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Protocol of a randomised controlled trial regarding the effectiveness of fluoroscopy-guided manual lymph drainage for the treatment of breast cancer-related lymphoedema (EFforT-BCRL trial)

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ABSTRACT

Objectives: Lymphoedema is a dreadful complication following breast cancer therapy. According to the International Society of Lymphology, the consensus treatment for breast cancer-related lymphoedema (BCRL) is the decongestive lymphatic therapy. This is a two-phase treatment and combines different treatment modalities including skin care, manual lymphatic drainage (MLD), compression therapy and exercise. However, the additional effect of MLD is debated since pooled data only demonstrated a limited non-significant additional value. A possible explanation is that in previous studies MLD has been applied blind, without knowledge of patient-specific lymphatic routes of transport. In addition, the MLD hand manoeuvres used by the therapists in previous studies, possibly did not optimally stimulate lymphatic transport. Recently, near-infrared fluorescence imaging has been introduced to visualise the superficial lymphatic network which allows MLD at the most needed location. The aim of the present study is to determine the effectiveness of the fluoroscopy-guided MLD, additional to the other parts of the decongestive lymphatic therapy and compared to the traditional or a placebo MLD, in the treatment of BCRL.

Study design: A three-arm double-blinded randomised controlled trial will be conducted in different university hospitals in Belgium. Based on a sample size calculation, 201 participants with chronic BCRL stage 1 or 2 of the arm or hand, with at least 5% difference between both sides (corrected for hand dominance) need to be recruited. All participants receive the standard treatment: skin care, compression therapy and exercises. The intervention group additionally receives fluoroscopy-guided MLD. One control group additionally receives the traditional 'blind' MLD and a second control group receives a placebo MLD. All subjects receive 3 weeks of daily intensive treatments and 6 months of maintenance treatment. Follow-up period is 6 months. The primary outcomes are the reduction in lymphoedema volume of the arm/hand and the change in stagnation of lymph fluid at level of the shoulder/trunk.

Introduction

Lymphoedema is an embarrassing and dreadful morbidity after breast cancer treatment. The incidence of breast cancer-related lymphoedema (BCRL) of the arm is 16% [1]. Lymphoedema does not only induce physical impairments such as swelling, heaviness

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and problems with performing household activities and mobility [2], but also psychosocial problems [3].

According to the recommendations of the International Society of Lymphology (ISL), lymphoedema needs to be treated with decongestive lymphatic therapy [4]. This is a two-stage treatment programme. During the first or intensive phase, lymphoedema is maximally reduced. This phase consists of skin care, manual lymph drainage (MLD), multi-layer bandaging and exercise therapy. The second or maintenance phase aims to conserve and optimise the results obtained in the first phase. It consists of skin care, compression by a low-stretch compression sleeve, exercises and MLD.

Due to the significantly improved screening and treatment modalities for breast cancer over the last few years, survival rates are growing resulting in a prevalence rate of BCRL which is still increasing as well [5]. In Belgium, almost all lymphoedema patients receive MLD as part of the physical treatment, which can be time-consuming for patients and entails a big financial cost for the patient as for the Health Care system [6]. However, a meta-analysis, including 6 randomised controlled trials (RCT's), and a Cochrane systematic review have questioned the effectiveness of MLD [7,8]. The meta-analysis showed an overall additional benefit of MLD to the treatment of BCRL of 75 ml, while the systematic review revealed that the individual contribution of MLD was limited to 7% [7,8]. Two recent RCT's were unable to demonstrate an additional effect of MLD to decongestive lymphatic therapy [9,10].

A possible explanation why MLD according to the method applied in previous studies, has a rather small benefit in addition to the other parts of decongestive lymphatic therapy, is that MLD is applied in an inefficient or 'blind' way. This method of MLD is further called 'traditional MLD'.

