# A Methodological Assessment of Lymphoedema Clinical Practice Guidelines

**Short title:** Lymphoedema Clinical Practice Guidelines

**Category:** Review

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## Abstract

**Objectives:** To determine the methodological quality of current lymphoedema clinical practice guidelines (CPGs) to assist healthcare professionals in selecting accessible, high-quality guidance and to identify areas for improvement in future CPGs.

**Methods:** Medline, EMBASE, online CPG databases and reference lists of included guidelines were searched up to 31st January 2020. Full-text CPGs reporting on evidence-based recommendations in lymphoedema diagnosis and/or management in English were included. CPGs based on expert consensus, CPG summaries or CPGs that were not freely available were excluded. Two reviewers identified eligible CPGs, extracted data and assessed their quality independently using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. Significant scoring discrepancies were discussed with a third reviewer. An overall scaled quality score of ≥80% was the threshold to recommend guideline use.

**Results:** Six relevant CPGs were identified. One was subsequently excluded as its full-text could not be obtained. Overall, there was very good inter-reviewer reliability of scores with ICC of 0.952 (95% CI, 0.921-0.974). No single CPG scored highest in all domains, with methodological heterogeneity observed. Poor performance was noted in domains 5 (mean scaled score 23.8±17.1%) and 6 (22.9±26.7%). No CPG achieved an overall scaled quality score of ≥80%, with the top CPG scoring 79.2%.

**Conclusions:** According to the defined threshold, no lymphoedema CPG was considered adequate for use in clinical practice. All current lymphoedema CPGs have areas for improvement with elements of methodological quality lacking, particularly with respect to rigour of development. A structured approach, guided by the use of CPG creation tools and checklists such as the AGREE II instrument, should help CPG development groups in improving the quality of future CPGs; this is of particular importance in a complex, multidisciplinary condition such as lymphoedema.

**Keywords**: lymphoedema, clinical practice guidelines, methodology

### Conflicting Interests

The authors declare that there is no conflict of interest.

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## Introduction

Lymphoedema, the accumulation of lymphatic fluid resulting in swelling of part of the body, is estimated to affect at least 100,000 people in the United Kingdom (UK) (1). While primary lymphoedema is rare (prevalence estimated at 0.17 per thousand (2)), secondary lymphoedema, particularly related to oncological treatment, such as in breast cancer, is considerably more common (3). Nonetheless, it has been argued that this prevalence is still underestimated, in part due to the variable patient description of lymphoedema and the difficulties in its recognition upon clinical assessment, leading to the undertreatment of patients suffering from this condition (4) and compounding the negative effects this has on quality of life (QoL). This complex condition requires multidisciplinary management from various specialties, including but not limited to nurses, physicians, vascular surgeons, and dermatologists. Studies have shown that patients with this “forgotten vascular disease” (5) often fail to receive the complex, comprehensive multidisciplinary care they require, with a recent review showing variable rates of treatment based on aetiology (6). Untreated lymphoedema is known to worsen over time (7) and it is therefore important for clinicians to recognise and treat these patients.

To aid clinicians in their diagnosis and management of complex conditions such as lymphoedema, efforts are made to consolidate available evidence into clinical practice guidelines (CPGs). These are developed by guideline committee groups for different healthcare professionals involved in lymphoedema care, including members from the specialties mentioned above. While not legally binding, these CPGs provide evidence based guidance which is used by healthcare professionals to diagnose and treat patients with lymphoedema, which makes their reliability of paramount importance.

The methodology involved in the creation of CPGs varies between guideline development groups. Differences include differential approaches employed in the literature search, consolidation of the available evidence and formulation of recommendations. Clearly, a sound methodology is required to ensure the evidence is appraised in a reliable, reproducible fashion. Shortfalls in methodological quality may be identified using CPG appraisal tools, of which the Appraisal of Guidelines for Research and Evaluation II (AGREE II) is an example (8). This instrument has been extensively validated and has been used for the assessment of guidelines in different specialties (9–11). The instrument only reports on methodological rigour of guideline formulation and clarity of presentation across seven domains (**Table 1**), and not the accuracy of the recommendations included in the assessed CPGs.

Utilising the AGREE II instrument, this review aims to:

1. Assess the quality of current lymphoedema CPGs to assist healthcare professionals in choosing an accessible, high-quality guideline to inform their practice, *and*
2. Identify areas for improvement in future versions of CPGs.

