory health insurance members and other interested people may suggest topics for the scientific assessment of medical interventions and technologies to the Institute for Quality and Efficiency in Health Care (IQWiG). The topics for these health technology assessment (HTA) reports can be submitted on the IQWiG website.

ThemenCheck Medizin aims to promote the involvement of the public in evidence-based medicine and answer questions which are particularly relevant in patient care.

Once yearly, IQWiG, in collaboration with patient representatives and members of the public, selects up to 5 topics on which HTA reports are to be prepared. IQWiG then commissions external experts to investigate the research question. The results prepared by the external experts and a publisher's comment by IQWiG are then published in the form of an HTA report.

IQWiG disseminates HTA reports to German institutions, for instance those deciding about healthcare services and structures. The HTA report will be made available to the professional community through the IQWiG website (www.iqwig.de). In addition, a lay summary of the results of the HTA report will be published under the title "HTA compact: The most important points clearly explained". This is done to ensure that the results of HTA reports will impact patient care.

1.2 Medical background

1.2.1 Definition

Lymphoedema is an independent chronic condition which tends to be progressive and is caused by impaired lymph flow due to lymphatic vessel system damage or disease [1].

The lymphatic vessel system is a network which spans the entire body and plays an important role in fluid transport [2]. Under physiological conditions, the amounts of fluid filtering through the blood vessel walls into the interstitium (particularly supporting and connective tissue) and fluid draining from the tissue are balanced [2]. An insufficient lymphatic system leads to accumulation and change in the interstitial fluid. Abnormal lymph flow causes various forms of initially painless swelling (oedema) [3].

Lymphoedema can develop on one or both sides (unilaterally or bilaterally) and affect the upper or lower limbs or even other body parts [4].

1.2.2 Causes and risk factors for the condition

Lymphoedema can be congenital or acquired. Congenital (primary) lymphoedema develops when lymphatic vessels develop incompletely or defectively, thereby reducing their drainage capacity [1]. Acquired (secondary) lymphoedema results from damage to the lymphatic vessels, e.g. by injury or radiation, lymph node removal, malignant diseases of the lymphatic vessels, or less commonly by bacterial or fungal infections or secondary to chronic venous insufficiency [1,3].

Risk factors for the development of lymphoedema include genetic predisposition as well as cancer and its treatment, advanced age, overweight, autoimmune diseases, and inflammatory arthritis [3].

In tropical regions, a parasitic infection (filariasis) transmitted by mosquitoes can cause secondary lymphoedema [1]. The present HTA report does not cover this special form of secondary lymphoedema (tropical lymphoedema, tropical elephantiasis) because it is an extremely rare occurrence in the German healthcare system.

1.2.3 Epidemiology

The condition's prevalence (proportion of the population who have the condition) and incidence (number of newly diagnosed lymphoedema cases) differ by cause, sex, and age. In the general population, the annual number of cases of chronic lymphoedema (lasting for more than 3 months) is 133 per 100 000 persons [5].

Primary lymphoedema dominates in children and adolescents. According to epidemiological data, 1.15 in 100 000 adolescents under the age of 20 years are newly diagnosed per year [6]. Girls are affected 3 times more commonly than boys [7].

The majority of cases of secondary lymphoedema are due to breast cancer and its treatment [3]. A systematic review including 72 studies reports the incidence of secondary arm lymphoedema in breast cancer patients as 16 600 per 100 000 patients. The incidence in cancers other than breast cancer is reported as 15 000 per 100 000 patients, with the incidence rate varying strongly by cancer type [8].

1.2.4 Individual disease burden

Alongside physical changes, patients often suffer from psychological disorders and reduced quality of life [9]. The affected limbs feel heavy and tight. Individual burden is further increased by reduced physical functioning (mobility restrictions), reduced ability to manage

daily tasks, and therapy sessions [4]. Women with lymphoedema after breast cancer treatment often experience anxiety as well as depression, sexual dysfunction, social phobias, or deterioration of existing psychological suffering [9].

1.2.5 Differentiation by severity

Through progressive tissue changes, lymphoedema leads to a chronic course of disease which can be classified into stages (also see Table 1) [4].

Initially, patients have no clinically demonstrable swelling (latent stage, stage 0) but may already subjectively perceive limbs as feeling heavy. In the first stage (stage I), protein-rich fluid accumulates in the tissue. At this point, limb volume can increase up to almost 20%. In this stage, oedema is still soft and typically resolves within 24 hours after elevation. In the course of disease, fibrosclerotic processes lead to progressive tissue hardening (stage II). Stage II lymphoedema typically does not resolve with elevation. Limb volume has increased by 20% to 40% and (initial) skin changes are visible (dermal fibroses). In stage III, limb volume has increased above 40%, and clearly visible skin and tissue changes exist (fat deposits, acanthosis, wart-like growths) [4,9]. Lymphoedema stage II and III are considered “advanced stages” [4].

Instead of staging by volume increase, the American Physical Therapy Association (APTA) classifies lymphoedema based on the maximum difference in circumference compared to the other limb: less than 3 cm difference (mild, corresponds to stage I), 3 to 5 cm difference (moderate, corresponds to stage II), and over 5 cm (severe, corresponds to stage III) [9]. Stage III lymphoedema has also been referred as debilitating “lymphostatic elephantiasis” [10], but this term is no longer in common use.

Table 1: Overview of disease stages

Stage [4,9,10]	Stage 0 (subclinical)	Stage I (initial stage)	Stage II (advanced stage)	Stage III (debilitating lymphostatic elephantiasis)
Volume increase		< 20%	20 to 40	> 40%
Difference in circumference		< 3 cm	3 to 5 cm	> 5 cm
Designation		Mild	Moderate	Severe

In the course of disease, various complications may occur, e.g. recurrent skin infections associated with redness, pain, and sensitivity to pressure. They include inflammation of the interstitial connective tissue (phlegmon, cellulitis) or of the lymph vessels (lymphangitis) or

erysipelas. Lymphangiosarcoma, a rare cancer presenting as purple skin discolouration may develop, particularly in advanced lymphoedema [9].

1.2.6 Diagnosis

Lymphoedema is diagnosed based on the patient's history and clinical examination. The patient history consists of a general part (questions about familial predisposition, surgeries, prior illnesses, skin changes, insect bites) and an oedema-specific part (questions about the time of oedema development, initial localization, and direction of spread, complaints, and symptoms) [4].

Afterwards, the patient is examined to determine the location of swelling as well as the difference in circumference and potentially length at the affected limb. In addition, the skin is examined for any trophic disorders, colouring, skin changes, lymphatic cysts, or deepened natural creases. Further, the patient is assessed regarding shortness of breath, sweating, and mobility [4].

Finally, the lymph nodes and oedema are examined through palpation. Lymph nodes are evaluated, in part, by their size and consistency. The oedema is rated by consistency (doughy soft, plump elastic, rough fibrotic, hardened). A finger is pressed on the skin to see whether the oedematous skin remains indented (pitting oedema). Tissue hardening is determined by checking whether the skin on the 2nd or 3rd toe can still be pinched (Stemmer sign).

1.2.7 Treatment

Treatment aims to achieve the alleviation of lymphoedema symptoms, regression of lymphoedema to a lower stage or an oedema-free condition, and slowing of the progression of disease [9].

Complete decongestive therapy

The standard treatment for lymphoedema is complete decongestive therapy (CDT), which consists of 5 components: (i) manual lymphatic drainage (MLD), (ii) compression therapy with special temporary bandages (and possibly compression stockings), (iii) decongestive exercise or movement therapy, (iv) skin care (and medical treatment where necessary), and (v) information and training on self-care [4].

(i) MLD, the first component of CDT, is a massage-like technique intended to mobilize excess tissue fluid by applying mild pressure. One of the goals is to stretch lymphatic vessel walls in order to stimulate their rate of pulsation. A suction effect increases lymph flow in the lymph collectors, leading to the draining of tissue fluid. In lymphoedema stages II and III, additional grip techniques are used to soften hardened tissue [4].

(ii) Following MLD, compression therapy using special bandages is intended, among other things, to stimulate inflow of tissue fluid into the lymph vessels and increase lymph flow in the remaining functioning lymph vessels [4].

(iii) Decongestive exercise or movement therapy increases interstitial pressure via muscle contraction and thereby increases lymph vessel motor function, which is to further promote decongestion. Suitable exercise includes Nordic walking, bicycling, swimming, and cross-country skiing [4].

(iv) Skin care serves to protect the skin, which is stressed by bandages, etc.; it involves daily cleaning with pH neutral soaps and applying with lipid-containing moisturisers and disinfection, if necessary. Skin treatment is performed where necessary, e.g. in wound (super)infections, after insect bites, allergic reactions, or eczematoid changes [4].

(v) Informing the patient about lymphatic system function, the clinical picture of lymphoedema, and the need for lifelong therapy as well as training on skin care, breathing techniques, decongestive exercise, and self-bandaging represent the 5th element of CDT [4].

CDT is broken down into phase 1 and phase 2. In the German healthcare system, phase 1 takes place in an inpatient or outpatient setting, with all components being administered once or twice daily. In stage III lymphoedema, it takes up to 35 days. In phase 2, the individual components are used depending on findings [4]. This phase serves to maintain the treatment results achieved in phase 1 [9].

Surgical measures

Surgical measures are used where conservative therapy was unsuccessful or for treating recurrent inflammations of the interstitial connective tissue (phlegmon, cellulitis). Malformations in primary lymphoedema can be surgically treated as well [11]. According to the guideline of the German Association of the Scientific Medical Societies (AWMF), patients should be offered surgical procedures only after at least 6 months of CDT (phase 1 and 2) because within this period, (a) transient oedema may regress and (b) the risk of secondary tissue changes increases [4].

Three surgical procedures are available: (i) reconstructive microsurgical procedures such as lymphatic vessel transplantation, lymphatic venous anastomosis, or lymph vessel flap transplant, (ii) deviating procedures such as connection to small veins (lymphovenous /lymphonodulovenous anastomoses) or autologous lymph node transplantation to restore the function of the lymphatic vessel system , (iii) resection procedures such as liposuction, removal of skin, subcutaneous tissue, or fascia, wound closure or skin and tissue transplantation (flap plasty, split-thickness skin graft). Resection procedures are suitable only for patients with advanced lymphoedema (stages II and III) on the limbs or genitals [4].

Other non-drug interventions

The section below lists other non-drug interventions used in the treatment of lymphoedema. Due to the large number of procedures used, this list is not complete.

(i) Intermittent pneumatic compression (IPC), also referred to as device-based intermittent compression, can be used as an adjunct to CDT in arm or leg lymphoedema. For this purpose, a cuff connected to a pump applies pressure at certain intervals to move tissue fluid [4]. The terms device-based intermittent compression and IPC are synonyms. For consistency purposes, the results part will use only the term intermittent pneumatic compression or IPC.

(ii) As an alternative to bandages or compression stockings, elastic tapes (lymph tapes) are in use [4]. The effect of compression is thought to be based on movement of fluid through tissue gaps, increased inflow of interstitial fluid into the initial lymphatic vessels, and reduction of venous pressure [4]. In the first method, Kinesio Taping is to lift the superficial skin to reduce pressure and open the initial lymph vessels. In a second method, Kinesio Taping is applied to muscle to improve the effectiveness of the deep lymph vessels by ensuring that the muscle can achieve maximum contraction and relaxation [12].

(iii) Low level laser therapy, also known as cold laser therapy, [13] is used as experimental therapy for soft tissue injury, chronic pain, and wounds [9].

(iv) Further non-drug interventions may include aquatic therapy, acupuncture, thermotherapy (heat and cold treatment), platelet-rich plasma (PRP), or deep oscillation [4,14]. Deep oscillation aims to reduce pain and oedema by the application of an electrostatic field [4]. Animal studies suggest that PRP leads, among other things, to increased lymphatic vessel formation and density and reduces lymphoedema in rats [15].

1.3 Health care situation

In Germany, the number of cases of lymphoedema classified as ICD-10 I89 and requiring inpatient care have increased between 2000 and 2017. A total of 2105 patients were admitted to fully inpatient care in the year 2000, compared to 5285 patients in 2017. Simultaneously, the average length of hospital stay decreased from 15.1 days in the year 2000 to 7.7 days in 2017 [16]. No separate data are available for patients with lymphoedema stages II and III.

Lymphoedema stages II and above are listed as diagnoses involving the long-term requirement of a remedy. CDT is reimbursable by the statutory health insurance (SHI) [17]. CDT is performed by physical therapists with the appropriate additional qualifications. For other non-drug interventions, no information is currently available to us with regard to the health care situation in Germany.

1.4 Concerns of those proposing the topic

A member of the public asked which therapies can be effective against the skin damage caused by lymph in stage III primary lymphoedema. The question was worded openly, without the member of the public limiting it to a specific non-drug therapy.

The *ThemenCheck Medizin* staff developed an HTA research question on the basis of this suggestion.

The research question was selected for analysis within an HTA report in part because lymphoedema is relatively common, particularly in patients with cancer, and it materially affects patients' lives due to both physical and psychological burdens.

2 Research questions

The aims of this investigation are to

- assess the benefit of treatment with non-drug interventions in comparison with one another, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema (stage II or above) with regard to patient-relevant outcomes,
- determine the (intervention) costs of treatment with non-drug interventions in comparison with each other, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema,
- assess the cost effectiveness of treatment with non-drug interventions in comparison with each other, with drug treatment, with sham treatment, or with no treatment in patients with advanced lymphoedema, and
- review ethical, social, legal, and organizational aspects associated with the medical intervention.

3 Methods

This HTA Report has been generated based on the *General Methods 6.0* [19].

3.1 Methods – benefit assessment

The target population of the benefit assessment is patients of any age who suffer from advanced primary or secondary lymphoedema (stage II or above) [4,20]. For inclusion, it was irrelevant in which location on the body lymphoedema had developed or whether it manifested unilaterally or bilaterally. Patients with lymphoedema due to parasite infections (e.g. filariasis) or leprosy as well as patients with secondary lymphoedema due to venous underlying conditions (e.g. venous insufficiency or postthrombotic syndrome) were excluded. Experimental interventions were CDT as well as individual components of CDT, surgical measures, or any other non-drug interventions such as IPC, lymph taping, low-level laser therapy, acupuncture, etc. (in the form of monotherapy or combination therapy). Comparator interventions were other non-drug interventions (in the form of monotherapy or combination therapy), drug treatment (in the form of monotherapy or combination therapy), sham treatment (e.g. placebo), or no treatment (e.g. waiting list). Variations of the same experimental interventions (e.g. the application of different pressures in compression) were not investigated as comparator interventions.

The investigation examined the following patient-relevant outcomes, which had been identified using prior searches and patient interviews:

- Mortality, such as
  - all-cause mortality
  - disease-specific mortality
- Morbidity, such as
  - swelling
  - pain
  - congestive symptoms
  - tension
  - mobility
  - severe late complications
- Health-related quality of life
- Health-related social functioning, including occupational and social participation
- Adverse events (AEs), such as

- type and number of adverse events related to the intervention
- treatment failure

As supplementary information, patient satisfaction with treatment – to the extent that it included health-related aspects – was analysed as well as the required intervention-related and disease-related effort.

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration. In each case, the latest time point within the experimental therapy phase or directly after the end of this phase was examined. For curative experimental interventions, such as surgical therapies, the latest follow-up time point was additionally analysed.

A systematic literature search for studies was conducted in the databases MEDLINE, Embase, and the Cochrane Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase and the Cochrane Database of Systematic Reviews. In addition, the reference lists of the identified systematic reviews from the past 2 years were reviewed. Furthermore, the following sources of information and search techniques were taken into account: trial registries (ClinicalTrials.gov and International Clinical trials Registry Platform Search Portal).

The selection of relevant studies from the bibliographical literature search and the trial registries was carried out by 2 people independently from each other. Any discrepancies were resolved by discussion between them; where necessary, a 3rd person was consulted. One person extracted the data into standardized tables, and another person reviewed them. To assess the qualitative certainty of results, criteria affecting the risk of bias at study and outcome levels for the patient-relevant outcomes were assessed, and the risk was rated as high or low in each case. The results of the individual studies were described, organized by experimental intervention and additionally by outcomes.

If the studies were comparable in terms of the research question and relevant characteristics and no relevant heterogeneity was observed, the individual results were pooled quantitatively by means of meta-analyses. Since fewer than 10 studies were pooled, it was impossible to conduct the originally planned subgroup analyses of the pooled studies with regard to experimental intervention, age, severity of disease, concomitant therapies, and affected limb.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: there was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or

the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

3.2 Methods – health economic assessment

3.2.1 Determination of intervention cost

To calculate intervention costs, the average resources required directly when performing the experimental and comparator intervention were estimated. In addition to the experimental and comparator interventions, the services directly associated with the intervention were included. Wherever possible, the relevant regulated or negotiated prices of these services were used, e.g. from the Uniform Value Scale (UVS) or the diagnosis-related group (DRG) catalogue. Where a therapy took more than 1 year, the average annual cost per patient was reported. Reimbursable and non-reimbursable costs were listed separately.

3.2.2 Health economic evaluation

To research the health economic aspects of non-drug therapy of lymphoedema, the hits found in the focused information retrieval via the systematic literature search in the MEDLINE and Embase databases were reviewed for relevance by 1 person. A 2nd person performed quality assurance of the result.

In addition to the benefit assessment’s inclusion criteria IB1–IB3, the inclusion criteria IE1–IE3 were used (see Table 6). Of interest were the short-term and long-term costs of intervention elements, particularly with regard to their associated changes in symptom severity, progression, and health-related quality of life. Comparative studies drawing conclusions on cost effectiveness, i.e. cost–effectiveness analyses, efficacy analyses, cost-utility analyses, or cost-benefit analyses (in the narrower sense), were taken into account. Since no such study types were found in the search, comparative health economic studies drawing conclusions on the cost of the intervention and comparator intervention, i.e. cost-cost analyses, were included. The inclusion and exclusion criteria with regard to the study population as well as the type of disease were the same as those used in the benefit assessment.

3.3 Methods – ethical aspects

To identify ethical aspects of non-drug therapies of lymphoedema, a scoping literature search was first conducted in the MEDLINE and ETHMED databases as well as with the aid of Google Scholar and Google.

Inclusion criteria were a publication date 2000 or later, the investigated patient groups including patients with lymphoedema after breast cancer, and the study's geographic focus being Europe or United States. One person reviewed hits for relevant ethical aspects and topics as described above. A 2nd person assured the quality of the result. Based on the information obtained in this manner, the questionnaire by Hofmann was worked through [21]. To supplement the literature searches, patient interview protocols were analysed. As an additional source of information, the reflective thoughts method, i.e. reflection informed by the authors' knowledge regarding potential ethical arguments and aspects, was applied [22].

3.4 Methods – social, legal, and organizational aspects

In the HTA, social and sociocultural aspects address the mutual interactions between examination/treatment methods and the social environment (e.g. resource distribution in society, access to technologies, patient preferences, social norms, and values). The information processing on social aspects was based on the comprehensive conceptional framework proposed by Mozygemba 2016 [23].

For the analysis of social aspects, a scoping search was carried out in the Medline (PubMED) database and supplemented by website-based searches. In addition, the studies included in the benefit assessment and the patient interview protocols were reviewed for social aspects. One person checked the documents for conclusions on social arguments and aspects of the technology to be investigated, and quality was assured by a 2nd person. As an additional source of information, the reflective-thoughts method, i.e. reflection informed by the authors' knowledge regarding potential social arguments and aspects, was applied [22].

All arguments and aspects necessary for information processing were extracted into tables.

The analysis of legal aspects first reviewed the existing legal provisions and applied them to individual cases. This concerns, firstly, regulations and guidelines applicable to the treatment method, and secondly, provisions regarding the treatment contract as well as the reimbursement of the treatment method in SHI members. Aspects of the guideline developed by Brönneke 2016 were included in this process [24]. The standards were applied to life circumstances using established legal interpretation methods. Furthermore, relevant comments were used in the presentation and assessment of the legal situation in order to explain the standards and, on this basis, incorporate key rulings as well further literature.

The organizational domain was analysed using scoping searches in MEDLINE as well as via Google on the Internet. In addition, studies included in the benefit assessment were reviewed for organizational aspects. The identified studies were viewed by 1 person. A 2nd person was tasked with quality assurance. All arguments and aspects necessary for information processing were extracted into tables and summarized as a narrative. In addition, “reflective thoughts” were used [22].

3.5 Patient interviews

During the generation of the HTA report protocol, patient-relevant aspects, relevant subgroups as well as relevant ethical, social, legal, and organizational aspects were discussed with patients. For this purpose, individual interviews were conducted with 2 patients using a predefined interview guide. Patient-relevant aspects reported by patients were used in the generation of the HTA protocol.

4 Results: benefit assessment

4.1 Results of the comprehensive information retrieval

From among 4005 hits, the information retrieval identified 23 randomized controlled trials resulting in 24 publications as relevant for the research question of this benefit assessment. In addition, 2 ongoing studies, 1 study of unclear status, 1 discontinued study, and 3 completed studies without reported results were found. Furthermore, 3 studies are in the planning stages. The registry entries did not show when results are to be expected for the ongoing and planned studies.

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 27 February 2020.