After dissection of the axillary lymph nodes, whether or not in combination with radiotherapy, the lymphatic system of the upper limb is damaged. Lymph nodes are removed and often fibrosis of the superficial lymphatic system follows [11,12]. As a result, reverse flow of lymph fluid coming from collecting vessels and going through precollecting vessels in direction of the dermal capillaries, can occur. This dysfunctional phenomenon is called dermal backflow [13]. Moreover, rerouting of lymphatic drainage via lymph collaterals and dermal capillaries, also called dermal rerouting, has been described in patients with lymphoedema [14,15]. This rerouting is patient-specific. Therefore, it is proposed that the traditional or 'blind' MLD needs to be abandoned and a tailored approach needs to be established. Near-infrared fluorescence imaging or lymphofluoroscopy can aid to apply a more efficient MLD. During this investigation, diluted Indocyanine Green (ICG) is injected intradermal in the hand; it visualizes the superficial transport of lymph from the hand up to the axilla and it demonstrates alternative pathways towards other lymph nodes [16].

A second possible explanation why traditional MLD has not proven to be effective, is that the therapist does not optimally stimulate lymphatic transport. The resorption of lymph capillaries has to be performed with the thumb (instead of with the hand in the traditional MLD, which gives a lower pressure). In addition, gliding (compared to no gliding) is hypothesised to be more effective to enhance lymphatic transport [17]. The physiological effect of one session of fluoroscopy-guided MLD was demonstrated in patients with BCRL [17,18]. Whether the application of different sessions of fluoroscopy-guided MLD has a clinical and long-lasting effect on the lymphoedema, superior to the traditional MLD, has yet to be established.

Further, clinical experience revealed that patients report a positive subjective feeling after MLD. Whether this is a real effect rather than a placebo-effect, needs to be investigated as well.

The objective of this trial is to examine the effectiveness of fluoroscopy-guided MLD versus traditional MLD and versus placebo MLD, applied as part of the decongestive lymphatic therapy, for the treatment of BCRL.

Methods

The RCT protocol used the recommended CONSORT guideline to report on the following items [19].

Trial design

The EFforT-BCRL trial is a multicentre double-blind three groups RCT. Fig. 1 gives an overview of the participant flow. All participants (n = 201) receive an intensive treatment lasting 3 weeks and a maintenance treatment for 6 months. Additionally, they are followed up for another 6 months. All participants receive a standard treatment consisting of skin care, compression therapy, exercises and information. Only the MLD differs among the three groups: the intervention group receives a fluoroscopy-guided MLD, control group one receives the traditional MLD and control group two receives a placebo MLD. The participants are assessed before the start of the trial, after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of additional follow-up.

All treatments and assessments are performed at the department of Physical Medicine and Rehabilitation (treatment and clinical assessment) and at the department of Vascular Surgery (lymphofluoroscopy) of the University Hospitals of Leuven, at the Multidisciplinary Breast Clinic in the Antwerp University Hospital, at the Lymphology Clinic in Saint-Pierre University Hospital in Brussels and at the Centre of Oncology in General Hospital Groeninge in Kortrijk.

The EFforT-BCRL trial has been approved by the Ethical Committee of the University Hospitals of Leuven (main Ethical Committee) and received positive advise from the Ethical Committees of all other participating centres (CME reference S58689, EudraCT Number 2015-004822-33). The study has been registered in clinicaltrials.gov (NCT02609724).

Randomisation and allocation sequence generation

All participants are allocated to one of the three groups. The random allocation sequence is computer-generated. Randomisation is performed by using 6-size permuted blocks. The allocation to the groups is concealed and performed by an independent physical therapist. The sequence of randomisation is determined by the participant's identification number, which he/she receives after inclusion in the study.

Blinding

All participants are blinded for the allocation to one of the three MLD groups.

Additionally, all clinical as well as fluoroscopic assessments are performed by investigators who are blinded for the allocation of the patients to the treatment groups. The therapists are blinded to participants' data, but are aware of the treatments provided to the three different groups.