## Materials and Methods

A systematic search was performed in accordance to PRISMA guidelines. Medline and EMBASE databases were searched using a predefined algorithm (**Supplement 1**) until 31st January 2020. To further ensure comprehensive inclusion of all available CPGs, online CPG databases (as previously listed on the AGREE Research Trust website) were also searched using the term “lymphoedema” or “lymphedema”. Reference lists of included CPGs were then hand searched to identify further relevant guidelines.

Two reviewers (M.T., S.S.) independently identified CPGs and performed data extraction. Any conflict between reviewers was referred to senior reviewers (S.O., T.L.) until agreement was met.

### Inclusion and Exclusion Criteria

Full text guidelines reporting evidence-based recommendations on primary and secondary lymphoedema diagnosis and/or management in English were included. CPGs solely based on consensus from expert opinion, CPG summaries or CPGs that were only available if purchased were excluded.

### AGREE II Assessment

Four reviewers (M.T., S.S., M.B., A.G.) independently assessed the CPGs, using the statements included in AGREE II instrument to rate guidelines from 1 (lowest quality) to 7 (highest quality) (**Table I**). Scores were added for each of the six domains to obtain a raw score, which was scaled to determine the quality score for each CPG using the following equation: [Obtained score - Minimum possible score / Maximum possible score - Minimum possible score] x 100. All assessments and scaling of scores were performed according to the guidance provided in the user manual available from the AGREE Research Trust website (12).

Inter-reviewer reliability was determined using a two-way mixed model to calculate intraclass correlation coefficients (ICC). An overall CPG assessment scaled score of ≥80% was considered of adequate quality to recommend use in clinical practice, a standard previously published by other studies (13,14).

Statistical analysis was performed using SPSS® Statistics V25 (IBM®, United States of America).

## Results

### Selected Guidelines

The literature search identified 400 articles, from which six CPGs were identified. One was subsequently excluded as the full text could not be obtained (15). A total of five CPGs were therefore included in the AGREE II assessment (16–20).

CPGs were published between 2006 and 2017. Guideline development group members included, but were not limited to, dieticians, occupational therapists, nurse specialists, general practitioners, dermatologists, and vascular surgeons. Three were national guidelines (16,18,20), while one originated from an Australian state (Queensland) (19) and the last was created by international collaborators (17). Further guideline characteristics are summarised in **Supplement 2**.

### Quality Scores

Inter-reviewer reliability varied between domain, ranging from moderate (domains 1 and 4) and good (domains 2, 5 and overall quality) to excellent reliability (domain 3) based on the ICCs calculated. Overall ICC of all scores, however, showed excellent reliability (ICC 0.952, 95% confidence interval 0.921-0.974) (**Table II**).

Raw and scaled quality scores can be found in **Table III**, with the distribution of scaled scores shown in **Figure I**. Significant methodological heterogeneity was shown, with a wide range of scores achieved by the various CPGs. As a whole, CPGs generally performed worst in domains 5 (23.8 ± 17.1%) and 6 (22.9 ± 26.7%) but performed relatively well in domain 1 (70.0 ± 15.3%).

### Individual Domain Performance

**Domain 1**

 Domain 1 includes statements that cover the scope of the CPGs, as well as their overall objectives. This extends to describing the health questions that are to be answered and defining the relevant patient populations.

 CPGs fared adequately in this domain, with no CPG scoring a scaled score of less than 50%. Scores in this domain were the least heterogenous, with the smallest interquartile range (**Figure I)**. Guidelines that did well in this domain clearly defined clinical situations in which they were meant to be applied and also specified the scope of broader terms. For example, the CPG created by Queensland Health explicitly defined “compression therapy” to include “compression bandaging, compression garments and intermittent pneumatic compression” which were to be applied to adults with “established lymphoedema” (19). Another CPG that performed well in this domain, the CREST guideline, provided a comprehensive list of questions used to frame the development of the recommendations, as well as clearly stating the relevant patient population to include primary lymphoedema, secondary lymphoedema, and lymphoedema secondary to complex syndromes (17). CPGs that performed less well in this domain had unclear aims, with broad non-specific terminologies used to define their areas of interest or CPG objectives.

**Domain 2**

 Domain 2 concerns the involvement of various parties in the CPG development process. This is essential to gain multidisciplinary input into complex conditions such as lymphoedema, as well as to consider the various aspects of healthcare provision that may be offered by different healthcare professionals. This domain also considers the health care professionals that the CPG might be relevant for.

