Oral nutritional supplements for treating venous leg ulcers (Protocol)

Holt IGS, Green SM, Nelson EA


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Oral nutritional supplements for treating venous leg ulcers (Protocol)
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Oral nutritional supplements for treating venous leg ulcers

Ian GS Holt, Sue M Green, E Andrea Nelson

1Department of Nursing, Oxford Brookes University, Oxford, UK. 2Faculty of Healthcare Sciences, University of Southampton, Southampton, UK. 3School of Healthcare, University of Leeds, Leeds, UK

Contact address: Ian GS Holt, Department of Nursing, Oxford Brookes University, Jack Straws Lane, Marston, Oxford, Oxon, OX3 0FL, UK. ian.holt@brookes.ac.uk.

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

To investigate the effects of oral nutritional supplements on venous leg ulcer healing in adults.

Background

Description of the condition

Venous leg ulcers are chronic wounds on the lower leg caused by poor venous return from the feet to the heart (due to varicose or blocked veins). They usually affect older people, with some estimates that up to 1% of people will be affected by a leg ulcer at some point in their life in industrialised countries (Graham 2003; O’Meara 2014) with higher prevalence in females aged over 70 years (Iglesias 2004). The average cost of treating a venous ulcer with dressings varied between EURO1332 and EURO2585 in Sweden and between EURO814 to EURO1994 in the United Kingdom (UK) (Ragnarson Tennvall 2005). The cost-of-illness of leg ulcer treatment in Hamburg revealed mean annual total costs of EURO9060/patient/year and associated high costs of leg ulcers for health insurances, patients and society (Augustin 2012). The prevalence in less industrialised countries is not fully described as yet, but it is likely that venous ulcers may also affect people across settings. Leg ulcers usually take months to heal completely and often recur after healing. Some people are affected by venous ulcers for many years and the leakage of wound fluid from the ulcer, smell, itch and pain can reduce quality of life and self image, and occasionally lead to low mood and depression (Briggs 2007; Briggs 2012).

Compression heals the majority of venous leg ulcers (Nelson 2014) as this tackles the underlying cause of the ulceration with other therapies such as nutritional support being adjunctive and the focus of this study. Venous ulcers are thought to heal quickest when the blood supply from the leg is supported by compression bandages or stockings (Nelson 2014) when the wound is covered in a dressing that keeps it moist (not wet and not dry), and when the person’s ability to repair wounds is supported, for example by making sure that the skin has sufficient resources supplied by the arteries, such as oxygen and nutrients available to repair the ulcer. Compression bandages or stockings are applied from toe to knee and these can interfere with washing and bathing, and are often bulky and unsightly. Scheduling treatment can affect quality of life as it usually includes very frequent dressings (so people need to arrange their life around visits to the nurse or doctor’s office, or
The body's ability to heal can be optimised by treatment of arterial disease to improve arterial blood supply; this aims to ensure that the tissue receives adequate oxygen and nutrients and waste products are removed. Surgery can improve venous insufficiency (Wittens 2015) and help prevent ulcers coming back with ambulatory compression but is not always possible due to the type of vein problem, or some people not wanting or feeling too unwell for surgery. As well as ensuring that the body's vascular supply can deliver oxygen and nutrients to the body, other potential limits to tissue repair, such as reduced oxygen (which may be caused by respiratory disease) and nutrient levels, may be considered.

The use of oral nutritional supplements containing a range of nutrients may be an effective way of increasing nutrient levels of people with leg ulcers and consequently improving the rate of leg ulcer healing. People with leg ulcers are at risk of malnutrition because, as well as losing nutrients from ulcers due to leakage of fluid from tissues, they are often older and their dietary intake may be poor. A high prevalence of protein-energy (‘calories’) malnutrition in older adults has been reported (Green 2005; Kaiser 2010). This type of malnutrition has been associated with a wide range of factors, including poor appetite and self reported health (van der Pols-Vijlbrief 2014). In addition to this, intake of micronutrients (vitamins and minerals) from habitual diet can be poor (ter Borg 2015). People over 50 years of age with chronic leg ulcers have been shown to have low levels of some micronutrients, namely vitamins and minerals, such as vitamins A and E and zinc (Rojas 1999). It is important that treatment of malnutrition is considered because it has been suggested that it affects the healing prognosis of people with leg ulcers (Wissing 2012).

