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Cost-effectiveness analysis of lymphaticovenous anastomosis in reducing cellulitis recurrence in 150 lymphoedema cases followed-up over 24 months

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Summary *Background:* Lymphoedema is a chronic condition that imposes ongoing costs on the patient and National Health Service (NHS). This study aimed to estimate the cost-effectiveness of lymphaticovenous anastomosis (LVA) in reducing cellulitis recurrence in 150 patients with lymphoedema who were followed-up for over 24 months.
Methods: Data were prospectively captured pre- and post-LVA surgery in 150 patients with unilateral lower or upper limb lymphoedema in a centre in the UK. Data collection included cellulitis resource utilisation with costs identified from the British National Formulary, Personal Social Services Research Unit, and a quality-of-life questionnaire (EQ-5D-5L).
Results: The mean overall costs for cellulitis and hospital admissions reduced by £1389.85, which was statistically significant ($p < 0.001$). Mean per patient reduction of costs across the 24-months was estimated at −£1405.62 (CI: −£1878.09, −£933.16). When the cost of LVA (£4551) was included, the reductions were offset to £3145.37 (CI: £2672.90, £3617.84). The mean EQ-5D-5L utility score ($n = 143$) increased from 0.743 (SD 0.168) to 0.800 (SD 0.196), being statistically significant ($p = < 0.001$). The incremental cost-effectiveness ratio (ICER) through costs and EQ-5D-5L changes was £54231, indicating that LVA costs more, but is more effective. LVA benefits patients for more than the 24-months captured, thus costs would be reduced based on the patients' life expectancy.

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Conclusion: This cost-effectiveness analysis provided an in-depth examination of a large cohort of LVA patients who were followed up for 24 months, highlighting decreased cellulitis recurrence.

Background

Lymphoedema is a progressive, chronic condition initiated by excess accumulation of protein rich fluid within the subcutaneous tissues. Lymphoedema diagnosis occurs when oedema lasts for a minimum of 3 months, due to lymphatic system dysfunction from a reduced transport capacity and/or increased capillary filtrate.[1-3] Those affected may experience pain, recurrent cellulitis requiring admittance into hospital, wounds, falls, reduced range of movement and heaviness.[4-6] Lymphoedema also affects the quality of life, extending into all aspects of normality and emotional well-being.[3,4,6-8]

Conservative lymphoedema treatment, including compression, skin care, exercises, weight management and massage, can improve the symptoms. Nevertheless, treatment requires lifelong patient compliance for wearing compression garments to maintain the improvements made and does not negate the need for continuous self-management.[3-6] Therefore, lymphoedema leads to detrimental health outcomes and its consequences, such as cellulitis, are a financial burden to the NHS.

In recent years, microsurgical procedures specifically lymphaticovenous anastomosis (LVA) have gained evidence and acceptance as a promising medical intervention for lymphoedema.[4,6,9-11] Recent studies with increasing participant numbers and longer follow-up times have suggested that LVA may also offer cost effective benefits as well as improved patient outcomes.[12-15] An American cost-minimisation decision analysis study[12] estimated the economic impact of post-operative lymphoedema among patients with breast cancer who underwent mastectomy with axillary lymph node dissection (ALND) alone or mastectomy with ALND and prophylactic LVA.

The N-LVA study,[16] SurLym trial[17] and Wolfs study[18] have commenced recruiting into the first randomised controlled trials using LVA in the Netherlands focusing on costs and outcomes. However, limited research, that focused on cellulitis recurrence in a large cohort of lymphoedema cases, has been conducted in the United Kingdom on the cost-effectiveness of LVA.

Since 2015, the Wales' NHS has supported a small cohort of patients with lymphoedema to undergo LVA. Two years of prospective data were captured for the first 150 patients undergoing LVA.[6] Within the eligibility criteria, patients must be under the care of the Lymphoedema Wales Clinical Network (LWCN) and have had at least 2 episodes of cellulitis requiring antibiotics in the previous 24 months prior to receiving LVA.

Aims and objectives

This study aimed to estimate the cost-effectiveness of LVA in reducing cellulitis recurrence in 150 lymphoedema cases that were followed-up over 24-months.

