Update to the Canadian Clinical Practice Guidelines for best-practice management of Breast Cancer Related Lymphedema: Study Protocol

Journal:	*CMAJ Open*
Manuscript ID	CMAJOpen-2021-0038
Manuscript Type:	Protocol
Date Submitted by the Author:	08-Feb-2021
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More Detailed Keywords:	lymphedema, breast cancer, Guidelines
Keywords:	Clinical Practice Guidelines, Women's health
Abstract:	Background: Lymphedema is a significant swelling of the arm, breast and chest wall that occurs on the side of the breast cancer and is one of the more frequent complications following treatment for breast cancer. The aim of this work is to update the 2001 Clinical Practice Guideline for the care and treatment of breast cancer related lymphedema. Methods: The objective of the clinical practice guideline is to provide information and recommendations for patients and their physicians when making decisions about diagnosis, risk reduction practices, and long-term management of lymphedema in women with breast cancer. The new

	guidelines will encompass a patient-oriented research approach with a focus on self-management. The methods for the proposed evidence-based guideline development will follow the levels of scientific evidence and will be undertaken with consideration of the standards outlined in the Appraisal of Guidelines Research and Evaluation II instrument (AGREE II). The literature will be appraised by evaluating: 1) existing guidelines from other countries and regions, 2) the evidence from systematic reviews and meta-analyses, and 3) direct evidence from clinical studies. Interpretation: Recommendations will be presented in an actionable statement format to guide users on what to do, when, and under what specific circumstances to facilitate implementation and measurement. Each recommendation statement will be linked to the level of evidence along with any relevant discussion or considerations used when informing the recommendation. A draft of the guidelines will be produced by the Steering Committee, then sent out to international experts and stakeholder groups for feedback.

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Funding: Research funding was provided by an internal grant from the Oncology Division of the Canadian Physiotherapy Association and Canadian Lymphedema Framework.

Data sharing: Raw data will be available through the University of Alberta Libraries' Dataverse Network

ABSTRACT

Background: Lymphedema is a significant swelling of the arm, breast and chest wall that occurs on the side of the breast cancer and is one of the more frequent complications following treatment for breast cancer. The aim of this work is to update the 2001 Clinical Practice Guideline for the care and treatment of breast cancer related lymphedema.

Methods:

The objective of the clinical practice guideline is to provide information and recommendations for patients and their physicians when making decisions about diagnosis, risk reduction practices, and long-term management of lymphedema in women with breast cancer. The new guidelines will encompass a patient-oriented research approach with a focus on self-management. The methods for the proposed evidence-based guideline development will follow the levels of scientific evidence and will be undertaken with consideration of the standards outlined in the Appraisal of Guidelines Research and Evaluation II instrument (AGREE II). The literature will be appraised by evaluating: 1) existing guidelines from other countries and regions, 2) the evidence from systematic reviews and meta-analyses, and 3) direct evidence from clinical studies.

Interpretation: Recommendations will be presented in an actionable statement format to guide users on what to do, when, and under what specific circumstances to facilitate implementation and measurement. Each recommendation statement will be linked to the level of evidence along with any relevant discussion or considerations used when informing the recommendation. A draft of the guidelines will be produced by the Steering Committee, then sent out to international experts and stakeholder groups for feedback.

INTRODUCTION

Lymphedema, a frequent complication following treatment for breast cancer, is a significant swelling of the arm, breast and chest wall that occurs on the side of the breast cancer. Breast cancer related lymphedema (BCRL) is a lifelong condition affecting approximately 20% of women who undergo treatment for their breast cancer.[1] Women with breast cancer are at increased risk of developing lymphedema after undergoing axillary surgery and/ or radiation therapy to lymph node regions.[1] There are currently no known curative treatments for lymphedema.[2] Nonsurgical therapies, including interventions such as compression therapies, specialized massage techniques, and pneumatic compression devices, are prescribed to reduce and maintain limb size, restore function, reduce pain, reduce infection risk, and improve the appearance of the limb.[2, 3] Although not widely available across Canada, specialized lymphedema microsurgical, liposuction and debulking techniques are options for patients when nonsurgical therapies are inadequate to control the condition.[4, 5] Following these specialized surgeries, however, individuals with BCRL must continue with lifelong nonsurgical therapies to maintain benefit.[6-8]