Programmes that promote changes in eating and drinking behaviour can improve dietary intake, but behavioural change is not always maintained (Fjeldsoe 2011). Oral nutritional supplement use is a health behaviour that may be adopted by people with venous leg ulcers (Miller 2014). Currently, people in the primary care setting in the UK may be prescribed oral nutritional supplements containing protein and energy if they are considered to have or be at risk of protein-energy malnutrition (NICE 2012). Patients are usually screened for risk of protein-energy malnutrition by nurses using a screening tool such as the British Association for Parenteral and Enteral Nutrition (BAPEN) Nutritional Care Tool (BAPEN 2016). Use of screening tools are recommended as best practice (NICE 2012) and are generally designed to detect protein-energy malnutrition rather than micronutrient deficiency. Therefore, those people of normal weight who consume a poor quality diet may not meet the criteria for protein and energy-containing oral nutritional supplement prescription.

People with leg ulcers may be prescribed multivitamin and mineral supplements if they are considered to be at risk of micronutrient deficiency (Johnston 2007). The use of oral nutritional supplements in those not with, or not at risk of malnutrition may be ineffective or detrimental (Johnston 2007). A previous Cochrane review considered oral zinc supplementation and concluded that there was insufficient evidence to determine whether zinc helped the healing of arterial and venous leg ulcers (Wilkinson 2014). However, the review was based on a small number of small studies which were mostly of poor quality (Wilkinson 2014).

Description of the intervention

We will review any interventions comprising oral products containing macronutrients (protein, fat and carbohydrate) and micronutrients (vitamins and minerals) alone or in combination, with the intention of supplementing the oral diet. The term ‘oral nutritional supplement’ is defined as a product for use in oral nutrition support with the aim of increasing nutritional intake (NICE 2006). Typically it describes a product containing a mix of macronutrients and micronutrients (Stratton 2010; Webster-Gandy 2012). In this review the term ‘oral nutritional supplement’ will include any products containing one or more nutrients for oral consumption and will include micronutrient supplements. Micronutrients include minerals and vitamins that are needed by the human body in small quantities (Webster-Gandy 2012). Minerals include zinc, iodine, iron, cobalt, chromium, copper, manganese, fluoride, sodium, selenium and molybdenum. Vitamins include vitamins A, C, D, E and K, as well as the B-complex vitamins. The frequency with which oral nutritional supplements are taken depends on the form that they take and is tailored to the individual (Webster-Gandy 2012). Micronutrient supplements are generally taken orally once daily in small quantities whilst supplements containing macronutrients are taken several times a day depending on need. We will only review nutritional supplements taken orally to supplement the diet as this is the normal route for providing nutritional supplementation in the primary care setting.

The British National Formulary (BNF) outlines types of oral nutritional supplements that can be prescribed in Sections A2 (food supplements) and Chapter 9 (vitamins and minerals) and this will inform our exclusion and exclusion criteria (BNF 2016). We are excluding in our definition of oral nutritional supplements all products given with the intention of exerting a pharmaceutical/pharmacokinetic effect, for example St. John's wort. Some of these may be licensed as food supplements or defined as nutritional products in other ways in some countries. In addition, there may not be the same way of classifying products in all jurisdictions, however, we will not include them in the review. We will exclude medicinal herbs, for example ginger, garlic, lavender, thyme, dandelion, peppermint and chamomile.

How the intervention might work

For the purpose of this review the potential links between chronic wound healing of venous leg ulcers and nutrients are outlined be-
low. The phases of wound healing rely on sufficient nutrients to progress and when nutrients are unavailable the normal wound healing process will be compromised (Brown 2010). Nutrients form the cell structure (Wild 2010) and enable the cell to grow, repair and divide. Therefore, it is logical to suggest that nutrient provision should improve wound healing where nutrients are lacking and nutrients are provided to replenish stores. A person’s nutrient intake may be less than is required because of poor dietary intake, increased loss from the body or increased use due to disease processes.