The specific objectives were to:

- Estimate the costs associated with the delivery of LVA.
- Measure changes in the cellulitis resource utilisation for patients before and after LVA focusing on appointments, admission and antibiotic medication.
- Describe the health-related quality of life (HRQoL) in service users before and after LVA.
- Generate an Incremental Cost Effectiveness Ratio (ICER) through costs and EQ-5D-5L changes after LVA.

Methods

Briefly, 150 patients were prospectively followed up at 3 set points: 3-, 12- and 24-month post-operatively. All patients were over 18 years of age and consented to anonymous data collection as part of the LVA service delivery. Briefly, the design was a prospective, interventional study with data collected before and after LVA surgery.[6] Patients with primary or secondary lymphoedema of cancer or non-cancer origin were included in the study consecutively following scanning of their lymphatics. All patients had to provide informed consent and comply with an existing lymphoedema management plan. Preoperatively, 150 patients were assessed, reducing to 147 at 3 and 12 months and 143 at 24 months. The attrition rate at 24 months was due to 2 patients who died and 5 who were lost to follow-up.

Ethics and research governance

The study design was reviewed by the Joint Study Review Committee at Swansea Bay University Health Board, Wales, and deemed a service evaluation/data audit. Swansea University College of Human and Health Sciences ethics committee provided permission to analyse the anonymised data sets (ethics application reference: 170419d).

Data collection measures

Data capture included clinical and subjective outcomes as previously published in 2023.[6] These data also included details on whether the cellulitis required hospitalisation and cost calculated using national sources.[19-21] The numbers of patients prescribed prophylactic antibiotics was also sourced.

Health related quality of life

The EQ-5D-5L a generic HRQoL questionnaire[22] was completed by patients throughout the study. These responses

generated a 5-figure profile that was converted to an individual utility score that was then used to estimate and generate an ICER. EQ-5D-5L and patient-reported outcome measure are routinely collected in LWCN as part of normal care pathways.

Intervention costs

Resources and associated costs of providing LVA for the 150 patients was estimated at £682 608 (£4551 per patient procedure). The intervention costs covered all the resources associated with the acquisition of the equipment, LVA procedure including theatre time, scanning process and all staff, plus one follow-up visit with a lymphoedema specialist (Table 1).

Cellulitis resource use

Resource use associated with cellulitis pre- and post-LVA treatment was summarised into relevant categories valued in £ sterling using the price year of 2021/2022. It was assumed that an episode of cellulitis would incur at least one visit to the General Practitioner (£39) and one course of oral antibiotics (£1.16). If a cellulitis infection was treated at the Emergency Department and incurred length of stays, then the cost was estimated to be £3070 (Table 2). The costs were determined from nationally published sources of unit costs.[20,21]

Data and statistical analysis

All continuous variables were reported as mean with standard deviation and categorical data as frequency. Differences in pre- and post-LVA means were analysed using the paired-samples *t*-test with a 95% confidence interval to examine the effects of LVA.

An incremental cost-effectiveness ratio (ICER) analysis was undertaken to assess the extent of potential changes in the main cost parameters and outcomes (EQ-5D-5L) to cost parameters per outcome increment. This was achieved using the mean difference, as well as the lower and upper bounds of the confidence intervals. A one-way sensitivity analysis ($\pm$ 30%) was undertaken to assess the extent of altering the main cost parameters on LVA impact. Results were analysed using MS EXCEL and IBM SPSS Statistics for Windows, version 26 (INM corp. ®, Armonk, N.Y., USA). A p-value < 0.05 was considered statistically significant. We employed complete case analysis and excluded cases where data were missing. Any participants lost to follow-up (e.g. due to death), excluded from the analysis. The analysis was conducted from the perspective of the UK NHS.[19]

Results

Among the 150 patients eligible for LVA surgery, 19 were men (13%) and 131 were women (87%), with an average age of 53.8 years (range 21–79 years). Table 3 presents the demographic data captured, including age, body mass index (BMI), lymphoedema classification, International Society Lymphology (ISL) staging and affected limb. The average BMI before surgery was 26.9 kg/m^2 (range 17.6–35.9 kg/m^2). In the cohort, 118 patients (79%) had secondary lymphoedema due to cancer, 21 (14%) had primary lymphoedema and the remaining 11 (7%) had secondary lymphoedema due to non-cancer causes. At the baseline, 150 patients were assessed, which reduced to 147 at 3 and 12 months and 143 at 24 months. The attrition rate at 24 months decreased because of death of 2 patients and 5 patients were lost to follow-up.

