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**A dual realist review: compression for leg swelling at the end of life has potential quality of life benefit**

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## **Abstract**

### **Aims**

To examine the evidence for the use of compression in the general population and determine how far it can be used to inform treatment at end of life.

### **Design**

In advanced illness, some patients suffer lower limb swelling and its resulting problems. In the general population, compression is used to treat lower limb swelling, but little is known about its use at end of life. This review is designed to deeply explore the available evidence and identify what is known and areas for further research.

**Data Sources:** Five databases were searched; CINAHL, MEDLINE, Embase, AMED and Cochrane, in November 2021. Reference lists for included studies were hand-searched. A web search was carried out.

### **Review Methods:**

Two parallel realist reviews were performed. The first reviewed the use of compression in the general population. The second explored lower limb swelling at end of life. Findings were screened using inclusion and exclusion criteria, quality assessed and qualitative and quantitative data extracted.

### **Results:**

The initial searches returned 1179 articles in review one and 839 articles in review two. Following screening, 10 articles remained in each review for analysis. A programme theory was drawn for each review. The theories had sufficient similarities to allow evidence from the general population to be used to make recommendations for those at end of life.

### **Impact:**

People with advanced illness and leg swelling suffer physically and psychologically. Compression delivers a reduction in swelling and a quality of life benefit in the general population. This study found people with advanced illness may experience the same benefits. A cautious approach should be taken and stockings or adjustable Velcro compression devices (AVCDs) are likely to be the best starter interventions. Existing guidelines should also be consulted. Further research to develop the right intervention in this group is needed.

**Keywords:** swelling, oedema, lower limb, leg, compression, quality of life, palliative, end of life

**No patient and public contribution:** as this is a review article.

## INTRODUCTION

### Rationale for review

People approaching the end of life suffer lower limb swelling. In this review, the term swelling is chosen to encompass oedema, lymphoedema and swelling of mixed or uncertain aetiology.

Little is known about the exact prevalence of swelling in people approaching the end of life, or about the best way to manage swelling in this group. Comprehensive guidelines exist for the management of lymphoedema in the general population, but they offer limited advice for those at the end of life, and the evidence to support it is weak (International Lymphoedema Framework (ILF), 2012, Lymphoedema Framework, 2006, Lymphoedema Support Network (LSN), 2015). Palliative care guidelines for the management of symptoms occurring at end of life, do not consider lower limb swelling (Health Improvement Scotland, 2017, National Institute for Health and Care Excellence, 2017, Royal College of Nursing, 2015).

This lack of research and guidance makes treatment decisions about lower limb swelling at end of life difficult. This is acknowledged by lymphoedema experts (Lymphoedema Framework, 2006, LSN, 2015).

This situation is concerning due to the negative impact of lower limb swelling. Resulting problems include pain, loss of function, reduced mobility, lymphorrhoea, ulceration, psychosocial problems and infection (Honnor, 2009, Todd, 2009). Failure to manage lower limb swelling adversely affects quality of life.

Compression therapy is the use of bandaging or hosiery to increase the pressure within the limb, to improve lymphatic drainage and venous return (Newton, 2013). In the general population, compression therapy is the main treatment for lower limb swelling, with a good body of evidence supporting its use (European Wound Management Association (EWMA), ILF, 2012).

In end of life care, there is no such evidence. Conducting research is difficult, recruitment and retention may be a problem, the population is vulnerable and the ethics are challenging (Bar-Sela et al., 2010, Jacobsen & Blinderman, 2011, Murtagh et al., 2007).

Nonetheless, compression cannot be used at end of life without a sound understanding of the benefits and potential complications (Todd, 2009).

Realist review may offer a way forward. It is hoped that by conducting two parallel reviews and analysing the results together, evidence from one population can suggest a way forward in another.

## BACKGROUND

### Rationale for realist synthesis

Realist synthesis is a relatively young approach to review, with its roots in philosophy, social science and evaluation (Pawson, 2002, Pawson et al., 2004). It has recently been adopted as an approach to the review of complex interventions in healthcare (Pawson et al., 2004, Rycroft-Malone et al., 2012).

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2  
3 Some interventions work, or do not work, due to a complex set of interrelated factors, such as  
4 context, individuals and setting. In this situation a traditional systematic review, asking “does it  
5 work?” is not useful. Realist review is different. It asks “what works, for whom and in what  
6 circumstances?” It examines the context, mechanism and outcome of an intervention (Pawson,  
7 2002, Pawson et al., 2004, Rycroft-Malone et al., 2012, The RAMESES project, 2014, Wong et al.,  
8 2010). Realist review helps to determine the complex set of circumstances necessary to maximise  
9 the success of the intervention.  
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11

12  
13 This review concerns the use of compression to deliver a quality of life benefit at end of life. This  
14 may seem suited to a traditional meta-analysis. However, as the scoping search demonstrated, there  
15 are no trials of compression in advanced disease to include in such a review. A different approach is  
16 therefore taken.  
17  
18

19 Realist review is used to extract complex information about compression in the general population  
20 and about swelling at end of life. It is hoped by taking this approach two parallel programme  
21 theories (context, mechanism, outcome models) may be drawn. If these have sufficient similarities,  
22 it may be possible to use information from one population to inform another.  
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24

## 25 **THE REVIEW**

### 26 **Aims, objectives and focus**

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29 Primary research question: what evidence is available to inform decisions about the use of  
30 compression to improve quality of life in lower limb swelling at end of life? This question is  
31 subdivided into two separate realist reviews. Review one: does compression reduce lower limb  
32 swelling and/or deliver a quality of life benefit in the general population? If so, how, for whom and in  
33 what way? Review two: what problems are caused by lower limb swelling at end of life? How, for  
34 whom and why do these problems occur? The results of the two reviews are analysed together.  
35  
36

37  
38 The review considered compression with layered bandaging systems, AVCDs and hosiery. Other  
39 forms of compression, such as intermittent pneumatic compression, were not included. Patients  
40 approaching the end of their lives are often cared for in hospices or the community, where there is  
41 not access to complex equipment or intensive monitoring.  
42  
43

44 The review focused on compression with bandages, hosiery or AVCDs used alone. When  
45 compression was used together with other interventions, such as exercise or manual lymphatic  
46 drainage, the study was excluded. This aimed to reduce confounding by other variables. Additionally,  
47 patients at end of life often have a poor functional status that would preclude these interventions.  
48  
49

### 50 **Design**

#### 51 **Scoping the literature**

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53  
54 A scoping search was performed to determine what was known about the management of lower  
55 limb swelling at end of life. The databases searched were; MEDLINE, CINAHL, Embase, AMED and  
56 Cochrane. The search identified 52 results. Following screening by abstract, 3 studies remained  
57 (Balzarini, 2011, Jacobsen & Blinderman, 2011, Lawrence, 2008). One small study of 14 patients  
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2  
3 offered evidence that might inform a treatment decision in lower limb swelling at end of life  
4 (Balzarini, 2011).  
5

6 A web search of the grey literature was performed. National guidelines for the management of  
7 lymphoedema were retrieved and contain some information about the management of lower limb  
8 swelling at end of life. However, this tends to be based on expert consensus, rather than research  
9 evidence, and is general in nature (ILF,2012, Lymphoedema Framework, 2006, LSN, 2015). The lack  
10 of research evidence to support these recommendations is acknowledged within them  
11 (Lymphoedema Framework, 2006).  
12  
13

14  
15 Overall, the scoping search confirmed a paucity of evidence to support treatment decisions in lower  
16 limb swelling at end of life, supporting the premise of the review.  
17

### 18 **Changes in the review process**

19  
20 While carrying out the review, it became clear some interventions not related to compression were  
21 being used to manage lower limb swelling at end of life. A sub-question was therefore added to the  
22 second review: what is currently being done to manage these problems? This was to allow  
23 comparison between these interventions and compression.  
24  
25

26 During the review, it became clear that there was a profound lack of evidence concerning lower limb  
27 swelling at end of life. It was not possible to find studies meeting the criteria of "rigorous  
28 methodology." Some studies were available with weaker methodology, including pilot studies and  
29 case reports. A decision was taken to include these studies, as long as they contained primary data  
30 and were peer reviewed. It was considered better to examine what little is known. A lack of rigour in  
31 these studies was addressed by quality assessment, and reference to quality in discussion and  
32 conclusion.  
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35