Participants

Participants are recruited from three university hospitals and one general hospital in Belgium: University Hospitals of Leuven (n = 90), Saint-Pierre University Hospital in Brussels (n = 20), Antwerp University Hospital (n = 51) and General Hospital

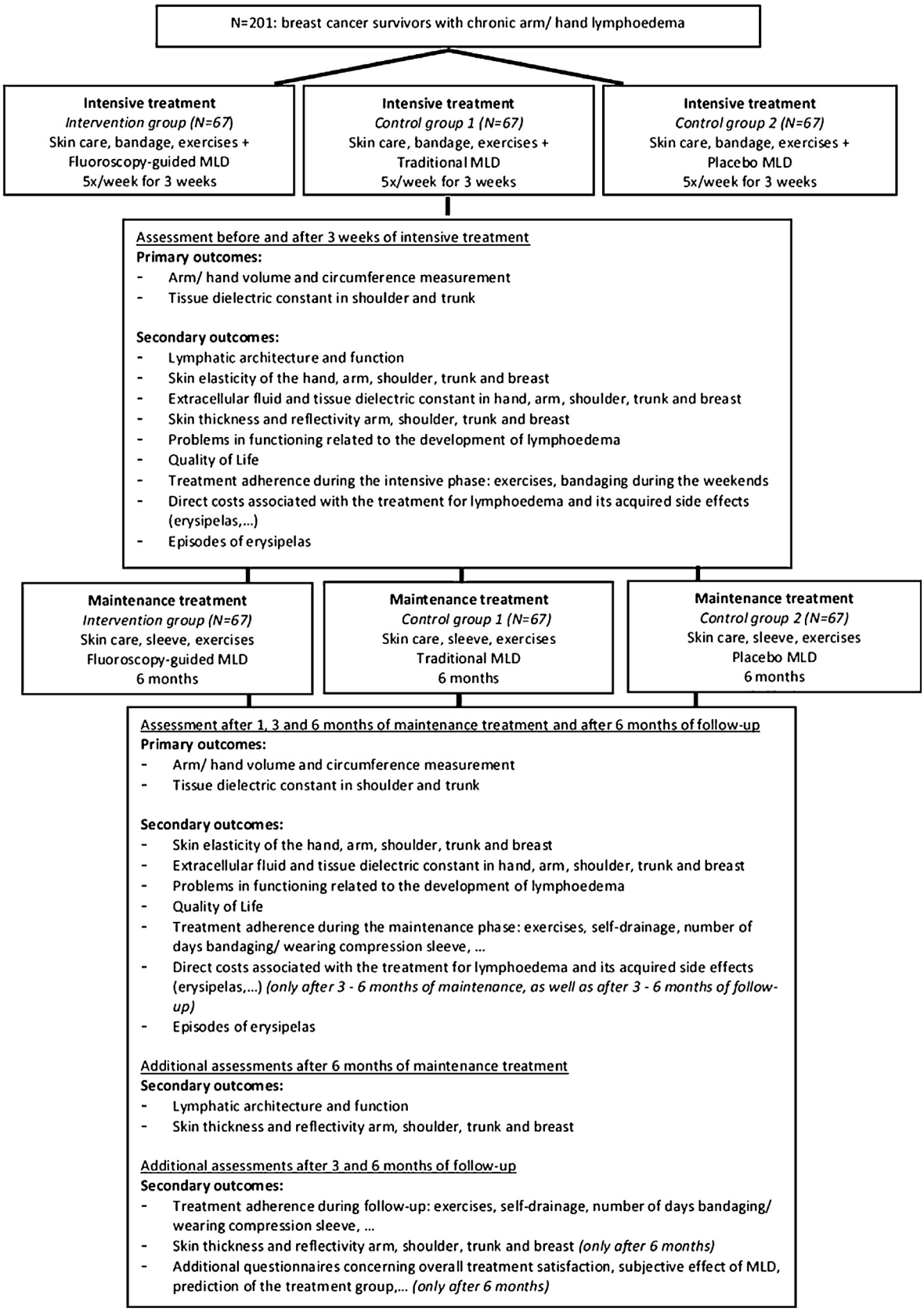


Fig. 1. Flow chart of the EFforT-BCRL trial.