Impact of lymphedema

Chronic BCRL is often associated with pain, limited range of motion, limb heaviness, loss of strength and functional limitations.[9, 10] Thus, the impact of BCRL is often profound, negatively impacting function, social relationships and quality of life.[11, 12] A major complication of lymphedema is the susceptibility of the affected arm to skin and soft tissue infections, particularly cellulitis. About one third of individuals with BCRL develop recurrent infections, with some progressing to systemic infections requiring hospitalization for intravenous antibiotic therapy.[13,14,13] Women with BCRL have been found to utilize over 30% more healthcare services

than women with breast cancer who have not developed lymphedema — with increased utilization found to persist for more than 10 years following diagnosis.[14]

Background: existing guidelines and reviews

In 2001, an expert panel of clinicians from across Canada published the first Canadian clinical practice guideline (CPG) for the care and treatment of BCRL.[15] The guideline was developed based on evidence from a systematic review of the literature performed by researchers at the British Columbia Cancer Agency, with dates encompassing 1966 to 2000. At the time, there was a lack of high-quality research in the field, namely randomized controlled trials (RCTs), limiting the evidence available to inform the guidelines. Since that time, over 100 RCTs and more than 50 systematic reviews have been published in the area of cancer related lymphedema. Given the growing cohort of survivors living with BCRL, new scientific research, improvements in breast cancer surgical and radiotherapy techniques, as well as new diagnostic and measurement technologies, an update to the CPG is long overdue. Supporting this need, a recent review of lymphedema-specific CPGs reported that none of the current CPGs could be recommended for clinical practice due to the poor methodological quality and lack of rigour of CPG development.[16]

Scope and purpose of the CPG

The proposed updated evidence-based guideline will serve as a tool on best practice and clinical decision-making for the long-term management of lymphedema related to breast cancer in Canada. Specifically, the objective of the CPG is to provide information and recommendations for patients and their physicians when making decisions about diagnosis, risk reduction practices, and long-term management of the condition. While the guidelines may also provide some direction for other healthcare professionals, as well as for patient advice and education,

practitioner education and training, and service standards, the main aim of the work is to provide recommendations for clinical practice based on the available evidence.

Models guiding methodology and decision-making

The new guidelines will encompass a patient-oriented research approach and focus on the ability of individuals with breast cancer to adapt and to self-manage their lymphedema.

Patient Oriented Research: We will follow the principles of patient-oriented research (POR) as per Canada's POR strategy.[17] Individuals with BCRL will be involved in all stages of the guideline development. We will work collaboratively with patients and stakeholders on the development and implementation of the guidelines. As well, we will ensure the guidelines are 1) responsive to areas of greatest need, 2) expand on existing knowledge, expertise and excellence in the field, and 3) foster a culture of new ideas and solutions. Importantly, we will ensure inclusivity, and make decisions through open, collegial and engaging discussion. Thus, the proposed guidelines will be developed by an interdisciplinary group with strong user and patient representation.

Positive Health Model: For the purposes of the guideline development and recommendations, we will follow the positive health model introduced in the Netherlands in 2011.[18] In this model, health is defined as the 'ability to adapt and to self-manage, in the face of social, physical and emotional challenges'. This definition of health focuses on the individual's capacity for resilience and for coping with new situations and chronic health conditions over the life span. This model aligns well with our intent to identify, where possible, effective self-management strategies for BCRL.

Development of Questions

Prior to undertaking the proposed guidelines update, a meeting was held in Toronto in November 2019 involving researchers, and healthcare practitioners with expertise in BCRL, as well as patient representatives, and was funded by the Oncology Division of the Canadian Physiotherapy Association. The purpose of the meeting was to discuss the need for an updated Canadian CPG and provide attendees with the opportunity to propose topic areas, identify key questions and discuss clinical issues to inform guideline development. Twenty stakeholders from across Canada, including individuals with BCRL took part in the initial meeting. A framework for the guidelines was developed based on four main categories: 1) diagnosis, 2) prevention/ risk reduction, 3) effective management, 4) measurement outcomes. A full list of identified key questions can be found in the Supplementary Material.

METHODS

Guideline Development Process

The methods for the proposed evidence-based guideline development will follow the levels of scientific evidence (Appraisal of Guidelines for Research and Evaluation, http://www.agreetrust.org) and will be undertaken with consideration of the standards outlined in the Appraisal of Guidelines Research and Evaluation II instrument (AGREE II).[19] Figure 1 illustrates the planned stages and timeline of the CPG development.

Eligibility Criteria

CPGs, systematic reviews and large-scale studies published in the last 7 years describing diagnosis, risk reduction, management and measurement outcomes involving individuals with breast cancer of any age who have or are at risk of developing lymphedema.