### 36 **Search methods**

37  
38 Two separate searches were undertaken, for two separate literature reviews.  
39

40 Search one was of the following databases; MEDLINE, CINAHL, Embase, AMED and Cochrane. This  
41 search was completed in September 2017 and updated November 2021. The free text terms used  
42 for all databases were; edema, oedema or swelling AND leg, lower limb, ankle, calf or thigh AND  
43 compression therapy, compression bandaging, compression garment, compression hosiery,  
44 compression stockings, multi-layer system, long-stretch or short-stretch. Keyword searches were  
45 performed using the following terms. For CINAHL; oedema, lower extremity, leg, compression  
46 garments, compression therapy and elastic bandages. For MEDLINE; edema, leg, lower extremity,  
47 compression bandages, stockings, compression. For Embase; edema, leg oedema, leg, lower leg,  
48 compression bandage, compression garment, compression stocking, compression therapy, leg  
49 compression. For AMED; edema, leg. Cochrane does not use keywords.  
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53

54 Search two was of the following databases; MEDLINE, CINAHL, Embase, AMED and Cochrane. The  
55 search was completed in September 2017 and updated in November 21. The free text terms used for  
56 all databases were; edema, oedema or swelling AND leg, lower limb, ankle, calf or thigh AND  
57 hospice, palliative, terminal, dying, end of life or advanced disease. Keyword searches were  
58 performed using the following terms. For CINAHL; edema, lower extremity, leg, hospice care,  
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3 hospice and palliative nursing, palliative care, terminal care. For MEDLINE; edema, leg lower  
4 extremity, hospice and palliative care nursing, palliative care, palliative medicine. For Embase;  
5 edema, leg edema, leg, lower leg, palliative therapy, conservative treatment. For AMED; edema, leg,  
6 palliative care, terminal care. Cochrane does not use key words.  
7  
8

9 In realist review, searching usually takes an iterative approach, until saturation is reached (Pawson  
10 et al., 2004, Wong et al., 2010). However, this study was carried out by a single researcher and  
11 iterative searching until saturation was not possible within the timeframe. Instead, an inclusion and  
12 exclusion criteria was applied, whilst maintaining a realist scientific approach. There is precedent for  
13 this hybrid use of realist enquiry (Rycroft-Malone et al., 2012). It is acknowledged that there is a risk  
14 some information may have been missed using this screening technique.  
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### 20 **Search outcome**

21  
22 Studies were screened by abstract, by a single researcher, against criteria shown in table one. The  
23 criteria are designed to screen for relevance and rigour (Wong et al., 2010).  
24

25 After screening by abstract, 140 articles remained in literature review one and 36 articles in  
26 literature review two. The full text of these articles was obtained, and the articles screened again  
27 against the above criteria. Reference lists were hand screened. A web search was performed.  
28  
29

30 Throughout, the main criteria for exclusion were documented, to allow insight into the exclusion  
31 process (Pawson et al., 2005, Rycroft-Malone et al., 2012). See figures 1 and 2. At the end of the  
32 process, 10 articles remained for analysis in each review.  
33  
34

### 35 **Quality appraisal**

36  
37 In keeping with realist methodology, a variety of study designs were included (Wong et al., 2010). As  
38 a result, it was not possible to use one pre-designed quality assessment tool. Instead a bespoke tool  
39 was created, based on a synthesis of leading evidence-based tools produced by the Critical Appraisal  
40 Skills Programme (CASP) (CASP, 2017), the Joanna Briggs Institute (2017) and the Cochrane  
41 Collaboration (Higgins & Green, 2011). The bespoke tool was given minor adaptations to suit three  
42 broad groups of studies; randomised controlled trials, other interventional studies and descriptive  
43 works.  
44  
45

46 Quality assessment data is summarised in table 2. A full breakdown of quality assessment by  
47 question is included, as the evidence does not support the use of aggregated scores (Higgins &  
48 Green, 2011).  
49  
50

### 51 **Data abstraction**

52  
53 In keeping with a realist approach, a data extraction tool was designed specifically for this review  
54 (Pawson et al., 2004). A slightly adapted version was used for each review.  
55  
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### 57 **Synthesis**

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3 Data was analysed by a single researcher. Key themes were documented as they emerged. Demi-  
4 regularities (patterns) were observed in the data and recorded. The demi-regularities were used to  
5 construct middle range programme theories. These were tested across the different studies and  
6 contexts and refuting evidence sought (Wong et al., 2010). The result was two distinct programme  
7 theories, one to represent each review.  
8  
9

## 10 RESULTS

### 11 Literature review one

#### 12 Document characteristics and main findings

13 See table 3

#### 14 Intervention and outcome: compression delivers a reduction in swelling and/or quality of life benefit

15 In all studies compression delivered a reduction in swelling and/or a quality of life benefit, even  
16 where this was not the primary goal.

17 The studies used a variety of different forms of compression, including compression stockings,  
18 compression bandages, AVCDs and elastic kits.

19 One study used a control group (Wu et al., 2017). Four studies compared one mode of compression  
20 against another (Badger et al., 2000, Mosti & Partsch, 2013, Mosti et al., 2015, Mosti et al., 2012).  
21 Two studies were quasi experimental, investigating a single type of compression (Franks et al., 2012,  
22 Midttun et al., 2010). Three studies were descriptive cross-sectional studies (Cataldo et al., 2012,  
23 Franks et al., 2006, Rabe et al., 2012). The studies did not have sufficient homogeneity to justify a  
24 meta-analysis, which supports the realist mode of enquiry.

25 Refuting evidence was sought for the outcome of a reduction in swelling and/or quality of life  
26 benefit. No interventional studies recorded withdrawals due to complications of compression. In the  
27 descriptive studies some patients withdrew due to difficulty applying the stockings, lack of  
28 improvement in symptoms, cosmetic concerns or not having the prescription filled (Cataldo et al.,  
29 2012, Rabe et al., 2012). None withdrew due to complications of compression.

30 In terms of negative outcomes, small numbers of patients experienced the following during the  
31 intervention; worsening of swelling, muscle cramps, cellulitis, deep vein thrombosis, although the  
32 link with compression was not clear (Badger et al., 2000, Cataldo et al., 2012). A small number of  
33 patients developed side effects which were linked to compression including; skin irritation, itching,  
34 sores under bandages (Franks et al., 2012, Wu et al., 2017). All of these problems were able to be  
35 treated and compression therapy continued.

#### 36 Mechanism: How does compression deliver a reduction in swelling and/or quality of life benefit?

37 The studies in the review describe swelling in the lower limb as a result of two problems, occurring  
38 together or separately. The first is venous hypertension. This occurs due to insufficiency of the veins  
39 in returning blood to the heart. This causes excessive capillary filtration from the vascular system  
40 into the interstitial space (Mosti et al., 2012).  
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3 The second problem is insufficient drainage of excess fluid from the interstitial space via the  
4 lymphatic system. Lymphatic flow is dependent on subtle changes in interstitial pressure, which  
5 prompt contractions. It is likely that in lymphoedema this system fails (Badger et al., 2000).  
6  
7

8 These vascular and lymphatic problems ultimately lead to excess fluid in the interstitial space, which  
9 causes swelling. The studies explain that compression works to address these problems in the  
10 following ways.  
11

12 In the venous system, pressure exerted by an inelastic bandage supports the calf muscle pump, by  
13 providing a rigid outer layer against which the muscle can push, increasing the force of the  
14 contraction. Blood is forced out of the limb and back towards the heart. Venous pressure reduces  
15 and the valves in the veins are supported to prevent back flow of blood (Badger et al., 2000, Wu et  
16 al., 2017). Stockings and elastic bandages work in a similar way, but the elastic materials pushing  
17 against the limb exert continuous pressure (Badger et al., 2000).  
18  
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20

21 In the lymphatic system, compression of all forms works in two ways. External compression of the  
22 limb reduces filtration from the capillaries into the interstitial space. External compression also  
23 increases pressure on the lymphatic system, stimulating contractions and enhancing the drainage of  
24 fluid into the circulation (Badger et al., 2000, Mosti & Partsch, 2013, Mosti et al., 2012).  
25  
26

27 **Context: What level of compression is required to offer a reduction in swelling and/or quality of life**  
28 **benefit?**  
29