Groeninge in Kortrijk (n = 40). The recruitment of participants started in February 2016. Eligibility criteria for the EFforT-BCRL trial are 1) patients with unilateral lymphoedema of the arm and/or hand, developed after treatment for breast cancer, 2) chronic lymphoedema stage I to IIb (duration of >3 months), 3) at least 5% difference between both arms, adjusted for hand dominance, and/or between both hands, and 4) no active metastases. Patients are excluded when one of the following criteria are present 1) age <18y, 2) oedema of the upper limb from another cause than breast cancer treatment, 3) cannot participate during the entire study period, 4) mentally or physically unable to participate in the study, 5) allergy for iodine, sodiumiodine, Indocyanine Green, 6) increased activity of the thyroid gland; benign tumours of the thyroid gland, 7) lymph node transplantation or lymphovenous shunt in the past, 8) bilateral axillary lymph node dissection.

All patients receive written as well as oral information. Only patients who signed the informed consent document prior to the start of the study, were included.

Assessments

Fig. 1 gives an overview of the different assessments and their timing in the EFforT-BCRL trial.

Near-infrared fluorescence imaging or lymphofluoroscopy

All lymphofluoroscopic assessments are performed by a vascular (ST) and plastic (LV) surgeon (the same surgeon for every patient) and assisted by a physical therapist (ND, NG, KD), who are experienced in performing this investigation. Both the surgeon and physical therapist are blinded to the participant's data as well as to the assigned therapy.

During a lymphofluoroscopy, Indocyanine Green (ICG) is injected intradermal in the first and fourth web space of the hand on the affected side. ICG emits fluorescence in the near-infrared spectrum (760 nm) and the signal is acquired using a camera with a Photo Dynamic Eye (PDE, Hamamatsu) system to visualise the superficial lymphatic system. The procedure consists of three consecutive phases. During the first part of the investigation, lymph flow is being evaluated at rest (3 min), after activity (3 min of dorsiflexion of the wrist) and after stimulating lymph transport with MLD (5 min). Phase two consists of a 60 min break in which exercise and rest are alternated. Last, in phase three, a scan of the limb (including arm, axilla, supraclavicular and scapular region) is performed with the PDE camera. Afterwards, pictures are taken of the ventral, lateral and dorsal side of the arm and trunk, and functional lymph nodes together with active lymphatic transport as well as dysfunctional rerouting patterns are designed on a body diagram. In Fig. 2 an example is shown.

All the information about the lymphatic transport is documented in a standard evaluation document. For a detailed description of the procedure and protocol of this investigation, see Table 1.

Lymphofluoroscopic assessments occur at baseline, post-intensive (3 weeks) and post-maintenance phase (6 months) in all participants to assess the lymphatic transport (i.e. a secondary outcome parameter). In addition, baseline lymphofluoroscopy is used to determine the procedure of MLD (i.e. which hand movements at which location [17]) in the group receiving fluoroscopy-guided MLD.

Clinical assessments

The clinical assessments are performed by three assessors (KD, LV, TDV), according to the institution of participation. Each assessor is assigned to a particular institution and every participant is being evaluated by the same assessor. A standardised protocol consisting of the consecutive measurements and procedures has been developed, in order to maintain standardisation between the different assessors. Multiple training sessions were performed to make the assessors familiar with the procedure. Participants are told not to mention information concerning their treatment during the evaluations, to ensure blinding of the assessor. In addition, the assessor is blinded to previous measurement data in order to avoid being influenced by previous results.

Clinical assessments occur at baseline, after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months follow-up. Tables 2 and 3 provide a detailed overview of the clinical evaluation methods and procedures performed in the EFforT-BCRL trial.

Primary outcomes

A first primary outcome measure is the change in lymphoedema volume at the level of the whole arm, hand, distal and proximal lower arm and upper arm. The volume of the arm is determined with the water displacement method on the one hand and is calculated from circumference measurements on the other

