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Underwood, Emma; Woods, Mary; Riches, Katie; Keeley, Vaughan; Wallace, Anita; Freeman, Jennifer

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Title Page:

Full Title

The Lymphoedema Research Prioritisation Partnership: A collaborative approach to setting research priorities for lymphoedema management.

Running Title

Lymphoedema Research Prioritisation Partnership

Authors

Emma Underwood DipCOT, MClinRes, Lymphoedema Specialist (OT), Royal Cornwall Hospital NHS Trust.

Mary Woods RGN, BSc (Hons), MSc, Nurse Consultant Lymphoedema, Royal Marsden Hospital, London.

Katie Riches BSc (Hons) RN, Lead Research Nurse, Derby Hospitals NHS Foundation Trust, Chair of the British Lymphology Society Scientific Committee at the time of the study.

Professor Vaughan Keeley PhD, FRCP, Consultant in Lymphoedema, Derby Teaching Hospitals NHS Foundation Trust and Hon. Professor, University of Nottingham.

Anita Wallace Chair of Lymphoedema Support Network.

Professor Jennifer Freeman B App Sc (Physiotherapy), PhD, Professor in Physiotherapy and Rehabilitation, Plymouth University.

Correspondence

Emma Underwood, Lymphoedema Clinic, Therapy Department, PAW, Royal Cornwall Hospital, Truro, Cornwall, TR1 3LJ UK. Tel 01872 252601 email emmaunderwood@nhs.net

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Key words

- Research prioritisation
- Patient and public involvement
- Lymphoedema

Abstract

Background: More research is needed in lymphoedema management to strengthen the evidence base and ensure patients receive clinically and cost-effective treatment. It is critical that patients and clinicians are involved in prioritising research to ensure it reflects their needs and is not biased by commercial interests. This study aimed to set the research priorities for lymphoedema management in the United Kingdom, through collaboration with patients, carers and clinicians.

Methods and Results: Following the James Lind Alliance's methodology, a national survey was conducted to identify unanswered questions about lymphoedema management from the perspective of patients, carers and clinicians. These were collated and verified against an in-depth evidence review. Unanswered questions were formatted into broad research questions, which were prioritised by a purposive sample of patients, carers and clinicians using an online Delphi survey.

The initial survey generated 631 submissions from 213 participants including 108 patients, 9 carers and 88 clinicians. Of these 485 met inclusion criteria and were grouped into 12 overarching themes. The evidence review demonstrated that 101 submissions were answered by existing research and identified an additional 78 questions. The remaining unanswered submissions were collated into 126 broad research questions which were prioritised over four rounds of the Delphi survey to produce the top 10 priorities.

Conclusions: This study is the first to attempt to systematically identify research priorities for lymphoedema management in the United Kingdom, from the perspective of patients, carers and clinicians. The results provide guidance for

researchers and funders to ensure future research meets the needs of those living with lymphoedema.

Condensed Abstract

This study aimed to set the research priorities for lymphoedema management in the United Kingdom, through collaboration with patients, carers and clinicians using the James Lind Alliance's methodology. A national survey was conducted to identify unanswered questions about lymphoedema management. The results were collated into 12 overarching themes, verified against an in-depth evidence review and formatted into 126 broad research questions, which were prioritised using an online Delphi survey to produce a top 10. These will be used to promote research into lymphoedema management that meets the needs of those living with lymphoedema.

Introduction

Lymphoedema results from a failure of the lymphatic system and causes swelling, skin and tissue changes and a predisposition to infection. It may affect any part of the body and occur at any age. Lymphoedema is classified as either primary, caused by genetic lymphatic dysplasia, or secondary, caused by damage to the lymphatic system by an extrinsic process such as cancer and cancer treatment, trauma, disease or infection (1). It is a chronic, progressive and disabling condition which impacts greatly on quality of life and requires life-long management (2, 3). Although probably underestimated it is thought that lymphoedema affects approximately 140-250 million people worldwide (4). In the United Kingdom (UK) lymphoedema is estimated to currently affect 3.93 per 1000 population, which increases with age to 10.31 /1000 in those aged 65–74, rising to 28.75 in those aged over 85 years (5).