30 The review found that relatively low pressures are likely to offer symptom benefits. Mosti and  
31 Partsch (2013) found that external pressure to reduce capillary filtration could be as little as 1-  
32 10mmHg. In bandages, swelling reduction positively correlates with increased pressure up to  
33 40mmHg, after which higher pressures do not lead to better volume reduction. In stockings, swelling  
34 reduction tends to positively correlate with volume reduction up to 30mmHg. 40mmHg is the  
35 highest pressure needed to provoke lymphatic contractions. Of note is that the pressures needed  
36 are much lower than those needed when treating venous ulcers, which would be 60-80mmHg at the  
37 ankle (Mosti & Partsch, 2013, Mosti et al., 2012).  
38  
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40

41 In four studies stockings were compared to bandages. In three studies stockings or AVCDs delivered  
42 lower pressures than bandages but resulted in comparable or better volume reductions (Mosti &  
43 Partsch, 2013, Mosti et al., 2015, Mosti et al., 2012). The fourth demonstrated better outcomes with  
44 bandages than stockings, but pressure differences were not documented (Badger et al., 2000). Also  
45 of note is that a number of studies found compression was comfortable for patients (Mosti &  
46 Partsch, 2013, Mosti et al., 2015, Wu et al., 2017).  
47  
48  
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50 **Context: who does compression work for?**  
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52 The studies show two main populations benefit from compression. The first is those with venous  
53 disease of all classes (Cataldo et al., 2012, Mosti & Partsch, 2013, Mosti et al., 2015, Mosti et al.,  
54 2012, Rabe et al., 2012) [for classes of venous disease see Beebe et al. (1996)]. The second is those  
55 with lymphoedema, stages II and III (Badger et al., 2000, Franks et al., 2012) [for classification of  
56 lymphoedema see Lymphoedema Framework (ILF, 2012)].  
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3 One study identified that the incidence of swelling due to venous insufficiency increases with age  
4 (Cataldo et al., 2012). The other studies were across all age groups.  
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6 In those with arterial insufficiency, Midttun et al (2010) cite a risk of pressure damage and reduced  
7 blood flow when compression is used. The study recommends measurement of arterial brachial  
8 pressure index (ABPI) prior to the use of compression. Several studies excluded those with any  
9 degree of arterial insufficiency (ABPI <0.8), and so risks for patients with arterial insufficiency cannot  
10 be determined (Badger et al., 2000, Cataldo et al., 2012, Mosti & Partsch, 2013, Mosti et al., 2015,  
11 Mosti et al., 2012,).

### 12 **Outcome: in what way does compression reduce swelling or increase quality of life?**

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17 Compression improved a wide variety of problems resulting from lower limb swelling. Feelings of  
18 heaviness, tightness and tension improved (Badger et al., 2000, Franks et al., 2012, Mosti et al.,  
19 2015, Rabe et al., 2012). Pain, burning and discomfort reduced (Badger et al., 2000, Cataldo et al.,  
20 2012, Franks et al., 2012, Mosti et al., 2015, Rabe et al., 2012). Itching and restless leg improved  
21 (Mosti et al., 2015). Inflammatory symptoms, skin thickness and firmness reduced (Badger et al.,  
22 2000, Franks et al., 2012, Mosti et al., 2012). Exudate was better controlled and tissue infection  
23 prevented (Franks et al. 2012). Wellbeing, psychological state and emotional status improved  
24 (Badger et al., 2000, Franks et al., 2000, Midttun et al., 2010).  
25

26  
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28 Some of the improvements recorded were striking. Rabe et al. (2012) found that 89.4% of patients  
29 receiving compression experienced less heaviness, 60.9% less pain and 78.9% less tension. In Cataldo  
30 et al. (2012) 90% of patients experienced improved pain, discomfort and burning. In Mosti et al.  
31 (2015) aggregated symptom scores including pain, heaviness, discomfort, itching and restless leg,  
32 dropped from 15 to 2.  
33

### 34 **Update of searches**

35  
36  
37 One article was included when the searches were updated (Sibbald et al., 2020). This was a small  
38 study of 25 patients, with chronic swelling due to venous disease, comparing a stockinette and a  
39 tubular bandage. Although these could be considered "garments," they are not hosiery or bandage  
40 systems, and would not usually be considered under the term compression. Therefore, this study  
41 does not affect the outcomes of this review.  
42

### 43 **Literature review two**

#### 44 **Document characteristics and main findings**

45  
46  
47 See table 4  
48

### 49 **Problem requiring intervention: does lower limb swelling occur in patients at the end of life?**

50  
51  
52  
53 There was no exact prevalence data for lower limb swelling in advanced cancer, but several studies  
54 described it as a "common" or "frequent" symptom (Balzarini, 2011, Bar-Sela et al., 2010, McGee et  
55 al., 2004, Mercadante et al., 2009). In renal failure, the prevalence of arm and leg swelling was 58%  
56 (Murtagh et al., 2007). In Woo et al. (2011), 85% of patients with renal failure, dementia, stroke,  
57 heart failure and COPD experienced symptoms of swelling. The studies are summarised in table 4.  
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60

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3 **Mechanism: why does lower limb swelling occur at the end of life?**  
4

5 The studies describe the same underlying mechanism causing swelling. At a cellular level, the  
6 delicate balance between capillary pressure, interstitial pressure and osmotic pressure, as described  
7 in the Starling equation, is disrupted. This can be caused by an excess of capillary filtrate, reduced  
8 venous reabsorption, a change in the constitution of the fluid or poor function of a damaged  
9 lymphatic system (Bar-Sela et al., 2010, Clein & Purgachev 2004, Jacobsen & Blinderman, 2011,  
10 Mercadante et al., 2009,).

11  
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14 In advanced disease, the wider causes are likely to be multifactorial, with several processes  
15 combining to disturb the extracellular fluid volume (Bar-Sela et al., 2010, McGee et al., 2004,  
16 Mercadante et al., 2009). As a result, it can be difficult to distinguish which factors are contributing  
17 to swelling (Mercadante et al., 2009).

18  
19  
20 Physical obstruction in the venous or lymphatic system by tumour infiltration, or damage caused by  
21 anti-cancer treatments, result in impaired drainage of fluid from the limb (Balzarini, 2011, Bar-Sela  
22 et al., 2010, Faily et al., 2007, Jacobsen & Blinderman, 2011, McGee et al., 2004). Venous flow  
23 specifically may be disrupted by the presence of thrombosis or thrombophlebitis (Balzarini, 2011,  
24 Bar-Sela et al., 2010).

25  
26  
27 Advanced disease can cause disruption to blood chemistry. In anorexia-cachexia syndrome, serum  
28 albumin is reduced, resulting in breakdown of the Starling equation (Balzarini, 2011, Bar-Sela et al.,  
29 2010, Faily et al., 2007, McGee et al., 2004, Mercadante et al., 2009).

30  
31  
32 End stage renal and cardiac disease can impact global fluid management (Bar-Sela et al., 2010, Faily  
33 et al., 2007, McGee et al., 2004). Conditions causing neurological dysfunction, reduced mobility,  
34 severe hyposthenia and long-term bed rest can contribute to swelling (Balzarini, 2011, Mercadante  
35 et al., 2009).

36  
37  
38 Finally, medications used in advanced illness can cause swelling, including non-steroidal anti-  
39 inflammatory drugs, corticosteroids and calcioantagonists (Balzarini, 2011).

40  
41 **Outcome: What impact does swelling have?**  
42

43 In terms of what patients said in the studies, in renal failure, 20% reported that swelling impacted  
44 them "quite a lot or very much" and 38% of patients reported that swelling impacted them "a little  
45 or somewhat" (Murtagh et al., 2007). In Bar-sela et al. (2010), 8 patients with advanced cancer  
46 reported swelling as their main symptom, causing a great deal of discomfort. In Clein and Purgachev  
47 (2004), a patient in the last days of life, reported that his remaining wish was that his swelling be  
48 reduced.

49  
50  
51 In terms of resulting problems, patients suffered reduced mobility, reduced activity and reduced  
52 ability to self-care. This led to feelings of burdening others and increased anxiety, fear and distress  
53 (Bar-Sela et al., 2010, Clein & Purgachev 2004, Faily et al., 2007, Jacobsen & Blinderman, 2011,  
54 McGee et al., 2004).  
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3 Patients suffered leakage from swollen limbs, causing discomfort and loss of dignity. The fluid  
4 resulted in frequent dressing changes and a constant feeling of cold (Clein & Purgachev., 2004, Faily  
5 et al., 2007., Jacobsen & Blinderman, 2011, Mercadante et al., 2009).