Table 2: Study pool for the benefit assessment

	Study	Available documents			
		Full publication (in professional journals)	**Registry entry**	**Results report from study registries**	**Clinical study report from manufacturer documents (not publicly available)**
1	Akgul 2020	Yes [14]	https://clinicaltrials.gov/ct2/show/NCT03080207?term=Akgul&draw=2&rank=3	-	-
2	Bao 2018	Yes [25]	https://clinicaltrials.gov/ct2/show/NCT01706081	Yes	-
3	Bergmann 2014	Yes [26]	-	-	-
4	Buragadda 2015	Yes [27]	-	-	-
5	Chmielewska 2016	Yes [28]	-	-	-
6	Dionyssiou 2016	Yes [29]	-	-	-
7	Dunn 2019	Yes [30]	https://www.clinicaltrials.gov/ct2/show/NCT03825263	No	-
8	Fukushima 2017	Yes [31]	-	-	-
9	Gradalski 2015	Yes [32]	-	-	-
10	Kilmartin 2020	Yes [33]	https://www.clinicaltrials.gov/ct2/show/study/NCT01351376	Yes	-
11	Li 2017	Yes [34]	-	-	-
12	Ligabue 2019	Yes [35]	-	-	-
13	Melgaard 2016	Yes [36]	-	-	-
14	Pekyavas 2014	Yes [12]	-	-	-
15	Ridner 2013	Yes [37]	https://clinicaltrials.gov/ct2/show/study/NCT00852930?term=ridner&draw=2&rank=5	Yes	-
16	Sanal-Toprak 2019	Yes [38]	-	-	-
17	Smykla 2013	Yes [39]	-	-	-
18	Szolnoky 2009	Yes [40]	-	-	-
19	Szuba 2002	Yes [41]	-	-	-
20	Tambour 2018	Yes [42]	https://clinicaltrials.gov/ct2/show/NCT02015897	No	-

Table 2: Study pool of the benefit assessment (continued)

	Study	Available documents			
		Full publication (in professional journals)	**Registry entry**	**Results report from study registries**	**Clinical study report from manufacturer documents (not publicly available)**
21	Tantawy 2019	Yes [43]	https://www.clinicaltrials.gov/ct2/show/NCT03401086?term=Nct03401086&draw=2	No	-
22	Taradaj 2016	Yes [44]	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12613001173785	No	-
23	Tsai 2009	Yes [45]	https://clinicaltrials.gov/ct2/show/NCT00155220	No	-

Table 3: Study pool for the health economic assessment

Study	Available documents [reference]
Dionyssiou, D. et al	[29]
Melgaard, D. et al	[36]

4.2 Characteristics of the studies included in the assessment

The 23 included RCTs investigated lymphatic drainage, compression, exercise or movement therapy, diverse CDT components, Kinesio Taping, intermittent pneumatic compression, vascularized lymph node transfer, laser, acupuncture, thermotherapy, and platelet-rich plasma for the treatment of lymphoedema in a total of 1223 patients [12,14,25–46]. The specific comparisons (experimental versus comparator intervention) are found in Table 4 as well as in the HTA details listed in Table 11 of the full HTA report.

A total of 19 of the 23 studies examined only women [12,25-29,31-37,39-44]. Two studies with 65 patients had a mixed population, of which 15 participants were male [14,30]. In 2 further studies with a total of 87 patients, no data were available on the percentage of men and women. Only 7 of the 23 studies reported the average age for the entire study population [26,30,31,36,37,41,42]. In these studies, the average participant age ranged from 49.8 years [30] to 66.9 years [41]. The studies used different criteria to describe lymphoedema stage or severity. Among the included studies, 10 provided data on their total study population [14,25,26,28-31,37,38,42]. Five studies included patients in International Society of Lymphology (ISL) stage 2 [25,28-31]. Two studies included patients in ISL stages 2 and 3 [14,38], and 1 study included patients in stages 1 through 3, with only slightly under 9% of patients being in stage 1

[14]. One study each described the extent of lymphoedema in percent [26] and in mL [42]. In 20 RCTs, the underlying condition was breast cancer, and in 1 RCT each, it was trauma or inflammation [14] or a gynaecological cancer [31]. One RCT provided no detailed information [30].

Most experimental interventions were applied for a period between 10 weeks and 3 months. Four studies individually adjusted the time period to patient response, without providing more detailed information on average duration (1 study on lymphatic drainage [37], 2 studies on laser [33,37], 1 study on acupuncture [25]). A study on exercise and movement therapy [31] investigated effects directly after 15 minutes.

Two studies with potentially curative effects (1 study on surgical therapy [29] and 1 study on laser therapy [33]) as well as 1 study with the primary objective of evaluating tumour recurrence under lymphoedema therapy [34] reported effects at the end of a follow-up period. In all 3 studies, the longest follow-up time was 1 year.

4.3 Overview of patient-relevant outcomes

From 23 studies, it was possible to extract data on patient-relevant outcomes. Table 4 presents an overview of the available data on patient-relevant outcomes from the included studies. The most common cause for unusability of reported effects was that studies reported insufficient or no information on relative effects between the study groups. None of the studies reported data on the outcomes of all-cause mortality, disease-specific mortality, skin damage (e.g. fibrosis, erysipelas), or treatment failure.

Table 4: Matrix of patient-relevant outcomes

Study	**Outcomes**								
Author_year	**Swelling**	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Social functioning**	**Further outcomes**	**Adverse events[a]**
CDT component 1 (lymphatic drainage)									
MLD versus no MLD (+ co-intervention in both study groups)									
Bergmann 2014 [26][b]	●	●	-	-	●	-	-	-	-
Gradalski 2015 [32][c]	●	-	-	-	-	-	-	-	-
Tambour 2018 [42][b]	●	●	●	●	●	-	-	●	-
Ridner 2013 [37][d]	o	-	-	-	-	o	-	o	-
CDT component 2 (compression)									
Compression versus no compression (+ co-intervention in both study groups)									
Pekyavas 2014 [12][e]	o	o	o	o	-	o	-	o	●
Compression versus placebo Kinesio Taping (+ co-intervention in both study groups)									
Smykla 2013 [39][f]	●	-	-	-	-	-	-	-	o
Taradaj 2016 [44][g]	●	-	-	-	●	-	-	●	o

(continued)

Table 4: Matrix of patient-relevant outcomes (continued)

Study	Outcomes								
Author_year	**Swelling**	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Social functioning**	**Other**	**Adverse events[a]**
CDT component 3 (exercise)									
Exercise versus no exercise (+ co-intervention in both study groups)									
Chmielewska 2016 [28][h]	●	-	-	-	-	-	-	-	-
Fukushima 2017 [31][i]	●	●	●	●	-	-	-	-	-
Diverse combinations of CDT components									
Home-based programme (LD + skin care + breathing exercises + exercise, each self-administered) versus no home-based programme (+ co-intervention in both study groups)									
Buragadda 2015 [27][j]	●	●	-	-	-	-	-	●	-
Home-based programme (MLD + compression + breathing exercises + exercise, each self-administered) versus standard therapy (information brochure) (+ co-intervention in both study groups)									
Ligabue 2019 [35][k]	●	●	-	-	-	-	-	-	-
Kinesio Taping									
Kinesio Taping versus compression (+ co-intervention in both study groups)									
Melgaard 2016 [36][l]	●	-	-	-	-	-	-	-	-
Pekyavas 2014 [12][m]	o	o	o	o	-	o	-	o	●
Smykla 2013 [39][f]	●	-	-	-	-	-	-	-	o
Tantawy 2019 [43][n]	●	●	-	-	-	●	●	●	o
Taradaj 2016 [44][g]	●	-	-	-	●	-	-	●	o
Tsai 2009 [45][o]	●	-	-	●	-	-	-	●	o
Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups)									
Smykla 2013 [39][f]	●	-	-	-	-	-	-	-	o
Taradaj 2016 [44][g]	●	-	-	-	●	-	-	●	o

(continued)

Table 4: Matrix of patient-relevant outcomes (continued)

Study	Outcomes								
Author_year	**Swelling**	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Social functioning**	**Other**	**Adverse events[a]**
Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)									
Pekyavas 2014 [12][l]	o	o	o	o	-	o	-	o	●
Intermittent pneumatic compression									
IPC versus no IPC (+ co-intervention in both study groups)									
Dunn 2019 [30][p]	●	-	-	-	-	●	-	-	o
Szuba 2002 [41][q]	●	-	-	-	o	-	-	-	o
IPC versus MLD (+ co-intervention in both study groups)									
Sanal-Toprak 2019 [38][r]	●	●	●	●	●	-	-	-	-
Szolnoky 2009 [40][s]	●	-	-	-	-	-	-	●	-
Surgical procedures									
VLNT versus no VLNT (+ co-intervention in both study groups)									
Dionyssiou 2016 [29][t]	●	●	●	-	-	-	-	●	●
Laser									
Laser versus no laser (+ co-intervention in both study groups)									
Akgul 2020 [14][p]	●	-	-	●	-	●	-	●	-
Ridner 2013 [37][q]	o	-	-	-	-	o	-	o	-
Laser versus placebo laser (+ co-intervention in both study groups)									
Kilmartin 2020 [33][u]	●	●	●	-	●	-	-	●	o
Laser versus MLD (+ co-intervention in both study groups)									
Ridner 2013 [37][q]	o	-	-	-	-	o	-	o	-
Laser versus PRP (+ co-intervention in both study groups)									
Akgul 2020 [14][p]	●	-	-	●	-	●	-	●	-
Further interventions									

(continued)

Table 4: Matrix of patient-relevant outcomes (continued)

Study	Outcomes								
Author_year	**Swelling**	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Social functioning**	**Other**	**Adverse events[a]**
Acupuncture									
Acupuncture versus waiting list (no co-intervention)									
Bao 2018 [25]	●	-	-	-	-	-	-	-	o
Thermotherapy									
Thermotherapy versus compression + skin care (no co-intervention)									
Li 2017 [34]	-	-	-	-	-	-	-	-	o
PRP (platelet-rich plasma)									
PRP versus no PRP (+ co-intervention in both study groups)									
Akgul 2020 [14][p]	●	-	-	●	-	●	-	●	-

● Data were reported and were usable.
o Data were reported but unusable for the benefit assessment.
- No data were reported (no further information). / The outcome was not surveyed.
a: No serious adverse events were reported.
b: Co-intervention: compression + exercise + skin care.
c: Co-intervention: compression + exercise + breathing exercises.
d: Co-intervention: laser + compression.
e: Co-intervention: Kinesio Taping + MLD + exercise + skin care.
f: Co-intervention: MLD + IPC + skin care.
g: Co-intervention: MLD + IPC.
h: Co-intervention: IPC.
i: Co-intervention: compression.
j: Co-intervention: MLD + compression (garments) + exercise + breathing exercises.
k: Co-intervention: arm guard.
l: Co-intervention: MLD + compression (garments) + exercise + skin care.
m: Co-intervention: MLD + exercise + skin care.
n: Co-intervention: training plan.
o: Co-intervention: MLD + IPC + exercise + skin care.
p: Co-intervention: MLD + compression + exercise + skin care.
q: Co-intervention: MLD + compression.
r: Co-intervention: compression + exercise.
s: Co-intervention: 30 min MLD (in comparison, a total of 60 min MLD) + compression + exercise + skin care.
t: Co-intervention: MLD + compression (garments).
u: Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management.
IPC: intermittent pneumatic compression; KT: Kinesio Taping; MLD: manual lymphatic drainage; PRP: platelet-rich plasma; QoL: (health-related) quality of life; VLNT: vascularized lymph node transfer

4.4 Assessment of the risk of bias of the results

All included studies had a high risk of bias at study and outcome levels. In all but 4 studies, either both patients and treatment providers were unblinded [12,26,30,36,38,42,45] or no information was provided and blinding was deemed impossible based on the type of intervention [25,27-29,31,32,34,37,40,41]. Two 3-arm studies blinded patients only for the comparison of Kinesio Taping versus placebo Kinesio Taping [39,44]. In 1 study, only patients were blinded [35]. In 1 other study, patients were blinded regarding treatment in the comparator intervention groups, even if they were not blinded regarding their own therapy [14].

In 13 studies, it was unclear whether group allocation was concealed [12,26-29,31,32,34,37,38,40,41,44]. In 1 study, the authors stated that group allocation was concealed to the physician who established the diagnosis, but no information was provided as to how this was ensured [14]. In the remaining 9 studies, group allocation was concealed [25,30,33,35,36,39,42,43,45]. For detailed information on the risk of bias on the study and outcome levels, see Section A3.2.2 as well as the respective sections on the detailed results for patient-relevant outcomes (Section A3.3).

4.5 Results on patient-relevant outcomes

The literature search for the benefit assessment included 23 studies which examined MLD, compression, exercise or movement therapy, diverse CDT components, Kinesio Taping, IPC, vascularized lymph node transfer (VLNT), laser therapy, acupuncture, thermotherapy, and PRP [12,14,25-45]. No studies were found which investigated the benefit of CDT as a whole or surgical procedures other than VLNT or deep oscillation. For an overview of the comparisons investigated in each case, see Table 4.

The results section is broken down into the experimental intervention examined in each case (e.g. MLD, Kinesio Taping). For each outcome (e.g. swelling), the results of all studies with this experimental intervention are reported.

The results for the respective outcomes are additionally grouped by treatment comparison (e.g. Kinesio Taping versus compression) and – where necessary – by similar co-interventions. For the outcome of swelling, for instance, all “Kinesio Taping versus compression” results are described. Studies with different co-interventions, e.g. “training plan” instead of ”MLD + IPC” are each summarized in separate, appropriately labelled sections. Table 11 of the full HTA report describes the co-interventions in detail.

co-interventions are therapies that both study groups received. In some 3-arm studies, where the experimental intervention represented a combination of the therapies from the other 2 study groups, the comparator therapies played the role of either co-intervention or

comparator therapy, depending on the comparison. Ridner 2013 [37], for instance, investigated (i) laser + MLD, (ii) laser alone, and (iii) MLD. Compression was a co-intervention in all 3 study groups, and for consistency purposes, it was presented as such in the results tables.

For the comparison of study groups 2 and 3, laser versus MLD (each with the co-intervention of compression), laser is the experimental intervention and MLD the comparator intervention, with compression acting as the co-intervention. However, in the comparison of the combination therapy of laser + MLD (+ compression) with study group 2 (laser + compression), for instance, laser plus compression represents the co-intervention. In this case, the study groups differ only in the additional MLD (in study group 1). Except for the characterization of the study and description of interventions, the results of these study groups' results are correspondingly listed as "MLD versus no MLD".

4.5.1 CDT component 1 (lymphatic drainage)

Table 16 through Table 19 of the full HTA report present all results on the intervention of CDT component 1 (lymphatic drainage, MLD).

4.5.1.1 Swelling

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

Three studies with similar co-interventions (see above) reported results on this outcome [26,32,37,42]. All 3 studies reported on the outcome of volume difference in mL between the healthy arm and the affected arm [26,32,42]. Only 1 study reported statistically significant effects in both study groups compared with baseline, showing an improvement in favour of the intervention of MLD [26]. The other 2 studies did not report on this topic [32,42]. Statistically significant differences between the respective study groups were not found for any of the studies. Two studies reported sufficient data for conducting a metaanalysis (see Section A3.3.12); the pooled mean difference was not statistically significant, at -95.22 mL (95% CI: -205.31, 14.87, p = 0.09) [26,32].

One study also reported on the outcomes of total volume and circumference of the affected arm. No data for a comparison with baseline were available. For the comparison between the 2 study groups, no statistically significant difference was found for either outcome [42].

One study reported results on the outcome of percent volume difference as well as on the categorical outcome of grade of reduction in swelling. No data for a comparison with baseline were available. For the comparison between the 2 study groups, no statistically significant difference was found [26].

No hint of benefit was found.

Co-intervention: laser + compression (Ridner 2013 [37])

One 3-arm study compared laser + MLD versus MLD versus laser regarding the outcome of circumference difference in percent. Compared with baseline, the effects in both study groups showed a statistically significant improvement. No statistically significant difference was found for the comparison between all 3 study groups (MLD versus no MLD). No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

4.5.1.2 Pain

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

Two studies reported results on pain [26,42].

One study used the 5-level EQ-5D version (EQ-5D-5L) questionnaire for the evaluation and reported a statistically significant improvement from baseline for the comparator intervention arm but did not provide any data for the experimental intervention. For the comparison between the 2 study groups, no statistically significant difference was found [42].

The 2nd study used a visual analogue scale (VAS) for evaluating pain. No results were available regarding the relevance of the change from baseline. For the comparison between the 2 study groups, no statistically significant difference was found [26]. However, no information was available on the range and the direction of the score [26].

No hint of benefit was found.

4.5.1.3 Congestive symptoms

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

Only 1 study reported about a sense of heaviness in the arm using a numerical rating scale. No data for a comparison with baseline were available. For the comparison between the 2 relevant study groups, no statistically significant difference was found [42].

No hint of benefit was found.

4.5.1.4 Tension

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

Only 1 study reported on the outcomes of tension in the arm, tension in the shoulder, and tension in the breast based on a numeric rating scale (0 = no tension; 10 = worst imaginable tension). Compared to baseline, the effects in the arm showed a statistically significant improvement in both study groups. For tension in the breast, a statistically significant improvement was found only for the comparator intervention group; for the experimental intervention group, the effects were not statistically significant. For the outcome of tension in the shoulder, the effects compared to baseline were not statistically significant for either group. For the comparison between the two study groups, a statistically significant difference showing superiority of the experimental intervention was found for the outcome of tension. For the outcomes of tension in the arm and tension in the breast, the effects were not statistically significant [42].

No hint of benefit was found.

4.5.1.5 Mobility

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

One study reported results on mobility using the EQ-5D-5L score. No data were available for a comparison with baseline. For the comparison between the 2 study groups, no statistically significant difference was found [42]. A 2nd study reported whether mobility remained normal, improved, or remained limited before and after therapy. For the comparison between the 2 study groups, no statistically significant difference was found [26]. The 3rd study mentioned above did not report any data on the outcome of mobility.

No hint of benefit was found.

4.5.1.6 QoL

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: laser + compression (Ridner 2013 [37])

One 3-arm study investigated health-related quality of life using the Upper Limb Lymphoedema 27 (ULL-27) score. The effects compared to baseline were not statistically significant for either study group. For the comparison between all 3 study groups, no statistically significant effect was found. No data were available for comparing the 2 relevant study groups [37].

The same study additionally investigated health-related quality of life based on the Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire. For the comparison with baseline, the differences between both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

4.5.1.7 Further patient-relevant outcomes

Physical functioning

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

One study reported on physical functioning using the EQ-5D-5L domains of self-care and usual activities. No data were available regarding the relevance of the effects compared with baseline. For the comparison between the 2 study groups, no statistically significant difference was found for either outcome [42].

No hint of benefit was found.

Health

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

Only 1 study reported on current health status (VAS score). No data were available for a comparison with baseline. For the comparison between the 2 study groups, no statistically significant difference was found [42].

No hint of benefit was found.

Co-intervention: laser + compression (Ridner 2013 [37])

One 3-arm study reported on the outcome of overall symptom burden based on the Lymphedema Symptom Intensity and Distress Survey – Arm (LSIDS-A) questionnaire. Compared with baseline, the effects in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

The same study reported on the number of symptoms reported by participants. No data were available for a comparison with baseline, but the study's authors state that there were no

substantial changes. For the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

Mood

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

One study reported on anxiety using EQ-5D-5L. No data were available for a comparison with baseline. For the comparison between the 2 study groups, no statistically significant difference was found [42].

No hint of benefit was found.

Co-intervention: laser + compression (Ridner 2013 [37])

One study reported on psychological distress based on the Short Form of the Profile of Mood Scales (POMS-SF) total score as well as depressive symptoms (Center for Epidemiological Studies—Depression [CES-D] score). No data were available for a comparison with baseline for either outcome. For the comparison between all 3 study groups, no statistically significant difference was found for either outcome. No data were available for a comparison between the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

4.5.1.8 Outcomes analysed for supplementary information

MLD versus no MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise + skin care (Tambour 2018 [42] and Bergmann 2014 [26]) and compression + exercise + breathing exercises (Gradalski 2015 [32])

One study reported the number of patients rating the value of treatment as “low to moderate” versus “very high”. For the comparison between the 2 study groups, no statistically significant difference was found [26].

The same study also reported on willingness to repeat the therapy if necessary. The difference between the number of patients answering “yes” versus “no” was not statistically significant between the 2 study groups [26].

The benefit assessment disregarded these outcomes because they are not directly associated with health-related outcomes.

4.5.2 CDT component 2 (compression)

All results from the studies on compression are found in Table 21 and Table 22 of the full HTA report.

4.5.2.1 Swelling

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported arm volume in mL. Compared with baseline, the effects in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Compression versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]), IPC + MLD (Taradaj 2016 [44])

Two 3-arm studies compared percent oedema reduction. Compared with baseline, the percent volume difference (affected versus healthy arm) showed a statistically significant improvement in both study groups. For the comparison of percent oedema reduction between the 2 relevant study groups by means of variance analysis, there was a statistically significant difference showing superiority of the experimental intervention [39,44].

A hint of benefit was found.

4.5.2.2 Pain

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on this outcome based on a VAS score. Compared with baseline, the effect in the experimental intervention group was not statistically significant, while the comparator intervention group showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.2.3 Congestive symptoms

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on this outcome based on a VAS score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.2.4 Tension

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on this outcome based on a VAS score. In the experimental intervention group, the effect compared with baseline was not statistically significant, while the comparator intervention group showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.2.5 Mobility

Compression versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD (Taradaj 2016 [44])

One 3-arm study reported on this outcome using measurements of shoulder and elbow mobility in a total of 5 different directions using a goniometer. Compared to baseline, the effect for the movement directions showed a statistically significant improvement in both study groups. In the comparison between the 2 study groups, the effects for all measured movements were statistically significant, showing superiority of the experimental intervention. However, the results are associated with uncertainties: the risk of bias is high due to lack of blinding in this subjective outcome, and it is unclear whether the observed differences represent a clinically relevant advantage for patients. Particularly in subjective outcomes, it is also questionable to what extent placebo Kinesio Taping is an adequate placebo to be compared with compression.

Overall, there was no hint of benefit.

4.5.2.6 QoL

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

A 3-arm study reported on this outcome using the 36-Item Short Form Survey (SF-36) questionnaires on physical health and mental health. Compared with baseline, the experimental intervention group exhibited a statistically significant improvement in the outcome of mental health, while the effect in the comparator intervention group was not statistically significant. For the outcome of physical health, the effects compared with baseline found in the 2 study groups were not statistically significant. In the comparison between all 3 study groups, the effects were not statistically significant for either outcome. No data were available for a comparison between the 2 relevant study groups regarding either outcome [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.2.7 Further patient-relevant outcomes

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

Limitations of usual activities

One 3-arm study reported on limitations of usual activities based on a VAS score. Compared with baseline, the effect in the experimental intervention group was not statistically significant, while the comparator intervention group showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant difference was found. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Numbness

The same 2-arm study reported on numbness using a VAS score. Compared with baseline, the effect was not statistically significant in either study group. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Stiffness

The same 3-arm study reported on stiffness using a VAS score. Compared with baseline, both study groups showed a statistically significant improvement. In the comparison between all

3 study groups, the effects were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Discomfort

The same 3-arm study reported on the outcome of discomfort using a VAS score. Compared with baseline, the experimental intervention group showed no statistically significant effect, while the comparator intervention group exhibited a statistically significant improvement. The effects shown in the comparison between the 3 study groups were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Compression versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD (Taradaj 2016 [44])

Grip strength

A 3-arm study reported on the outcome of grip strength measured in Newton. Compared with baseline, both study groups showed a statistically significant improvement. In the comparison between study groups, the effects were statistically significant, showing superiority of the experimental intervention. However, the results are associated with uncertainties: The risk of bias is high due to lack of blinding regarding this subjective outcome, and it is unclear whether the observed differences represent a clinically relevant advantage for patients. Particularly in subjective outcomes, it is also questionable to what extent placebo Kinesio Taping is an adequate placebo to be compared with compression.