Lymphoedema remains a poorly evidenced speciality, relying largely on expert review and consensus (6) with a paucity of randomised controlled studies and satisfactory meta-analysis (3, 7) resulting in a weak and inconclusive evidence base (8, 9). Further research is therefore needed to strengthen the evidence base and ensure patients receive the optimum treatment. In order to best utilise research funding, clinical research needs to ensure that it addresses priority questions that have not already been answered, are representative of patient's needs (10), and not driven by commercial interests and priorities (11) which are not necessarily those of patients and clinicians (12).

Research prioritisation has been conducted in many specialities. In lymphoedema, priorities for breast cancer related lymphoedema have been established by an

international expert consensus group (13) and for lymphoedema in general for the UK by clinicians (14). These studies, however, are no longer current and did not involve patients or carers. A more recent study, which established research priorities for morbidity control of lower limb lymphoedema in India (Narahari et al., 2017), successfully involved patients to prioritise seven research questions. These are however, specific to filariasis affected countries and though western healthcare can learn much from this, our priorities are likely to be different.

The Lymphoedema Research Prioritisation Partnership (LRPP) aimed to set research priorities for the treatment and management of lymphoedema in the UK, through collaboration with patients, carers and clinicians, to inform research funding strategies and policies.

Methods and materials:

Governance:

The study was conducted in collaboration with the Lymphoedema Support Network (LSN), a UK charity which represents patients with lymphoedema and their carers and the British Lymphology Society (BLS), a UK charity that represents clinicians, academics and researchers in lymphoedema. Both organisations were represented on the study steering group.

Ethical approval was gained from the Faculty of Health and Human Sciences Ethics Committee, Plymouth University (30/6/2016); and undertaken in line with the Declaration of Helsinki. All data was kept in accordance with the Data Protection Act (15).

Methods:

The study used the internationally accepted James Lind Alliance (JLA) methodology (16), which is recognised as the gold standard in research prioritisation (Smith and Morley, 2015). This involves four stages: initiation, engagement and generation of research ideas; collation, analysis, verification and formatting of submissions; prioritisation; evaluation and dissemination, which are detailed below.

Data collection

Phase One – Generation of Research Questions

A national qualitative, online and paper survey was conducted over a 10-week period in 2016, with the aim of generating research questions. Surveys have been used in many other research prioritisation studies (17, 18) and have been shown to generate more top 10 research priorities, reach a wider audience, provide greater breadth of information and were more cost effective than other methodologies (19).

To gain as many wide ranging perspectives as possible, the survey was presented at both the LSN and BLS conferences and advertised via their newsletters, website and social media forums, which has proved an effective method of recruitment in other studies (20, 21). In addition, individuals with lymphoedema and clinicians were asked to publicise to their local support groups and the Children's Lymphoedema Special Interest Group promoted the research during its Lymphaletics event for children and young people with lymphoedema and their carers.

As this was a qualitative survey a high number of respondents would not necessarily result in more or better research questions (16) and therefore the focus was to ensure a representative sample of participants. Those eligible to complete the survey were people with lymphoedema aged over 16 years, unpaid carers of individuals with lymphoedema, clinicians treating patients with lymphoedema, academics or

researchers with an interest in lymphoedema and lymphoedema support groups, with no geographical boundaries. All those who expressed an interest were provided with a participant information sheet; consent was presumed by virtue of them completing and returning the survey. Participants could complete the survey anonymously or add their contact details to enable them to be contacted to participate in phase three, the Delphi study, at which time the participants completed a separate consent and declaration of interest's form.

The survey was completed and returned either in paper form or online (cloud-based Bristol Online Surveys). Both versions were distributed at the LSN and BLS conferences and could be returned at the conference, by post, or online. The survey asked a single open-ended question, paraphrased to ensure clarity for the respondent: "What questions about the treatment of Lymphoedema do you feel need to be answered by research?" or "What questions about lymphoedema treatment have you and your healthcare professional been unable to answer?". Respondents were asked to submit up to five questions. Examples of questions from other unrelated JLA partnerships were also provided. Demographic data indicating the role of the participant (patient, carer, clinician, academic, researcher or support group) and their country of residence, was also collected.