6  
7  
8 Some suffered pain, breakdown in skin integrity, infection, and feelings of heaviness in the limb  
9 (Clein & Purgachev, 2004, Faily et al., 2007, Jacobsen & Blinderman, 2011, Maleux et al., 2016,  
10 Mercadante et al., 2009).

### 11 **Context: who suffers swelling at end of life?**

12  
13 Limited information was available on which types of patients suffer lower limb swelling at end of life.  
14 Balzarini (2011) reported lower limb swelling in patients with advanced cancer. Murtagh et al. (2007)  
15 reported half of patients with conservatively managed chronic kidney disease experience (CKD)  
16 lower limb swelling. Woo et al (2011) report that 85% of patients experience swelling in a population  
17 of five major non-cancer end stage diseases.  
18  
19

### 20 **Context: Approaches already in use**

#### 21 Diuretics

22  
23 Studies reported limited evidence for the effectiveness of diuretics in lower limb swelling at end of  
24 life (Mercadante et al., 2009). There is a high likelihood of side effects (Bar-Sela et al., 2010) Fluid  
25 and electrolyte balance must be closely monitored (Faily et al., 2007).  
26  
27

#### 28 Treating low albumin

29  
30 There are few options to treat low albumin in advanced illness, where nutritional intake is often  
31 poor (Bar-Sela et al., 2010). Replacement of albumin artificially is expensive and unsuccessful  
32 (Mercadante et al., 2009).  
33

#### 34 Stenting of inferior vena cava obstruction

35  
36 Small case studies documented the use of this procedure and the quality of the evidence was poor.  
37 Maleux et al. (2016) and McGee et al. (2004) found that the procedure was safe and that leg swelling  
38 decreased significantly. Patients in these studies were required to spend time in hospital, to lie  
39 supine, receive sedation and some required anti-coagulation. Potential complications included pain,  
40 unsatisfactory expansion of the stent, stent migration, thromboembolism, subsequent occlusion of  
41 the stent. There is also a risk the procedure shortens life.  
42  
43

#### 44 High dose furosemide and hypertonic saline

45  
46 One small study (Mercadante et al., 2009) found a reduction in leg circumference, weakness and  
47 heaviness with this procedure. No adverse effects were reported. The procedure was invasive,  
48 requiring daily bloods, a urethral catheter, cannulation, twice daily infusions and the administration  
49 of potassium replacement therapy. It would need to take place in the inpatient setting.  
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#### 52 Subcutaneous drainage

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3 Small case studies reported positive outcomes, including reduction in limb size, increased  
4 movement, reduced heaviness, improvement in comfort, dignity and appearance (Bar-Sela et al.,  
5 2010, Clein & Purgachev, 2004, Faily et al., 2007, Jacobsen & Blinderman, 2011).  
6  
7

8 Negative outcomes were recorded. Some patients' symptoms did not improve and some had  
9 ongoing post procedure leakage, requiring dressings or an ostomy bag. Patients' mobility was  
10 reduced due to the requirement for bed rest during the procedure and in some cases swelling  
11 reoccurred.  
12

13  
14 The procedure is untested and it is difficult to counsel patients on the risks. Optimum timing and  
15 technique are not known (Faily et al., 2007, Jacobsen & Blinderman, 2011) Credentialing is a  
16 problem (Jacobsen & Blinderman, 2011). Patients are required to undergo blood tests and to have  
17 normal coagulation and platelets (Bar-Sela et al., 2010).  
18  
19

### 20 Compression

21  
22 One small study of compression reported positive outcomes (Balzarini, 2011). All patients had a  
23 favourable response to compression and saw a reduction in limb volume and circumference.  
24 Resulting positive outcomes included; better skin status, reduced skin tension, improved range of  
25 motion and mobility. The treatment was well tolerated with no reported side effects.  
26  
27

### 28 Manual lymphatic drainage

29  
30 One study explained this treatment may not be possible in advanced disease, due to the need for  
31 forced prolonged elevation of the limb (Balzarini, 2011).  
32

### 33 Update of searches

34  
35 Two additional articles were retrieved when searches were updated. The first concerned the use of  
36 compression therapy together with furosemide in hypersaline intravenous infusion (Gradalski,  
37 2017). This study was of 19 patients found a clinically meaningful reduction in limb volume, and the  
38 treatment was well tolerated. However, it was invasive, requiring IV infusions, regular blood tests  
39 and hospital admission.  
40  
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42  
43 The second study concerned the prevalence of lower limb swelling in patients being admitted to the  
44 hospice in Australia (Best et al., 2018). The study of 59 patients found that 50.8% had lower limb  
45 swelling present for at least 3 months. Primary diagnosis was cancer, cardiac or lung failure or  
46 neurological disease. This is in keeping with previous findings, that lower limb swelling at end of life  
47 appears to be a "common" symptom, present across multiple diseases.  
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### 50 DISCUSSION

51  
52 As expected, the evidence to support the use of compression to reduce swelling or give a quality of  
53 life benefit in the general population was good. Also, as expected, the evidence concerning the  
54 management of lower limb swelling in the end of life population is poor. Therefore, the premise of  
55 the review was supported.  
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58 From the results of the two parallel reviews, programme theories were drawn. Programme theory  
59 one (figure 3) demonstrates the use of compression in the form of stockings, bandages or AVCDs, to  
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3 improve venous and lymphatic return. This produces the outcome of a reduction in swelling and/or a  
4 quality of life benefit. The quality of life benefits obtained were broad and, in some cases, striking.  
5 This question is whether these benefits could also be seen in patients who are approaching the end  
6 of life.  
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9 Here, we look to programme theory two, drawn from the results of the second parallel review  
10 (figure 4). This theory describes the evidence concerning lower limb swelling in patients at the end of  
11 life. Swelling in this population is shown to be caused by the mechanism of a failing lymphatic or  
12 venous system, the root of which may be multifactorial. The outcomes produced significantly reduce  
13 quality of life, both physically and psychologically. These outcomes are complex, multifaceted and  
14 not easily managed.  
15  
16

17 At this point it becomes possible to draw parallels between the two programme theories. Both  
18 theories describe the same mechanism at work in the venous and lymphatic system. Both theories  
19 consider the same outcomes, which affect quality of life. Given this similarity of mechanism and  
20 outcome, we can begin to compare contextual factors between the two models.  
21  
22

23 The first contextual factor concerns population. We see in programme theory one, that compression  
24 delivers a quality of life benefit for those with impaired function of the venous and/or lymphatic  
25 system. In the second programme theory, those with advanced cancer, organ failure and  
26 neurological conditions are suffering from lower limb swelling. These disease processes impact the  
27 venous and lymphatic systems in a variety of ways, from reduction in activation of the calf muscle  
28 pump, to tumour obstructing the limb root. But ultimately, the underlying process, of circulatory  
29 insufficiency, is the same in both the general population and those at the end of life. It is therefore  
30 reasonable to suggest that compression at end of life may confer some of the same quality of life  
31 benefits as in the general population. In the general population, the quality of life benefits of  
32 compression are shown to be significant and well supported. Negative outcomes are small and have  
33 minimal impact.  
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38 However, there is another contextual factor that must be considered. Patients in the studies in the  
39 general population tend to have swelling of simple aetiology. By contrast, those at the end of life  
40 often have swelling caused by multiple factors impacting the venous and lymphatic systems at the  
41 same time. This makes it more difficult to predict how compression would work in this population  
42 and there is little in the literature to help answer this question. Thus, any use of compression at end  
43 of life would need to take a very cautious approach. Careful monitoring of effects and side effects  
44 would be required. This is in line with the best available guidance for compression at end of life,  
45 which suggests a “start low and go slow” approach (ILF, 2012).  
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50 Another important contextual factor is the impact of co-morbidities. In the studies obtained  
51 concerning the general population, patients with co-morbidities were largely excluded. Patients at  
52 end of life, frequently suffer from multiple co-morbidities. This means it is not possible to fully  
53 understand the impact compression would have in patients with multimorbidity, again indicating  
54 caution.  
55  
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57 This does not mean those at the end of life should be excluded from the benefits of compression,  
58 but the approach should be careful. Patients would need to be informed of the uncertainty of risk  
59 when consenting to the intervention. Those at the highest risk may need the intervention to be  
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3 initiated in a setting where regular monitoring were possible. Accepting a degree of risk is in line  
4 with other practices in the literature, such as subcutaneous drainage of fluid (Bar-Sela et al., 2010,  
5 Clein & Purgachev., 2004, Faily et al., 2007., Jacobsen & Blinderman, 2011).