Identified outcomes

The primary outcomes considered for each of the four proposed categories of this guideline include:

1) Diagnosis: sensitivity and specificity
2) Risk reduction/ prevention: incidence rates related to risk reduction strategies and practices.
3) Effective lymphedema management: limb volume
4) Measurement outcomes: valid, reliable and sensitive methods to detect and monitor lymphedema and associated symptoms, and recommended surveillance timelines

Additional outcomes that will be considered include breast, chest wall and trunk lymphedema, upper limb function, lymphedema related symptoms, and quality of life as well as associated costs related to lymphedema diagnosis, assessment and management.

Critical appraisal

The literature will be appraised by evaluating: 1) existing guidelines from other countries and regions, 2) the evidence from systematic reviews and meta-analyses, and 3) direct evidence from clinical studies. The need for a new or updated systematic review, as identified by the Steering Committee, will be registered in Prospero (https://www.crd.york.ac.uk/PROSPERO/). At each stage, the findings will be mapped to the list of clinical questions from the November Stakeholders meeting. We will strive for a balance between rigor and pragmatism to maintain efficiency.[11] Table 1 provides details on the proposed methods as per the AGREE II tool. At each stage of the review findings will be presented to the Steering Committee for feedback and approval.

Stage 1 Literature search: A search of the following electronic databases from January 2015 to August 1st 2020 will be performed including MEDLINE, EMBASE, SCOPUS, CINAHL,

Dissertation Abstracts, PEDro, Occupational Therapy Systematic Evaluation of Evidence, EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews), Agency for Healthcare Research and Quality, and the National Guideline Clearing House. We will use search terms related to breast cancer (e.g. breast neoplasms, axillary dissection, lymph node excision), lymphedema (e.g. lymphedema, lymphoedema, edema), surgical treatments (e.g. vascularized lymph node transplant, vascularized lymph node transfer, lymphaticovenous anastomosis and lymphaticolymphatic bypass, liposuction), conservative treatments (e.g. stockings, compression, manual lymph drainage, kinesiotaping), and publication type (e.g. practice guideline, government publication, random allocation, clinical trial, systematic review, meta-analysis). Published and unpublished studies are eligible for inclusion, with no language restrictions. To locate unpublished research, we will review proceedings from lymphedema conferences and search websites housing clinical trial details, theses, or dissertations. In addition, we will hand-search the reference lists of all potentially relevant studies and contact experts to identify relevant articles. In this stage, we will review existing CPGs from within and outside of Canada: the quality of existing CPGs will be assessed by four appraisers using the AGREE II instrument, and domains will be scored. The objective of this stage is to determine the quality of the CPG, its relevance to, and appropriateness for use given the Canadian context, and to identify any gaps requiring further research evidence. Guidelines will be considered for adaptation to the Canadian context if scoring 75% or higher on the Rigour of Development, 60% or higher on stakeholder involvement and editorial independence, and 50% or higher for all other domains. The recommendations of existing CPGs will be mapped to the relevant category along with information on AGREE II scores.

Survey and focus group work to engage patients

To facilitate a larger number of individuals with BCRL in the guideline engagement process, we will conduct a series of surveys (modified DELPHI) and focus group sessions. Our aim is to establish consensus on the top 10 questions from the perspective of individuals with, and at risk of BCRL, as well as to identify any additional barriers and facilitators to seeking lymphedema care that may have been missed at the original stakeholders meeting. A survey will be created using the secure REDCap web platform for managing online databases and surveys, supported by the Women's and Children's Health Research Institute, and housed in the Faculty of Medicine and Dentistry at the University of Alberta. Potential participants will be identified through recruitment emails sent by the Canadian Lymphedema Framework and the Canadian provincial lymphedema associations. Ethics approval will be sought from the Health Research Ethics Board of Alberta: Cancer Committee. All participants in the survey and focus groups will be required to provide informed consent.

Stage 2 of the project will involve evaluating the research evidence from systematic reviews, meta-analyses and large-scale studies (published in the last 7 years) relevant to the identified gaps in ***Stage 1.*** The objective of this stage is to inform the need for, and conduct of any new or updated systematic reviews in areas where research is lacking or outdated.

Stage 3 of the project will involve a final synthesis of the evidence that will be performed with consideration given to the Canadian healthcare context (e.g. cost, availability of diagnostic test or service across provinces) as well as the alignment of the guideline to a self-management focus where appropriate. This stage will also involve the formation of the draft recommendations. We will use the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to ensure rigorous and transparent practice guidelines and recommendations. When the level of evidence is strong, benefit/harm is clearly established, findings are consistent across

studies and appropriate to the Canadian context, a recommendation will be formulated. The Steering Committee will vote on the recommendation, 80% agreement will be required for the recommendation to be included in the CPG. As necessary, where there is little evidence to guide the answers or when findings are contentious, we will aim to establish expert consensus on recommended diagnostic and risk reduction practices, treatment and long-term management strategies. Eighty percent agreement on a statement will be required to reach consensus.[11] When consensus cannot be reached, a modified-Delphi process will be administered by reaching out to the larger lymphedema community and stakeholder groups.