Phase Two – Collation, Verification and Formatting

Anonymised results from the online and paper-based versions of the survey were downloaded into a single Microsoft Excel spreadsheet; to ensure transparency and maintain an audit trail, all submissions were given a unique code. The data were

then screened for out-of-scope questions against agreed exclusion criteria by two researchers (EU, KR), and the outcome verified by the steering group. Other studies have found that this screening process can potentially reduce the contribution of patients and carers, who may not have phrased their submission as a research question (22), therefore to ensure equity submissions relating to broad themes were included. The agreed out-of-scope submissions were removed and service dissatisfaction submissions were passed to the LSN and BLS to be used as illustrations of the impact of poor service provision. The remaining questions were then collated and analysed, using an inductive approach to group similar questions into themes (23). This informed the evidence review, which in turn informed the thematic analysis.

The JLA (16) state that a treatment uncertainty is a question that has not been answered by a systematic review of the evidence. An in-depth literature review was undertaken to verify the submissions, identify evidence gaps and add additional unanswered questions identified in the research. Healthcare databases (AMED, BNI, CINAHL, Cochrane Database of Systematic Reviews, EMBASE, JBI Library, MEDLINE, PubMed, Web of Science) were searched from 2006-2017 for systematic reviews, nationally or internationally accepted clinical practice guidelines and future research needs documents relating to the treatment or management of lymphoedema; robust literature reviews were considered in the absence of a systematic review. In addition, consensus documents and clinical guidelines from the International Lymphoedema Framework, International Lymphology Society and British Lymphology Society were also included.

The systematic reviews were assessed for methodological validity by the primary researcher (EU) using the AMSTAR measurement tool (24) adapted to provide a score for each systematic review; areas of conclusive evidence were identified and research questions extracted. The second reviewer (MW), reviewed any paper where the confidence interval crossed the line of no effect to clarify its clinical relevance in the absence of statistical significance and this was agreed in discussion with the primary researcher (16), areas of uncertainty were discussed with a third person (JF). Questions relating to areas of conclusive evidence with established effectiveness and those questions known to have been answered in the expert opinion of the steering group were excluded from phase three and were provided to the LSN and BLS to highlight the lack of awareness by the respondents of available evidence. The research recommendations from the literature were then added to the submitted questions.

The themes were then transformed into broad research questions, using population, intervention, comparator and outcome (PICO) (25) where relevant. The steering group reviewed these questions to ensure they reflected the submissions and were understandable and meaningful to patients, clinicians and researchers. The questions were refined following discussion, and a glossary of terms developed to help patients and carers understand the medical terminology.

Phase Three – Prioritisation

An online Delphi survey was used in the prioritisation phase to allow recruitment of a more representative sample from a wide geographical area at low cost, negating

difficulties with travelling and time away from work or caring responsibilities (Jones & Hunter, 1995). This approach also avoided issues of dominance in the group due to status or ability to articulate (Murphy et al., 1998; Owens, Ley & Aitken, 2008).

The agreed list of research questions from phase two, were prioritised over four rounds of the Delphi, with a purposive, representative sample of patients and carers and clinicians, who volunteered in phase one, to gain consensus on a ranked list of the top 10 priorities. The sample for patients and carers was based on current estimated lymphoedema prevalence figures: 78% Female, 20% Male, 2% Children, 60% Non-Cancer and 40% Cancer (26), with maximum variation based on age, diagnosis and time from diagnosis and geographical spread based on the UK population. Round one of the Delphi was an item reduction round and participants were asked to rate the importance of the question for research on a three-point Likert scale. The subsequent rounds asked the participant to rank the remaining questions in order of priority.

Results

Phase One and Two

Overall 213 participants, including 118 patients/carers and 88 clinicians, completed the survey, which generated 631 submissions (illustrated in figure1). After screening for out-of-scope questions, 488 remained. These were analysed and collated into 12 broad themes and 30 sub-themes, which informed the evidence review. The evidence review excluded 103 submissions as there was adequate evidence in the literature to answer these and an additional 78 unanswered research questions were added as a result of the evidence review. The final 463 submissions were formulated into 126 broad research questions.

Phase Three

A purposive sample of 27 patients, 3 carers and 31 clinicians were selected from volunteers, to ensure broad representation. Round one of the Delphi received 51 responses, however the item reduction was not successful as no questions were excluded by the participants. During this round, the JLA Cellulitis priority setting partnership published their priorities (27) and to avoid duplication four questions were excluded. Round two reduced the questions to a priority list of 31, which were ranked in rounds three and four, to reach final consensus on a ranked, top ten research priorities (Table 1).