7  
8 The next contextual area of importance is the pressures at which compression delivers a reduction in  
9 swelling and a quality of life benefit. The most established area of research into compression  
10 therapy is venous leg ulcer healing, where there have been large systematic reviews (O'Meara et al.,  
11 2012). This review found that significantly lower pressures are required to deliver a quality of life  
12 benefit, than are needed for venous ulcer healing (Mosti & Partsch, 2013). In fact, several studies  
13 found that stockings or AVCDs, with lower pressures than inelastic bandages, delivered comparable  
14 outcomes in terms of swelling reduction and quality of life. One study even suggests pressures as  
15 low as 1-10mmhg will deliver some swelling reduction (Mosti & Partsch, 2013, Mosti et al., 2015,  
16 Mosti et al., 2012).

17  
18 This means we can begin to reframe how we think about compression for those approaching the end  
19 of life, where the goals are comfort and relief of suffering (World Health Organisation, 2017).

20  
21 Clinicians worry about whether high levels of compression would be suitable for those at the end of  
22 life. But this review suggests lower, gentler pressures may still deliver a quality of life benefit.

23  
24 In terms of devices, it seems light stockings or liners are likely to be comfortable but deliver a quality  
25 of life benefit (Mosti & Partsch, 2013). AVCDs may also be beneficial. AVCDs deliver a comparable  
26 swelling reduction to inelastic bandages, but are able to be adjusted for comfort at any time by the  
27 patient or carer (28). The advantage is that the adjusted AVCD remains in place, and so some benefit  
28 is maintained. This allows for the titration of compression to achieve maximum benefit, for that  
29 specific patient, in their current condition.

30  
31 A contextual factor that represents a complication is vascular impairment. Patients with vascular  
32 impairment can be harmed by compression, because the application of pressure to the limb can  
33 restrict arterial blood flow to the tissue. The Leg Ulcer Advisory Board suggest that patients with  
34 arterial insufficiency receive reduced compression or none if the insufficiency is severe (Stacey et al.,  
35 2002). In order to prevent damage related to arterial insufficiency, patients are screened prior to the  
36 application of compression by the measuring of the ankle brachial pressure index (ABPI) (EWMA,  
37 2005, ILF, 2012,). Those with an ABPI of <0.8 require reduced compression (EWMA, 2005, Stacey et  
38 al., 2002). Those with an ABPI of <0.5 are considered to have an absolute contraindication to  
39 compression (ILF, 2012). The studies in review one largely excluded those with any degree of  
40 vascular impairment and therefore cannot provide information about how to manage this group.

41  
42 The importance of this discussion is that some patients at the end of life will have a degree of  
43 arterial insufficiency. To identify this, patients require an ankle brachial pressure index (ABPI)  
44 measurement. A clinician skilled in the ABPI procedure is required (Shilangu & Bliss, 2013). It is  
45 acknowledged that palliative care professionals require broad training in a variety of symptoms  
46 (Woo et al., 2011). But the palliative workforce may not currently skilled to carry out ABPI  
47 measurement.

48  
49 A further concern, is that measurement of ABPI can be uncomfortable or even painful in gross  
50 swelling. Those at the end of life may need adapted assessment (Lymphoedema Framework, 2006).  
51 The LSN (2015) suggest a limb examination and history may be adequate for the palliative patient.

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3 Further research is needed to ensure that patients do not miss out on symptom benefit because of  
4 difficulties with the assessment process.  
5

6 A further contextual factor of importance is prevalence. The prevalence of venous and lymphatic  
7 diseases causing swelling in the general population is known (LSN, 2014, Robertson et al., 2014).  
8 However, the prevalence of lower limb swelling at the end of life is less well understood. Best et al  
9 (2018) found a prevalence of 50.8% in those being admitted to the hospice with cancer, cardiac and  
10 lung failure and neurological disease. For those with CKD managed conservatively, 58% of patients  
11 suffered swelling (Murtagh et al., 2007) and in Woo et al. (2011), those with five non-cancer end  
12 stage diseases, 85% suffered swelling. The number of studies retrieved discussing lower limb  
13 swelling at the end of life goes some way to support the existence of the problem. The published  
14 guidance also identifies swelling at end of life (ILF, 2012, LSN, 2015). Further prevalence data would  
15 be helpful.  
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20 The final contextual area of interest concerns interventions already being trialled to manage lower  
21 limb swelling at the end of life. Stenting of inferior vena cava obstruction was shown to be very  
22 effective but carries serious risks and requires hospitalisation. High dose furosemide and hypertonic  
23 saline also demonstrated good outcomes, but is invasive and requires inpatient care. The same is  
24 true for furosemide and hypertonic saline with compression. Subcutaneous drainage reported mixed  
25 outcomes, and again requires inpatient care.  
26  
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28 A small study of compression in palliative patients showed good outcomes, with no side effects,  
29 good tolerance and the intervention was minimally invasive. It could be argued further exploration  
30 of compression therapy should be prioritised over riskier, more invasive interventions.  
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32

### 33 **Strengths and limitations**

34 Lower limb swelling at end of life is poorly understood and difficult to study. This review offers  
35 insights which can direct future research and better inform treatment decisions.  
36  
37

38 This was a large review, including 20 studies for analysis, and screening a large portion of the  
39 evidence base. This suggests the outcomes are based on the best available evidence.  
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42 The project uses the novel approach of two parallel realist reviews analysed together, to test how  
43 well evidence from one population can inform another. This approach requires further testing and  
44 examination, but in this case has generated useful outcomes in a hard to study population.  
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46

47 There are limitations to this review. The project was carried out by a single researcher, increasing  
48 the risk of bias. This was mitigated by including as much information as possible about the searching  
49 and quality assessment process to aid transparency and reproducibility.  
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52 The iterative nature of the searches was limited by using an inclusion and exclusion criteria, rather  
53 than by mining the literature to saturation. The review therefore acknowledges the possibility that  
54 studies were missed. A larger team, enabling a more iterative search strategy, would better fit the  
55 realist methodology for future studies of this kind (Pawson et al., 2004).  
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3 It is acknowledged that some low-quality studies were included in the second review. This is because  
4 there were no higher quality studies available. It was judged better to include what little is known.  
5 The quality of these studies was considered throughout analysis and discussion.  
6  
7

8 Finally, little prevalence data was found for swelling at end of life, although it was clear from the  
9 review the symptom does exist within this population. Further work is urgently required to  
10 document the prevalence of swelling at end of life.  
11

### 12 **Comparison with existing literature**

13 Little is known about the use of compression at the end of life and this is an investigative review.  
14 There are existing guidelines which consider the use of compression for lower limb swelling at end of  
15 life, but the statements are general, and not well supported by research evidence (ILF, 2012, LSN,  
16 2015, Lymphoedema Framework, 2006). Nonetheless, the findings of this review agree with existing  
17 guidelines.  
18  
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20 One small study by Balzarini (2011) shows that compression at the end of life delivers a reduction in  
21 swelling and improved quality of life, is well tolerated and has no adverse effects. The findings of this  
22 review are broadly in line with findings of this study. However, this review identifies a greater degree  
23 of complexity surrounding the use of compression at end of life.  
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### 27 **CONCLUSION**