Table 1 Intervention costs of LVA.

Cost items	Cost per procedure	Unit cost source/Description	Comments/Assumptions made
LVA Surgery Equipment Acquisition	£233	Welsh Government	Acquisition cost £158 500. Equivalent annual annuity for 10 years at 3.5% = £34 908.26
LVA Treatment (such as Inc. Equipment, Staff, and theatre)	£4243	UK Costing Centre from Business Case	Estimated cost of LVA surgery (supplied by LWCN Business Case)
Lymphoedema Specialist Band 8a	£75	PSSRU (2021) Band 8a - Page 104	Based on one follow-up visit
Number of LVA participants			150
Overall cost of LVA procedure			£682 608
Cost of LVA Intervention per participant			£4551

Table 2 Unit costs used in the analysis.

Health service resource	Unit cost (£)	Source
GP surgery visit (Per surgery consultation lasting 9.22 min)	£39	PSSRU 2021 page 111
Inpatient: *Cellulitis* Unspecified oedema with CC score 2+ (non-elective long stay)	£3070	NHS reference costs (2020/2021)
Medication-oral antibiotics (Flucloxacillin (as Flucloxacillin sodium) 250 mg)	£1.16	BNF[23]

Table 3 Patient demographics.

Variable	Category	n	(%)
Age group, years	21-30	10	(7)
	31-40	12	(8)
	41-50	32	(21)
	51-60	51	(34)
	61-70	31	(21)
	70+	14	(9)
BMI, kg/m^2	Underweight (< 18.5)	1	(1)
	Normal weight (18.5-24.9)	49	(33)
	Overweight (25-29.9)	64	(43)
	Obese Class 1 (30-34.9)	34	(23)
	Obese Class 2 (35-39.9)	2	(1)
Lymphoedema classification	Primary	21	(14)
	Secondary Cancer	118	(79)
	Secondary Non-Cancer	11	(7)
ISL staging	Stage 0 (Latent)	1	(1)
	Stage I (Mild)	27	(17)
	Stage II a (Pitting)	49	(33)
	Stage II b (Non-pitting)	73	(49)
Affected limb	Upper Limb	101	(67)
	Lower Limb	49	(33)
Affected side	Right	69	(46)
	Left	81	(54)

Cellulitis resource use and costs (baseline to three-month follow-up) (n = 147)

The mean number of cellulitis infections pre-LVA was 4.2 (SD 6.02), compared to post-LVA mean at three months of 0.1 (SD 0.24) with a mean difference of −4.16 (CI: −3.19, −5.13; $p < 0.001$). The mean number of patients hospitalised for cellulitis pre-LVA was 0.5 (SD 1.01), compared to 0 (SD 0.08) at three-month post-LVA, with a mean difference of −0.46 (CI: −0.30, −0.62; $p < 0.001$). The number of days off work significantly decreased from 5.8 pre-LVA (SD 13.34) to a mean of 0.2 (SD 1.29) with a mean difference of −5.64 (CI: −3.45, −7.83; $p < 0.001$). The use of prophylactic antibiotics slightly decreased from 0.1 (SD 0.33) to 0.1 (SD 0.24) with a mean difference of −0.08 (CI: −0.01, −0.13; $p = 0.029$).

Cellulitis resource use (Baseline to 12-month follow-up) (n = 147)

The mean number of cellulitis infections pre-LVA was 4.4 (SD 6.05), compared to post-LVA mean at 12 months of 0.1 (SD 0.35) with a mean difference of −4.07 (CI: −3.08, −5.06; $p < 0.001$). The mean number of patients hospitalised for cellulitis pre-LVA was 0.5 (SD 1.02) compared to 0 (SD 0.12) at 12 months, with a mean difference of −0.46 (CI: −0.29, −0.62; $p < 0.001$). The number of days off work significantly decreased from 5.9 (SD 13.46) pre-LVA to 0.2 (SD 0.93) post-LVA with a mean difference of −5.75 (CI: −3.53, −7.97; $p < 0.001$). The use of prophylactic antibiotics slightly reduced from 0.1 (SD 0.32) to 0.1 (SD 0.30) post-LVA with a mean difference of −0.02 (CI: −0.04, 0.08; $p = 0.493$).