Stage 4 will involve external review of the recommendations. Recommendations will be presented with a clear purpose and in an actionable statement format to guide users on what to do, when, and under what specific circumstances, using unambiguous language that facilitates implementation and measurement.[11] Each recommendation statement will be linked to the level of evidence along with any relevant discussion or considerations used when informing the recommendation. A draft of the guidelines will be produced by the Steering Committee, then sent out to international experts and stakeholder groups (Table 2) for feedback. Following external review, the Steering Committee will refine and release the guidelines for a period of public comment and review, prior to being finalized.

Research Management Team

The project will be guided by the Alberta Health Services Guideline Resource Unit (GURU), Steering Committee, and a working management team. A Steering Committee has been comprised that includes broad stakeholder representation, with diversity of experience and perspectives. The Steering Committee includes researchers, individuals with BCRL, clinicians and specialists in lymphedema and end-users, with representation from across Canada. The

Steering Committee will be responsible for evaluating the evidence at each stage of the review, and for directing next steps. A knowledge management specialist member of GURU will guide the steps involved in the development of this CPG, ensure adherence to methodological standards. The Steering Committee will meet at 4 monthly intervals starting in March 2021. The management team will include an experienced researcher, an expert clinician coordinator, a postdoctoral fellow, and three graduate students. This group will meet regularly and a project platform has been created to identify milestones, organize daily tasks and monitor overall work progress (https://canadalymph.ca/project/research/). Working groups (and subgroups as needed) will be established for each of the following categories: 1) diagnosis, 2) risk reduction/ prevention, 3) effective management, and 4) measurement outcomes. Stakeholder groups will be invited to be involved in the process as the project progresses.

DISCUSSION

This research will identify best evidence to inform the updated CPG recommendations for individuals with or at risk of breast cancer related lymphedema and their physicians. As part of the dissemination and implementation of the CPG, Steering Committee members will share the findings at both national and international level conferences. A webinar will be hosted by the Canadian Lymphedema Framework for both patient and healthcare professional groups. In addition, we will apply for funding to support the creation of videos to disseminate our key findings to the targeted users of the guideline: 1) individuals with breast cancer related lymphedema, and 2) physicians and other healthcare professionals. To increase reach, the professional and patient series of videos will be hosted on the websites of the Oncology Division of the Canadian Physiotherapy Association, and the Canadian Lymphedema Framework in both official languages.

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SUPPLEMENTARY MATERIAL

Questions from Stakeholders Group Meeting: Toronto, November 2019

Prevention

1. What is the effect of Radiotherapy?
2. What are the differences in risk based on surgical techniques?
3. What is the value of new surgeries aimed at prevention of BCRL?
4. Is there an impact from breast reconstruction?
5. What is the effect of Chemotherapy protocols and effects of chemotherapy?
6. What is the impact of other impairments (i.e. shoulder dysfunction)?
7. What is the impact of other comorbid diseases?
8. Can lymphedema be prevented?
9. What is the value of prophylactic measures (i.e. compression sleeve)?
10. What is the value of self-monitoring?

Risk Reduction

11. When should we be introducing risk reduction strategies?
12. What are the risks associated with taking blood pressure, venipuncture, and medical procedures involving the 'at risk' arm or region?
13. Should patients be advised to wear a garment for travel?
14. Should advice be tailored by varying degree of risk?
15. What is the critical time for surveillance of lymphedema?
16. What is the importance of weight control / management?
17. What should we advise re: exercise parameters: restrictions – what is safe?
18. What is the impact of cellulitis? What is the value of infection prevention strategies?
19. What is the value of nutrition counseling?
20. Are there considerations related to the work environment?

Diagnosis/ Assessment

21. What constitutes a diagnosis?
22. When is there a need to rule out sinister causes? What percent/ symptoms may be related to recurrence?
23. What is the best diagnostic method to diagnose LE?
24. Is there a gold standard of measurement/ assessment protocol: Percentage, cm, Pitting? Stemmer?
25. What is the role of bioimpedance in the diagnosis of lymphedema?
26. Is there a universal definition of LE – percent/ volume? Is there a critical cut-point? i.e. 5%
27. What is the value of self-reported sensory changes?
28. Is there value in limb segment assessment?
29. Is there value in obtaining pre-operative measures?
30. Is there a simple questionnaire for early identification of LE?