28 The review found compression delivers a reduction in lower limb swelling and a quality of life benefit  
29 in the general population. Those at the end of life may experience the same benefits. A cautious  
30 approach needs to be taken due to the probable multifactorial aetiology of their swelling, the impact  
31 of multimorbidity and the possibility of vascular impairment. However, these risks are comparable to  
32 those of interventions already being trialled to manage lower limb swelling in this group.  
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36 At end of life, lower pressures delivered by stockings, liners or AVCDs are likely to be the most  
37 appropriate starter interventions. They may deliver the best outcomes with minimum impact on  
38 comfort and quality of life. Guidelines already in existence for the management of lower limb  
39 swelling at end of life should be considered (ILF, 2012, LSN, 2015, Lymphoedema Framework, 2006).  
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43 Further research into the prevalence of lower limb swelling at the end of life is urgently required.  
44 Research is also required to develop the complex intervention of compression therapy for those with  
45 lower limb swelling at end of life.  
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48 Finally, the method of dual realist review was successful here, to begin to inform practice in a  
49 difficult to study area. This approach requires further evaluation, but may be of use in other difficult  
50 to study areas.  
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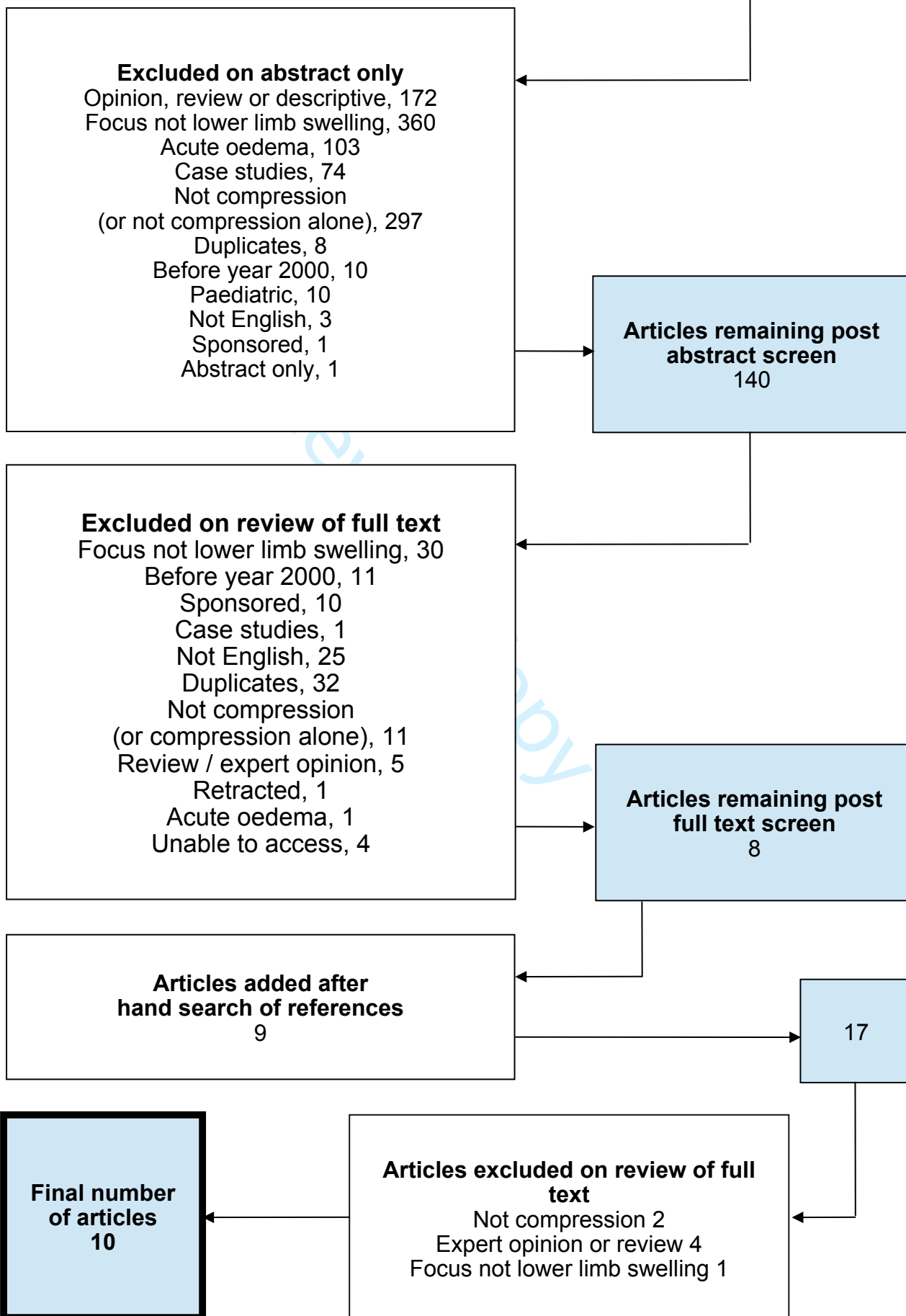
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**Figure 1: Articles retrieved by initial search, 1179**



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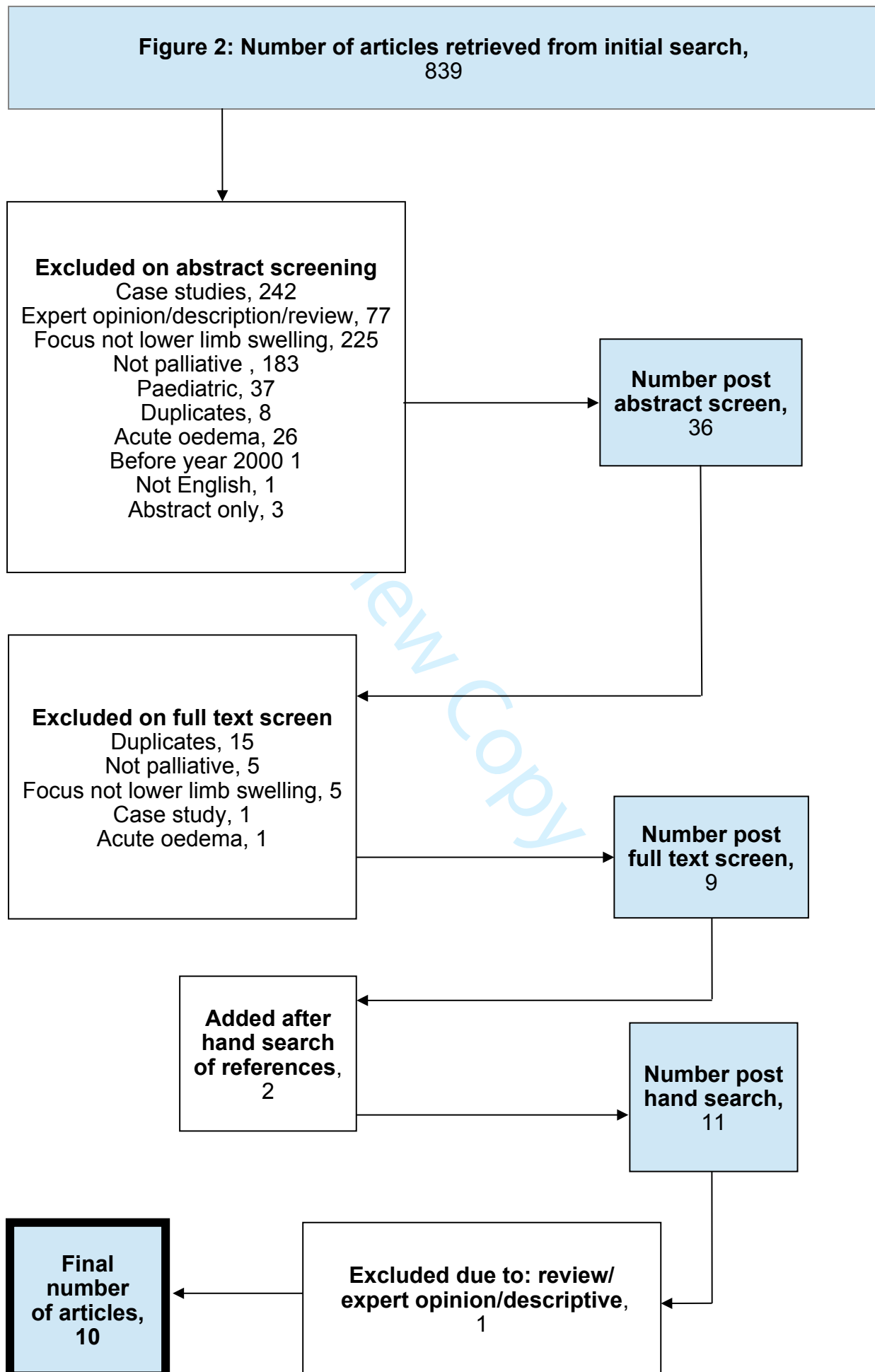
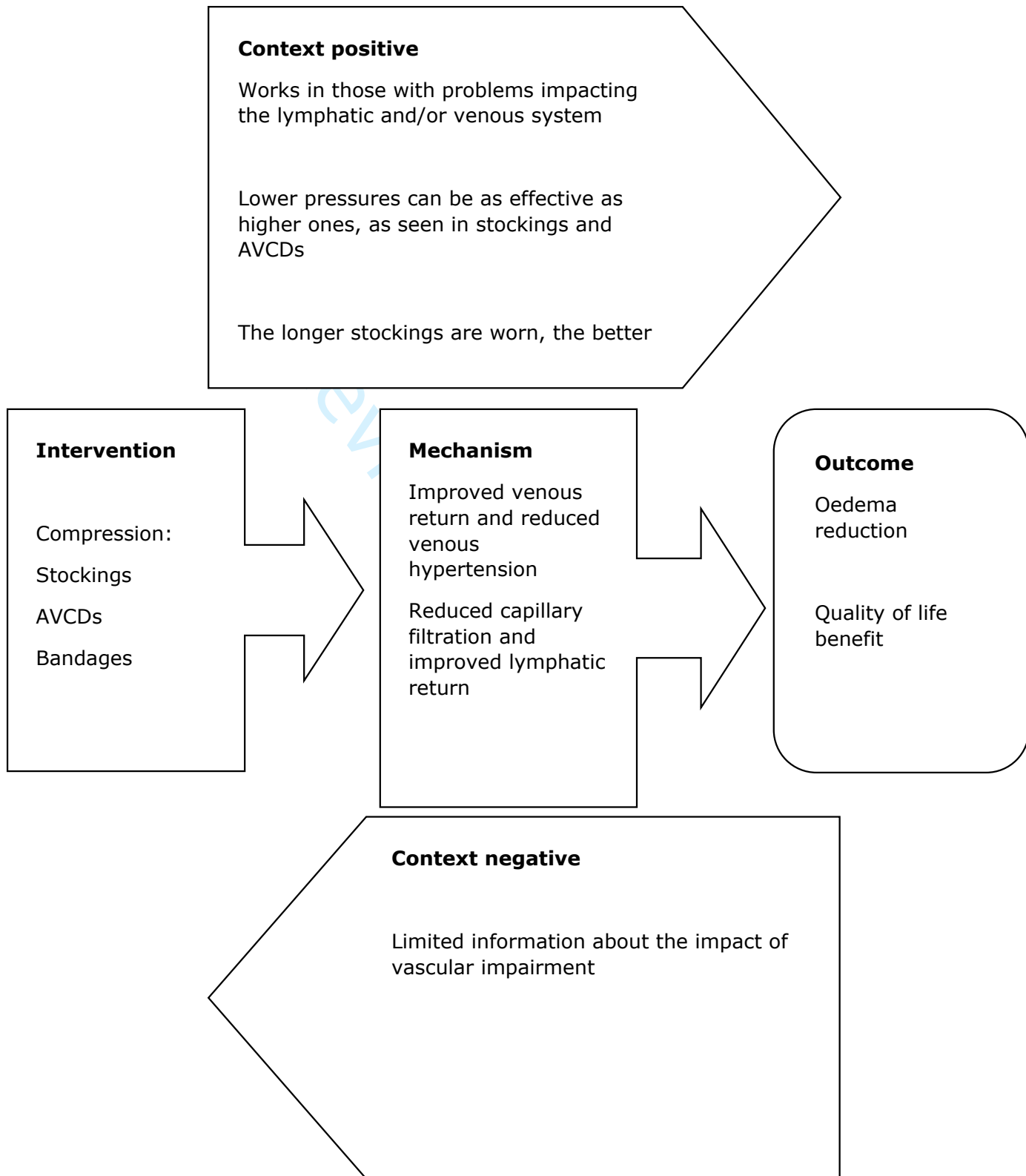