Cellulitis resource use (Baseline to 24-month follow-up) (n = 143)

Finally, the mean number of cellulitis reduced from 4.3 (SD 6.11) pre-LVA to 0.1 (SD 0.31) at 24-month post-LVA with a mean difference of −4.15 (CI: −3.14, −5.16; $p < 0.001$). The mean number of patients hospitalised for cellulitis pre-LVA was 0.5 (SD 1.03) compared to 0 (SD 0.28) at 24 months, with a mean difference of −0.42 (CI: −0.26, −0.58; $p < 0.001$). The mean number of days off work saw a statistically significant decrease from 5.9 (SD 12.26) to 0.2 (SD 0.87) with a mean difference of −5.24 (CI: −3.20, −7.28; $p < 0.001$). Prophylactic antibiotics again decreased from 0.1 (SD 0.33) to 0.1 (SD 0.32) with a mean difference of −0.14 (CI: −0.05, 0.08; $p = 0.656$) (Table 4).

Patient HRQoL outcomes

Table 5 details the mean EQ-5D-5L utility score increased from 0.739 (SD 0.18) baseline to 0.786 (SD 0.20) at three-month follow-up with a mean difference of 0.047 (CI: 0.020, 0.070), which was statistically significant ($p < 0.001$). At 12-month follow-up, the mean EQ-5D-5L utility score increased to 0.802 (SD 0.19) with a mean difference of 0.060 (CI: 0.036, 0.086; $p < 0.001$). At 24-month follow-up, the mean EQ-5D-5L utility score remained at 0.800 (SD 0.20) with a mean difference of 0.058 (CI: 0.030, 0.085; $p < 0.001$). These results indicate a statistically significant increase in the perceived quality of life of the patients from pre- to post-LVA.

One-way sensitivity analysis

A one-way sensitivity analysis (±30%) was undertaken (Table 6) to assess the extent of altering the main cost parameters on LVA impact. When the main cost drivers of cellulitis were subject to 30% changes either way, they indicated that the results remained consistent and in favour of LVA. This was also favourable when we used the estimated 24-month cost savings of −£1405.62. However, when we included the mean patient intervention cost (£3145.37), the LVA treatment became unfavourable.

Incremental cost-effectiveness ratio analysis

An ICER analysis was undertaken (Table 7) to assess the extent of potential changes in the main cost parameters and outcomes (EQ-5D-5L) to cost per outcome increment using the mean difference, lower and upper bounds of the confidence intervals. When the base-case results of the costs of the intervention (£3145.37) are used with the results of the EQ-5D-5L scores (0.058), the cost per unit of improvement was £54231, indicating that the intervention costs more and was more effective. When all the scenarios were tested, all the outcomes indicated that the intervention cost more, but was more effective. Thus, LVA was not cost-effective

Table 4 Cellulitis events, hospitalisation costs and impact.

	Baseline		Baseline to 3 months (n = 147)			Baseline to 12 months (n = 147)			Baseline to 24 months (n = 143)		
	Mean	(SD)	Mean	(SD)	p-value	Mean	(SD)	p-value	Mean	(SD)	p-value
Number of cellulitis pre-LVA	4.22	−6.02	0.06	−0.24	< 0.001	0.20	0.44	< 0.001	0.31	0.61	< 0.001
Cellulitis cost (£)	169.53	−241.72	2.43	−9.6	< 0.001	5.74	−14.1	< 0.001	4.21	−12.35	< 0.001
Hospitalised for cellulitis	0.46	−1.01	0.01	−0.08	< 0.001	0.02	0.14	< 0.001	0.06	0.31	< 0.001
Hospitalisation cost (£)	1421.68	−3101.44	20.6	−251.5	< 0.001	41.77	−356.86	< 0.001	107.34	−847.64	< 0.001
Days off work due to cellulitis	5.81	−13.34	0.17	−1.29	< 0.001	0.34	1.59	< 0.001	0.5	1.8	< 0.001
Prophylactic antibiotics	0.12	−0.33	0.06	−0.24	0.029	0.1	−0.29	0.493	0.11	−0.32	0.656
Impact of cellulitis on life	2.3	−0.69	3.92	−0.36	< 0.001	3.78	−0.59	< 0.001	3.77	−0.71	< 0.001

Table 5 Health-related quality of life.