Overall, there was no hint of benefit.

4.5.2.8 Adverse events

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcomes of itching and treatment-related wound formation. No data were available for a comparison with baseline. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for a comparison between the 2 relevant study groups [12]. Based on IQWiG calculations, no statistically significant difference was found for the comparison between the 2 relevant study groups.

There was no hint of harm, although it must be noted that Kinesio Taping was used in both study groups.

Compression versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]), IPC + MLD (Taradaj 2016 [44])

Two 3-arm studies reported on health-related study discontinuation. In the first study, 3 patients were transferred to other hospitals due to complications unrelated to the treatment and dropped out of the study. One of these patients died of stroke. In the comparator intervention group, only 1 patient was excluded from the analyses since the study authors presumed that the patient's high body mass index (BMI) would increase the standard deviation [39]. In the second study, 1 patient discontinued therapy due to complaints during compression therapy. In the comparator intervention group, 2 patients discontinued therapy due to discomfort at the time of IPC, and 2 other patients were excluded from further participation due to viral infections. The authors did not report on any effect estimation [44].

Therefore, the reported data do not allow a benefit assessment.

4.5.2.9 Outcomes analysed for supplementary information

Compression versus no compression (+ co-intervention in both study groups)

Co-intervention: Kinesio Taping + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on patient satisfaction with nighttime treatment based on a VAS score. No data were available for a comparison with baseline. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups. IQWiG calculations for the comparison between the 2 relevant study groups demonstrated a statistically significant effect, showing superiority of the experimental intervention [12].

This outcome was disregarded in the benefit assessment because it does not directly concern health-related outcomes.

4.5.3 CDT component 3 (exercise or movement therapy)

All results from the studies on exercise and movement therapy are found in Table 24 of the full HTA report. This component was referred to briefly as "exercise", without differentiating between exercise, physical therapy, or other therapeutic exercises. Table 11 of the full HTA report describes the interventions in detail.

4.5.3.1 Swelling

Exercise versus no exercise (+ co-intervention in both study groups)

Co-intervention: compression (Fukushima 2017 [31])

A 3-arm randomized cross-over study reported results on the outcome of volume difference before and after the intervention, in each case comparing high-load exercise + compression versus low-load exercise + compression versus compression-only therapy. Compared to

baseline, all 3 study groups showed a statistically significant improvement. For the comparison of (low-load) exercise + compression versus compression-only therapy, the effects were not statistically significant. For the comparison of (high-load) exercise + compression versus compression-only therapy, the difference was statistically significant [31].

No hint of benefit was found.

Co-intervention: IPC (Chmielewska 2016 [28])

One study reported results on circumference in 11 different locations at the upper limb (base of phalanx proximalis, metacarpophalangeal joint, wrist, 5 cm proximal to wrist, lateral epicondyle, 10 cm distal to lateral epicondyle, 10 cm proximal to lateral epicondyle, axillary line). Compared with baseline, the effects in the experimental intervention group were statistically significant only at the base of the 3rd finger as well as 10 cm distal to and 10 cm proximal to the lateral epicondyle. For the comparator intervention, the changes from baseline were statistically significant for all locations except the base of the 1st, 3rd, and 4th phalanx, metacarpophalageal articulation as well as 10 cm distal to the lateral epicondyle [28].

No data were available for the comparison between the 2 study groups. IQWiG calculations showed no significant difference in the comparison between the 2 study groups at any location [28].

No hint of benefit was found.

4.5.3.2 Pain

Exercise versus no exercise (+ co-intervention in both study groups)

Co-intervention: compression (Fukushima 2017 [31])

A 3-arm randomized cross-over study reported results on the outcome of pain based on the change in a VAS score before and after the intervention, comparing high-load exercise + compression versus low-load exercise + compression versus compression-only therapy. Compared to baseline, all 3 study groups showed a statistically significant improvement. No statistically significant differences were found for the comparison between the 2 study groups of (low-load) exercise + compression versus compression or for the comparison of (high-load) exercise + compression versus compression-only therapy [31].

There were no hints of benefit.

4.5.3.3 Congestive symptoms

Exercise versus no exercise (+ co-intervention in both study groups)

Co-intervention: compression (Fukushima 2017 [31])

One 3-arm, randomized cross-over study reported results on the outcome of feeling of heaviness based on a VAS score before and after the intervention, comparing high-load exercise + compression versus low-load exercise + compression versus compression-only therapy. Compared to baseline, all 3 study groups showed a statistically significant improvement. No statistically significant differences were found in the comparison between the study groups of (low-load) exercise + compression versus compression-only therapy or for the comparison of (high-load) exercise + compression versus compression-only therapy [31].

No hint of benefit was found.

4.5.3.4 Tension

Exercise versus no exercise (+ co-intervention in both study groups)

Co-intervention: compression (Fukushima 2017 [31])

One 3-arm randomized cross-over study reported results on the outcome of skin elasticity before and after the intervention. In all 3 study groups, the effects compared to baseline were not statistically significant. No statistically significant differences were found for the comparison between the study groups of (low-load) exercise + compression versus compression-only therapy or for the comparison of (high-load) exercise + compression versus compression-only therapy [31].

No hint of benefit was found.

4.5.4 Diverse combinations of CDT components

This section reports on the results of studies which compared different combinations of CDT components. All results from the studies on the diverse combinations are found in Table 26 and Table 27 of the full HTA report.

4.5.4.1 Swelling

Home-based programme (LD + skin care + breathing exercises + exercise, each in self-application, following conventional therapy) versus no home-based programme (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + breathing exercises (Buragadda 2015 [27])

One study investigated this outcome based on arm volume in cm^3. No data were available for a comparison with baseline. For the comparison of effects between study groups, there was a statistically significant difference showing superiority of the experimental intervention [27].

The same study investigated this outcome based on measured circumference (in cm) at 5 different locations on the arm (wrist, middle forearm, elbow, middle arm, axial line) after 6 weeks. The study's reporting is slightly unclear. On the one hand, the authors report that a comparison between study groups revealed significant improvements in circumference. However, they then specifically state that the proximal arm circumference was significantly reduced post-test when compared with the pre-test value. This raises the question whether the authors actually meant pre-therapy and post-therapy [27]. Based on IQWiG calculations, the differences between the study groups were statistically significant at all measuring points, showing superiority of the experimental intervention.

A hint of greater benefit was found.

Home-based programme (MLD + compression (tape) + breathing exercises + exercise, each self-applied following conventional therapy) versus standard therapy (information brochure) (+ co-intervention in both study groups)

Co-intervention: arm guard (Ligabue 2019 [35])

One study investigated this outcome based on volume difference in the arm as well as the hand, each in percent. Compared to baseline, the effects for both outcomes in the experimental intervention group showed a statistically significant improvement. Compared with baseline, the effects for both outcomes were not statistically significant for the comparator intervention group. The comparison of effects between both study groups showed no statistically significant difference for either outcome [35].

The same study also reports the change in arm circumference in cm for this outcome. Compared to baseline, the effects in both study groups were not statistically significant. In the comparison between the 2 study groups, no statistically significant difference was found [35].

The study additionally reported the percentage of patients who exhibited a change in volume difference between arms as well as between hands, each based on a minimal clinically important difference (MCID) of 5%. For this purpose, patients were categorized in 3 study groups, "stable", "worse", and "better". For the comparison between the 2 study groups, a statistically significant difference showing superiority of the experimental intervention was found for the outcome of changes in arm volume difference. In the comparison between the 2 study groups, no statistically significant difference was found for the outcome of changes in hand volume difference [35].

No hint of benefit was found.

4.5.4.2 Pain

Home-based programme (LD + skin care + breathing exercises + exercise, each in self-application, following conventional therapy) versus no home-based programme (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + breathing exercises (Buragadda 2015 [27])

One study investigated pain using a VAS score. No data were available for a comparison with baseline. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [27].

A hint of greater benefit was found.

Home-based programme (MLD + compression (tape) + breathing exercises + exercise, each self-applied following conventional therapy) versus standard therapy (information brochure) (+ co-intervention in both study groups)

Co-intervention: arm guard (Ligabue 2019 [35])

One study investigated this outcome based on a numerical rating scale. Compared with baseline, the effects in the experimental intervention group showed a statistically significant improvement. Compared with baseline, the effects for the comparator intervention were not statistically significant. In the comparison between the study groups, there was a statistically significant difference showing superiority of the experimental intervention [35].

A hint of benefit was found.

4.5.4.3 Further patient-relevant outcomes

Physical functioning

Home-based programme (LD + skin care + breathing exercises + exercise, each in self-application, following conventional therapy) versus no home-based programme (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + breathing exercises (Buragadda 2015 [27])

One study investigated functional limitations in the shoulder, arm, and hand based on the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire. No data were available for a comparison with baseline. In the comparison between the study groups, the effects were statistically significant, showing superiority of the experimental intervention [27].

A hint of greater benefit was found.

4.5.5 Kinesio Taping

All results from the studies on Kinesio Taping are found in Table 29 and Table 30 of the full HTA report.

4.5.5.1 Swelling

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported on this outcome using the sum of arm circumferences in cm. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [43].

A hint of greater benefit was found.

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One study reported on this outcome using arm volume difference in mL. Compared with the values at the end of a 1-month control period without therapy, the effect in the experimental intervention group was not statistically significant, while the effect in the comparator intervention group showed a statistically significant effect improvement. For the comparison between the 2 study groups, the study's authors compared only the difference between changes during the control period (without therapy) and the changes under therapy (after the control period); no statistically significant difference was found [45]. Based on IQWiG calculations, the comparison between the 2 study groups showed no statistically significant difference.

Another 3-arm study reported on this outcome using the volume of the affected arm in cm3. Compared with baseline, the effects in both study groups showed a statistically significant improvement. The difference between study groups was reported using percent reduction in the volume of the upper limb, but the reported values were not quite plausible. In the comparison between the 2 relevant study groups, there was a statistically significant difference showing superiority of the experimental intervention arm [44].

Another 3-arm study compared percent oedema reduction. Compared with baseline, the percent volume difference (between affected and healthy arm) showed a statistically significant improvement in both relevant study groups. In comparison of percent oedema reduction between both relevant study groups using variance analysis, there was a statistically significant difference showing superiority of the comparator intervention [39].

There was a hint of lesser benefit.

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported arm volume in mL. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping 2 x weekly versus compression (tape) 4 x weekly (+ co-intervention in both study groups)

Co-intervention: compression (garments) + MLD + exercise + skin care (Melgaard 2016 [36])

One study reported on this outcome, measuring circumference in cm at 7 different locations of the affected arm (metacarpophalangeal joint, wrist, wrist + 8 cm and + 15 cm, elbow, elbow + 10 cm, deltoid). Compared with baseline, statistically significant differences were found only for the experimental intervention group and, within it, only for the measurement at the metacarpophalageal joint and at elbow + 10 cm. For all other measuring sites and all measurements in the comparator intervention group, effects compared with baseline were not statistically significant. No data were available for a comparison between the 2 study groups [36]. Based on IQWiG calculations, no statistically significant differences between the study groups were found for any of the measuring sites.

No hint of benefit was found.

Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]) and IPC + MLD (Taradaj 2016 [44])

One study reported on this outcome based on the volume of the affected arm in cm3. Compared with baseline, the effects in both study groups were statistically significant showing improvement. The difference between study groups was reported using percent reduction in the volume of the upper limb, but the reported values were not entirely plausible. In the comparison between study groups, no statistically significant difference was found [44].

The second 3-arm study compared percent oedema reduction. Compared with baseline, the percent volume difference (between affected and healthy arm) showed a statistically significant improvement in both study groups. The comparison of percent oedema reduction between both relevant study groups using variance analysis showed no statistically significant difference [39].

No hint of benefit was found.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported arm volume in mL. Both study groups exhibited a statistically significant volume change compared with baseline. For the comparison between all 3 study groups, the difference was not statistically significant. No data are available for the comparison between the relevant study groups at the end of the intervention [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.2 Pain

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported on this outcome based on the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Cancer 30 (QLQ-C30) pain scale. In comparison with baseline, the effects were statistically significant showing improvement in the experimental intervention group, while they were not statistically significant in the comparator intervention group. In the comparison between the 2 study groups, there was a statistically significant effect showing superiority of the experimental intervention [43].

A hint of greater benefit was found.

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on pain measured with a VAS score. Compared with baseline, a statistically significant improvement was found for the experimental intervention group. For the comparator intervention group, the change from baseline was not statistically significant. In the comparison between all 3 study groups, the differences were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on pain measured with a VAS score. Compared with baseline, no statistically significant difference was found for either study group. In the comparison between all 3 study groups, the differences were not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.3 Congestive symptoms

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on heaviness based on a VAS score. Compared with baseline, the changes in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One study reported on heaviness using a VAS score. Compared with baseline, the changes in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.4 Tension

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One study reported on tension based on a VAS score. Compared to the end of the control period (after 1 month without therapy), the effects in both study groups showed a statistically significant improvement. For the comparison between the 2 study groups, no statistically significant difference was found [45].

No hint of benefit was found.

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on tension based on a VAS score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on tension based on a VAS score. Compared with baseline, no statistically significant effect was found in the experimental intervention group, while the comparator intervention group showed a statistically significant improvement. For the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.5 Mobility

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One 3-arm study reported on this outcome, measuring shoulder mobility based on flexion, abduction, horizontal flexion, horizontal extension as well as elbow flexion. Compared with baseline, the effects for all outcomes in both study groups showed a statistically significant improvement. In the comparison between the 2 relevant study groups, the study found statistically significant differences showing superiority of the experimental intervention at all measuring sites [44].

There was a hint of lesser benefit.

Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]) and IPC + MLD (Taradaj 2016 [44])

One study reported on this outcome, measuring shoulder mobility based on flexion, abduction, horizontal flexion, horizontal extension as well as elbow flexion. Compared with baseline, statistically significant improvement was found for all outcomes in both study groups. For the comparison between the 2 relevant study groups, there were no statistically significant differences for any of the measuring sites [44].

No hint of benefit was found.

4.5.5.6 QoL

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported on this outcome using the EORTC QLQ-C30. Compared with baseline, statistically significant improvement was found in both study groups. In the comparison

between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [43].

A hint of greater benefit was found.

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on health-related quality of life with regard to physical health (SF-36.p) and mental health (SF-36.m). Compared with the baseline values, statistically significant improvement was found only for the outcome of SF-36.m in the comparator intervention group, while no statistically significant effects were found in the experimental intervention group or for the outcome of SF-36.p in either study group. In the comparison between all 3 study groups, the difference was not statistically significant for either outcome. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One study reported on health-related quality of life with regard to physical health (SF-36.p) and mental health (SF-36.m). Compared with baseline, a statistically significant improvement was found in both study groups for the outcome of SF-36.m, while no statistically significant effect was found in either study group for the outcome of SF-36. No results were available for comparing the therapies at the end of the intervention, but for the comparison between all 3 study groups, the difference was not statistically significant for either outcome [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.7 Level of social functioning

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported results on this outcome based on the domain in the EORTC QLQ-C30 questionnaire. Compared with baseline, a statistically significant improvement was found for both study groups. For the comparison between the 2 study groups, no statistically significant differences were found [43].

No hint of benefit was found.

4.5.5.8 Further patient-relevant outcomes

Shoulder pain and disability

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported on the Shoulder Pain and Disability Index (SPADI). Compared with baseline, a statistically significant improvement was found for the experimental intervention group, while no statistically significant effect was found for the comparator intervention group. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [43].

A hint of greater benefit was found.

Activities of daily living

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on limitations of activities of daily living based on a VAS score. Compared with baseline, the experimental intervention group exhibited statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. No results were available for comparing the therapies at the end of the intervention. However, the difference between the 3 study groups was not statistically significant. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on limitations of activities of daily living based on a VAS score. Compared with baseline, the effects in both study groups were not statistically significant. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Grip strength

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: training plan (Tantawy 2019 [43])

One study reported on this outcome based on grip strength in kg. Compared with baseline, a statistically significant improvement was found in the experimental intervention group, while

no statistically significant effect was found in the experimental intervention group. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [43].

A hint of greater benefit was found.

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One 3-arm study investigated grip strength in Newton. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 relevant study groups, there was a statistically significant difference showing superiority of the comparator intervention [44].

There was a hint of lesser benefit.

Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]) and IPC + MLD (Taradaj 2016 [44])

One 3-arm study investigated grip strength in Newton. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 relevant study groups, the differences were not statistically significant [44].

No hint of benefit was found.

Discomfort / feeling of fullness

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One study reported on a feeling of fullness and discomfort using a VAS score. For both outcomes, a statistically significant improvement was found in comparison with the values at the end of a 1-month control period without therapy. For the comparison between the 2 study groups, the study's authors compared only the difference between changes during the control period (without therapy) and changes under therapy (after the control period); no statistically significant difference was found [45]. Based on IQWiG calculations for the comparison between the 2 study groups, no statistically significant difference was found.

Discomfort/inconvenience seems to have been measured again in a further patient survey using a VAS score for rating bandages and/or Kinesio Taping; in this case, the differences were statistically significant [45].

No hint of benefit was found for feeling of fullness or discomfort.

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of discomfort using a VAS scale. Compared with baseline, the effects in both study groups showed a statistically significant improvement. For the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of discomfort using a VAS scale. Compared with baseline, the experimental intervention group showed no statistically significant effect, while the comparator intervention group exhibited a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Numbness

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of numbness using a VAS scale. Compared with baseline, the effects in both study groups were not statistically significant. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of numbness based on a VAS scale. In the comparison with baseline, the effects in the 2 study groups were not statistically significant. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Stiffness

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of stiffness using a VAS scale. Compared with baseline, the experimental intervention group exhibited statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of stiffness based on a VAS scale. Compared with baseline, the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12].

Therefore, the reported data do not allow a benefit assessment.

4.5.5.9 Adverse events

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: Training plan (Tantawy 2019 [43])

One study reported 7 dropouts – 3 in the experimental intervention group, of which 1 did not regularly come in and 2 without specific reasons as well as 4 in the comparator intervention group, 1 due to discomfort, 1 due to a health problem, and 2 for personal reasons [43].

No harm assessment is possible based on the reported data.

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One study reported on itching and on wounds forming from the wearing of Kinesio Tape and/or bandages. In the comparison between the 2 study groups, no statistically significant difference was found for the outcome of itching. In the comparison between the 2 study groups regarding the outcome of number of wounds forming due to bandages or Kinesio Tape, a statistically significant difference was found, showing inferiority of the experimental intervention [45]. Regarding the frequency of itching and the number of wounds, it is unclear what exactly was recorded. The text states that more wounds formed in the Kinesio Taping

group, suggesting that the number of wounds was analysed in relation to the number of patients, but this would have required the analyses to take into account the associated cluster formation.

Therefore, the reported data do not allow assessing harm.

One 3-arm study reported on study discontinuation for health reasons. In the experimental intervention group, 6 patients discontinued therapy due to inflammatory skin reactions under Kinesio Taping, and 1 patient was excluded due to myocardial infarction. In the comparator intervention group, 1 patient discontinued therapy due to discomfort and poor tolerance of compression therapy. No systematic data were available on adverse events [44].

Therefore, the reported data do not allow assessing harm.

One study reported the reasons for study discontinuation. In the experimental intervention group, health reasons for discontinuation included allergic skin reaction in 4 of 26 patients, and 1 woman had a myocardial infarction. In the comparator intervention group, only 1 patient was excluded from the analyses because the study's authors presumed that the patient's high BMI would increase the standard deviation. Systematic data on adverse events were missing [39].

Therefore, the reported data do not allow assessing harm.

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on itching and wound formation, using a VAS score for each. No data were available for the comparison between the 2 relevant study groups [12]. IQWiG calculations comparing the 2 study groups found no statistically significant difference for either outcome.

There was no hint of harm.

Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: IPC + MLD + skin care (Smykla 2013 [39]) and IPC + MLD (Taradaj 2016 [44])

One 3-arm study reported on study discontinuation for health reasons (also see comparison of Kinesio Taping versus compression). In the experimental intervention group, 6 patients discontinued therapy due to inflammatory skin reactions under Kinesio Taping, and 1 patient was excluded due to myocardial infarction. In the comparator intervention group, 2 patients discontinued therapy due to discomfort at the time of IPC, and 2 other patients were excluded from further participation due to viral infections. The authors did not report any relative effects [44].

One 3-arm study reported on the reasons for study discontinuation (also see comparison of Kinesio Taping versus compression). In the experimental intervention group, health reasons for discontinuation included allergic skin reaction in 4 of 26 patients , and 1 woman had a myocardial infarction. In the comparator intervention group, 1 patient was excluded from the analysis due to high BMI. No systematic data were available on adverse events [39].

Therefore, the reported data do not allow assessing harm.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One study reported on itching and wound formation, using a VAS score for each. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [12]. IQWiG calculations comparing the 2 study groups found no statistically significant difference for either outcome.

There was no hint of harm.

4.5.5.10 Outcomes analysed for supplementary information

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + IPC (Taradaj 2016 [44]), MLD + IPC + skin care (Smykla 2013 [39]), MLD + IPC + exercise + skin care (Tsai 2009 [45])

One study investigated duration of use, during the day and during the night, each measured in hours, as well as the difficulty and inconvenience of bandage use. No data were available for a comparison with baseline. In the comparison between the two study groups, a statistically significant difference showing longer use of the experimental intervention was found for the duration of daytime use. In the comparison between the 2 study groups regarding the outcome of “nighttime use”, no statistically significant difference was found [45].

With regard to difficulty and inconvenience of use, statistically significant differences between the 2 study groups were found, showing superiority of the experimental intervention [45].

Since these outcomes are not directly health-relevant, they were disregarded in the benefit assessment.

Kinesio Taping versus compression (+ co-intervention in both study groups)

Co-intervention: MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of patient satisfaction with nighttime treatment using a VAS score. No data were available for a comparison with baseline. In the comparison between all 3 study groups, no statistically significant differences were found. No data were

available for comparing the 2 relevant study groups [12]. IQWiG calculations for the comparison between the 2 study groups found no statistically significant difference.

Since the outcome of patient satisfaction is not directly health-relevant, it was disregarded in the benefit assessment.

Kinesio Taping versus no Kinesio Taping (+ co-intervention in both study groups)

Co-intervention: compression + MLD + exercise + skin care (Pekyavas 2014 [12])

One 3-arm study reported on the outcome of patient satisfaction with regard to nighttime treatment using a VAS score. No data were available for a comparison with baseline. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [12]. IQWiG calculations for the comparison between the 2 study groups found no statistically significant difference.