Assessment: other

31. What are the important variables related to lymphedema: onset, extent?
32. What is the value of ROM and strength measures?
33. What is the significance of scar tissue, fibrosis -association with lymphedema

34. What key symptoms, quality of life, functional scales – should be captured? What value do they add? (e.g. body mass index, axillary web syndrome, exercise levels, function, cellulitis assessment)
35. What is the importance of capturing the patient's goals of treatment/ care?

Management:

36. What is the value of surgery for existing lymphedema?
37. What is evidence on diuretics and other medications?
38. What is the gold standard for conservative treatment?
    a. What are the key components of treatment?
    b. What is evidence of: timing/ timelines of treatments?
    c. What is the evidence on the needed frequency of treatment in acute phase?
39. What are the personal lifestyle factors that impact LE?
40. Evidence behind skin care advice/ treatment?
41. What is the evidence on?
    a. Manual lymph drainage
    b. Compression therapies, how do you decide type (flat knit, etc), compression level? When do you need to replace sleeves?
    c. Compression bandaging: initiation when? Criteria for appropriateness?
    d. Lymphedema pumps
    e. Kinesiotaping
    f. Laser therapy and modalities
    g. Exercise: divided by stage of healing
    h. Evidence for aquatic therapy
    i. Night-time compression: what is the evidence?
42. What is available from industry commercially?
43. Can we better deliver care by using technology – assessment/ standardized reporting?

Outcomes:

44. What is the needed frequency of follow-up/ surveillance?
45. How do we promote self-management, self-monitoring?
46. How do we support a client centred approach (e.g. rural patients, disease status)?
47. Should outcomes be based on patient goals?
48. What is different for those with malignant/ palliative LE outcomes and treatment?
49. What are the best measurements?
    a. What are the recommended questionnaires? How often should they be administered?
    b. What about other measures (e.g. strength, psychosocial impact, adherence, function, quality of life)?
50. What constitutes a significant clinically meaningful improvement, stable, progression (worsening) of lymphedema?