Paired-samples statistics	Baseline		Baseline to 3 months				Baseline to 12 months				Baseline to 24 months			
Health-related quality of life	Mean Score	(SD)	Mean Score	(SD)	Mean Diff	p-value	Mean Score	(SD)	Mean Diff	p-value	Mean Score	(SD)	Mean Diff	p-value
EQ-5D-5L Index	0.74	(0.18)	0.79	(0.20)	0.05	< 0.001	0.80	(0.19)	0.06	< 0.001	0.80	(0.20)	0.06	< 0.001
Health Score (0-100)	74.07	(19.50)	77.56	(18.35)	3.50	0.032	77.56	(17.98)	3.43	0.032	78.75	(18.89)	4.18	0.003

Table 6 Results of one-way sensitivity analysis.

	LVA			
Parameter	Base-case	Lower Range	Upper Range	Result
Cost of cellulitis (24 Months)	£166.82	−£116.77	−£216.87	In favour of LVA
Cost of hospital stay (24 Months)	−£1288.11	−£901.68	−£1674.54	In favour of LVA
Total LVA cost difference (24 months) (not including the intervention costs)	−£1405.62	−£983.93	−£1827.31	In favour of LVA
Total LVA cost difference (24 months) (including intervention costs)	£3145.37	£2201.76	£4088.98	Not in favour of LVA

Table 7 Incremental cost effectiveness ratio (ICER) analysis.

Analysis	Incremental cost (£)	Incremental effect	ICER (£)	Result
Base-case	£3145.37 (£2672.90, £3617.84)	0.058 (0.030, 0.085)	£54 231	Usual Care is Dominant
Upper 95% bound of net cost/Upper 95% bound of net utility	£3617.84	0.085	£42 563	Usual Care is Dominant
Upper 95% bound of net cost/Lower 5% bound of net utility	£3617.84	0.030	£120 595	Usual Care is Dominant
Lower 5% bound of net cost/Lower 5% bound of net utility	£2672.90	0.030	£89 097	Usual Care is Dominant
Lower 5% bound of net cost/Upper 95% bound of net utility	£2672.90	0.085	£31 446	Usual Care is Dominant

and usual care dominates. Among all the scenarios that got close to being cost effective between £20 000 and £30 000 per QALY threshold as adopted by NICE (National Institute for Health and Clinical Excellence), was using the lower 5% bound of net cost/Upper 95% bound of net utility. This produced an ICER of £31 446, which was close to the upper threshold of £30 000 per outcome increment. Importantly, the cost of the equipment was shared among the patients with LVA, but the benefit lasted longer than the 24 months and could be used for other patients as well.

Discussion

A strength of this study is that it involved the largest population with the longest follow-up at 3-, 12- and 24-months. This prospective study of 150 patients with upper and lower limb lymphoedema who were followed up for 24 months demonstrated statistically significant improvements in the quality of life and decreased episodes of cellulitis from pre- to post-LVA. Results indicated that health care costs are also significantly reduced in the key areas of hospital admissions and length of stays due to cellulitis reduction. Mean per patient reduction in costs across the 24 months was estimated at −£1405.62 (CIs −£1878.09, −£933.16). While the analysis provides no indication of whether such costs are sustained over 24 months, this snapshot provides a tentative indication that LVA surgery significantly reduced resource use.

While appropriate caution must be taken, the findings indicated that most health care contacts had an observed trend of decreasing (from baseline, 3-months, 12-months and at 24-months). This is an exciting finding as it has massive implications for financial savings and avoidance of NHS expenditure supporting forthcoming LVA services.

Although there was a cost avoidance of admissions, when the mean per patient cost of LVA (£4551) was added to the analysis, the cost reductions were offset by the cost of the treatment (£3145.37 [CIs £2672.90, £3617.84]). In the short term, the costs of delivering the LVA treatment would be at their highest, particularly given the intensive nature of delivering a complex intervention to this patient population with chronic, complex and (likely) fluctuating health care needs.[3] Thus, investment in LVA treatment as an upstream intervention, particularly to support patients in managing their lymphoedema, could realise downstream costs and benefits in the future.[12] The acquisition cost of the equipment was £158 500. The equivalent annual annuity for 10 years at 3.5% interest results in an equipment cost of £34 908.26. Therefore, even though the treatment may cost £233 per procedure for 150 patients in this cohort, the machine could be used for more than 1000 patients across the Wales NHS. In addition, the machines could be used for breast reconstruction and other preventative operations.[11,12] Therefore, the costs would be absorbed throughout the lifetime of the equipment.