Since the outcome of patient satisfaction is not directly health-relevant, it was disregarded in the benefit assessment.

4.5.6 Intermittent pneumatic compression

All results from the studies on intermittent pneumatic compression are found in Table 32 and Table 33 of the full HTA report.

4.5.6.1 Swelling

IPC versus no IPC (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Dunn 2019 [30]) and MLD + compression (Szuba 2002 [41])

One study reported on this outcome based on percent volume reduction. No data were available for comparison with baseline. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [41].

Another study investigated the outcome using volume reduction in mL. In the comparison with baseline, the statistical relevance of effects was not reported. In the comparison between study groups, no statistically significant difference was found [30].

No hint of benefit was found.

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise (Sanal-Toprak 2019 [38])

One study reported on circumference differences in cm at 5 different measuring sites of the upper limb (metacarpophalangeal joint, wrist, 15 cm distal to medial epicondyle, medial

epicondyle, and 15 cm proximal to medial epicondyle). Compared to baseline, statistically significant improvement was found for each measuring site in both study groups. In the comparison between the 2 study groups, none of the effects were statistically significant [38].

No hint of benefit was found.

Co-intervention: MLD + compression + exercise + skin care (Szolnoky 2009 [40])

One study compared IPC versus 30-minute MLD. In both study groups, patients received said co-interventions including 30-minute MLD, meaning that patients in the comparator intervention arm received complete CDT treatment including 60 minutes of MLD. Regarding this outcome, the study reported volume reduction in mL or percent volume for the comparison between the 2 study groups. Compared with baseline, a statistically significant improvement was found for both study groups. For the comparison between the 2 study groups, there was a statistically significant difference showing superiority of IPC compared with (longer) MLD [40].

A hint of benefit was found.

4.5.6.2 Pain

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise (Sanal-Toprak 2019 [38])

One study reported results on shoulder pain based on a VAS score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, none of the differences were statistically significant [38].

No hint of benefit was found.

4.5.6.3 Congestive symptoms

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise (Sanal-Toprak 2019 [38])

One study reported on heaviness using a VAS score. In the comparison with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, the difference was not statistically significant [38].

No hint of benefit was found.

4.5.6.4 Tension

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise (Sanal-Toprak 2019 [38])

One study reported on a feeling of tension using a VAS score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, no statistically significant difference was found [38].

No hint of benefit was found.

4.5.6.5 Mobility

IPC versus no IPC (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Dunn 2019 [30]) and MLD + compression (Szuba 2002 [41])

One study investigated the range of motion of the shoulder, elbow, wrist as well as forearm supination in patients who had limited mobility at baseline. Compared with baseline, the mobility of the total population, i.e. of both study groups analysed jointly, improved in a statistically significantly manner. According to the study's authors, both study groups were combined since the comparator intervention group included very few patients with limited mobility at baseline. No separate data for each study group were available for conducting a comparison with baseline or with each other [41].

Assessing benefit is not possible based on the reported data.

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: compression + exercise (Sanal-Toprak 2019 [38])

One study reported on shoulder range of motion measured in degrees (abduction, adduction, flexion, extension as well as internal and external rotation). Compared with baseline, statistically significant improvements were found, except for extension and internal rotation in the experimental intervention group and internal and external rotation in the comparator intervention group. For the comparison between the 2 study groups, the authors did not explicitly report differences, but their general conclusion regarding the comparison between the 2 therapies states that neither was superior to the other [38]. Based on IQWiG calculations, the differences between the 2 study groups were not statistically significant.

No hint of benefit was found.

4.5.6.6 QoL

IPC versus no IPC (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Dunn 2019 [30]) and MLD + compression (Szuba 2002 [41])

One study reported on this outcome using the Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) questionnaire. No data were available for a comparison with baseline. In the comparison between the 2 study groups, the differences were not statistically significant [30].

No hint of benefit was found.

4.5.6.7 Further patient-relevant outcomes

Reduction of lymphoedema-associated subjective symptoms

IPC versus MLD (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Szolnoky 2009 [40])

One study reported on the reduction of lymphoedema-associated subjective symptoms using a score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, no statistically significant difference was found [40]. No data were available on point estimators and confidence intervals.

No hint of benefit was found.

4.5.6.8 Adverse events

IPC versus no IPC (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Dunn 2019 [30]) and MLD + compression (Szuba 2002 [41])

One study reported that a patient in the comparator intervention group repeatedly suffered from headache and hypertension [41]. This likely applies to the period after study completion, when all participants were offered the option of using IPC at home.

The second study reported that 1 patient dropped out of the study because IPC was too unpleasant. In the control intervention arm, 3 patients dropped out of the study without reported reasons [30].

Assessing harm is not possible based on the reported data.

4.5.6.9 Outcomes analysed for supplementary information

IPC versus no IPC (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Dunn 2019 [30]) and MLD + compression (Szuba 2002 [41])

One study additionally investigated the user friendliness rating of IPC. At a maximum of 60 points, the mean equalled 58, with 1 patient (of 10) dropping out of the study group early because IPC was too uncomfortable [30].

Since this outcome is not directly health-relevant, it was disregarded in the benefit assessment.

4.5.7 Surgical procedures

Only 1 study investigated a surgical procedure, specifically VLNT. All results from the studies on VLNT are found in Table 35 of the full HTA report.

4.5.7.1 Swelling

VLNT versus no VLNT (+ co-intervention in both study groups)

Co-intervention: MLD + compression (garments) (Dionyssiou 2016 [29])

One study investigated percent volume difference between affected and healthy limb in VLNT as an add-on to the co-interventions in comparison with the co-interventions alone. The co-interventions were carried out for 6 months; both study groups had no further therapy in the subsequent follow-up period. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, there was a statistically significant difference showing superiority of the experimental intervention [29].

A hint of greater benefit was found.

4.5.7.2 Pain

VLNT versus no VLNT (+ co-intervention in both study groups)

Co-intervention: MLD + compression (garments) (Dionyssiou 2016 [29])

One study investigated the outcome of pain using a VAS scale. Compared with baseline, the experimental intervention group exhibited statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. In the comparison between the 2 study groups, statistically significant effects showing superiority of the experimental intervention were found [29].

A hint of greater benefit was found.

4.5.7.3 Congestive symptoms

VLNT versus no VLNT (+ co-intervention in both study groups)

Co-intervention: MLD + compression (garments) (Dionyssiou 2016 [29])

One study investigated the outcome of congestion symptoms using a VAS scale. In the comparison with baseline, the experimental intervention group showed a statistically significant improvement, whereas the effect was not statistically significant in the comparator intervention group. In the comparison between the 2 study groups, statistically significant effects showing superiority of the experimental intervention were found [29].

A hint of greater benefit was found.

4.5.7.4 Further patient-relevant outcomes

Physical functioning

VLNT versus no VLNT (+ co-intervention in both study groups)

Co-intervention: MLD + compression (garments) (Dionyssiou 2016 [29])

One study investigated the outcome of limb functioning based on a VAS scale. Compared with baseline, the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. In the comparison between the 2 study groups, statistically significant effects showing superiority of the experimental intervention were found [29].

A hint of greater benefit was found.

4.5.7.5 Adverse events

VLNT versus no VLNT (+ co-intervention in both study groups)

Co-intervention: MLD + compression (garments) (Dionyssiou 2016 [29])

One study reported on infection rates. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between the 2 study groups, statistically significant effects showing superiority of the experimental intervention were found [29].

A hint of greater benefit or lesser harm was found.

4.5.8 Laser

All results from the studies on laser treatment are found in Table 37 through Table 39 of the full HTA report.

4.5.8.1 Swelling

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One 3-arm study compared laser + MLD versus MLD versus laser regarding the outcome of circumference difference in percent. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

Assessing benefit is not possible based on the reported data.

Another 3-arm study compared laser + co-intervention versus PRP + co-intervention versus co-intervention alone and reported on the circumference difference of the lower limb in mL. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the 2 study groups were not statistically significant.

No hint of benefit was found.

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study investigated this outcome based on the percentage of patients with a volume difference of at least 5%. This cutoff served to define lymphoedema. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus the end of the follow-up period, the effects in the 2 study groups were likely not statistically significant. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we expect that it is in fact a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations comparing the 2 study groups found no statistically significant difference for either time point.

No hint of benefit was found.

Laser versus MLD (+ co-intervention in both study groups)

Co-intervention: compression (Ridner 2013 [37])

One 3-arm study compared laser + MLD versus MLD versus laser and reported on this outcome using between-arm difference in circumference in percent. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for a comparison between the 2 relevant study groups [37].

Assessing benefit is not possible based on the reported data.

Laser versus PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14])

Another 3-arm study compared laser + co-intervention versus PRP + co-intervention versus co-intervention alone, reporting on the circumference difference in the lower limb in mL. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the difference was not statistically significant. No data were available for comparing the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the 2 study groups were not statistically significant.

No hint of benefit was found.

4.5.8.2 Pain

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study compared pain/discomfort between the affected and healthy limbs [33]. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus the end of the follow-up period, the effects in the 2 study groups were likely not statistically significant. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we expect that it is in fact a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations found no statistically significant difference between the study groups at the end of the follow-up period.

No hint of benefit was found.

4.5.8.3 Congestive symptoms

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study investigated fluid accumulation using a Likert scale, comparing the affected versus the healthy limb and defining a difference of ≥ 2 cm as fluid accumulation. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus the end of the follow-up period, the effects in the 2 study groups were likely not statistically significant. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we presume that it is, in fact, a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations found no statistically significant difference between the study groups at the end of therapy and at the end of the follow-up period.

No hint of benefit was found.

4.5.8.4 Tension

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One 3-arm study reported on the outcome of tension using a numeric rating scale. Compared with baseline, statistically significant improvements were found in both study groups. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. IQWiG calculations comparing the 2 study groups found no statistically significant differences.

No hint of benefit was found.

Laser versus PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14])

One 3-arm study reported on the outcome of tension using a numeric rating scale. Compared with baseline, statistically significant improvements were found in both study groups. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. IQWiG calculations comparing the 2 study groups found no statistically significant differences.

No hint of benefit was found.

4.5.8.5 Mobility

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study investigated mobility limitations based on the percentage of patients who reported 2 or more symptoms of limited limb mobility. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus the end of the follow-up period, the effect in the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we expect that it is in fact a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations found no statistically significant difference between the study groups at the end of therapy and at the end of the follow-up period.

No hint of benefit was found.

4.5.8.6 QoL

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One 3-arm study investigated health-related quality of life using the ULL-27 score. The effects compared to baseline were not statistically significant for either study group. In the comparison between all 3 study groups, no statistically significant effect was found. No data were available for comparing the 2 relevant study groups [37].

The same study additionally investigated health-related quality of life using the FACT-B questionnaire. In the comparison with baseline, the differences between both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for comparing the 2 relevant study groups [37].

Therefore, the data reported in this study do not allow a benefit assessment.

Another 3-arm study investigated the outcome of health-related quality of life using the Lymphoedema Quality of Life (LYMQOL) questionnaire. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the effects in the 2 study groups were not statistically significant.

No hint of benefit was found.

Laser versus MLD (+ co-intervention in both study groups)

Co-intervention: compression (Ridner 2013 [37])

One 3-arm study investigated health-related quality of life using the ULL-27 score. The effects compared to baseline were not statistically significant for either study group. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

The same study additionally investigated health-related quality of life using the FACT-B questionnaire. In the comparison with baseline, the differences between both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, the effects were not statistically significant. No data were available for comparing the 2 relevant study groups [37].

Therefore, the data reported in this study do not allow a benefit assessment.

Laser versus PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14])

Another 3-arm study investigated the outcome of health-related quality of life using the LYMQOL questionnaire. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the effects in the 2 study groups were not statistically significant.

No hint of benefit was found.

4.5.8.7 Further patient-relevant outcomes

Health

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One 3-arm study reported on the outcome of overall symptom burden based on the LSIDS-A questionnaire. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

The same study reported on the number of symptoms reported by participants. No data were available for a comparison with baseline, but the study's authors state that there were no substantial changes. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study investigated the number of reported lymphoedema symptoms using the breast cancer and lymphedema symptom experience index (BCLE-SEI) questionnaire. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus the end of the follow-up period, the effect in the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we expect that it is in fact a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations found no statistically significant difference between the study groups at the end of therapy and at the end of the follow-up period.

No hint of benefit was found.

Laser versus MLD (+ co-intervention in both study groups)

Co-intervention: compression (Ridner 2013 [37])

One 3-arm study reported on the outcome of overall symptom burden using the LSIDS-A questionnaire. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

The same study reported on the number of symptoms reported by participants. No data were available for a comparison with baseline, but the study's authors state that there were no substantial changes. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

Walking distance

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One 3-arm study investigated the 6-minute walking test (walking distance in meters). Compared with baseline, the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. No data were available for a comparison between all 3 study groups or for a comparison between the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the study groups were not statistically significant.

No hint of benefit was found.

Laser versus PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14])

One 3-arm study investigated the 6-minute walking test (walking distance in meters). Compared with baseline, the experimental intervention group showed a statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. No data were available for a comparison between all 3 study groups or for a comparison between the 2 relevant study groups [14]. Based on IQWiG calculations, the differences between the study groups were not statistically significant.

No hint of benefit was found.

Mood

Laser versus no laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14]) and MLD + compression (Ridner 2013 [37])

One study investigated psychological suffering based on the POMS-SF total score as well as the CES-D score. No data for a comparison with baseline were available for either outcome. In the comparison between all 3 study groups, no statistically significant difference was found for either outcome. No data were available for the comparison between the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

The same study also investigated mood (sadness) as well as self-image using the BLCE-SEI questionnaire. Regarding both outcomes, data for conducting a comparison between baseline and the time point after the end of therapy were missing. Compared with baseline, the experimental intervention group showed a statistically significant improvement at the end of the follow-up period, whereas the effect in the comparator intervention group was not statistically significant. In the body of text, the authors of the study used said p-values, but the reporting is ambiguous since authors did so, depending on the outcome, not only for comparisons with baseline, but also for assessing the differences between both study groups. Given the manner in which it is presented, the comparison is presumably with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. Based on IQWiG calculations, no statistically significant difference was found between study groups at the end of therapy versus at the end of the follow-up period for either outcome.

No hint of benefit was found.

Laser versus MLD (+ co-intervention in both study groups)

Co-intervention: compression (Ridner 2013 [37])

One study investigated psychological suffering using the POMS-SF total score as well as the CES-D score. No data for a comparison with baseline were available for either outcome. In the comparison between all 3 study groups, no statistically significant difference was found for either outcome. No data were available for comparing the 2 relevant study groups [37].

Therefore, the reported data do not allow a benefit assessment.

4.5.8.8 Adverse events

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

One study reported on this outcome. In the experimental intervention group, 1 person discontinued therapy due to skin problems at the trunk, and 1 patient left the country after completing therapy. The comparator intervention group had 4 dropouts: 1 patient discontinued therapy due to surgery, 1 patient dropped out due to wrist fracture after completion of therapy, and 2 patients missed the final follow-up visit [33]. No data were available for a comparison between the 2 study groups.

Therefore, the reported data do not allow a benefit assessment.

4.5.8.9 Outcomes analysed for supplementary information

Laser versus placebo laser (+ co-intervention in both study groups)

Co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management (Kilmartin 2020 [33])

Furthermore, the study reported the percentage of patients adhering to CDT therapy. No data were available for comparing baseline versus the time point after the end of therapy. In the comparison of baseline versus end of follow-up period, the effect in the experimental intervention group was not statistically significant, whereas the comparator intervention group showed statistically significant deterioration. However, this is unclear because in the body of their text, the study's authors used these p-values for evaluating effects compared with baseline in some outcomes, but for evaluating differences between the 2 study groups in other outcomes. Based on the presentation in the tables, however, we expect that it is in fact a comparison with baseline. Due to the ambiguous reporting, it is unclear whether effects were compared between the 2 study groups [33]. IQWiG calculations found no statistically significant difference between the study groups at the end of therapy and at the end of the follow-up period.

Since the outcome is not directly health-relevant, it is disregarded in the benefit assessment.

4.5.9 Acupuncture

Only 1 study investigated acupuncture treatment. All results from the study on acupuncture are found in A3.3.9.

4.5.9.1 Swelling

Acupuncture versus waiting list (no co-intervention, Bao 2018 [25])

One study reported on this outcome based on the circumference difference between arms in cm as well as the responder rate, defined as the number of patients with a decrease in arm circumference difference by > 30%. No data were available on the comparison with baseline for either outcome. In the comparison between the 2 study groups, no statistically significant differences were found for either outcome [25].

No hint of benefit was found.

4.5.9.2 Adverse events

Acupuncture versus waiting list (no cointervention, Bao 2018 [25])

One study reported the number of events in all participants. While participants were on the waiting list, no adverse events were reported. After study completion, acupuncture treatment was offered to participants on the waiting list as well. In the 77 patients who received acupuncture, 45 pressure marks, 2 haematomas, 2 cases of pain, and 1 skin infection were reported. The study's authors report the frequency in percent of events per patient, but without stating whether any patients had more than 1 event. No data were available for a comparison between the 2 study groups [25].

Assessing benefit is not possible based on the reported data.

4.5.10 Thermotherapy

Only 1 study investigated thermotherapy. All results from the studies on thermotherapy are found in Table 44 of the full HTA report.

4.5.10.1 Adverse events

Thermotherapy versus compression + skin care (no co-intervention, Li 2017 [34])

One study investigated whether patients undergoing thermotherapy versus compression exhibited the following side effects after 1 year: enlarged lymph nodes in the liver, spleen, kidneys, chest, axillary region, or supraclavicular region, scalding, local infections, pyrexia, complaints, or pain [34]. No adverse events were reported for the experimental intervention group or for the comparator intervention group.

Based on the reported data, it is not possible to assess harm.

4.5.11 PRP (platelet-rich plasma)

Only 1 study investigated PRP treatment. All results from the study on PRP therapy are found in Table 46 of the full HTA report.

4.5.11.1 Swelling

PRP versus no PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + exercise + skin care (Akgul 2020 [14])

One 3-arm study reported on the difference in circumference of the lower limbs in patients treated with PRP as an add-on to MLD + compression + exercise + skin care. Compared with baseline, both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. IQWiG calculations found no statistically significant difference between the 2 study groups.

No hint of benefit was found.

4.5.11.2 Tension

PRP versus no PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + skin care + exercise (Akgul 2020 [14])

A 3-arm study reported on tension using a numeric rating scale. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for a comparison between the 2 relevant study groups [14]. IQWiG calculations found no statistically significant difference between the 2 study groups.

No hint of benefit was found.

4.5.11.3 QoL

PRP versus no PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + skin care + exercise (Akgul 2020 [14])

One 3-arm study investigated health-related quality of life using the LYMQOL score. Compared with baseline, the effects in both study groups showed a statistically significant improvement. In the comparison between all 3 study groups, no statistically significant differences were found. No data were available for comparing the 2 relevant study groups [14]. IQWiG calculations found no statistically significant difference between the 2 study groups.

No hint of benefit was found.

4.5.11.4 Further patient-relevant outcomes

Walking distance

PRP versus no PRP (+ co-intervention in both study groups)

Co-intervention: MLD + compression + skin care + exercise (Akgul 2020 [14])

One study investigated walking distance in meters using the 6-minute walking test. Compared with baseline, the experimental intervention group exhibited statistically significant improvement, whereas the effect in the comparator intervention group was not statistically significant. No data were available for a comparison between all 3 study groups or for a comparison between the 2 relevant study groups [14]. IQWiG calculations found no statistically significant difference between the 2 study groups.

No hint of benefit was found.

4.6 Evidence map

Table 5 below shows the evidence map regarding patient-relevant outcomes.