How a nutritional supplement might improve wound healing will depend on a number of factors:

1. A deficiency of a nutrient essential to wound healing will limit wound healing even if there is an abundance of other nutrients. The classic example of this is vitamin C, where a deficiency will prevent the normal rate of collagen production (Jacob 2002). There is little evidence to suggest that providing nutrients in excess of that required will increase the rate of wound healing (Thomas 1997). Providing an abundance of nutrients other than the one or ones that are deficient is also unlikely to promote wound healing.

2. A recent review has suggested that there is a need for protein supplementation as an intervention to encourage wound healing and tissue repair (Cawood 2012). However, the issue of whether provision of protein in excess of an individual’s daily requirement promotes healing needs investigation.

3. It has been suggested that some nutrients have a specific role to play in wound healing. An example of this is the amino acid arginine (Arnold 2006), which is thought to have a role in cell growth.

4. Transport of nutrients to the site of healing could be influenced by the provision of nutrients that can improve tissue perfusion, for example by increasing blood oxygen capacity and hydration.

5. The impact of nutritional support on wound healing is likely to differ between acute and chronic wounds (Stechmiller 2010). In conclusion, "optimal wound healing requires adequate nutrition" (Stechmiller 2010 p61) and poor nutritional intake may delay healing and impair wound strength.

**OBJECTIVES**

To investigate the effects of oral nutritional supplements on venous leg ulcer healing in adults.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCTs) including cluster trials and cross-over trials (the latter only to the point of cross-over).

**Types of participants**

Eligible participants will include people aged 18 years of age or over, treated in any care setting, including in their own home, with a venous leg ulcer however defined by the trialists. We will include RCTs where the baseline nutritional status of participants has been defined as adequate or inadequate; we will also include RCTs where the baseline nutritional status has not been defined.

**Types of interventions**

We will include evaluations of oral nutritional supplements. This will include oral nutritional supplements in any dose or form (e.g. drink, dessert or tablet) from any product where contents such as proteins and vitamins are stated. We will include RCTs comparing standard clinical practice (e.g. dressings and compression) plus nutritional supplement with standard clinical practice alone or with placebo. We will also include RCTs comparing different types of nutritional supplements added to standard clinical practice. We will exclude trials where the only comparison is between standard diet and any of the following:
• medicinal herbs (e.g. ginger, garlic, lavender, thyme, dandelion, peppermint, chamomile);
• herbal therapies (e.g. St John's wort, cranberry, soy isoflavones, garlic, black cohosh, ginkgo biloba etc);
• homeopathic extracts of substances derived from botanical, animal or mineral sources in micro doses intended to assist the body's natural mechanisms for protecting and healing itself;
• zinc supplements.

Types of outcome measures

Primary outcomes
Trialists measure and report wound healing in many different ways, including: time to complete wound healing, proportion of wounds healed during follow-up and rates of change of wound size. For this review we will include trials that report one or more of the following.
• Time to complete healing of the reference venous ulcer.
• Time to complete healing of all ulcers (where there is more than one ulcer).
• Number of venous ulcers completely healed during trial follow-up (frequency of complete healing).
• Change (and rate of change) in venous ulcer area during trial follow-up period.

Secondary outcomes
• Treatment costs.
• Cost-effectiveness.
• Acceptability for the patient, such as taste, gastric upset, where recorded from a tool or by narrative.
• Adverse events.
• Adherence to the indicated use and dosage for the supplement.
• Health-related quality of life, as measured by a validated tool, such as SF-36 or EQ5D and/or disease-specific quality of life instruments (Palfreyman 2010) designed for use with venous ulcer patients, such as the Charing Cross Venous Ulcer Questionnaire (CXVUQ), the Venous Leg Ulcer-Quality of Life Questionnaire (VLU-QoL), the Loftus questionnaire, or the Quality of Life Leg Ulcer Questionnaire (QoLFUQ).

Search methods for identification of studies

Electronic searches
We will search the following electronic databases for relevant studies:
• The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) (latest issue);
• Ovid MEDLINE (1946 to present);
• Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (latest issue);
• Ovid EMBASE (1974 to present);
• Ovid AMED (1985 to present);
• EBSCO CINAHL Plus (1937 to present).