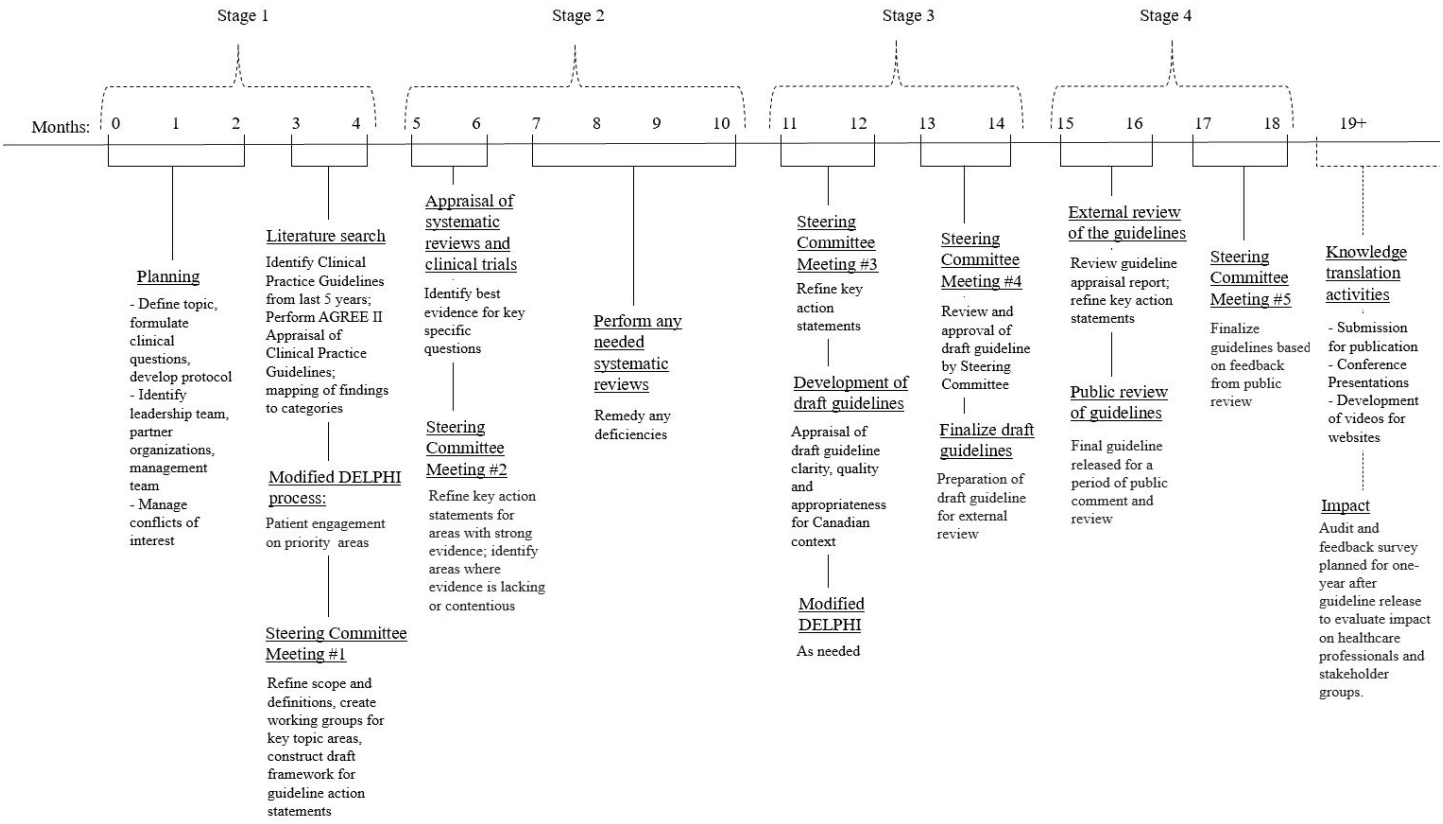

Figure 1. Timeline for CPG Development

Table 1. Clinical Practice Guidelines Methodology: AGREE II CHECKLIST

AGREE II Checklist Item	Reporting Criteria	Planned Guidelines Protocol
Domain 1: Scope and Purpose		
1. Guideline Objectives	Health intent, expected benefit and targets	• To provide information and recommendations for women and their physicians when making decisions about the diagnosis, prevention/ risk reduction, management and outcomes related to BCRL in women
2. Questions	Target population Interventions/ exposures Outcomes Context	• Women with breast cancer with/ at risk of developing lymphedema • Diagnosis, risk reduction, management and outcomes • Improve the care of women with BCRL; focus on self-management • Canadian Healthcare system
3. Population	Target population Clinical condition Severity of disease	• Adult women with breast cancer • Breast cancer – from diagnosis to palliative stages, all ages • Lymphedema – all stages and severity of the condition
Domain 2: Stakeholder Involvement		
4. Group membership	Participants Membership expertise Institutions/ organizations Geographical location Members' roles	• Guideline Development Group: Researchers, clinicians, specialists, methodologist, research librarian, and patient representatives from across Canada. • Partners: Canadian Physiotherapy Association Oncology Division, CancerControl Alberta's Guideline Resource Unit (GURU) and the Canadian Lymphedema Framework • Member roles will be defined and shared.
5. Target population preferences/ views	Patients' views and preferences	• Patient representatives on Guideline Development Group • Modified Delphi Survey, focus groups and consultation with patient groups
6. Target Users	Intended audience Use of guidelines	• Primary: Physicians and women with/ and at risk of breast cancer related lymphedema • Secondary: other healthcare professional groups • Inform clinical decisions and standards of care
Domain 3: Rigour of Development		
7. Search methods	Electronic databases; time periods of searches; search Terms and strategy	• MEDLINE, PubMed, EMBASE, SCOPUS, CINAHL, Dissertation Abstracts, PEDro, Occupational Therapy Systematic Evaluation of Evidence, EBM Reviews, Agency for Healthcare Research and Quality, and the National Guideline Clearing House • Guidelines and Systematic Reviews, RCTs: last 7 years • Further details on the search terms and strategy are provided in Appendix A.

8. Evidence selection criteria	Target population; study design; outcomes; languages	• Breast cancer related lymphedema • Clinical Practice Guidelines; Systematic Reviews; Cross-sectional studies (diagnosis); Cohort Studies (prognosis); RCTs (treatment/ management) • Diagnosis/assessment; risk reduction/ prevention; management/treatment; outcomes/ surveillance • No language restrictions
9. Strengths and limitations of evidence	Study methodology to evaluate quality	• Clinical Practice Guidelines: AGREE II appraisal; Systematic Reviews: AMSTAR; Cross-sectional studies: AXIS Tool; Cohort Studies: Newcastle-Ottawa Scale; RCTs: risk of bias • Rating of evidence: we will use the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to grade the quality of evidence and strength of recommendations in the guidelines. • Tables detailing the level of evidence, consistency of results, direction of results, magnitude of benefit (versus harm) and applicability to practice context in Canada will be developed
10. Formulation of recommendations	Recommendation development process	• Non-contentious findings: Voting of Steering Committee in the situation where the level of evidence and benefit/harm is established, findings are consistent across studies, and the recommendation is applicable to the Canadian context • Contentious findings/ no evidence: Modified DELPHI process involving larger Guideline Development Group and stakeholders - 80% level required; with a virtual/ face-to-face meeting as needed to reach consensus
11. Consideration of health benefits, side effects and risks	Data supporting benefits, harms/ side effects, balance of benefits/ harms	• Tables will be developed to outline the benefits and risks • Recommendations will consider the balance between benefits/ risks as appropriate
12. Link between recommendations and evidence	Link between evidence and recommendations	• The recommendations will be supported by the level of evidence, extent of the evidence (total number of studies/ total number of subjects), direction of effect, magnitude of effect, and where possible, with consideration given to the stage and severity of lymphedema.
13. External review	Purpose and intent of external review	• Feedback from external experts and stakeholder groups will be solicited to improve the CPG quality, and to obtain feedback on the draft recommendations.
14. Updating procedure	Statement on when the CPG will be updated	• The steering group will determine the timeline and outline criteria for future updates
Domain 4: Clarity of Presentation		