Table 5: Evidence map regarding patient-relevant outcomes

Morbidity					**Health-related quality of life and psychosocial aspects**		**Further outcomes**	**Adverse events**
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
MLD versus no MLD (+ co-intervention in both study groups) *co-intervention: compression + exercise + skin care ([42] and [26]); compression + exercise + breathing exercises [32]*								
⇔	⇔	⇔	⇔	⇔	-	-	⇔ Physical functioning ⇔ Health ⇔ Mood	-
MLD versus no MLD (+ co-intervention in both study groups) *co-intervention: laser + compression [37]*								
o	-	-	-	-	o	-	o Health o Mood	-
Compression versus no compression (+ co-intervention in both study groups) co-intervention: KT + MLD + exercise + skin care [12]								
o	o	o	o	-	o	-	All: o	⇔
Compression versus placebo Kinesio Taping (+ co-intervention in both study groups) co-intervention: IPC + MLD + skin care [39], IPC + MLD [44]								
⇗	-	-	-	⇔	-	-	⇔ Grip strength	o

(continued)

Table 5: Evidence map regarding patient-relevant outcomes (continued)

Morbidity					Health-related quality of life and psychosocial aspects		Further outcomes	Adverse events
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
Exercise versus no exercise (+ co-intervention in both study groups) co-intervention: compression [31]								
⇔[a]	⇔	⇔	⇔	-	-	-	-	-
Exercise versus no exercise (+ co-intervention in both study groups) co-intervention: IPC [28]								
⇔	-	-	-	-	-	-	-	-
Home-based programme (LD + skin care + breathing exercises + exercise, each in self-application) vs. no home-based programme (+ co-intervention in both study groups) co-intervention: MLD + compression (garments) + exercise + breathing exercises [27]								
⇗	⇗	-	-	-	-	-	⇗ Physical functioning	-
Home-based programme (MLD + compression + breathing exercises + exercise, each self-administered) versus standard therapy (information brochure) (+ co-intervention in both study groups) co-intervention: arm guard [35]								
⇔	⇗	-	-	-	-	-	-	-
Kinesio Taping versus compression (+ co-intervention in both study groups) *co-intervention: training plan [43]*								
⇗	⇗	-	-	-	⇗	⇔	⇗ SPADI ⇗ Grip strength	o

(continued)

Table 5: Evidence map regarding patient-relevant outcomes (continued)

Morbidity					Health-related quality of life and psychosocial aspects		Further outcomes	Adverse events
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
Kinesio Taping versus compression (+ co-intervention in both study groups) *co-intervention: MLD + IPC [44], MLD + IPC + skin care [39], MLD + IPC + exercise + skin care [45]*								
↘	-	-	⇔	↘	-	-	⇔ Feeling of fullness ⇔ Discomfort ↘ Grip strength	o Wounds o Itching o Health complaints
Kinesio Taping versus compression (+ co-intervention in both study groups) *co-intervention: MLD + exercise + skin care [12]*								
o	o	o	o	-	o	-	All: o	⇔ Itching ⇔ Wound formation
KT versus compression (bandage) (+ co-intervention in both study groups) *co-intervention: Compression (garments) + MLD + exercise + skin care [36]*								
⇔	-	-	-	-	-	-	-	-
Kinesio Taping versus placebo Kinesio Taping (+ co-intervention in both study groups) *co-intervention: IPC + MLD + skin care [39], IPC + MLD [44]*								
⇔	-	-	-	⇔	-	-	⇔ Grip strength	o
KT versus no KT (+ co-intervention in both study groups) *co-intervention: Compression + MLD + exercise + skin care [12]*								
o	o	o	o	-	o	-	All: o	⇔ Itching ⇔ Wound formation

(continued)

Table 5: Evidence map regarding patient-relevant outcomes (continued)

Morbidity					**Health-related quality of life and psychosocial aspects**		**Further outcomes**	**Adverse events**
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
IPC versus no IPC (+ co-intervention in both study groups) *co-intervention: MLD + compression + exercise + skin care [30]; MLD + compression [41]*								
⇔	-	-	-	o	⇔	-	-	o
IPC versus MLD (+ co-intervention in both study groups) *co-intervention:* 30 min MLD (in comparator intervention, total of 60 min MLD) + compression + exercise + skin care *[40]*								
⇗	-	-	-	-	-	-	⇔	-
IPC versus MLD (+ co-intervention in both study groups) *co-intervention: compression + exercise [38]*								
⇔	⇔	⇔	⇔	⇔	-	-	-	-
VLNT versus no VLNT (+ co-intervention in both study groups) *co-intervention: MLD + compression* [29]								
⇗	⇗	⇗	-	-	-	-	⇗ Physical functioning	⇗

(continued)

Table 5: Evidence map regarding patient-relevant outcomes (continued)

Morbidity					Health-related quality of life and psychosocial aspects		Further outcomes	Adverse events
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
Laser versus no laser (+ co-intervention in both study groups) *co-intervention: MLD + compression + exercise + skin care [14]; MLD + compression [37]*								
⇔	-	-	⇔	-	⇔	-	⇔ Walking distance o Health o Mood	-
Laser versus placebo laser (+ co-intervention in both study groups) *co-intervention: MLD + compression (tape + garments) + exercise + IPC self-management [33]*								
⇔	⇔	⇔	-	⇔	-	-	⇔ Health ⇔ Mood	o
Laser versus MLD (+ co-intervention in both study groups) *co-intervention: compression [37]*								
o	-	-	-	-	o	-	o Health o Mood	-
Laser versus PRP (+ co-intervention in both study groups) co-intervention: MLD + compression + exercise + skin care [14]								
⇔	-	-	⇔	-	⇔	-	⇔ Walking distance	-
Acupuncture versus waiting list (no co-intervention, [25])								
⇔	-	-	-	-	-	-	-	o

(continued)

Table 5: Evidence map regarding patient-relevant outcomes (continued)

Morbidity					**Health-related quality of life and psychosocial aspects**		**Further outcomes**	**Adverse events**
Swelling	**Pain**	**Congestive symptoms**	**Tension**	**Mobility**	**QoL**	**Level of social functioning**		
Thermotherapy versus compression + skin care (no co-intervention, [34])								
-	-	-	-	-	-	-	-	o
PRP versus no PRP (+ co-intervention in both study groups) *co-intervention: MLD + compression + skin care + exercise [14]*								
⇔	-	-	⇔	-	⇔	-	⇔ Walking distance	-

⇗: Hint of (greater) benefit or hint of lesser harm.
⇘: Hint of lesser benefit or hint of (greater) harm.
⇔: No hint, indication, or proof; homogeneous result.
o: Reported data are unusable for the benefit assessment.
-: No data reported.
a: Statistically significant effects for high-load exercise, but not for low-load exercise.
IPC: intermittent pneumatic compression; KT: Kinesio Taping; MLD: manual lymphatic drainage; PRP: platelet-rich plasma; QoL: (health-related) quality of life; SPADI: Shoulder Pain and Disability Index; VLNT: vascularized lymph node transfer

4.7 Discussion of clinical relevance

Ideally, benefit should be assessed not solely on the basis of the statistical significance of effects, but also taking into account their clinical relevance. A systematic review published in 2018 investigated MCIDs in the management of lymphoedema [47]. Depending on treatment phase, the review distinguished between 3 measurement time points: (1) immediate changes following a single intervention, (2) changes following intensive therapy, and (3) changes during the maintenance therapy phase.

This report includes only one 3-arm study which reported immediate changes directly following a single therapy session, i.e. high-load/low-load exercise, each with and without compression [31]. However, the differences between study groups found in this comparison were not statistically significant for any of the outcomes except swelling [31]. In the comparison of (high-load) exercise versus compression, statistically significant differences were found only for the outcome of swelling. Since the investigation of changes during or after maintenance therapy was outside the scope of this report, all other included studies reported on effects found during or after the end of intensive therapy.

Swelling

The systematic review regarding MCIDs identified 3 studies which reported clinically relevant effects for the outcome of volume [47]. One of the studies arbitrarily defined a clinically relevant effect as a 50% reduction in lymphoedema volume [48]. The study found that the percentage of patients who achieved a 50% reduction in lymphoedema volume varied by baseline volume. Depending on baseline volume, the study's authors formed 3 study groups: (1) patients with a baseline lymphoedema volume ≤ 250 mL, (2) patients with a baseline lymphoedema volume of 250–500 mL, and (3) patients with a baseline lymphoedema volume > 500 mL [48]. In the group of patients with the smallest baseline volume, a 50% volume change therefore equalled a maximum of 125 mL. In the study group with the highest baseline volume, a 50% reduction from baseline required a volume reduction by more than 250 mL.

A 2nd study defined a clinically relevant change as an arm volume reduction by at least 200 mL, but it did not justify its chosen cutoff [49]. The 3rd study was also included in this systematic review and reported clinically relevant changes from baseline without describing the criteria used to make this decision [37].

For the maintenance therapy phase, however, the systematic review also reported smaller changes, which were used. For instance, 2 studies defined "stable" lymphoedema in the upper limb as increases by less than 10% within 3 or 6 months, and a 3rd study defined it for the lower limb as an increase by less than 15% within 3 months. Five studies defined deterioration as a ≥ 5% increase in relative limb volume during the intervention, whereas the cutoff was 3%

and 20%, respectively, in 1 study each [47]. One of the studies on home-based programmes which was included in this report also used an MCID of 5% for data interpretation [35].

Low MCID cutoffs in particular must be viewed in the context of minimal detectable change (MDC). Any effects of therapy which measure below the MDC would fall within the range of a measurement error, and such changes cannot be assumed to correspond to true effects of therapy.

Measurement error will differ depending on both the employed measuring method – particularly in case of subjective measuring methods – and the investigator's experience [47]. The systematic review on MCIDs also investigated the reliability of volume measurements, and in this case as well, the suggested cutoffs varied widely. Based on 3 studies, the estimated MDCs for total arm volume, for instance, range from 55 mL to 218.4 mL [47]. Since each of the studies used a different measuring method, the representativeness of these estimates for the individual measuring methods remains unclear. Based on 1 study, the variability of volume measurements of the lower limb (volume estimate based on circumference measurements and truncated cone method) is estimated to equal 270 mL for repeated measurements by a single examiner and 1000 mL for different investigators [47].

Diverse CDT components

One study investigated the added benefit of a home-based programme with self-administered lymphatic drainage, breathing exercises, and physical therapy subsequent to conventional therapy [27]. Based on IQWiG calculations, the 2 study groups differed in total arm volume by -187.7 cm^3 (95% CI: *-294.05; -81.35)* [27]. Given MCIDs of between 125 mL and 250 mL, all values lie within the confidence interval; in all scenarios, it is therefore safe to assume that some of the treated patients experienced a clinically relevant benefit from therapy.

Kinesio Taping versus compression

For the comparison of Kinesio Taping versus compression including the co-intervention of training plan, 1 study reported statistically significant differences between 2 study groups regarding the sum of arm circumferences [43]. Based on IQWiG calculations, the difference was -9.9 cm (95% CI: 16.29; -3.51). While the identified systematic review did not report MCIDs for the outcome during the intensive therapy phase, the authors found 1 study on MCIDs during the maintenance therapy phase which assumed an MCID of 25% reduction in the sum of arm circumferences [47]. However, this study measured circumference in 7 locations rather than 8, as in the Tantawy study [43,47].

In the comparison of Kinesio Taping versus compression including the co-intervention MLD + PIC and possibly additional co-interventions, 2 of the 3 studies exhibited statistically significant effects showing better reduction of swelling after compression [39,44,45]. At 45.02%, 1 study reported statistically significant effects for percent volume reduction of the

affected upper limb for compression therapy in comparison with Kinesio Taping (22.45%) [44]. No data were available on confidence intervals; therefore, it cannot be assessed whether they include an assumed clinically relevant effect of 50% reduction. A similar situation was found in a 2nd included study which reported 53.21% oedema reduction for the compression arm versus 24.45% for the Kinesio Taping arm [39]. The mean difference would have been above the MCID. However, since the difference between the 2 study groups was calculated using variance analysis [39], neither means nor confidence intervals are available, and parametric tests were potentially inappropriate. Hence, the clinical relevance of the differences cannot be assessed in this case either. In the 3rd study, effects did not differ to a statistically significant extent, although they were better in the arm with compression [45].

Compression versus placebo Kinesio Taping [39,44]

The above studies, which reported percent oedema reduction by means of variance analysis for Kinesio Taping versus compression, additionally reported on the comparison of compression versus placebo Kinesio Taping. They found a mean of 53.21% or 45.02% in the experimental intervention group and a mean of 24.78% or 24.04% for placebo Kinesio taping. Here, the same considerations apply regarding the poor interpretability of the clinical relevance of effects.

IPC versus MLD [40]

One study compared IPC plus 30-minute MLD versus each of the co-interventions of 30-minute MLD, compression, exercise, and skin care. Compared with baseline, a volume reduction of 7.93% was found for IPC and 3.06% for MLD. The difference between the 2 study groups was 4.87%. Again, no data are available on confidence intervals in each case, but these values are much smaller than the above-mentioned clinically relevant reduction by 50%, rendering a clinical effect unlikely at this cutoff.

Surgery – vascularized lymph node transfer (VLNT) [29]

The included study on VLNT reported reductions in percent lymph oedema volume in the experimental intervention group; compared with baseline, the differences were 20.88% and 6.77%. The difference between study groups was 14.11%. No data were reported on the spread, making it impossible to assess whether the confidence interval includes the MCID.

Further patient-relevant outcomes

The studies on VLNT [29], on the home-based programme [27], and on diverse CDT components [35] investigated pain using VAS or numerical rating scales (NRS) ranging from 0 to 10, while 1 study on Kinesio Taping investigated pain using the EORTC QLQ-C30 questionnaire scale [43]. The systematic review on MCIDs, however, found no studies investigating VAS scores or NRS or the EORTC QLQ-C30 questionnaire as instruments for measuring the severity of pain [47]. The systematic review further did not report MCIDs

regarding the following outcomes: congestive symptoms (scale from 0 to 10) [29], mobility (percent range of motion, measured using a goniometer) [44], grip strength (in Newton [44] or kg [43]), SPADI questionnaire [43], DASH questionnaire [27], limb function (VAS) [29], and health-related quality of life (QLQ-C30 of the EORTC questionnaire) [43].

The systematic review reported MCIDs for infection rates but found no studies which defined MCIDs for the intensive therapy phase. For the maintenance therapy phase, 2 studies used an infection rate of 1 or 0 infections in the prior 3 months as the criterion for stable lymphoedema, while 1 study strived for a < 29% annual incidence of hospitalizations due to cellulitis [47]. For the study on VLNT, the mean number of infectious episodes per year and patient was calculated; this parameter was reduced by 1.66 in the experimental intervention group compared with the year prior to therapy ($p < 0.001$) and by 0.44 in the comparator intervention group ($p = 0.016$) [29]. In the comparison between the 2 study groups, IQWiG calculations found a difference of -0.883 for the incidence rates at the study end. No confidence intervals were reported [29], making it impossible to assess the relation to the proposed MCIDs.

5 Results: Health economic assessment

5.1 Intervention costs

In lymphoedema treatment, it is essential to take into account patients' individual circumstances. Therefore, the intervention costs listed below might depart from those incurred in clinical routine, or additional costs might arise. For all treatment types, it was also assumed that lymphoedema had already been diagnosed. This means that the costs of all pretherapeutic diagnostics for confirming lymphoedema were disregarded. Lymphoedema treatment typically takes a long time (often lifelong).

Section A4.1 discusses example intervention costs for lymphoedema management in the German healthcare context.

To determine the cost of hypothetical oedema treatment, patients were assumed to have lymphoedema of an upper limb, e.g. after breast cancer treatment. The following illustration of typical costs of potential courses of treatment are purely descriptive. The listed costs are always based on the reimbursements from the treatment provider perspective.

Generally, all costs are reimbursable, but remedies, therapeutic appliances, drugs, and surgical dressings in the outpatient sector are subject to various copayment rules based on total amount (typically 10% of costs) and medical prescription (often €10 per prescription), which, in turn, are subject to various caps (e.g. maximum of €10 per prescription). Chronically ill patients can additionally apply to be exempted from copayments. Treatment processes are based on the relevant "Diagnostics and therapy of lymphoedema" guideline [50]. Costs are based on the relevant price lists.

The first step in the treatment of oedema is to reduce it as far as possible using intensive outpatient or inpatient decongestive therapy with daily manual lymphatic drainage and subsequent compression bandaging (since the oedema is not yet sufficiently stable to allow fitting a tailored compression stocking). The cost of this 1-month treatment equals €1532.72 (also see Table 47 and Table 49 of the full HTA report).

This initial phase is followed by maintenance therapy with less frequent (in the chosen example 3 times weekly) manual lymphatic drainage and the wearing of a suitable compression arm sleeve. These costs equal €6158.52 for 11 months (see Section A4.1.1 for details on all data provided here).

In addition, the applicable laws and current literature provide for the possibility of supplying the patient with an intermittent pneumatic compression device for home use as supportive therapy. This device rents for about €1595 for 11 months, bringing the total annual cost of treatment to €8359.56 € (also A4.1.1).

The total cost for CDT per patient and year (1-month decongestive phase followed by an approximately 11-month maintenance phase) equals €7691.24, or €9286.24 if an IPC device is additionally rented. These figures do not include the cost for further CDT components (decongestive exercise / movement therapy, skin care products, patient information and training on individualized self-care) because utilization of services differs greatly between patients. Patients often have to pay these costs out of pocket.

The frequency of recurrence is unknown; recurrence may be due to noncompliance with maintenance therapy, but also due to infections after skin injuries which are impossible to fully prevent and each lead to oedema progression. Any recurrence requires another decongestive phase.

According to guidelines, surgical therapy should be weighed as an option if a patient suffers or exhibits increased secondary tissue changes despite guideline-compliant conservative therapy and treatment adherence. Surgical therapy aims to permanently restore impaired lymphatic drainage and hence at least reduce the need for decongestive therapy. For lymphoedema following (partial) mastectomy (with lymphadenectomy, stage II), the measure is reimbursed via DRG J22Z. The reimbursement amount for the procedure equals €3128.71. Subsequently, further costs can be incurred by postoperative rehabilitation as well as a continued need for lymphoedema treatment depending on treatment success.

5.2 Systematic review of health economic evaluations

5.2.1 Results of the information retrieval

Overall, the information retrieval identified 224 potentially relevant studies. Among these, 2 RCTs, which also ended up being included in the benefit assessment, were deemed relevant and included in the assessment [29,36]. Both studies are comparative cost-cost studies. The check of the reference lists of identified systematic reviews did not produce any further hits.

5.2.2 Characteristics and results of the studies included in the assessment

Only 2 cost-cost studies were found for the health economic evaluation [29,36].

Table 51 (Section A4.2.2) of the full HTA report presents the study characteristics and results of the included health economic study. Both studies investigated relatively small patient cohorts (N = 36 [29] and N = 10 [36] patients) and were based on healthcare systems in European countries (Denmark and Greece) [36]. The 2 studies were conducted relatively recently (in 2016) and evaluated patients suffering from breast cancer-related lymphoedema. One study compared surgical lymph node transfer followed by MLD and compression versus MLD and compression alone [29]. The second study compared Kinesio Taping and compression versus bandages – with both study groups receiving *compression (garments), MLD, exercise, and skin care* [36].

Based on 36 breast cancer patients in Greece, Dionyssiou et al. [29] reported the cost of lymph node transfer with postoperative MLD and compression for 6 months (€6944) and compared it with the cost of MLD and compression for the patient's remaining lifetime (34.9 years, €28 115). The study failed to prove the equivalence of these treatment alternatives' benefits; therefore, the costs incurred during these different time horizons (6 months versus the remaining lifetime) are not comparable.

For 10 breast cancer patients in Denmark, Melgaard et al. [36] report on the treatment alternatives of compression via bandage + co-interventions (5 days a week for 4 weeks, €1122) versus Kinesio Taping + co-interventions (twice weekly for 4 weeks, €458). This study likewise failed to provide adequate proof of the equivalence of the treatment alternatives. Both studies list material and personnel costs from the perspective of the respective healthcare system. The cost figures presented here have been adjusted for inflation using the German Federal Statistical Office's Harmonized Index of Consumer Prices.

6 Results: Ethical, social, legal, and organizational aspects

6.1 Results on ethical aspects

Ethical aspects regarding the use of therapeutic procedures such as the non-drug interventions investigated in this report for the treatment of lymphoedema include, among others, questions regarding the medical risk-benefit profile, burdens and advantages associated with each treatment from the patient perspective, e.g. feasibility in everyday life, effects on patients' self-determination, and questions regarding any discrimination or preferential treatment of certain patient groups, equal access to therapy, and the cost of the therapy for the insured community. Therefore, many of the research questions and investigations of the HTA report, e.g. the central question about the effectiveness of non-drug therapies, also qualify as ethical questions. In this section explicitly entitled "ethical aspects", the focus should lie on topics which the literature explicitly designates and treats as "ethical" aspects of lymphoedema therapy or on topics which address problems difficult to adequately integrate in other parts of this report.

Inclusion criteria for the search were a publication date of 2000 or later, the investigated patient groups including patients with lymphoedema after breast cancer, and the study's geographic focus being Europe or United States. The approximately 60 hits identified in this manner were reviewed for relevant ethical aspects and topics as described above. The resulting list of relevant publications is found in Section A9.3.1. Four publications were included. The information obtained based on this literature was systematically organized with the aid of the questionnaire by Hofmann [51]. Five relevant ethical aspects can be identified.

1. Relevance and difficulty of recording disease-related psychological and social burdens

The literature emphasizes the fact that lymphoedema is associated not only with physical impairments, but also with psychological and social burdens [52]. Fu and Kang point out that these psychosocial consequences are massive and might also be inadequately depicted by existing category systems used in quantitative studies [52]. Patient interview protocols confirm that lymphoedema leads to substantial pain and mobility limitations, making it impossible to work full time, complicating the management of everyday life, and leading to situations perceived as embarrassing.

2. Inadequate provision of care to certain patient groups

Patients whose lymphoedema is not due to cancer or treatment thereof are believed to receive poorer care because they do not benefit from established aftercare programmes. Published evidence supporting this assumption was found for Great Britain [53]. In the opinion of this report's scientific advisor, these findings can be extrapolated to the German healthcare situation.

In view of cost carriers' reluctant approval practice concerning inpatient rehabilitation, it is furthermore conceivable that not all patients whose phase of disease and treatment requires inpatient care actually receive adequate care. This issue is likely to affect particularly patients who lack the resources to appeal denied applications. The German Association for the Promotion of Lymphoedema Therapy describes such challenges on the basis of individual cases [54]. Patient interview protocols also include corresponding experiences.

This ethical aspect is likewise of social relevance. It is included and discussed in further detail in Section 6.2, "Sociocultural aspects of the implementation of the intervention and organization of use".

The inadequate provision of care to certain groups of patients may result, in part, from an unclear disease definition and inadequate diagnostics. This topic is discussed under social aspects in Section 6.2.

3. Self-stigmatization and withdrawal from social activities

Lymphoedema can lead to patients withdrawing from social situations and relations. This response can be described as a type of self-stigmatization: patients believe that others will reject them and therefore withdraw from social activities. Health consequences such as depression, may ensue [55].

4. Physical therapies' disruption of daily life and the potential alternative of surgical procedures

Physical therapy must be administered regularly for the patient's remaining lifetime. These measures are associated with burdens in everyday life as well as psychosocial burdens. Against this backdrop, patients may deem surgical measures which might reduce these burdens a more attractive alternative. Dionyssiou 2016 [29] mentions permanent reduction in limb volume as a long-term advantage of the microsurgical procedure. This study provides for no further therapy until the 12-month follow-up visit, revealing that the objective was to provide curative therapy. The advantage of having to undergo only a single procedure might lead to patients preferring surgical procedures even if assessments of surgical procedures' direct physical benefit and harm or quantitative QoL parameters have shown no advantages over physical therapies. In its presentation of surgical procedures, the German Association for the Promotion of Lymphoedema Therapy, a patient organization, accordingly expresses favourable interest [54].

Section 6.2 discusses in more detail the patient acceptance of different types of therapy.

5. Failure to provide adequate care due to budgetary specifications

The budgetary rules governing service providers such as physicians, rehabilitation centres, and physical therapists can lead to physical therapies not being carried out to the required extent

or in the necessary setting (inpatient versus outpatient). Even in cases where the rules actually allow for good provision of care, the care provided may still be inadequate, e.g. when physicians do not know these rules in detail [54]. The website of the German Association for the Promotion of Lymphoedema Therapy details the economic problems physicians may face when prescribing lymphoedema therapies [54].

6.2 Results on social aspects

The information obtained from 22 included publications was assessed based on the comprehensive conceptual framework suggested by Mozygemba 2016 [23]. Alongside the outlined ethical aspects, e.g. the medical risk–benefit profile and the burdens or advantages of the interventions from the patient perspective, this subsection focuses on 3 social aspects of non-drug interventions for the treatment of lymphoedema: (1) social construct and perception of lymphoedema, (2) patient understanding of the interventions and their use, (3) international sociocultural aspects of the interventions' implementation and organization of their use. Totalling 22 publications, the available literature on social aspects is quite robust with regard to the desired research and care situation identified below.