The draft search strategy for CENTRAL is presented in Appendix 1. We will adapt this strategy to search the other databases listed above. We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE; sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE search with the Ovid EMBASE randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL search with the randomised trials filter terms developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). We will not restrict studies with respect to language, date of publication or study setting.
We will also search the following clinical trials registries for ongoing and unpublished studies:
• ClinicalTrials.gov (http://www.clinicaltrials.gov/)
• WHO International Clinical Trials Registry (ICTRP) (http://apps.who.int/trialsearch/Default.aspx)
• ISRCTN registry (http://www.isrctn.com/)

Searching other resources
We will search the bibliographies of all retrieved and relevant publications identified by the database searches for further studies. We will identify and contact nutrition supplement companies, as well as experts/authors in this field who are familiar with the literature, to enquire about unpublished or ongoing studies.
We will also search websites and search engines such as Open Grey (www.opengrey.eu), Zetoc (http://zetoc.mimas.ac.uk/) and Google Scholar (http://scholar.google.com) to identify grey literature reports and conference proceedings.

Data collection and analysis
Two review authors will independently perform study selection, data extraction and 'Risk of bias' assessment. We will undertake meta-analysis where feasible and appropriate.

Selection of studies
We will assess the titles and abstracts of publications identified as a result of the search against the inclusion criteria for relevance. Two review authors will independently do this and a third review author will be available for consultation where differences arise between the initial two review authors.
We will obtain full copies of publications identified as potentially relevant. We will obtain publications identified through reference lists if the title is considered relevant. We will appraise publications meeting the inclusion criteria. Two review authors will independently assess full-text publications for inclusion, with disagreements resolved by discussion with a third review author.

Data extraction and management

Two review authors will independently extract data, recording relevant items using the latest version of the Review Manager software (RevMan 2014). We will include duplicate studies found in the multiple databases or reported in different publications only once, ensuring that all relevant data are extracted. We will discuss any disagreement within the review team. We will extract the following data when possible on those trial arms that are relevant to the review:

- Trial identifier (first author, year of publication).
- Country of origin.
- Trial design (e.g. parallel, cluster).
- Unit of randomisation and analysis.
- Patient selection criteria.
- Baseline information (e.g. ulcer size and duration, nutritional status of patient).
- Number of participants randomly assigned to each trial arm.
- Details of treatment regimen received by each group, including details of the oral nutritional supplement(s).
- Details of any co-interventions provided (e.g. compression therapy).
- Care setting.
- Duration of treatment.
- Primary and secondary outcome(s) (with definitions).
- Measurement tools used for assessing healing and other outcomes.
- Outcome data for primary and secondary outcomes (by group).
- Duration of follow-up.
- Number of withdrawals (by group).
- Publication status of study.
- Source of funding for trial.

When data are missing from reports, we will attempt to contact the study authors to obtain this information. When a study with more than two intervention arms is included, we will only extract data from the intervention and control groups that meet the eligibility criteria of the review.

Assessment of risk of bias in included studies

Two review authors will independently assess each included study using The Cochrane Collaboration tool for assessing risk of bias (Higgins 2011a). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance) (see Appendix 2 for details of criteria on which the judgement will be based). We will assess blinding of outcome assessment and completeness of outcome data for each outcome separately. We will complete a 'Risk of bias' table for each eligible study. We will discuss any disagreement amongst all review authors to achieve a consensus.

Blinding of participants, care providers and outcome assessors will be assessed by looking for explicit statements that these parties were blind and not aware of treatment allocation. Low risk, high risk or unclear will be recorded as detailed in Appendix 2.

RCTs will be classified as being at overall high risk of bias if they are rated as having high risk in relation to at least any one of three key domains (allocation concealment, blinding of outcome assessors and completeness of outcome data - use of intention-to-treat analysis). If none of the key domains are rated as high risk, but one or more are rated as having an unclear risk of bias, the RCT will be rated overall as having an unclear risk of bias. To attain an overall low risk of bias, all three key domains will have to be rated as low risk individually.

Risk of bias data will be extracted by one review author and independently checked for accuracy by a second review author. Disagreements about ratings will be resolved by discussion with the third team member.

We will seek to identify selective outcome reporting by initially seeking the protocol for each included RCT. Where available, the protocol will be reviewed and compared to the published RCT report to identify if all pre-specified (primary and secondary) outcomes relevant to the review have been reported in the pre-specified way. Where the trial protocol is not available the published report will be examined to: identify whether outcomes specified in the methods section correspond to those reported in the results section and; determine whether all expected outcomes are reported. We will note any pre-specified or expected outcomes which have not been reported, also if any outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified or expected.