Scores in this domain were more heterogenous with scores ranging from 30.6% to 77.8% (mean 50.3±18.8%). CPGs scoring highly in this domain involved a variety of healthcare professionals ranging from primary to tertiary care (17). CPGs that scored better in this domain also involved the views of patients, for example through the use of consumer representatives in the guideline development groups (19) or obtaining views from patient support networks (17). CPGs were largely differentiated by their scores regarding the definition of target users. For example, Queensland Health specified that the CPG was for the use of “occupational therapists, physiotherapists and registered nurses” as well as “‘new’ lymphoedema-trained clinicians” (19), while vaguer terms such as to “inform clinical practice” were used in CPGs that scored poorly.

**Domain 3**

Domain 3 contains eight statements which determine the evidence-based rigour of the CPGs assessed. These include statements concerning the strategies of evidence selection and evaluation, as well as the recommendation formulation methods, together with procedures to update the guideline.

There was once again heterogeneity in scores, ranging from 21.4% to 70.8% (mean 42.9 ± 23.2%). Good evidence-based CPGs performed robust systematic literature reviews (17–19) and also provided the search algorithms in the document (17,19). These CPGs gave clear inclusion and exclusion criteria, made use of validated methods of critical appraisal and evidence grading systems, and made efforts for the CPG to be peer reviewed by experts in the field prior to publication. Poorer scoring CPGs mostly failed to inform users of the methodology involved in the creation of the CPG altogether.

**Domain 4**

Domain 4 describes how comprehensible the CPGs are, including statements assessing whether included recommendations are unambiguous and how easy it is for CPG users to identify important recommendations in the document.

Overall, CPGs generally performed well in this domain, with higher mean score (69.7 ± 16.1%) and lower variability observed (**Figure I**). Guidelines scoring highly in this domain clearly signposted their recommendations and the related evidence (16,17), with clear formatting allowing easier identification of recommendations relevant to specific clinical scenarios (16,17,19,20). Failure to perform well in this domain was largely due to poor formatting making recommendations difficult to isolate from the body of the text.

**Domain 5**

CPGs performed inadequately in this domain, which describes applicability (mean 23.8 ± 17.1%). Statements in this domain concern how recommendations translate into clinical practice, including consideration of the barriers and facilitators of implementing such recommendations, as well as resources required for implementation.

The majority of CPGs included in this assessment failed to address this domain. The CPG from CREST performed best, with a section considering audit criteria and future research questions that should be addressed to improve the available evidence, as well as service provision (17). The CPG from Queensland Health also considered the need for state-wide funding models for compression garments (19).

**Domain 6**

Similarly, CPGs scored poorly in this domain, concerning editorial independence, with an average score of 22.9 ± 26.7%. The variability in scores was also greatest in this domain (**Figure I**). This domain concerns questions on competing interests both on the individual (conflicts of interests of individual CPG development group members) and institutional level (involvement of funding bodies). CPGs that clearly stated the competing interests of CPG development group members as well as the extent of involvement of funding agencies scored reasonably in this domain (19,20). The other CPGs often failed to declare these potential sources of bias.

**Overall Guideline Assessment**

The Overall Guideline Assessment contains two components: the overall quality rating of the CPG, and whether the reviewer would recommend use of the CPG in clinical practice. While two CPG scores approached the predefined threshold for recommending use in clinical practice (79.1% (19) and 70.8% (17) respectively), none were rated of adequate quality to enable this.

## Discussion

This study highlights the performance of existing lymphoedema CPGs against the AGREE criteria, assessing their methodological robustness and highlighting a number of issues in methodological quality. Such issues are not isolated to lymphoedema guidelines and variability in CPG quality has been reported in various fields of medicine, including cardiology (9), orthopaedics (10), and venous disease (11). The applicability of the guidelines is an area of particular weakness, as reported in this study for the lymphoedema CPG, with lower scores in this domain. Despite this, a proportion of CPGs assessed have been found to be adequate for use in clinical practice (e.g. four among the chronic venous disease CPGs) (11)), in our study no lymphoedema CPG met the predefined score threshold to recommend its use in clinical practice. This lack of methodological quality may be particularly marked in lymphoedema as, despite increasing efforts to research this “forgotten vascular disease” (5), there are still many gaps in the evidence pertaining to this topic. The epidemiology is poorly characterised (4), the pathophysiology poorly understood (5), and the methodological rigour of existing CPGs has now been found to be variable. There are a number of factors that may have affected this.