Social construct and perception of lymphoedema

Despite evidence demonstrating that lymphoedema is associated with not only physical disability but also psychological and social burdens (e.g. [56-59]), global awareness of the number of patients affected by lymphoedema and the effects of the disease (e.g. hidden mortality) continues to lack, as does knowledge about effective treatment options [60]. While lymphoedema diagnostics and therapy have been defined in national and international guidelines (e.g. AWMF in Germany), a current international analysis identifies the establishment of a clear, international definition of lymphoedema as a continued central problem [60,61]. Overall, the internationally unclear definition of lymphoedema and the associated lack of clarity regarding the diagnosis lead to a worldwide dearth of investment in the treatment and research of the causes and treatment of lymphoedema and consequently to low cultural, scientific, economic, and social capital [61].

Knowledge about the interventions and their utilization

Furthermore, patient knowledge about and understanding of lymphoedema and its treatment currently seems to be limited: Several of the identified studies show that patients knew little about lymphoedema before they contracted the disease themselves – and even some of the lymphoedema patients lack knowledge about lymphoedema risks, the types of (breast cancer related) lymphoedema, treatment approaches and methods as well as self-administered therapies [62-67]. Since diagnosing lymphoedema early and informing patients about treatment options are key steps toward recognizing the physical and emotional dimensions of the disease and improving its treatment [62,68], it is important to promote knowledge about lymphoedema and its treatment. The studies included in the benefit assessment supply

sporadic evidence regarding the target group's acceptance of the different interventions, which likely depends on the patients' personal experiences: High acceptance was found for pneumatic compression devices and physical therapy with and without manual lymphatic drainage [26,30]. Acceptance was higher for Kinesio Taping than for bandages [45].

Sociocultural aspects of the intervention's implementation of and organization of use

Lymphoedema management has often been exclusively associated with cancer therapy; only in recent years has the focus increasingly included other causes as well [60]. The publications found in this search likewise focus primarily on breast cancer-related lymphoedema and are largely from Anglo-American countries. Currently, diagnosis and therapy seem to be influenced by sociocultural location and the associated diagnostic and treatment options: Moffatt et al. [60], for instance, report that, in countries where lymphoedema is recognized primarily as a tropical filariasis-induced disease, there is a tendency of assuming that all patients suffer from filariasis-induced lymphoedema and treating them accordingly. Filiariasis is a rare cause of lymphoedema and is therefore not the subject matter of this report (see Section 3.1). Conversely, in some other countries, the cost of lymphoedema treatment is covered only for patients who are simultaneously receiving cancer treatment or who suffer from a primary form as confirmed by clinical investigation [60].

Joint decision-making by patients and treatment providers is characterized by the above-mentioned lack of awareness of lymphoedema and its treatment – both among patients and among treatment providers: Consequently, initial swelling is often ignored by both patients and professionals until complications occur [60]. Furthermore, various investigations show that physicians (1) do not routinely provide sufficient patient information about lymphoedema [58,65], (2) lack knowledge regarding surgical procedures [69], and (3) create a key barrier to successful self-management through this poor patient information about treatment options and risk reduction [70]. In addition, many medical professionals are unaware of central elements of lymphoedema prevention and treatment [71]. In a survey conducted in Turkey, for instance, the majority of general practitioners reported that lymphoedema was not discussed during their studies [72], and nurses in Great Britain were worried about their lack of knowledge [73]. In Great Britain, patients with lymphoedema are typically referred to a specialist, where available [74]. In Turkey as well, 55% of general practitioners referred women with breast cancer-related lymphoedema to a general surgeon, followed by an oncologist (28%) and specialists for physical medicine and rehabilitation (17%) [72]. However, the outlined lack of knowledge may delay any referral, which in turn can lead to deterioration of symptoms and longer treatment durations [74]. For Germany, Lulay 2017 postulates a high number of unrecorded lymphology patients and an overall unsatisfactory care situation, e.g. in secondary lymphoedema and treatment-resistant courses [75]. This situation as well as scenarios where failure to provide adequate care might

arise owing to budgetary constraints are critically questioned from an ethical perspective as well (see Section 6.1).

Consequently, there is a substantial need to improve professionals' knowledge and skills to facilitate adequate treatment [74]. The risk of lymphoedema increases with age. Particularly given our ageing society, approaches that close the existing gaps are therefore needed. This could be achieved, for instance, through a collaborative approach in which medical specialists offer support, consultation, and instruction [74].

The identified literature underlines the fact that both professional and societal discussion of lymphoedema and its treatment should be promoted.

6.3 Results on legal aspects

The specific treatment of lymphoedema can be individually agreed in the treatment contract. The duties arising from said contract are governed by German Civil Code (BGB) Section 630c, et seq. Reimbursement is based on the contract, with privately insured patients typically being reimbursed directly, whereas for SHI members, the treatment provider receiving a claim under the German Social Code against the Association of Statutory Health Insurance Physicians. Treatment must be in accordance with professional standards, i.e. it must be based on regulations such as the AWMF guidelines [50]. From a legal perspective, surgical measures meet this standard whenever the conservative treatment approach has not resulted in an adequate improvement after at least 6 months of treatment. In these cases, patients should be informed about surgical alternatives even if conservative treatment is to be preferred. Surgical therapy is indicated where conservative therapy has not alleviated the patient's suffering or even an increase of secondary tissue changes is recorded [50], or if the therapy presents an excessive burden for patients. The patient must be comprehensively informed about potential risks, obligations to cooperate, etc., particularly in case of surgical therapy, which is associated with greater risks, but also in case of other therapies. Any violations of contractual obligations, including inadequate patient information, may be associated with liability risks, in some cases even risks under criminal law. With regard to reimbursement by health insurance funds, private health insurers must follow the German Medical Fee Schedule (GOÄ). For the SHI, Section 11 SGB V applies, with the corresponding list by the Federal Joint Committee (G-BA) being relevant. In this regard, it must be noted that, in 2017, the G-BA decided to list the diagnosis of lymphoedema stage II and above for long-term remedy needs to thereby facilitate patients' long-term care of the disease [76]. No such decision has been taken for surgical measures.

6.4 Results on organizational aspects

The information processing on organizational aspects followed the grid template proposed by Perleth et al. 2014 [77] for the assessment of organizational consequences of treatment

methods. The analysis of organizational aspects is based on 17 publications. The list of the relevant publications is found in Section A9.3.4.

Influence on the prerequisites of service provision and the organizational processes

Most of the therapies investigated in the studies are performed on an outpatient basis or possibly on an inpatient basis as part of rehabilitation therapy and must be performed by appropriately trained professionals. Depending on the specific intervention, non-drug interventions are performed by medical professionals with appropriate additional qualifications. Service providers include particularly physical therapists (with additional qualifications, e.g. in Kinesio Taping), physicians with corresponding additional qualifications (e.g. in acupuncture or laser therapy/medicine), or medical specialists (e.g. in physical and rehabilitation medicine or surgery). Due to the large array of conservative and surgical treatment options, good interdisciplinary collaboration is important.

In view of the typically chronic nature of lymphoedema, most physical therapy procedures must be applied regularly and life-long. For patients, they are therefore associated with substantial burdens in everyday life. The only treatment options which patients and family members might be able to self-administer at home following appropriate training are the home-based programme / self-CDT, IPC, and Kinesio Taping. It is unclear whether self-administration represents a relief for patients since self-administration of therapies is time-intensive and requires self-discipline. Only PRP infusion and surgery must be performed on an inpatient basis. However, undergoing a single invasive surgical procedure might offer the advantage of a potential cure, making other long-term therapies unnecessary. Based on the identified studies, it is impossible to determine whether and to what extent no further therapies are in fact needed postoperatively. Since the mechanism of action of laser therapy is also assumed to include structural changes, this therapy has the potential of curing or permanently improving the condition. However, very few comparative clinical studies are currently available which examine the benefit of surgical measures and laser therapy in patients with moderate to severe lymphoedema (see Section 4.5.7 and Section 4.5.8).

The new remedies list includes CDT and its components as reimbursable therapies [78]. According to AWMF, this includes self-CDT. Since the training needed for this purpose is not explicitly listed in the remedies catalogue, however, it remains unclear whether health insurance funds pay for it [50,78,79]. Kinesio Taping and laser therapies are not covered by SHI[80]. Acupuncture treatment, in contrast, is covered by some SHI funds (see Table 57 of the full HTA report) [81].

Due to the associated high “organizational” effort, IPC is unique among the non-drug treatments. It requires that a physician inform the patient about the specific advantages and disadvantages of use, risks, side effects as well as potential alternatives. Alongside the more

complex devices for use at hospitals and practices, devices for home use are available. Particularly in patients with long-term indication, a device for home use could be helpful and promote self-management as well as patient autonomy. Said devices can be prescribed and paid for by the health insurance fund. Prescriptions may be for both loan devices for limited-time use and permanent devices in case of long-term or life-long use [82].

7 Synthesis of results

The literature search for the benefit assessment included 23 studies which examined MLD, compression, exercise or movement therapy, diverse CDT components, Kinesio Taping, IPC, VLNT, laser therapy, acupuncture, thermotherapy, and PRP [12,14,25-45]. None of the studies investigated the effectiveness of the entire CDT programme, despite the fact that it represents the standard therapy according to the AWMF guideline. A total of 1083 patients were enrolled in the studies [12,14,25-45]. A total of 19 of the 23 studies examined only women [12,25-29,31-37,39-44]. Two studies with 65 patients had a mixed population, of which 15 participants were male [14,30]. In 2 further studies with a total of 87 patients, no data were available on the percentage of men versus women [38,45]. In 20 of the 23 studies, participants suffered from breast cancer [12,25,27-29,32-45]. Most studies (16 of 20) further restricted the breast cancer population based on 1 or more criteria. Excluded were patients with recurrent breast cancer, (lymph node) metastases, and/or "active cancer", likely defined as cancer which is not deemed cured. In 1 study each, the underlying conditions were gynaecological tumours [31], inflammations or trauma [14], or were unreported [30]. Consequently, most available data concern arm lymphoedema, while little to no data are available on lymphoedema in other locations such as the legs, trunk, or head and neck area. Likewise, no robust data were found on the question posed by the person suggesting the topic, i.e. regarding adverse events, particularly on skin damage caused by lymph fluid.

The available evidence was very heterogeneous due to the multitude of populations, experimental, comparator, and co-interventions as well as different outcomes, and for the most part, it had to be summarized as a narrative. The studies on surgery (VLNT) and laser therapy (in part) aimed to achieve curative effects, and for thermotherapy, the primary objective was to investigate the associated risk of tumour recurrence. Consequently, the longest follow-up time point was analysed for these studies [29,33,34]. For the other studies, only the latest follow-up time point during or at the end of the experimental intervention was evaluated in an effort to avoid additional heterogeneity between the studies due to variable maintenance therapies. Hence, the follow-up period was typically short: For most studies it equalled between 10 days and 3 months.

The varying combinations of the above-mentioned factors in nearly all studies make it difficult to assess the causality of the observed effects.

Hints of benefit were found for compression, IPC, home-based programmes, as well as vascularized lymph node transfer [27,29,35,39,40]. For the comparison of Kinesio Taping versus compression, contradictory effects were found depending on the co-intervention [12,36,39,43-45].

In the comparison of compression versus placebo Kinesio Taping based on 2 studies in patients with breast cancer as the underlying condition, a hint of greater benefit was found regarding the outcome of swelling [39,44]. Another study in patients with breast cancer as the underlying condition investigated the comparison of compression versus no compression, finding no hint of benefit regarding the outcome of adverse events [12].

One study each in patients with breast cancer as the underlying condition investigated the effectiveness of a home-based programme. One of the studies found a hint of greater benefit regarding the outcomes of swelling, pain, and physical functioning for a home-based programme with lymphatic drainage, skin care, breathing exercises, and exercise in comparison with no home-based programme [27]. All patients in this study received the other CDT components as a co-intervention. A 2nd study compared the home-based programme with the existing standard therapy for patients with breast cancer – an information brochure containing adapted exercises as well as behavioural and hygiene standards. This study found a hint of benefit only for the outcome of pain [35].

One study investigated vascularized lymph node transfer versus no vascularized lymph node transfer in patients with breast cancer as the underlying condition. Both groups received the co-interventions of MLD and compression for 6 months, followed by no further therapies for the subsequent 6 months. At the end of the follow-up period, hints of greater benefit were found for the outcomes of swelling, pain, congestive symptoms, limb functionality, and adverse events (infection rates) [29].

Results were inconsistent for the experimental intervention of Kinesio Taping. All studies investigated the effects in patients with breast cancer as the underlying condition. In the comparison of Kinesio Taping versus compression, opposite effect directions were found depending on the type of co-intervention, particularly for the outcomes of swelling and grip strength, which were investigated in both comparisons [39,43-45].

In the comparison of Kinesio Taping versus compression, with several co-interventions including MLD+IPC as well as further therapies in some cases, hints of a superiority of compression were found for the outcomes of swelling [39,44,45], mobility, and grip strength [44]. In a study with the co-intervention of training plan, however, Kinesio Taping showed better results regarding the outcomes of swelling, pain, health-related quality of life, grip strength, and the Shoulder Pain and Disability Index (SPADI) [43]. Two further studies with different co-interventions found no hints of benefit [12,36]. In the comparison of Kinesio Taping versus no Kinesio Taping [12] as well as Kinesio Taping versus placebo Kinesio Taping [44], no hint of benefit was found.

In the comparison of exercise versus no exercise in women with gynaecological cancer and lymphoedema of the lower limb, a 3-arm study showed, for the comparison of high-load

exercise versus compression, a statistically significant difference between study groups regarding the outcome of swelling. The difference between low-load exercise versus compression was not statistically significant, however [31]. The different results found for the 2 comparisons may be due to chance, or the data may be explained by 2 other conceivable interpretations: (1) the differences may be due to a dose-response effect, or (2) the effects may not be in the same direction since the 2 comparisons did not both exhibit significant effects. Regarding the other investigated outcomes, no statistically significant differences were found in either study group [31]. Another study in patients with breast cancer as the underlying condition, which likewise compared exercise versus no exercise but used IPC as co-intervention and was therefore analysed separately, likewise found no statistically significant difference regarding the outcome of swelling [28]. Given the absence of other comparable included studies on these interventions, benefit was assessed consistent with the general approach of the latter interpretation. Correspondingly, it was assumed that there is no hint of benefit in each case.

One study each was found for the comparison of IPC versus MLD or longer MLD. In 1 study, patients with breast cancer as the underlying condition received the co-interventions of 30-minute MLD, compression, exercise, and skin case in both study groups. For the outcome of swelling, a statistically significant difference was found. For the other investigated outcome – reduction of lymphoedema-associated subjective symptoms – there was no statistically significant difference *[40].* A hint of benefit was found only for the outcome of swelling.

However, a 2nd study on IPC versus MLD investigating patients with breast cancer as the underlying condition and involving compression and exercise as co-interventions found no statistically significant differences between study groups [38]. The comparison of IPC versus no IPC based on 2 studies showed no hint of benefit regarding the outcomes of swelling and health-related quality of life [30,41]. If IPC were superior to longer MLD, one would expect the other comparisons with IPC to provide evidence of benefit as well, but the studies failed to deliver this confirmation.

No hints of benefit were likewise found for MLD, laser, acupuncture, thermotherapy, or PRP.

MLD was investigated in 4 studies with patients with breast cancer as the underlying condition, with the comparator intervention group not receiving MLD. No hint of benefit was found for any of the investigated outcomes [26,32,37,42].

Laser treatment was compared with placebo laser, no laser, MLD, and PRP. No hint of benefit was found for any of these comparisons [14,33,37], with the reported data not allowing a benefit assessment for the comparison of laser versus MLD in patients with breast cancer as the underlying condition [37]. One study each compared acupuncture versus waiting list [25], thermotherapy versus compression and skin care [34], and PRP versus no PRP [14]. The study

on PRP investigated patients with lymphoedema of the lower limb following trauma and/or inflammation, while the 2 other studies included patients with breast cancer as the underlying condition. No hint of benefit was found for any of these comparisons [14,25,34], with the reported data not allowing a benefit assessment for the comparison of thermotherapy versus compression and skin care [34].

Due to small study size, high risk of bias, and the absence of minimal [clinically] important differences (M[C]IDs), this benefit or harm assessment is associated with high uncertainty as well. It is based almost exclusively on the statistical significance of effects, which are, however, not automatically associated with a noticeable symptom improvement for the patient. The reporting of the included studies was often ambiguous and incomplete. Although all included studies were RCTs or randomized cross-over studies, results on differences between the investigated study groups were often reported incompletely or not at all. Most commonly, the studies reported changes from baseline. Here, they often found statistically significant changes.

Where possible, IQWiG calculated relative effects between study groups based on the data provided on effects at the end of therapy. The number of analysed patients was likewise in part based on assumptions, particularly in cases where these figures were not clearly reported but, based on short study duration and no evidence of dropouts, it seemed likely that all randomized patients were in fact analysed. A disadvantage of analysing effects at the end of the intervention instead of effects based on changes from baseline is that, in small studies, an imbalance in the study groups at baseline may lead to misjudgement of effects.

A definitive health economic evaluation was impossible due to missing data. Based on the example of arm lymphoedema after breast cancer, however, it was possible to partially estimate costs. Costs were estimated for parts of CDT. The annual cost for a 1-month decongestive phase and subsequent maintenance phase (taking into account only MLD and compression) equals €7691.24.

When including an additional IPC device for home-use, which is optionally available according to guidelines, the cost equals €9286.24.

The reimbursement for surgical lymph node transfer (DRG J22Z) equals about €3128.71.

However, due to missing data, it was impossible to estimate the cost of additional long-term treatment, e.g. due to deterioration or complications as well as progression of disease.

A lack of suitable studies likewise makes it impossible to estimate the cost effectiveness of the interventions. The 2 identified cost-cost studies merely report costs for different time horizons (study on vascularized lymph node transfer) and treatment frequencies (study comparing Kinesio Taping versus compression). Specifically, the first study compared vascularized lymph

node transfer + 6 months of co-interventions versus no vascularized lymph node transfer, but with co-interventions for the patient's remaining lifetime. In both study groups, co-interventions were manual lymphatic drainage and compression. The second study compared Kinesio Taping 2 x weekly versus 5 x weekly compression (bandaging), each including co-interventions. The co-interventions in both study groups were compression (garments), manual lymphatic drainage, exercise, and skin care. Neither study provided proof of the equivalence of the treatment options. Hence, the studies cannot be used to draw any conclusions for the present report.

In the ethical and social domain – as in the benefit and health economic domain – long-term burdens resulting from the fact that most of the investigated therapies are not expected to cure the disease represent a very important aspect. In addition to health-related and financial burdens, burdens such as self-stigmatization and organizational aspects, e.g. the feasibility of therapies in everyday life, play a major role. This is one of the reasons why the patient organization "German Association for the Promotion of Lymphoedema Therapy" is interested the potentially curative surgical procedures [54].

Interestingly, 1 study reported higher acceptance of Kinesio Taping versus compression with bandages [45], despite the fact that in the benefit domain, more studies showed a hint of benefit of compression [39,43-45].

Another important aspect identified in the domains on ethical and social aspects were diverse obstacles which might delay or prevent access to adequate therapy. Examples include treatment providers' and patients' poor knowledge of the disease as well as ambiguities in its definition and diagnostics. Access to adequate therapy might be more difficult or insufficient due to cost carriers' reluctance to approve inpatient rehabilitation stays, budgetary specifications, and physicians' potential lack of knowledge about said specifications. In January 2021, the GB-A issued a new Remedies Directive intended to simplify the prescription of these therapies and hopefully facilitate access to these therapies [78]. Currently, patients whose lymphoedema is not due to cancer or its treatment are suspected to receive poorer care because they do not benefit from established aftercare programmes.

The focus on breast cancer as the cause of lymphoedema was also reflected by the identified literature for the benefit and health economic domains. In the benefit domain, the problem of unclear disease definition and diagnostics was reflected by the varying patient inclusion criteria. The different classification systems in part used different criteria for the classification of lymphoedema severity. This can lead to patients being classified as exhibiting advanced or severe lymphoedema according to one classification system but only mild lymphoedema by another. For instance, the Tambour study included patients with lymphoedema > 2 cm and stage II or III. Despite these inclusion criteria, they found that, with regard to the aspect of lymphoedema volume, 57% of participants ultimately had "mild" severity based on additional

limb volume (i.e. < 20%) [42]. This issue complicates not only the diagnosis of lymphoedema but also the comparison of study results.

From a legal perspective, one problem area is the handling of specific treatment methods in connection with informed consent and in view of the standard of due care. Treatment providers are responsible for providing comprehensive information and treating only after obtaining valid consent. Doing so is also a prerequisite for avoiding criminal liability. In this context, the applicability of non-governmental guidelines and their relevance for the law are a worthy topic of discussion. Rather than constituting classic national law, these guidelines represent standards defined by certain professional or interest groups which do affect the law (e.g. with regard to negligence) – a practice which certainly warrants critical questioning. However, this report deliberately discussed the current legal situation and practice first.

For these therapies, which are often needed for life, relevant organizational aspects include the setting in which they are to be administered. Most therapies are administered in an outpatient or inpatient setting, e.g. during rehabilitation, and therefore require patients to travel to a therapist for each session. Even if they are prescribed by a physician, the majority of therapies are provided by professionals other than physicians. Only surgical interventions must be carried out by a physician.

Following appropriate briefing by trained staff, some interventions, particularly self-MLD, compression, and other CDT components, possibly even IPC, can also be administered at home [30,41,50]. Since self-administration is time-intensive and requires self-discipline, it remains unclear whether in view of the chronic nature of the condition, this represents a relief for patients.

8 Discussion

8.1 HTA report compared with other publications

The classifications used for lymphoedema severity as well as for the various treatment comparisons and co-interventions used in the RCTs are highly heterogeneous. As a result, even at the level of systematic reviews, seemingly minor changes in the defined inclusion criteria based on these and potentially other criteria can lead to widely differing study pools, including in comparison with this report.

In terms of accepted experimental interventions, the systematic review by Jeffs et al, whose inclusion criteria accepted all forms of decongestive therapy, had most broad research question. However, it included only studies in which women were treated within 12 months of the onset of breast cancer-related lymphoedema. The authors included 7 studies, 5 of which were RCTs [83]. Three RCTs investigated CDT and active resistance exercise as an add-on to CDT, and 1 further study investigated laser therapy. However, only 1 RCT was found which was relevant for this report as well. While the study pool therefore differed substantially, the authors reported similar limitations: high risk of bias in the studies, heterogeneity of treatment methods and protocols, and, in part, imprecise reporting. The review's authors concluded that there is weak evidence for the effect of decongestive therapy in patients with early lymphoedema and that said evidence does not allow drawing any conclusions regarding the most effective therapy [83].