Figure 3

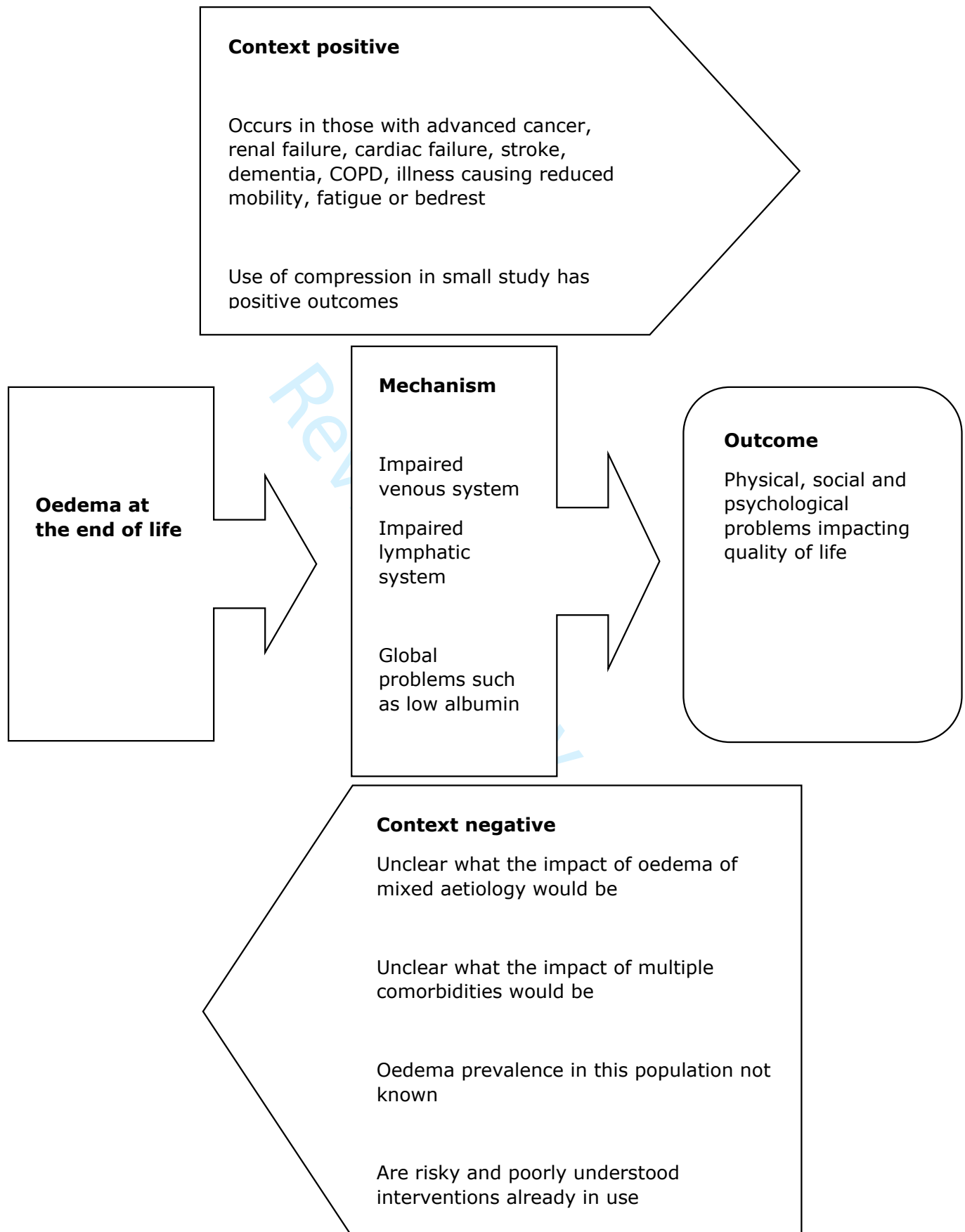
Programme theory one



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Figure 4

## Programme theory 2



**Table one – inclusion and exclusion criteria**

<b>Review one</b> Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Type - primary research with rigorous methodology, primary data included, peer reviewed</li> <li>• Population – patients with lower limb swelling, swelling must be chronic (present for more than 3 months), hospital, community and hospice patients</li> <li>• Intervention – compression bandaging or compression garments (versus no treatment or other types of treatment)</li> <li>• Outcome – symptom control or improved quality of life</li> <li>• In English and published after 2000</li> </ul>	<ul style="list-style-type: none"> <li>• Anecdotal evidence, expert opinion, case studies</li> <li>• Sponsored by companies producing compression products</li> <li>• Acute swelling (present for less than 3 months)</li> </ul>
<b>Review two</b> Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> <li>• Type – primary research with rigorous methodology, primary data included, peer reviewed</li> <li>• Population – receiving palliative care (may be alongside treatment), patients with lower limb swelling, must be chronic (present for more than 3 months), hospital, community and hospice patients</li> <li>• Data of interest – prevalence of lower limb swelling at end of life, aetiology of swelling in this population, resulting problems, impact on quality of life</li> <li>• In English and published after 2000</li> </ul>	<ul style="list-style-type: none"> <li>• Anecdotal evidence, expert opinion, case studies</li> <li>• Sponsored by companies producing compression products</li> <li>• Acute oedema (present for less than 3 months)</li> </ul>