15. Specific and unambiguous recommendations	Recommendations are specific with circumstances and relevant populations identified	• Recommendations will be presented with a clear purpose and in an actionable statement format • Areas of uncertainty, and those requiring further research will be identified • A lay summary of the findings will be shared with stakeholder groups
16. Management options	Describe management options for the condition	• Management options will be articulated given the Canadian Healthcare context, and the focus on self-management of lymphedema
17. Identifiable key recommendations	Easily identified key recommendations	• Key recommendations will be highlighted in an executive summary • Algorithms and flow charts will be created to highlight findings
Domain 5: Applicability		
18. Facilitators and barriers to application	Description of the facilitators and barriers to the CPG's application	• Information on barriers and facilitators to the CPG will be sought at the draft CPG stage • The CPG will be pilot testing in Alberta Canada prior to widespread implementation
19. Implementation advice/ tools	Tools to support application of the CPG	• Materials will be created to support CPG implementation • Short videos will be created for healthcare professionals and patients – videos will be housed on the Oncology Division of the Canadian Physiotherapy Association and Canadian Lymphedema Framework websites.
20. Resource implications	Potential resource implications of recommendations	• Where possible, costs related to diagnosis and management will be collected • Costs will be considered within the Canadian context
21. Monitoring/ auditing criteria	Provide auditing criteria	• Operational definitions will be determined to inform auditing and measurement of impact. We will assess impact of the guideline's recommendations based on stakeholder a stakeholder follow-up questionnaire one year following publication.
Domain 5: Editorial Independence		
22. Funding body	Influence of funding body on guideline recommendations	• Initial funding for the stakeholders meeting was received from the Oncology Division of the Canadian Physiotherapy Association • The CPG will be completed without influence from any funding body
23. Competing interests	All group members must declare competing interests	• All CPG guideline members will be required to provide written documentation declaring any competing interests • Individuals associated with industry, private business or declaring significant competing interests that could influence the guideline process or development will not be eligible to participate. A management plan will be formulated to address any other potential competing interests among group members.

Table 2. Definitions for Key Stakeholders

Stakeholders	Definition
Women with breast cancer	Women diagnosed with breast cancer with / at risk of developing lymphedema
Clinicians	Physical therapists, occupational therapists, nurses, oncologists, surgeons, and physiatrists with clinical experience who are actively practicing in their field
Researchers	Perform research in the area of lymphedema related cancer
Lymphedema Therapists (Private Sector)	Therapists that are certified in lymphedema such as massage therapists and physical therapists in private practice
Schools offering lymphedema certification	Schools offering specialized training, courses and post-graduate certification to medical and allied health professionals in advanced lymphedema care.
Industry representatives	Representatives from a private organization or business with a vested interest in the area of lymphedema
Provincial Benefit Programs	Publicly funded programs that aid people with disabilities to maintain an independent lifestyle. e.g. universal benefits programs providing compression garments for lymphedema.
Professional organization representatives	Representatives from professional organizations with relevant scope and practice
End-users	Representatives from the community or organizations external to academia that will directly use or benefit from the recommendations