Table 1: Top 10 Research Priorities for the treatment and management of Lymphoedema in the UK pg 18

Conclusions

Although research prioritisation has been carried out in many specialities, this is the first attempt at systematically identifying the evidence gaps and treatment uncertainties for the management of lymphoedema in the UK from the perspective of patients, carers and clinicians and prioritising them for research.

The strengths of this study are its use of the robust, structured and transparent JLA methodology, the collaboration with the LSN and BLS and the involvement of patients, carers and clinicians nationally, throughout the process. Of the 126 final questions, patients and carers contributed to 75 questions and clinicians to 82 questions. Only 15 questions were derived from the literature alone, which demonstrates the value of patient, carer and clinician involvement in generating meaningful research questions. Finally the use of a steering group with patient,

clinician and researcher / academic representation to guide the study provided invaluable clinical and research expertise, reduced the risk of bias, ensured transparency, provided methodological rigour and ensures that the developed research priorities are relevant and feasible (28).

The results of this study should, however, be interpreted within the context of its limitations. The survey was predominantly internet based and was only available in English which may have excluded some individuals from participating and although membership of the LSN or BLS was not necessary to participate, they were the main source of advertising and therefore non-members may have not engaged in the study. The study was conducted in the UK and may therefore be most relevant to the UK healthcare setting. However, the evidence review included international research and whilst the priorities may differ the unanswered questions are likely to be similar; the list of potential research questions may therefore be of international relevance to other high-income countries.

This study has reached consensus on the top 10 research priorities for lymphoedema management in the UK through collaboration with patients, carers and clinicians. Through dissemination of these research priorities it is hoped that research is generated that addresses questions that are important to patients with lymphoedema and the clinicians that treat them, with the goal of improving lymphoedema management.

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Author Disclosure Statement

No competing financial interests exist

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Generation of Research Questions	<p>National Survey</p> <p>213 Participants</p> <p>(108 Patients, 10 Carers, 92 Clinicians, 7 Academics/Researchers, 5 Support Groups – some participants had multiple roles)</p> <p>631 Submissions</p>
Collation, Verification and Formatting	<p>Collation</p> <p>143 submissions excluded against criteria</p> <p>12 overarching themes and 30 subthemes</p>
	<p>Evidence Review</p> <p>103 submissions excluded</p> <p>78 submissions added</p>
	<p>Formatting</p> <p>126 final questions</p>
Prioritisation	<p>Delphi</p> <p>Round One: 51 participants - 4 questions excluded</p> <p>Round Two: 47 participants – 31 priority questions remain</p> <p>Round Three: 50 participants - consensus not reached</p> <p>Round Four: 50 participants - top 10 agreed</p>

Figure 1: Summary of results for the Lymphoedema Research Prioritisation Partnership

Table 1:

Top 10 Research Priorities for the treatment and management of Lymphoedema in the UK

1. What early intervention modalities are the most effective in preventing or controlling lymphoedema and preventing long-term complications?
2. How effective are self-management regimes on the long-term management of lymphoedema?
3. Is it possible to promote the re-routing of lymphatic vessels with non-invasive treatment modalities to improve lymphatic drainage in lymphoedema?
4. How does exercise affect lymphatic flow, what exercises are the most beneficial for improving lymphatic drainage in upper and lower limb lymphoedema and mid-line lymphoedema (head and neck, trunk and genital) and what is the optimum protocol for these?
5. What are the differential diagnostic criteria for cellulitis, erysipelas, inflammation and bilateral red legs and how can these be utilised to enable prompt diagnosis and treatment by all care providers?
6. What predictive risk factors are there for developing cancer-related lymphoedema and how could these be assessed to reduce risk and inform cancer treatment decisions?
7. Is MLD an effective treatment to improve the symptoms of and manage lymphoedema and what are the long-term benefits of a course of MLD?
8. What are the indications for surgical treatment of lymphoedema and at what stage should each surgical technique optimally be used?
9. Is ongoing specialist review needed for long-term management of lymphoedema or can patients be safely discharged with self-management and review by generalist services?
10. Which specific exercise regimes (i.e. swimming, walking, Pilates, yoga, weight training) are the most beneficial in improving lymphatic drainage of the upper and lower limb and which are contraindicated?