The systematic review by Kasawara et al. investigated the effects of Kinesio Taping in women with breast cancer related lymphoedema and included 7 RCTs, of which 5 were also included in this report. They concluded that each of the studies showed improvements from baseline, but not in comparison with other interventions. For this purpose, however, they pooled studies with placebo control and active control [84], an approach which, for clinical reasons, would not have been chosen in this report, despite the fact that statistical heterogeneity was low in this case.

A Cochrane review investigated surgical interventions for the prevention and therapy of breast cancer related lymphoedema, and for the latter research question, it included the same study which was found in this report. While the authors rated the study's risk of bias only as unclear despite the lack of blinding of patients, treatment providers, and outcome recorders, they assumed the evidence for the outcomes of arm volume reduction, pain score, feeling of heaviness, mean number of infection, and improvement in overall function score to be of very low quality [85]. This assessment is similar to the one arrived at in this report, albeit in the latter, allocation concealment was additionally rated as unclear since the description of this aspect was missing. On the other hand, the authors downgraded the quality of evidence for being indirect because patients in the control arm did not receive any physical or compression

therapy after the 6-month conservative therapy phase, and hence did not receive the therapy standard. As described in the study, however, this also applied to patients in the experimental intervention group. Further reasons listed for downgrading the quality of evidence were risk of bias as well as imprecision due to small study size and broad confidence intervals [85].

Further current systematic reviews on MLD [86] and acupuncture [87] had a study pool which substantially differed from the study pool for this review.

The systematic review by Müller et al. [86] included 8 RCTs, 2 of which were also included in this report [32,37]. In their opinion, the number, quality, and heterogeneity of the studies do not permit drawing definitive conclusions. Because there is no evidence to suggest that MLD might have unfavourable effects on health-related quality of life, however, the study's authors recommend that that physicians and treatment providers should emphasize to their patients the benefit of volume reduction and the potential favourable effects on health-related quality of life [86].

The review by Chien et al. included 3 RCTs on acupuncture, 1 of them being the study by Bao, which was also included in this report. The authors assessed the quality of the included RCTs as moderate to high based on the modified Jadad scale and concluded that acupuncture is safe and that there is a trend to improve the symptoms [87]. The systematic review rated the risk of bias for the Bao study as low although the study staff was explicitly documented to have been unblinded and the types of therapies make it safe to assume that the same was true for patients [25,87]. As limitations of the evidence, they list differences in the quality of the studies as well as small study sizes and differences between the studies, e.g. with regard to patients' lymphoedema status, therapies, and measuring methods for classifying lymphoedema [87].

The guideline issued by the Association of the Scientific Medical Societies in Germany (AMWF) on the therapy of lymphoedema notes that among the therapies investigated in this report, IPC, lymph taping, low-level laser, and thermotherapy are used as additional measures, but the available evidence is insufficient for recommending them in the guideline [50]. CDT represents the standard conservative treatment; according to the guideline, the isolated use of individual CDT components is not recommended, and the entire CDT programme is to be preferred. In this context, the frequency of administration and number of sessions for each of the CDT components must be adapted to the lymphoedema stage and clinical findings. When determining whether CDT is indicated, it must be noted that there are absolute contraindications (e.g. decompensated heart failure, acute deep vein thromboses) and relative contraindications. In addition, treatment modification is recommended in case of certain comorbidities [50]. According to the guideline, surgical measures should be "offered only after guideline-compliant outpatient and/or inpatient complete decongestive therapy (CDT) phases I and II have been administered for at least 6 months" [50]. However, the

guideline lists a series of other surgical interventions alongside vascular lymph node transfer and mentions potential normalization of lymphatic drainage as a proven effect of vascularized lymph node transfer [50].

9 Conclusion

For the benefit assessment, 23 studies – 21 RCTs and 2 randomized cross-over studies – were found. Three RCTs were 3-arm studies. A total of 1083 patients were enrolled in the studies. A total of 19 of the 23 studies examined only women. Only 2 studies with a total of 65 participants had mixed populations and included 15 male participants, while 2 other studies with a total of 87 participants provided no data on the percentages of female versus male participants. In 20 of the 23 studies, participants suffered from breast cancer. In 1 study each, the underlying conditions were gynaecological tumours, inflammations or trauma, or were not reported. Consequently, most available data concern arm lymphoedema, while little to no data are available on lymphoedema in other locations such as the legs, trunk, or head and neck area.

Investigated experimental interventions comprised manual lymphatic drainage, compression, exercise or movement therapy, diverse components of CDT, Kinesio Taping, intermittent pneumatic compression, vascularized lymph node transfer, laser therapy, acupuncture, thermotherapy, and platelet-rich plasma. While none of the identified studies investigated CDT in its entirety, studies were found which evaluated at least several CDT components or combinations of components.

In 1 study each on acupuncture and thermotherapy, patients received no co-interventions. In all other studies, patients received co-interventions – typically CDT components such as compression, exercise, or skin care – alongside the experimental or comparator intervention.

Hints of benefit regarding individual patient-relevant outcomes were derived for the comparison of compression versus placebo Kinesio Taping, home-based programmes, vascularized lymph node transfer as well as intermittent pneumatic compression versus (longer-term) manual lymphatic drainage. For the comparison of Kinesio Taping versus compression, contradictory effects were found depending on the co-intervention. For all other experimental interventions, there were no hints of benefit in comparison with the respective comparator intervention.

In 2 studies, *compression* treatment was compared with placebo Kinesio Taping in patients with breast cancer as the underlying condition. For this comparison, there was a hint of compression + co-interventions reducing swelling more effectively than placebo Kinesio Taping + co-interventions. In this case, the co-intervention consisted of intermittent pneumatic compression and manual lymphatic drainage with or without skin care. Adverse events data were unusable for the benefit assessment. Therefore, it was impossible to definitively weigh benefits versus harm.

Two studies on patients with breast cancer as the underlying condition investigated the effectiveness of a *home-based programme (self-administered [manual] lymphatic drainage, breathing exercises, exercise, and skin care or compression)* following conventional therapy. In 1 of these studies, the comparator was no home-based programme; there was a hint of the home-based programme as an add-on to the co-interventions achieving greater improvements in swelling, pain, and physical functioning than the co-intervention alone. The co-intervention consisted of manual lymphatic drainage, compression (garments), exercise, and breathing exercises. For the second study, there was a hint of pain being alleviated by the home-based programme + co-intervention when compared with standard therapy consisting of an information brochure + co-intervention. In this case, the co-intervention consisted of an arm guard. Neither study recorded adverse events, which made it impossible to definitively weigh benefits versus harm.

Six studies on patients with breast cancer as the underlying condition compared *Kinesio Taping* versus compression; participants were allocated to 4 groups based on co-interventions. This comparison found opposing directions of effect in some cases, with statistically significant differences being found only in 2 groups. In the group with only 1 study (co-intervention of training plan), there were hints of Kinesio Taping + co-intervention improving swelling, pain, health-related quality of life, grip strength, and the Shoulder Pain and Disability Index (SPDI) better than the co-intervention alone. However, in the other group, where co-interventions included manual lymphatic drainage and intermittent pneumatic compression, there was a hint of compression with Kinesio Taping being superior in the outcomes of swelling, mobility, and grip strength – based on the results of 3 studies and of 1 study, respectively. In the other 2 groups with 1 study each, no hint of benefit or harm was found. These opposing effects might be due to differences in the execution of the interventions, differences in co-interventions, or simply chance. For the comparison between Kinesio Taping versus no Kinesio Taping and Kinesio Taping versus placebo Kinesio Taping (+ co-interventions in each case), no hint of benefit of Kinesio Taping was found for any of the investigated patient-relevant outcomes.

The 2 studies comparing *intermittent pneumatic compression* versus manual lymphatic drainage in patients with breast cancer were analysed separately based on co-interventions. One study investigated intermittent pneumatic compression versus (longer) manual lymphatic drainage taking 30 minutes; co-interventions in both study groups were 30-minute manual lymphatic drainage, compression, exercise, and skin care. For the outcome of swelling, there was a hint of benefit. For the outcome “reduction of lymphoedema-related subjective symptoms”, no differences were found, and adverse events were not investigated. Therefore, it was impossible to definitively weigh benefits versus harm. A second study, conducting a similar comparison, compared intermittent pneumatic compression versus manual lymphatic

drainage using the co-interventions of compression and exercise. In this case, no hint of benefit was found for any of the investigated outcomes.

One study investigated vascularized lymph node transfer in comparison with no vascularized lymph node transfer in patients with breast cancer as the underlying condition. Both groups received the co-interventions of manual lymphatic drainage and compression for 6 months, followed by no further therapies for the subsequent 6 months. At the end of the follow-up period, there was a hint of lymph node transfer in combination with the co-interventions achieving greater improvements in swelling, pain, congestive symptoms, and limb function than the co-interventions alone. Likewise, there was a hint of adverse events (infection rates) occurring less commonly in the vascularized lymph node transfer group than in the comparator group without lymph node transfer. No studies were found on other surgical methods, such as lymphovenous anastomosis.

Due to the high risk of bias, small study sizes, study heterogeneity, e.g. regarding co-interventions, the outcome definitions as well as the uncertainty regarding the size of clinically relevant changes. Section 4.7 presents in detail the reported effects in relation to reported minimal clinically important differences.

It is unclear whether the data can be extrapolated to different patient populations because the included studies enrolled almost exclusively patients with breast cancer-related arm lymphoedema. In addition, it is unclear whether the results can be extrapolated to the general healthcare context in Germany: According to clinical experts, combined treatment with manual lymphatic drainage and compression is important to achieve an optimal effect. While this combination was found in all but 1 of the studies investigating compression or manual lymphatic drainage as an experimental or comparator intervention, the combinations of the various CDT components as well as the execution of the diverse interventions often varied markedly between studies. According to clinical experts, the provision of services, even within Germany, appears to vary greatly, in part due to marked (quality) differences. It was impossible to establish clear criteria for assessing transferability to the German healthcare context. None of the studies investigated the effectiveness of the entire CDT programme despite the fact that it represents standard therapy according to the AWMF guideline. Likewise, no robust data were found on adverse events, particularly on skin damage caused by lymph fluid. Generating robust evidence requires methodologically high quality RCTs as well as markedly improved reporting. Some factors affecting the risk of bias, such as blinding of outcome recorders and the implementation of the ITT principle, are relatively easy to address, while blinding of treatment providers, in particular, can be very difficult at the least. Although this report included only randomized controlled trials, results on differences between study groups are often missing. Likely of almost equal practical importance is developing core outcome sets, reaching a consensus regarding relevant classifications of

lymphoedema as well as specifying relevant subgroups based on these classifications on which systematic reporting is to be achieved. Alongside further standardization of lymphoedema classification and improved reporting, this is a prerequisite for the development of robust evidence.

A definitive health economic evaluation was impossible due to missing data. Intervention costs were estimated based on the example of arm lymphoedema after breast cancer. Estimating cost was possible only for some components of CDT, specifically for manual lymphatic drainage and compression; for a 1-month decongestive phase with a subsequent approximately 11-month maintenance phase, they equalled about €7691 annually. The cost of further CDT components (movement therapy, skin care, information, and training) are not reflected because utilization of services differs greatly between patients. The cost of the optional additional supply of a device for intermittent pneumatic compression for home use equals €1595 for about 11 months. Including intermittent pneumatic compression, the cost for 52 weeks of treatment therefore equals about €9286. The reimbursement for surgical lymph node transfer is about €3129.

However, in light of missing data, it was impossible to estimate the cost of additional long-term treatment, e.g. due to deterioration or complications as well as progression of disease.

A lack of suitable studies likewise makes it impossible to estimate the cost effectiveness of the interventions. The 2 identified cost-cost studies merely report costs for different time horizons (study on vascularized lymph node transfer) and treatment frequencies (study comparing Kinesio Taping versus compression). Specifically, the first study compared vascularized lymph node transfer + 6 months of co-interventions versus no vascularized lymph node transfer, but with co-interventions for the patient's remaining lifetime. In both study groups, co-interventions were manual lymphatic drainage and compression. The second study compared Kinesio Taping 2 x weekly versus 5 x weekly compression (bandaging), each including co-interventions. The co-interventions in both study groups were *compression (garments), manual lymphatic drainage, exercise, and skin care.* Neither study provided proof of the equivalence of the treatment options. Hence, the studies cannot be used to draw any conclusions for the present report.

The ethical and social domain identified a series of causes for long-term burden. In addition to purely health-related and financial burdens, they also cited burdens due to self-stigmatization or the feasibility of therapies in daily life, for instance. Patients report the condition to be associated with severe pain and mobility restrictions and leading to limitations in work and everyday life. Currently, patients whose lymphoedema is not due to cancer or its treatment are suspected to receive poorer care because they do not benefit from established aftercare programmes. Access to adequate therapy might be more difficult to obtain or insufficient due to cost carriers' reluctance to approve inpatient rehabilitation stays,

budgetary specifications, and physicians' potential lack of awareness about said specifications. An unclear disease definition and insufficient diagnostics might present further obstacles to adequate care. The risk of lymphoedema increases with age. In view of these problems and against the background of an ageing society, a collaborative approach, where medical specialists offer support, consultation, and instruction, might be an option for facilitating adequate treatment. The new German Remedies Directive dated 21 January 2021 is likewise intended to facilitate the prescription of these therapies and might provide easier access to these therapies.

From a legal perspective, one problem area is the handling of specific treatment methods in connection with informed consent and in view of the standard of due care. Treatment providers are responsible for providing comprehensive information and treating only after obtaining valid consent. Doing so is also a prerequisite for avoiding culpability. In this context, the applicability of non-governmental guidelines and their relevance for the law are a worthy topic of discussion. Rather than constituting classic national law, these guidelines represent standards defined by certain professional or interest groups which do affect the law (e.g. with regard to negligence) – a practice which certainly warrants critical questioning.

With regard to the interventions examined herein, it should be noted, firstly, that from a legal perspective, surgical measures represent a treatment alternative if the conservative treatment approach does not achieve sufficient improvement after at least 6 months of therapy. Improvement is insufficient if the patient's suffering is not alleviated by the conservative therapy, an increase in secondary tissue changes is recorded, or the therapy presents an excessive burden for the patient. In these cases, patients should be informed about surgical alternatives even if conservative treatment is to be preferred. The legal provisions regarding medically indicated procedures, i.e. the corresponding provisions of the German Civil Code, become applicable in this case, with specific consequences including regarding liability. Secondly, it should be noted that in 2017, the Federal Joint Committee decided to list the diagnosis of lymphoedema stage II or above for long-term remedy needs to thereby facilitate patients' long-term care for the disease. No such decision has been taken for surgical measures.

Relevant organizational aspects of these often-lifelong therapies include the setting in which they are to be carried out as well as the need for interdisciplinary collaboration. Most therapies are administered in an outpatient or inpatient setting, e.g. during rehabilitation, and therefore require patients to travel to a therapist for each session. Some interventions, particularly self-manual lymphatic drainage, compression, other CDT components, and possibly also intermittent pneumatic compression, may also be carried out at home by trained persons. However, because self-administration is time-intensive and requires self-discipline,

it remains unclear whether, in view of the chronic nature of the condition, this represents relief for patients.

Seen from the social domain, the assessment of the various therapies must take into account that physical therapies are apparently well accepted, with evidence showing that Kinesio Taping is better accepted than compression. However, acceptance might depend on patients' individual experiences. In the ethical domain, the discussion involves patients potentially preferring surgical procedures over symptomatic therapy due to the former's potential curative effect. Currently, no data on this topic are available, and the existing evidence regarding patient preferences is based on the conclusions from a small number of studies. While the diagnosis of lymphoedema stage II or above has been listed for long-term remedy needs, no corresponding decision has been taken for surgical measures. From a legal perspective, therefore, surgical measures represent the state of medical science as per professional standard based, among others, on AWMF guidelines, only after 6-month therapy with the conservative treatment approach has failed to achieve adequate improvement. From an organizational perspective, curative surgical therapy is less human resource-intensive than lifelong physical therapy. Based on the available studies, however, it is not possible to determine whether and to what extent patients in fact need no further therapies postoperatively. The required professional qualifications differ markedly, so that bottlenecks would probably occur if surgical therapy were found to be associated with substantial added benefit and patients preferred it over other therapies. Currently, however, robust evidence on benefit and harm is missing for all interventions, including the entire CDT programme; therefore, this essential information cannot be taken into account when determining preferences.

References

Please see full HTA report for the full reference list.

1. Hinterseer M, Knez A. Erkrankungen der Lymphgefäße. In: Baenkler H-W, Goldschmidt H, Hahn J-M et al (Ed). Kurzlehrbuch Innere Medizin. Georg Thieme Verlag; 2015. p. 120-121.

2. Fritsch H, Kühnel W. Systematik der Lymphgefäße und -knoten. In: Fritsch H, Kühnel W (Ed). Taschenatlas Anatomie, Band 2: Innere Organe. Georg Thieme Verlag; 2018. p. 92-100.

3. Mehrara B. Clinical features and diagnosis of peripheral lymphedema [online]. 2019 [Accessed: 26.11.2019]. URL: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-peripheral-lymphedema.

4. Lymphologen GD. S2k Leitlinie: Diagnostik und Therapie der Lymphödeme [online]. 2017 [Accessed: 25.11.2019]. URL: https://www.awmf.org/uploads/tx_szleitlinien/058-001l_S2k_Diagnostik_und_Therapie_der_Lymphoedeme_2019-07.pdf.

5. Moffatt CJ, Franks PJ, Doherty DC et al. Lymphoedema: an underestimated health problem. QJM : monthly journal of the Association of Physicians 2003; 96(10): 731-738. https://dx.doi.org/10.1093/qjmed/hcg126.

6. Smeltzer DM, Stickler GB, Schirger A. Primary Lymphedema in Children and Adolescents: A Follow-up Study and Review. Pediatrics 1985; 76(2): 206-218.

7. Dale RF. The inheritance of primary lymphoedema. Journal of Medical Genetics 1985; 22(4): 274-278. https://dx.doi.org/10.1136/jmg.22.4.274.

8. Cormier JN, Askew RL, Mungovan KS et al. Lymphedema beyond breast cancer. Cancer 2010; 116(22): 5138-5149. https://dx.doi.org/10.1002/cncr.25458.

9. Mehrara B. Clinical staging and conservative management of peripheral lymphedema [online]. 2019 [Accessed: 26.11.2019]. URL: https://www.uptodate.com/contents/clinical-staging-and-conservative-management-of-peripheral-lymphedema.

10. Földi E, Baumeister RGH, Bräutigam P et al. Zur Diagnostik und Therapie des Lymphödems. Dtsch Arztebl International 1998; 95(13): A-740.

11. Mehrara B. Surgical treatment of primary and secondary lymphedema [online]. 2019 [Accessed: 26.11.2019]. URL: https://www.uptodate.com/contents/surgical-treatment-of-primary-and-secondary-lymphedema.

12. Pekyavas NO, Tunay VB, Akbayrak T et al. Complex decongestive therapy and taping for patients with postmastectomy lymphedema: a randomized controlled study. European Journal of Oncology Nursing 2014; 18(6): 585-590. https://dx.doi.org/https://dx.doi.org/10.1016/j.ejon.2014.06.010.

13. Hamblin MR. Photobiomodulation or low-level laser therapy. Journal of Biophotonics 2016; 9(11-12): 1122-1124. https://dx.doi.org/10.1002/jbio.201670113.

14. Akgul A, Tarakci E, Arman N et al. A Randomized Controlled Trial Comparing Platelet-Rich Plasma, Low-Level Laser Therapy, and Complex Decongestive Physiotherapy in Patients with Lower Limb Lymphedema. Lymphatic Research &Biology 2020; 19: 19. https://dx.doi.org/https://dx.doi.org/10.1089/lrb.2019.0064.

15. Forte AJ, Boczar D, Huayllani MT et al. Use of Autologous Blood Components in Lymphedema Treatment: A Systematic Review. Cureus 2019; 11(9): e5638. https://dx.doi.org/https://dx.doi.org/10.7759/cureus.5638.

16. Gesundheitsberichtserstattung des Bundes. Diagnosedaten der Krankenhäuser ab 2000 (Eckdaten der vollstationären Patienten und Patientinnen) [online]. [Accessed: 09.12.2019]. URL: http://www.gbe-bund.de.

17. Gemeinsamer Bundesausschuss. Lymphödeme ab Stadium II als Diagnosen für langfristigen Heilmittelbedarf gelistet [online]. [Accessed: 25.11.2019]. URL: https://www.g-ba.de/downloads/34-215-674/08-2017-03-16_Heilmittel-RL_Lymphdrainage.pdf.

18. Physio Deutschland. Deutscher Verband für Physiotherapie (ZVK) e.V. [online]. [Accessed: 09.12.2019]. URL: https://www.physio-deutschland.de/patienten-interessierte/wichtige-therapien-auf-einen-blick/manuelle-lymphdrainage.html.

19. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden 6.0. Köln: IQWiG; 2020.

20. Information DIfMDu. ICD-10-GM Version 2020. 2019. URL: https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2020/index.htm.

21. Hofmann B, Droste S, Oortwijn W et al. Harmonization of ethics in health technology assessment: a revision of the Socratic approach. Int J Technol Assess Health Care 2014; 30(1): 3-9. https://dx.doi.org/10.1017/S0266462313000688.

22. Lysdahl KB, Mozygemba K, Burns J et al. Guidance for assessing effectiveness, economic aspects, ethical aspects, socio-cultural aspects and legal aspects in complex technologies [online]. [Accessed: 29.07.2019]. URL: https://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

23. Mozygemba K, Hofmann B, Lysdahl KB et al. Guidance to assess socio-cultural aspects [online]. 2016 [Accessed: 29.07.2019]. URL: https://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

24. Lysdahl KB, Mozygemba K, Burns J et al. Guidance for assessing effectiveness, economic aspects, ehtical aspects, socio-cultural aspects and legal aspects in complex technologies. . 2016. URL: https://www.integrate-hta.eu/wp-content/uploads/2016/08/IPP_Guidance-INTEGRATE-HTA_Nr.3_FINAL.pdf.

25. Bao T, Iris Zhi W, Vertosick EA et al. Acupuncture for breast cancer-related lymphedema: a randomized controlled trial. Breast Cancer Research &Treatment 2018; 170(1): 77-87. https://dx.doi.org/https://dx.doi.org/10.1007/s10549-018-4743-9.

26. Bergmann A, da Costa Leite Ferreira MG, de Aguiar SS et al. Physiotherapy in upper limb lymphedema after breast cancer treatment: a randomized study. Lymphology 2014; 47(2): 82-91.