Other costs of lymphoedema management should also be considered. As discussed in our previous paper,[6] compression garment usage (numbers of days and hours per week) was reduced, which also decreases the need and eventually the costs. Further, the more expensive garments, such as made-to-measure options, decreased from 27% pre-LVA to 10% post-LVA, and similarly, class 2 knit garments decreased

from 45% to 15%, and 31% stopped wearing garments altogether. Although the costs of cellulitis included admissions and antibiotic usage, it is important to consider the overall impact of LVA in potentially reducing sepsis and supporting antimicrobial effective stewardship.

Similar to other studies,[11,13] the positive differences in EQ-5D 5L scores in patients after they have received the LVA treatment (across the 3 time periods) were encouraging and should be considered as an indication of the success and effectiveness of the treatment. To be considered cost effective, the National Institute for Health and Care Excellence (NICE) uses an ICER cost-effectiveness threshold of £20 000-£30 000.[24] The cost per unit of improvement was £54 231 indicating that the intervention costs more, but was more effective. When we used the lower 5% bound of net cost/upper 95% bound of net utility, an ICER of £31 446 was produced, which is close to the upper threshold of £30 000.

This analysis has provided a first in-depth examination of the impact of LVA treatment on a relatively large cohort of 150 patients with lymphoedema. This evidence indicated that LVA treatment could make differences to the management of lymphoedema within the NHS. From a decision makers' perspective, the analysis demonstrates that evidence should relate to the local health economy and patient health outcomes.

Limitations

The limitations of the study include the relatively narrow cellulitis perspective adopted (Direct NHS costs) and the population is limited to one area of the UK. If more detailed resources such as primary care usage (including practice nurse and carers), decrease in compression garments costs, reduction in lymphoedema services appointments and indirect costs were linked to factor such as time taken off work and family responsibilities, had been collected, then a wider, more societal perspective could have been used and a broader range of costs collected to offset against the cost of LVA. If we had explored the cost of time off work pre- and post-LVA and surmised the 5.8 days based on Mitchell and Bates, then the loss would be $2255 or £1741.[25] This additional loss might have altered the ICER results and made LVA more cost-effective. Widening the perspective of the analysis could also provide a clearer picture of the long-term HRQoL gains, if, for example, we had performed subgroup analysis on whether patients had upper or lower lymphoedema or differing ISL staging. Another limitation regarding the results is the sole use of the EQ-5D-5L to assess cost-effectiveness. In the previous paper,[6] we reported HRQoL outcomes using the EQ-5D-5L and lymphoedema-specific tool LYMPROM.[8] For this study, we aimed to align the analysis as close to the NICE guidelines as possible for cost-effectiveness analysis; therefore, only the EQ-5D-5L was used. For any future research, it may be beneficial to use the EQ-5D-5L and LYMPROM to assess the cost-effectiveness of LVA from a more cost-consequences approach.

The study was limited to a single hospital, representing this nation (Wales), and all plastic surgeries are centralised. This is due to a relatively small population requiring a centre of excellence to perform super-micro-surgery. Pricing is thus standardised for theatre use and staffing which negates the need for additional highly skilled theatre staff and specialist surgical equipment elsewhere, saving the additional costs for NHS Wales.

Conclusion

This economic analysis has provided one of the first in-depth examinations of the economic and patient impact of LVA treatment on cellulitis recurrence. Findings suggest an observed trend of significant reductions in patient-related costs to the NHS in terms of episodes of cellulitis and hospital inpatient stays. Importantly, the cost reductions indicate the minimum expected savings, and if a more holistic view, including compression therapy and patient time off work, had been considered, this would be potentially more substantial. The significant HRQoL gains over time are also testament to the impact that LVA has on the patient's journey to recovery.

Ethical approval

The study design was reviewed by the Joint Study Review Committee at Swansea Bay University Health Board, Wales, and deemed a service evaluation/data audit. Swansea University College of Human and Health Sciences ethics committee provided permission to analyse the anonymised data sets (ethics application reference: 170419d).

Conflicts of interest

None declared.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bjps.2025.04.032.

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