Table 1. Clinical Practice Guidelines Methodology: AGREE II CHECKLIST

AGREE II Checklist Item	Reporting Criteria	Planned Guidelines Protocol
Domain 1: Scope and Purpose		
1. Guideline Objectives	Health intent, expected benefit and targets	• To provide information and recommendations for women and their physicians when making decisions about the diagnosis, prevention/ risk reduction, management and outcomes related to BCRL in women
2. Questions	Target population Interventions/ exposures Outcomes Context	• Women with breast cancer with/ at risk of developing lymphedema • Diagnosis, risk reduction, management and outcomes • Improve the care of women with BCRL; focus on self-management • Canadian Healthcare system
3. Population	Target population Clinical condition Severity of disease	• Adult women with breast cancer and their physicians • Breast cancer – from diagnosis to palliative stages • Lymphedema – all stages and severity of the condition
Domain 2: Stakeholder Involvement		
4. Group membership	Participants Membership expertise Institutions/ organizations Geographical location Members' roles	• Guideline Development Group: Researchers, clinicians, specialist and patient representatives from across Canada. • Partners: Canadian Physiotherapy Association Oncology Division, CancerControl Alberta's Guideline Resource Unit (GURU) and the Canadian Lymphedema Framework • Member roles will be defined and shared.
5. Target population preferences and views	Patients' views and preferences	• Patient representatives on Guideline Development Group • Literature review of patient values and preferences • Survey, focus groups and consultation with patient groups
6. Target Users	Intended audience Use of guidelines	• Physicians and women with/ and at risk of breast cancer related lymphedema • Inform clinical decisions and standards of care
Domain 3: Rigour of Development		
7. Search methods	Electronic databases; time periods of searches; search Terms and strategy	• MEDLINE, PubMed, EMBASE, SCOPUS, CINAHL, Dissertation Abstracts, PEDro, Occupational Therapy Systematic Evaluation of Evidence, EBM Reviews, Agency for Healthcare Research and Quality, and the National Guideline Clearing House • Guidelines and Systematic Reviews: last 5 years; RCTs: 2000-present • Further details on the search terms and strategy are provided in Appendix A.

8. Evidence selection criteria	Target population; study design; outcomes; languages	• Breast cancer related lymphedema • Clinical Practice Guidelines; Systematic Reviews; Cross-sectional studies (diagnosis); Cohort Studies (prognosis); RCTs (treatment/ management) • Diagnosis/assessment; risk reduction/ prevention; management/treatment; outcomes/ surveillance • No language restrictions
9. Strengths and limitations of evidence	Study methodology to evaluate quality	• Clinical Practice Guidelines: AGREE II appraisal; Systematic Reviews: AMSTAR; Cross-sectional studies: AXIS Tool; Cohort Studies: Newcastle-Ottawa Scale; RCTs: risk of bias • Rating of evidence: Oxford Centre for Evidence-Based Medicine Levels of Evidence. • Tables detailing the level of evidence, consistency of results, direction of results, magnitude of benefit (versus harm) and applicability to practice context in Canada will be developed
10. Formulation of recommendations	Recommendation development process	• Non-contentious findings: Voting of Steering Committee in the situation where the level of evidence and benefit/harm is established, findings are consistent across studies, and the recommendation is applicable to the Canadian context • Contentious findings/ no evidence: Modified DELPHI process involving larger Guideline Development Group and stakeholders - 80% level required; with a virtual/ face-to-face meeting as needed to reach consensus
11. Consideration of health benefits, side effects and risks	Data supporting benefits, harms/ side effects, balance of benefits/ harms	• Tables will be developed to outline the benefits and risks • Recommendations will consider the balance between benefits/ risks as appropriate
12. Link between recommendations and evidence	Link between evidence and recommendations	• The recommendations will be supported by the level of evidence, extent of the evidence (total number of studies/ total number of subjects), direction of effect, magnitude of effect, and where possible, with consideration given to the stage and severity of lymphedema.
13. External review	Purpose and intent of external review	• Feedback from external experts and stakeholder groups will be solicited to improve the CPG quality, and to obtain feedback on the draft recommendations.
14. Updating procedure	Statement on when the CPG will be updated	• The steering group will determine the timeline and outline criteria for future updates
Domain 4: Clarity of Presentation		
15. Specific and unambiguous recommendations	Recommendations are specific with circumstances and relevant populations identified	• Recommendations will be presented with a clear purpose and in an actionable statement format • Areas of uncertainty, and those requiring further research will be identified • A lay summary of the findings will be shared with stakeholder groups

16. Management options	Describe management options for the condition	• Management options will be articulated given the Canadian Healthcare context, and the focus on self-management of lymphedema
17. Identifiable key recommendations	Easily identified key recommendations	• Key recommendations will be highlighted in an executive summary • Algorithms and flow charts will be created to highlight findings
Domain 5: Applicability		
18. Facilitators and barriers to application	Description of the facilitators and barriers to the CPG's application	• Information on barriers and facilitators to the CPG will be sought at the draft CPG stage • The CPG will be pilot testing in Alberta Canada prior to widespread implementation
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