We will assess other sources of bias such as baseline imbalance of prognostic variables (ulcer surface area, ulcer duration, patients' nutritional status in cases of RCTs recruiting participants with differing characteristics); we will also record source of funding where recorded.

We will present our assessment of risk of bias using a 'Risk of bias' summary figure, which presents all of the judgements in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study.

Measures of treatment effect

Where data are available from trial reports or trial authors we will
calculate measures of treatment effect from individual RCTs using the latest version of Review Manager (RevMan 2014). For trials reporting the number of people/ulcers healed we will summarise effects using the risk ratio (RR) and 95% CI. This is in preference to the odds ratio (OR), as at event rates greater than 30% the OR (if interpreted as RR) can give an inflated impression of the effect size (Deeks 2002).

For trials reporting continuous outcome measures such as rate of reduction in area (expressed as absolute or relative changes in area), or costs of care, we will summarise effects using mean difference (MD) with 95% CI. We do not plan to dichotomise continuous data or transform data into arbitrary categories, and we will therefore retain the maximum amount of information reported in the primary studies.

For studies reporting time to healing we will present the results as a hazard ratio (HR) with associated 95% confidence interval (CI) where available. If the time to healing data are presented (incorrectly) as a continuous variable, then, where feasible, we plan to estimate the effects using other reported outcomes, such as the numbers of events, through the application of available statistical methods (Tierney 2007).

**Unit of analysis issues**

Unit of analysis issues may arise when: multiple limbs or ulcers on the same individual are studied in a trial and such highly correlated data are regarded as independent; and/or if multiple assessments of the same outcome are presented. We will record whether trials presented outcomes in relation to a venous ulcer, limb or participant, or as multiple venous ulcers/limbs on the same participant. For wound healing, unless otherwise stated, when the number of wounds appears to equal the number of participants, we will treat the participant as the unit of analysis.

When a cluster-randomised trial has been conducted and correctly analysed, effect estimates and their standard errors may be meta-analysed using the generic inverse variance method in Review Manager (RevMan 2014). When outcomes from a cluster-randomised trial have been incorrectly analysed (i.e. at the individual rather than the cluster level), we will approximate the correct analyses if possible, in accordance with Chapter 16 of the Cochrane Handbook for Systematic Reviews of Interventions, using the information as suggested in Higgins 2011b:

- Number of clusters (or groups) randomly assigned to each intervention group, or the average (mean) size of each cluster.
- Outcome data ignoring the cluster design for the total number of individuals (e.g. number or proportion of individuals with events, means and standard deviations).
- Estimate of the intracluster (or intraclass) correlation coefficient (ICC).

**Dealing with missing data**

It is common to have data missing from trial reports. Excluding participants from the analysis post randomisation or ignoring participants who are lost to follow-up compromises the randomisation and potentially introduces bias into the trial. If it is thought that study authors might be able to provide some missing data, we will contact them; however, it is likely that data will often be missing because of loss to follow-up. In individual studies, when data on the proportion of venous ulcers healed are presented, we plan to assume that randomly assigned participants not included in an analysis had an unhealed venous ulcer at the end of the follow-up period (i.e. they will be considered in the denominator but not in the numerator). When a trial does not specify participant group numbers before dropout, we will present only complete case data and make that clear in our narrative. For time-to-healing analysis using survival analysis methods, dropouts should be accounted for as censored data. Hence all participants will be contributing to the analysis. We acknowledge that such analysis assumes that dropouts are missing at random. We will present data for area change of venous ulcer and for all secondary outcomes as a complete case analysis.