<b>Table Two - Quality Assessment Results</b>																				
<b>Key</b> Y = Yes N = No U = Unclear NA = Not applicable	Wu et al 2017	Mosti and Partsch 2013	Mosti et al 2015	Badger et al 2000	Mosti et al 2012	Franks et al 2012	Midttun et al 2010	Franks et al 2006	Rabe et al 2012	Cataldo et al 2012	Murtagh et al 2007	Woo et al 2011	Bar-Sela et al 2010	McGee et al 2004	Maleux 2016	Mercadante et al 2009	Jacobsen and Blinderman 2011	Failey et al 2007	Clein and Purgachew 2004	Balzarini 2011
Aims and study type appropriate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	N	Y
Good quality blinding and randomization	U	U	U	U	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Appropriate recruitment and sample	Y	Y	Y	Y	Y	N	N	U	Y	Y	U	N	N	N	N	U	U	U	N	N
Exposure / condition measured appropriately	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	N	N	N	N
Appropriate outcome measures and data collection	Y	Y	U	U	U	N	N	Y	U	Y	Y	N	N	N	N	N	N	N	N	U
Data analysis appropriate and rigorous	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	N
All outcomes and participants accounted for	Y	Y	U	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y	Y	N	U	Y	Y	Y
Confounding factors considered	Y	Y	Y	Y	Y	Y	Y	Y	U	U	U	U	Y	Y	N	U	U	U	U	U
Finds clear and well supported	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	U
Research questions answered or accounted for	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ethics and cost benefit considered	Y	U	Y	U	Y	Y	Y	N	U	Y	Y	Y	N	N	Y	U	U	U	U	N
Complexities of swelling considered	y	U	Y	U	Y	Y	N	N	Y	U	U	U	Y	Y	N	Y	U	Y	U	U
Total quality score	11	9	9	8	11	9	9	9	8	9	9	7	5	5	5	4	2	5	3	4

Table three

Study	Type of study	Type of compression	Sample size	Outcome
Rabe et al, 2012	Cross sectional	Medical compression stockings	3072	71.3% said they had improved symptoms
Cataldo et al, 2012	Cross sectional	Elastic medical stockings	3414	90% patients felt they had a good improvement in symptoms and self-assessed that their oedema was reduced
Wu et al, 2017	Double blind RCT	Mild compression diabetic socks	80	Statistically significant reduction in calf and ankle volume in compression group with no statistically significant reduction in control group
Mosti and Partsch, 2013	RCT	Inelastic compression bandages or elastic compression sock kit	40	Both types of compression reduced leg volume significantly (p=0.002)
Mosti et al, 2015	RCT	Inelastic compression bandages or adjustable Velcro compression devices	40	A statistically significant volume reduction was seen in both forms of compression (p=0.0001)
Badger et al, 2000	RCT	Multi-layer compression bandaging followed by compression hosiery or compression hosiery alone	83	All patients in both groups saw a highly statistically significant decline in limb volume
Mosti et al, 2012	RCT	Inelastic compression bandage or ready-made compression stocking	42	Both forms of compression gave a statistically significant reduction in leg volume (p=0.0001)
Franks et al, 2012	Prospective cohort study	Compression bandage system	24	Leg patients achieved a mean volume reduction of 14.9% (p=0.0001)

1 2 3 4 5 6 7	Midttun et al, 2010	Quasi experimental	Short stretch bandage	10	All patients had a 2 point reduction on a +3 to -3 visual swelling scale
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Franks et al, 2006	Epidemiological	Active compression therapy	228	The group having active compression therapy showed the greatest improvements in healthy related quality of life

Review Copy

**Table four**

Study	Type of study	Sample size	Intervention tested, if any	Population experiencing oedema symptoms
Balzarini, 2011	Observational prospective	14	Short stretch bandages	Patients with advanced cancer
Clein and Purgachev, 2004	Case Series	8	Subcutaneous drainage	Patients with advanced cancer
Faily et al, 2007	Case report	1	Subcutaneous drainage	Palliative cancer patients
Jacobsen and Blinderman, 2011	Case series	2	Subcutaneous drainage	Patients with advanced cancer
Mercadante et al, 2009	Prospective longitudinal	24	High dose furosemide and hypertonic saline	Patients with advanced cancer
Maleux, 2016	Retrospective	19	Iliac vein or inferior vena cava stenting	Patients with advanced cancer
McGee et al, 2004	Case series	5	Stenting of inferior vena cava	Patient with advanced cancer
Bar-Sela et al, 2010	Case series	8	Subcutaneous drainage	Patients with advanced cancer
Murtagh et al, 2007	Longitudinal	66	None	Patients with chronic kidney disease stage 5, on a palliative management pathway
Woo et al, 2011	Survey	80	None	Patients with dementia, COPD, heart failure, stroke, renal failure

<b>RAMESES List of items to be included when reporting a realist synthesis</b>	<b>Page no</b>
TITLE	Title page
1 In the title, identify the document as a realist synthesis or review	
ABSTRACT	1
2 While acknowledging publication requirements and house style, abstracts should ideally contain brief details of: the study's background, review question or objectives; search strategy; methods of selection, appraisal, analysis and synthesis of sources; main results; and implications for practice.	
INTRODUCTION	2
3 Rationale for review Explain why the review is needed and what it is likely to contribute to existing understanding of the topic area.	
4 Objectives and focus of review State the objective(s) of the review and/or the review question(s). Define and provide a rationale for the focus of the review.	3
METHODS	4
5 Changes in the review process Any changes made to the review process that was initially planned should be briefly described and justified.	
6 Rationale for using realist synthesis Explain why realist synthesis was considered the most appropriate method to use.	2
7 Scoping the literature Describe and justify the initial process of exploratory scoping of the literature.	3
8 Searching processes While considering specific requirements of the journal or other publication outlet, state and provide a rationale for how the iterative searching was done. Provide details on all the sources accessed for information in the review. Where searching in electronic databases has taken place, the details should include, for example, name of database, search terms, dates of coverage and date last searched. If individuals familiar with the relevant literature and/or topic area were contacted, indicate how they were identified and selected.	4
9 Selection and appraisal of documents	5
Explain how judgements were made about including and excluding data from documents, and justify these.	
10 Data extraction Describe and explain which data or information were extracted from the included documents and justify this selection.	5
11 Analysis and synthesis processes Describe the analysis and synthesis processes in detail. This section should include information on the constructs analyzed and describe the analytic process.	6

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4	<b>RESULTS</b>	
5	12 Document flow diagram Provide details on the number of documents assessed for	Figures 1 & 2
6	eligibility and included in the review with	
7	reasons for exclusion at each stage as well as an indication of their source of origin (for	
8	example, from	
9	searching databases, reference lists and so on). You may consider using the example	
10	templates (which are	
11	likely to need modification to suit the data) that are provided.	
12	13 Document characteristics Provide information on the characteristics of the	Tables 3 & 4
13	documents included in the review.	
14	14 Main findings Present the key findings with a specific focus on theory building and	6
15	testing.	
16		
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18	<b>DISCUSSION</b>	
19	15 Summary of findings Summarize the main findings, taking into account the review's	11
20	objective(s), research question(s), focus and	
21	intended audience(s).	
22	16 Strengths, limitations and future	14
23	research directions	
24	Discuss both the strengths of the review and its limitations. These should include (but	
25	need not be	
26	restricted to) (a) consideration of all the steps in the review process and (b) comment	
27	on the overall	
28	strength of evidence supporting the explanatory insights which emerged.	
29	The limitations identified may point to areas where further work is needed.	
30	17 Comparison with existing literature Where applicable, compare and contrast the	15
31	review's findings with the existing literature (for example,	
32	other reviews) on the same topic.	
33	18 Conclusion and recommendations List the main implications of the findings and	15
34	place these in the context of other relevant literature. If	
35	appropriate, offer recommendations for policy and practice.	
36	19 Funding Provide details of funding source (if any) for the review, the role played by	Title page
37	the funder (if any) and any	
38	conflicts of interests of the reviewers.	
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