Firstly, defining the target population is complicated by a two-tiered system, with significant focus on secondary lymphoedema related to cancer and provision of lymphoedema treatment often limited to this group of patients (22) and patients suffering from lymphoedema of other causes neglected (1). For example, a review considering the treatment gap in lymphoedema showed that 94% of patients with breast cancer-related lymphoedema received treatment for limb swelling, compared to 82% of venous leg ulcer patients with phlebolymphoedema (6). Anecdotally, a survey of United Kingdom and Canadian practitioners noted that the profile of patients with lymphoedema was changing and was increasingly non-cancer related (23). Patients with non-cancer related lymphoedema were also less likely to be satisfied with their first consultation for this problem (24). Interestingly, the review also highlighted a paucity of treatment for other cancer-related lymphoedema (including pelvic cancers, melanomas, prostate), suggesting that the higher rate of treatment in breast cancer may be in part due to it being a better recognised complication by both patients and physicians (6) – of note, a number of guidelines exist solely for the diagnosis and management of post-breast cancer lymphoedema (25,26) while no CPG focusing on primary lymphoedema was identified in this review. Future iterations of CPGs need to recognise this disparity of focus and healthcare provision between primary and secondary lymphoedema and define unique target populations to help decrease this treatment gap.

Secondly, poor understanding of the pathophysiology may lead to confusion as to which specialities should be involved in the management of this complex condition and, by extension, which members of the multidisciplinary team should be involved in the formulation of CPG recommendations. This is evident in the myriad of healthcare professionals involved across the CPGs assessed. While a 2006 paper by Tiwari *et al.* suggested that lymphoedema treatment teams should include vascular surgeons, lymphoedema physiotherapists, dermatologists and vascular nurses (27), representation of these individuals was not seen consistently across the CPGs. This may be in part due to lymphoedema coming under the domain of different specialities in different healthcare systems and complicated by the lack of evidence for effective treatment methods that come under the purview of the vascular teams. Of note, specialist nurse/therapist led lymphoedema services are being developed in various countries including the United Kingdom (23). While establishment of these services is still considered to be far from adequate, this may represent a unique team that could be integrated into the CPG development groups in the future.

Finally, the lack of appreciation of lymphoedema prevalence may have led to underestimation of resources required to implement CPG recommendations. Lymphoedema, as with most chronic health conditions, is associated with significant direct and indirect costs, which in one study was estimated to cost an average of over €5,000 per year per patient in Germany (28). While domain 5 (concerning applicability) was not the poorest performing domain in this review, the scope for improvement here should be highlighted. The underappreciation of such costs may have in turn led to the poor performance in this domain, suggesting that lymphoedema CPGs fail to identify resource shortfalls and obstacles that might hinder the implementation of good evidence-based recommendations, resulting in limited clinical impact. This is a concern as without the translation of recommendations into clinical practice, high quality recommendations are of little use. It is therefore imperative that future CPG developers consider such issues to improve uptake of recommendations into clinical practice.

In this assessment of lymphoedema CPG development methodology, no single CPG scored highest in all domains. All CPGs showed areas of merit, but also exhibited shortcomings that should be addressed in future iterations of these CPGs. It must be noted that this paper only analysed the methodological quality of the current lymphoedema CPGs and has not considered the accuracy of the recommendations included within these guidelines. Future work should consider comparing recommendations between CPGs, assessing their accuracy and establishing consensus between guidelines.

While there was no clear characteristic that had a significant impact on the scores, a strong performance in domain 1 appeared to set a higher standard for scores in the other domains. Having a clear objective, precise health questions considered, and a specific patient population to apply recommendations to understandably provided a framework for further meticulous methodology. That said, no statistical inter-domain correlation within each CPG was noted, reminding authors of future CPGs that methodological rigour in each domain is independent and therefore, independent efforts have to be made to correct all issues identified. Clear methods outlined in the CPG development process will potentially help improve methodological quality of newer CPGs. This may be assisted through the use of guideline development frameworks – the AGREE II instrument, G-I-N Standards (29), or Guidelines 2.0 (30) are some examples. It is also suggested that the international community agree upon a specific framework to reduce methodological heterogeneity for future CPG development.

## Conclusion

This methodological assessment has shown that current lymphoedema guidelines demonstrate shortfalls in various aspects of CPD methodology and are not adequate for use in clinical practice according to their scores – CPG development groups of future versions should strive to correct these issues. With newer iterations of the CPGs, guideline development groups must be cognisant that rigorous methodology can only be achieved through deliberate effort – good quality in a current version does not necessarily translate to high quality in future versions and vice versa. The want of rigour provides avenues for bias, preventing formulation of accurate recommendations. A structured approach is inherently important to an organised outcome, and development groups should take note of the available instruments that may be used to improve methodological rigour, making use of these tools to improve clinicians’ confidence in the validity of CPGs for use in their clinical practice.

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