**Assessment of heterogeneity**

We will consider clinical heterogeneity (i.e. the degree to which RCTs vary in terms of participant, intervention and outcome characteristics) and statistical heterogeneity. Inspection of the trials by the authors will determine the likelihood of clinical heterogeneity. We will assess statistical heterogeneity using the Chi² test (we will consider a significance level of p-value less than 0.10 to indicate statistically significant heterogeneity) in conjunction with the I² statistic (Higgins 2003). I² examines the percentage of total variation across RCTs that is due to heterogeneity rather than to chance (Higgins 2003). We will consider that I² values of 40% or less indicate a low level of heterogeneity, and values of 75% or more indicate very high heterogeneity (Higgins 2011c). We will apply the following decision rules for pooling:

- low heterogeneity (I² 40% or less) - use fixed effect model;
- moderate heterogeneity (I² above 40% but less than 75%) - use random effects model;
- high heterogeneity (I² 75% or more) - refrain from pooling and;
- any instance of clinical heterogeneity (regardless of I² estimation) - refrain from pooling.

**Assessment of reporting biases**

Reporting biases arise when dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of ‘small-study effects’, that is, a tendency for estimates of the intervention effect to be more beneficial in smaller RCTs. Funnel plots allow a visual assessment of whether small-study effects may be present in a meta-analysis.
A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of the size or precision of each trial (Sterne 2011). We plan to present funnel plots for meta-analyses comprising 10 or more RCTs using the latest version of Review Manager (RevMan 2014).

Data synthesis
We will combine details of included studies in a narrative review according to the comparators. In terms of meta-analytical approach, we will not perform a meta-analysis in the presence of clinical heterogeneity but we will present the results graphically, without pooling, to allow the reader to appreciate the effect sizes and heterogeneity in the trials. We will explore the sources of that heterogeneity, for example, by considering whether subgroups of trials may differ, with an aim of identifying the causes of clinical heterogeneity. In the absence of clinical heterogeneity we will select a meta-analysis method according to the decision rule described above Assessment of heterogeneity.

For dichotomous outcomes, we will present the summary estimate as a risk ratio (RR) with 95% CI. When continuous outcomes are measured in the same way across studies, we plan to present a pooled mean difference (MD) with 95% CI. We plan to pool standardised mean difference (SMD) estimates when studies have measured the same outcome using different methods. We will present pooled data using forest plots. For time-to-event data, we plan to plot (and, if appropriate, pool) estimates of HR and 95% CIs as presented in the study reports using the generic inverse variance method in the latest version of Review Manager (RevMan 2014). We will obtain pooled estimates of treatment effect by using the latest version of Review Manager (RevMan 2014).

Subgroup analysis and investigation of heterogeneity
When possible, we will perform a subgroup analysis informed by type and/or dose of supplement to explore the influence on effect sizes, and subgroup analysis on baseline nutritional status where trials record participants of adequate nutritional status versus trials recruiting those with sub-optimal nutritional status. Type of supplement will include oral nutritional supplements in any form (drink, dessert or tablet). When possible, we will assess whether there are differences stated between the effect of types of oral nutritional supplements on venous ulcer healing.

Sensitivity analysis
When possible, we will perform sensitivity analyses to explore the influence of overall risk of bias classification on effect sizes. We will assess this by removing RCTs with overall high or unclear risk of bias from the meta-analysis. We will only include studies that are assessed as having low risk of bias in all three key domains (allocation concealment, blinding of outcome assessors and completeness of outcome data - use of intention-to-treat analysis).

'Summary of findings' tables
We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined and the sum of available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b).

We plan to present findings related to the primary outcomes in the 'Summary of findings' tables, namely the following.
- Time to complete healing of the reference venous ulcer.
- Time to complete healing of all ulcers (where there is more than one ulcer).
- Number of venous ulcers completely healed during trial follow-up (frequency of complete healing).
- Adverse effects.

Where findings are identified in relation to the secondary outcomes, we will describe these prior to analysis within the 'Summary of findings' tables.

Acknowledgements
The guidance of the editorial team and the exemplars from Dumville 2015, O’Meara 2012, and O’Meara 2014.

The contribution of peer reviewers Duncan Chambers, Gill Worthy, Lillian Kao, Karen Zulkowski and Stephanie Krug and copy editor Jenny Bellorini.