27. Buragadda S, Alhusaini AA, Melam GR et al. Effect of complete decongestive therapy and a home program for patients with post mastectomy lymphedema. Journal of Physical Therapy Science 2015; 27(9): 2743-2748. https://dx.doi.org/https://dx.doi.org/10.1589/jpts.27.2743.

28. Chmielewska DD, Stania M, Blaszczak E et al. Intermittent pneumatic compression in patients with postmastectomy lymphedema. Family medicine and primary care review 2016; 18(4): 419-424. https://dx.doi.org/10.5114/fmpcr.2016.63694.

29. Dionyssiou D, Demiri E, Tsimponis A et al. A randomized control study of treating secondary stage II breast cancer-related lymphoedema with free lymph node transfer. Breast Cancer Research &Treatment 2016; 156(1): 73-79. https://dx.doi.org/https://dx.doi.org/10.1007/s10549-016-3716-0.

30. Dunn N, Williams EM, Fishbourne M et al. Home management of lower limb lymphoedema with an intermittent pneumatic compression device: a feasibility study. Pilot &Feasibility Studies 2019; 5: 113. https://dx.doi.org/https://dx.doi.org/10.1186/s40814-019-0496-4.

31. Fukushima T, Tsuji T, Sano Y et al. Immediate effects of active exercise with compression therapy on lower-limb lymphedema. Supportive Care in Cancer 2017; 25(8): 2603-2610. https://dx.doi.org/https://dx.doi.org/10.1007/s00520-017-3671-2.

32. Gradalski T, Ochalek K, Kurpiewska J. Complex Decongestive Lymphatic Therapy With or Without Vodder II Manual Lymph Drainage in More Severe Chronic Postmastectomy Upper Limb Lymphedema: A Randomized Noninferiority Prospective Study. Journal of Pain &Symptom Management 2015; 50(6): 750-757. https://dx.doi.org/https://dx.doi.org/10.1016/j.jpainsymman.2015.06.017.

33. Kilmartin L, Denham T, Fu MR et al. Complementary low-level laser therapy for breast cancer-related lymphedema: a pilot, double-blind, randomized, placebo-controlled study. Lasers in Medical Science 2020; 35(1): 95-105. https://dx.doi.org/https://dx.doi.org/10.1007/s10103-019-02798-1.

34. Li K, Xia L, Liu NF et al. Far infrared ray (FIR) therapy: An effective and oncological safe treatment modality for breast cancer related lymphedema. Journal of Photochemistry &Photobiology B - Biology 2017; 172: 95-101. https://dx.doi.org/https://dx.doi.org/10.1016/j.jphotobiol.2017.05.011.

35. Ligabue MB, Campanini I, Veroni P et al. Efficacy of self-administered complex decongestive therapy on breast cancer-related lymphedema: a single-blind randomized controlled trial. Breast Cancer Research &Treatment 2019; 175(1): 191-201. https://dx.doi.org/https://dx.doi.org/10.1007/s10549-019-05136-9.

36. Melgaard D. What is the effect of treating secondary lymphedema after breast cancer with complete decongestive physiotherapy when the bandage is replaced with Kinesio Textape? - A pilot study. Physiotherapy Theory &Practice 2016; 32(6): 446-451.

37. Ridner SH, Poage-Hooper E, Kanar C et al. A pilot randomized trial evaluating low-level laser therapy as an alternative treatment to manual lymphatic drainage for breast cancer-related lymphedema. Oncology Nursing Forum 2013; 40(4): 383-393. https://dx.doi.org/https://dx.doi.org/10.1188/13.ONF.383-393.

38. Sanal-Toprak C, Ozsoy-Unubol T, Bahar-Ozdemir Y et al. The efficacy of intermittent pneumatic compression as a substitute for manual lymphatic drainage in complete decongestive therapy in the treatment of breast cancer related lymphedema. Lymphology 2019; 52(2): 82-91.

39. Smykla A, Walewicz K, Trybulski R et al. Effect of Kinesiology Taping on breast cancer-related lymphedema: a randomized single-blind controlled pilot study. BioMed Research International 2013; 2013: 767106. https://dx.doi.org/https://dx.doi.org/10.1155/2013/767106.

40. Szolnoky G, Lakatos B, Keskeny T et al. Intermittent pneumatic compression acts synergistically with manual lymphatic drainage in complex decongestive physiotherapy for breast cancer treatment-related lymphedema. Lymphology 2009; 42(4): 188-194.

41. Szuba A, Achalu R, Rockson SG. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema. A randomized, prospective study of a role for adjunctive intermittent pneumatic compression. Cancer 2002; 95(11): 2260-2267.

42. Tambour M, Holt M, Speyer A et al. Manual lymphatic drainage adds no further volume reduction to Complete Decongestive Therapy on breast cancer-related lymphoedema: a multicentre, randomised, single-blind trial. British Journal of Cancer 2018; 119(10): 1215-1222. https://dx.doi.org/https://dx.doi.org/10.1038/s41416-018-0306-4.

43. Tantawy SA, Abdelbasset WK, Nambi G et al. Comparative Study Between the Effects of Kinesio Taping and Pressure Garment on Secondary Upper Extremity Lymphedema and Quality of Life Following Mastectomy: A Randomized Controlled Trial. Integrative Cancer Therapies 2019; 18: 1534735419847276. https://dx.doi.org/https://dx.doi.org/10.1177/1534735419847276.

44. Taradaj J, Halski T, Rosinczuk J et al. The influence of Kinesiology Taping on the volume of lymphoedema and manual dexterity of the upper limb in women after breast cancer treatment. European Journal of Cancer Care 2016; 25(4): 647-660. https://dx.doi.org/https://dx.doi.org/10.1111/ecc.12331.

45. Tsai HJ, Hung HC, Yang JL et al. Could Kinesio tape replace the bandage in decongestive lymphatic therapy for breast-cancer-related lymphedema? A pilot study. Supportive Care in Cancer 2009; 17(11): 1353-1360. https://dx.doi.org/https://dx.doi.org/10.1007/s00520-009-0592-8.

46. Tambour M, Tange B, Christensen R et al. Effect of physical therapy on breast cancer related lymphedema: protocol for a multicenter, randomized, single-blind, equivalence trial. BMC Cancer 2014; 14: 239. https://dx.doi.org/https://dx.doi.org/10.1186/1471-2407-14-239.

47. Tidhar D, Armer JM, Stewart BR. What Is Clinically Important in Lymphedema Management? A Systematic Review. Rehabilitation Oncology 2018; 36(1): 13-27. 13. https://dx.doi.org/10.1097/01.Reo.0000000000000093.

48. Ramos SM, O'Donnell LS, Knight G. Edema volume, not timing, is the key to success in lymphedema treatment. Am J Surg 1999; 178(4): 311-315. https://dx.doi.org/10.1016/s0002-9610(99)00185-3

49. Carati CJ, Anderson SN, Gannon BJ et al. Treatment of postmastectomy lymphedema with low-level laser therapy: a double blind, placebo-controlled trial. Cancer 2003; 98(6): 1114-1122.

50. online A. S2k Leitlinie Diagnostik und Therapie der Lymphödeme. AWMF Reg.-Nr. 058-001: 2017. URL: https://www.awmf.org/uploads/tx_szleitlinien/058-001l_S2k_Diagnostik_und_Therapie_der_Lymphoedeme_2019-07.pdf.

51. Hofmann B, Droste S, Oortwijn W et al. Harmonization of ethics in health technology assessment: a revision of the Socratic approach. Int J Technol Assess Health Care 2014; 30(1): 3-9. https://dx.doi.org/10.1017/S0266462313000688.

52. Fu MR, Kang Y. Psychosocial Impact of Living With Cancer-Related Lymphedema. Seminars in Oncology Nursing 2013; 29(1): 50-60. https://dx.doi.org/https://doi.org/10.1016/j.soncn.2012.11.007.

53. Moffatt CJ, Franks PJ, Doherty DC et al. Lymphoedema: an underestimated health problem. QJM: An International Journal of Medicine 2003; 96(10): 731-738. https://dx.doi.org/10.1093/qjmed/hcg126.

54. e.V. VzFdL. Verein zur Förderung der Lymphoedemtherapie e.V. [online]. [Accessed: 09.11.2020]. URL: https://www.lymphverein.de/index.html.

55. Rhoten B, Radina M, Adair M et al. Hide and seek: Body image-related issues for breast cancer survivors with lymphedema. Journal of Womens Health, Issues & Care 2015; 4(2): 1-7.

56. Symvoulakis EK, Anyfantakis DI, Lionis C. Primary lower limb lymphedema: a focus on its functional, social and emotional impact. Int J Med Sci 2010; 7(6): 353-357. https://dx.doi.org/10.7150/ijms.7.353.

57. McWayne J, Heiney SP. Psychologic and social sequelae of secondary lymphedema: a review. Cancer 2005; 104(3): 457-466. https://dx.doi.org/10.1002/cncr.21195.

58. Woods M. Patients' perceptions of breast-cancer-related lymphoedema. Eur J Cancer Care (Engl) 1993; 2(3): 125-128. https://dx.doi.org/10.1111/j.1365-2354.1993.tb00181.x.

59. Ridner SH. The psycho-social impact of lymphedema. Lymphat Res Biol 2009; 7(2): 109-112. https://dx.doi.org/10.1089/lrb.2009.0004.

60. Moffatt C, Keeley V, Quere I. The Concept of Chronic Edema-A Neglected Public Health Issue and an International Response: The LIMPRINT Study. Lymphat Res Biol 2019; 17(2): 121-126. https://dx.doi.org/10.1089/lrb.2018.0085.

61. Nairn S, Dring E, Aubeeluck A et al. LIMPRINT: A Sociological Perspective on "Chronic Edema". Lymphat Res Biol 2019; 17(2): 168-172. https://dx.doi.org/10.1089/lrb.2018.0082.

62. Bosompra K, Ashikaga T, O'Brien PJ et al. Knowledge about preventing and managing lymphedema: a survey of recently diagnosed and treated breast cancer patients. Patient Education and Counseling 2002; 47(2): 155-163. 155. https://dx.doi.org/10.1016/s0738-3991(01)00193-8.

63. Kwan ML, Shen L, Munneke JR et al. Patient awareness and knowledge of breast cancer-related lymphedema in a large, integrated health care delivery system. Breast Cancer Res Treat 2012; 135(2): 591-602. https://dx.doi.org/10.1007/s10549-012-2199-x.

64. Deng J, Fu MR, Armer JM et al. Self-reported information sources and perceived knowledge in individuals with lymphedema. Lymphology 2013; 46(4): 173-183.

65. Paskett ED, Stark N. Lymphedema: Knowledge, Treatment, and Impact Among Breast Cancer Survivors. Breast J 2000; 6(6): 373-378. https://dx.doi.org/10.1046/j.1524-4741.2000.99072.x.

66. Radina ME, Armer JM, Culbertson SD et al. Post-breast cancer lymphedema: understanding women's knowledge of their condition. Oncol Nurs Forum 2004; 31(1): 97-104. https://dx.doi.org/10.1188/04.ONF.97-104.

67. Krzywonos A, Ochalek K, Krzywonos-Zawadzka A et al. Assessment of knowledge of cancer and lymphoedema among breast cancer survivors. Prz Menopauzalny 2014; 13(5): 273-279. https://dx.doi.org/10.5114/pm.2014.45170.

68. Thomas R, Hamilton R. Illustrating the (in)visible: understanding the impact of loss in adults living with secondary lymphedema after cancer. Int J Qual Stud Health Well-being 2014; 9: 24354. https://dx.doi.org/10.3402/qhw.v9.24354.

69. Fahradyan A, El-Sabawi B, Patel KM. Understanding Patient Expectations of Lymphedema Surgery. Plast Reconstr Surg 2018; 141(6): 1550-1557. https://dx.doi.org/10.1097/PRS.0000000000004417.

70. Ostby PL, Armer JM, Smith K et al. Patient Perceptions of Barriers to Self-Management of Breast Cancer-Related Lymphedema. West J Nurs Res 2018; 40(12): 1800-1817. https://dx.doi.org/10.1177/0193945917744351.

71. Logan V, Barclay S, Caan W et al. Knowledge of lymphoedema among primary health care teams: a questionnaire survey. British Jounal of General Practice 1996; 46(411): 607-608.

72. Mete Civelek G, Aypak C, Turedi O. Knowledge of Primary Care Physicians About Breast-Cancer-Related Lymphedema: Turkish Perspective. J Cancer Educ 2016; 31(4): 687-692. https://dx.doi.org/10.1007/s13187-015-0880-6.

73. Morgan PA, Moody M, Franks PJ et al. Assessing community nurses' level of knowledge of lymphoedema. Br J Nurs 2005; 14(1): 8-13. https://dx.doi.org/10.12968/bjon.2005.14.1.17365.

74. Pugh S, Ives A, Stubbs C. Challenges of lymphoedema management in an ageing population. Br J Community Nurs 2018; 23(Sup10): S6-12. https://dx.doi.org/10.12968/bjcn.2018.23.Sup10.S6.

75. Lulay GR. Sekundäre Lymphödeme: Diagnose und Therapie weiterhin unbefriedigend. Deutsches Ärzteblatt 2017; 114(5): 14-16. https://dx.doi.org/10.3238/PersOnko/2017.02.03.03.

76. Bundesausschuss G. Lymphödeme ab Stadium II als Diagnosen für langfrstigen Heilmittelbedarf gelistet. URL: https://www.g-ba.de/presse/pressemitteilungen-meldungen/674/.

77. Perleth M, Gibis B, Velasco Garrido M et al. Organisationsstrukturen und Qualität. In: Perleth M, Busse R, Gerhardus A et al (Ed). Health Technology Assessment: Konzepte, Methoden, Praxis für Wissenschaft und Entscheidungsfindung. Berlin: Medizinisch Wissenschaftliche Verlagsgesellschaft; 2014. p. 265-279.

78. Bundesvereinigung K. Die Heilmittel-Richtlinie des Gemeinsamen Bundesausschusses. 2021. URL: https://www.g-ba.de/downloads/62-492-2471/HeilM-RL_2021-03-18_iK-2021-04-01.pdf.

79. Lymphology ECotISo. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology 2020; 53(1): 3-19.

80. Heringen H. Kinesiotape-Jetzt auch im Hausarztzentrum Heringen. URL: http://www.hausarztzentrum-heringen.de/files/Kinesiotape_hp.pdf.

81. Bundesausschuss G. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie „Methoden vertragsärztliche Versorgung“ in Anlage I „Anerkannte Untersuchungs- oder Behandlungsmethoden“ und in Anlage II „Methoden, die nicht als vertragsärztliche Leistungen zulasten der Krankenkassen erbracht werden dürfen“: Akupunktur. Deutsches Ärzteblatt 2006; 103(50): A 3429-3430.

82. Schwahn-Schreiber C, Reich-Schupke S, Breu FX et al. S1-Leitlinie Intermittierende pneumatische Kompression (IPK, AIK). AWMF Reg.-Nr. 037/007: 2018. URL: https://www.awmf.org/uploads/tx_szleitlinien/037-007l_S1_Intermittierende-pneumatische-Kompression-IPK-AIK_2018-07.pdf.

83. Jeffs E, Ream E, Taylor C et al. Clinical effectiveness of decongestive treatments on excess arm volume and patient-centered outcomes in women with early breast cancer-related arm lymphedema: a systematic review. JBI Database Of Systematic Reviews And Implementation Reports 2018; 16(2): 453-506. https://dx.doi.org/https://dx.doi.org/10.11124/JBISRIR-2016-003185.

84. Kasawara KT, Mapa JMR, Ferreira V et al. Effects of Kinesio Taping on breast cancer-related lymphedema: A meta-analysis in clinical trials. Physiotherapy Theory &Practice 2018; 34(5): 337-345. https://dx.doi.org/https://dx.doi.org/10.1080/09593985.2017.1419522.

85. Markkula SP, Leung N, Allen VB et al. Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. Cochrane Database of Systematic Reviews 2019; 2: CD011433.
https://dx.doi.org/https://dx.doi.org/10.1002/14651858.CD011433.pub2.

86. Muller M, Klingberg K, Wertli MM et al. Manual lymphatic drainage and quality of life in patients with lymphoedema and mixed oedema: a systematic review of randomised controlled trials. Quality of Life Research 2018; 27(6): 1403-1414. https://dx.doi.org/https://dx.doi.org/10.1007/s11136-018-1796-5.

87. Chien TJ, Liu CY, Fang CJ. The Effect of Acupuncture in Breast Cancer-Related Lymphoedema (BCRL): A Systematic Review and Meta-Analysis. Integrative Cancer Therapies 2019; 18: 1534735419866910. https://dx.doi.org/https://dx.doi.org/10.1177/1534735419866910.

88. European Network for Health Technology Assessment. EUnetHTA Joint Action 2: work package 8; HTA Core Model; version 3.0 [online]. [Accessed: 30.07.2019]. URL: https://www.eunethta.eu/wp-content/uploads/2018/03/HTACoreModel3.0-1.pdf.

89. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

90. Lefebvre C, Manheimer E, Glanville J. Searching for studies [online]. 2011 [Accessed: 05.09.2018]. URL: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm.

91. Glanville J, Fleetwood K, Yellowlees A et al. Development and testing of search filters to identify economic evaluations in MEDLINE and EMBASE. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

The full HTA report (German version) is published under

https://www.iqwig.de/sich-einbringen/themencheck-medizin-thema-vorschlagen/hta-berichte/ht19-01.html

Appendix A – Topics of the EUnetHTA Core Model

The European Network for Health Technology Assessment (EUnetHTA) is a network of European HTA agencies. EUnetHTA promotes the exchange of HTA information between its members and developed the core model [88] for this purpose. IQWiG is also a member of the network.

In order to make it easier for readers of this HTA report to find information on the superordinate domains of the EUnetHTA Core Model, Table 6 indicates where the relevant information can be found. The original names of the domains of the core model are used to describe the topics.

Table 6: Domains of the EUnetHTA Core Model

EUnetHTA domain	**Information in chapters and sections of the HTA report**
Health problem and current use of the technology (CUR)	**Background** Chapter 1
Description and technical characteristics of technology (TEC)	
Safety (SAF)	**Benefit assessment** Section 3.1; Chapter 4; Section A2.1; Chapter A3
Clinical effectiveness (EFF)	
Costs and economic evaluation (ECO)	**Health economic evaluation** Section 3.2; Chapter 5; A2.2; Chapter A4
Ethical analysis (ETH)	**Ethical aspects** Section 3.3; Section 6.1; Section A2.3 Section A5.1
Patients and social aspects (SOC)	**Social aspects** Section 3.4; Section 6.2; Section A2.4; Section A5.2
Legal aspects (LEG)	**Legal aspects** Section 3.4; Section 6.3; Section A2.4 Section A5.3
Organizational aspects (ORG)	**Organizational aspects** Section 3.4; Section 6.4; Section A2.4; Section A5.4

Appendix B – Search strategies

B.1 – Search strategies for the benefit assessment

B.1.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to February Week 3 2020
- Ovid MEDLINE(R) Daily Update February 26, 2020

The following filters were adopted:

- Systematic review: Wong [89] – High specificity strategy
- RCT: Lefebvre [90] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	Searches
1	exp Lymphedema/
2	(lymphedema* or lymphoedema*).ti,ab.
3	elephantiasis*.ti,ab.
4	or/1-3
5	randomized controlled trial.pt.
6	controlled clinical trial.pt.
7	(randomized or placebo or randomly or trial or groups).ab.
8	drug therapy.fs.
9	or/5-8
10	9 not (exp animals/ not humans.sh.)
11	cochrane database of systematic reviews.jn.
12	(search or MEDLINE or systematic review).tw.
13	meta analysis.pt.
14	or/11-13
15	10 or 14
16	4 and 15
17	16 not (comment or editorial).pt.
18	17 and (english or german).lg.

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to February 26, 2020
- Ovid MEDLINE(R) Epub Ahead of Print February 26, 2020

#	Searches
1	(lymphedema* or lymphoedema*).ti,ab.
2	elephantiasis*.ti,ab.
3	or/1-2
4	(clinical trial* or random* or placebo).ti,ab.
5	trial.ti.
6	(search or meta analysis or medline or systematic review).ti,ab.
7	or/4-6
8	3 and 7
9	8 not (comment or editorial).pt.
10	9 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 February 26

The following filters were adopted:

- Systematic review: Wong [89] – High specificity strategy
- RCT: Wong [89] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp lymphedema/
2	(lymphedema* or lymphoedema*).ti,ab.
3	elephantiasis*.ti,ab.
4	or/1-3
5	(random* or double-blind*).tw.
6	placebo*.mp.
7	or/5-6
8	(meta analysis or systematic review or MEDLINE).tw.
9	or/7-8
10	4 and 9
11	10 not medline.cr.
12	11 not (exp animal/ not exp human/)
13	12 not (Conference Abstract or Conference Review or Editorial).pt.
14	13 and (english or german).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews, Issue 2 of 12, February 2020
- Cochrane Central Register of Controlled Trials, Issue 2 of 12, February 2020

#	Searches
#1	[mh "Lymphedema"]
#2	(lymphedema* or lymphoedema*):ti,ab
#3	elephantiasis*:ti,ab
#4	#1 OR #2 OR #3 in Cochrane Reviews, Cochrane Protocols, Trials

B.1.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
lymphedema OR lymphoedema

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch
- Type of search: Standard Search

Search strategy
lymphedema OR lymphoedema

B.2 – Search strategies for the health economic evaluation

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL <1946 to February 26, 2020>

The following filter was adopted:

- Glanville [91] – Emory University (Grady)

#	Searches
1	exp Lymphedema/
2	(lymphedema* or lymphoedema*).ti,ab.
3	elephantiasis*.ti,ab.
4	or/1-3
5	(economic$ or cost$).ti.
6	cost benefit analysis/
7	treatment outcome/ and ec.fs.
8	or/5-7
9	8 not ((animals/ not humans/) or letter.pt.)
10	4 and 9
11	10 not (comment or editorial).pt.
12	11 and (english or german).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2020 February 26

The following filter was adopted:

- Glanville [91] – Embase G

#	Searches
1	exp lymphedema/
2	(lymphedema* or lymphoedema*).ti,ab.
3	elephantiasis*.ti,ab.
4	or/1-3
5	(Cost adj effectiveness).ab.
6	(Cost adj effectiveness).ti.
7	(Life adj years).ab.
8	(Life adj year).ab.
9	Qaly.ab.
10	(Cost or costs).ab. and Controlled Study/
11	(Cost and costs).ab.
12	or/5-11
13	4 and 12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 and (english or german).lg.