Dan Bader who conceived the review question and completed the first draft of the protocol.
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**Additional references**

Arnold 2006

Augustin 2012

BAPEN 2016

BNF 2016

Briggs 2007

Briggs 2012

Brown 2010

Cawood 2012

Deeks 2002

Dumville 2015

Fjeldsoe 2011

Graham 2003

Green 2005

Higgins 2003

Higgins 2011a

Higgins 2011b

Higgins 2011c

Iglesias 2004

Jacob 2002

Johnston 2007

Kaiser 2010

Lefebvre 2011
Oral nutritional supplements for treating venous leg ulcers (Protocol)
van der Pols-Vijlbrief 2014

Webster-Gandy 2012

Wild 2010

Wilkinson 2014
Wilkinson EAJ. Oral zinc for arterial and venous leg ulcers.

*Indicates the major publication for the study*

**APPENDICES**

**Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL) provisional search strategy**

#1 MeSH descriptor: [Dietary Supplements] explode all trees
#2 MeSH descriptor: [Micronutrients] explode all trees
#3 MeSH descriptor: [Dietary Proteins] explode all trees
#4 MeSH descriptor: [Dietary Carbohydrates] explode all trees
#5 MeSH descriptor: [Dietary Fats] explode all trees
#6 MeSH descriptor: [Energy Intake] explode all trees
#7 (diet* near/3 (supplement* or fortification or capsule* or tablet* or liquid*)):ti,ab,kw
#8 (nutrient* near/3 (supplement* or fortification or capsule* or tablet* or liquid*)):ti,ab,kw
#9 ((micronutrient* or micro-nutrient* or vitamin* or multivitamin* or mineral* or trace next element* or zinc or iodine or iron or cobalt or chromium or copper or manganese or fluoride or sodium or selenium or molybdenum) near/3 (supplement* or fortification or capsule* or tablet* or liquid*)):ti,ab,kw
#10 ((macronutrient* or macro-nutrient* or protein* or amino next acid* or carbohydrate* or calorie* or energ* or fat* or lipid*) near/3 (supplement* or fortification or capsule* or tablet* or liquid*)):ti,ab,kw
#11 ((food or diet) near/3 (intake or fortif*)):ti,ab,kw
#12 (or #1-#11)
#13 MeSH descriptor: [Leg Ulcer] explode all trees
#14 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (stasis next ulcer*) or (crural next ulcer*) or “ulcus cruris” or “ulcer cruris”):ti,ab,kw
#15 (or #13-#14)
#16 [and #12, #15] in Trials

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Appendix 2. Risk of bias criteria

1. Was the allocation sequence randomly generated?

Low risk of bias
The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias
The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear
Insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias
Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially-numbered drug containers of identical appearance; sequentially-numbered, opaque, sealed envelopes.

High risk of bias
Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear
Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias
Any one of the following:
- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
High risk of bias

Any one of the following:
- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following:
- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following:
- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following:
- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- ‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following:
- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following:
• The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
• The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

High risk of bias
Any one of the following:
• Not all of the study’s pre-specified primary outcomes have been reported.
• One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
• One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
• One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
• The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear
Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias
The study appears to be free of other sources of bias.

High risk of bias
There is at least one important risk of bias. For example, the study:
• had a potential source of bias related to the specific study design used; or
• has been claimed to have been fraudulent; or
• had some other problem.

Unclear
There may be a risk of bias, but there is either:
• insufficient information to assess whether an important risk of bias exists; or
• insufficient rationale or evidence that an identified problem will introduce bias.
CONTRIBUTIONS OF AUTHORS

Ian Holt: developed and co-ordinated the protocol. Wrote, edited and advised on the protocol. Approved the final version of the protocol prior to submission. Is a guarantor of the protocol.

Sue M Green: conceived the review question and developed the protocol. Completed the first draft, wrote and edited the protocol. Advised on the protocol and approved the final version prior to submission.

E Andrea Nelson: conceived the review question and developed the protocol. Completed the first draft, wrote and edited the protocol. Advised on the protocol and approved the final version prior to submission.

Contributions of the Editorial base

Susan O’Meara, Editor: edited the protocol; advised on methodology, interpretation and protocol content; approved the final protocol prior to submission.

Sally Bell Syer and Gill Rizzello, Managing Editors: co-ordinated the editorial process; advised on content; edited the protocol.

Rocio Rodriguez-Lopez and Reetu Child, Information Specialists: designed the search strategy, edited the search methods section and ran the searches.

DECLARATIONS OF INTEREST

Ian Holt - none known.

Sue M Green - none known

Andrea Nelson - none known.

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