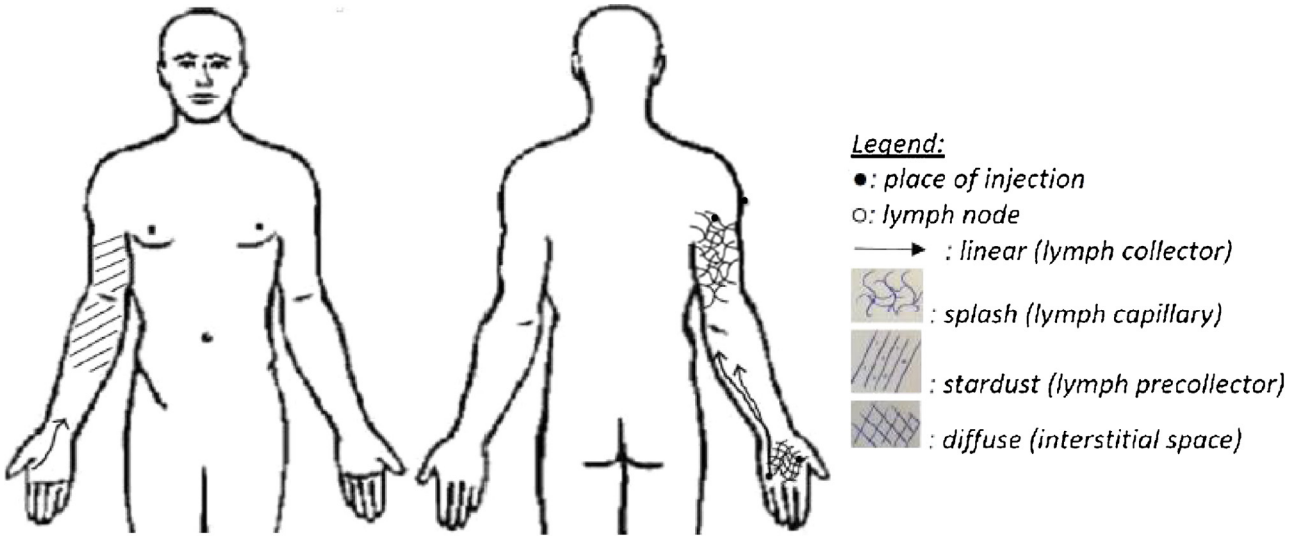


Fig. 2. Example of body diagram.

Table 1
Protocol near-infrared fluorescence imaging.

	STEP	DURATION	DESCRIPTION	REPORTING
Preparation	0.1 Dilution of ICG		Suspended ICG in 25 ml pure water and subsequently diluted with saline water to reach a final concentration of 0.20 mg/ml	
	0.2 Camera		Camera is held perpendicular to the observed skin at distance of 15 cm (best focus)	
	0.3 Injection of ICG		Intradermal injection in 1st (ulnar injection point) and 4th web space (radial injection point) dorsally in the hand 0.2 ml of the diluted solution is injected in each injection point	Time of injection
Early phase	1.1 Rest	3 min	Hand in resting position on table	- Linear transport starting from ulnar injection point: Yes/No (if "yes", after . . . . . sec) - Linear transport starting from radial injection point: Yes/No (if "yes", after . . . . . sec)
	1.2 Activity	3 min	Subject performs flexion/extension of the hand, with a large range of motion and lower arm stable on table Lymph flow and spreading pattern is observed from the injection point	- Fill of lymph collector, starting from injection point: Yes/No (if "yes", after . . . . . min) - Fill-in lymph collector after activity, starting from injection point: Yes/No (if "yes", after . . . . . min)
	1.3 Stimulation	5 min	Lymph capillaries at the level of the injection points are filled and transport through the lymph collectors and dermal rerouting is stimulated by therapist	
	1.4 Scan with camera	20 s	1) of the arm and shoulder with hand in pronation: starting at hand up to the retroclavicular region, 2) of the arm and axilla with hand in supination and abduction of the shoulder: starting at hand up to the axilla, together with the pectoral region: from the ipsilateral to the contralateral axilla, 3) of the scapular region: from the ipsilateral to the contralateral axilla, 4) of the pectoral region: from the ipsilateral to the contralateral axilla	After scan, reporting: - Number of lymph collectors - Of each lymph collector: length (measured with tapeline in cm), location and normal versus dilated situation - Presence of splash, stardust and diffuse pattern and location (fingers, hand, proximal/distal and ventral/dorsal lower or upper arm, breast and trunk) - Number of lymph nodes (cubital, humeral, axillary, retroclavicular)
	1.5 Measuring		Length of each lymph collector is measured	Length of each lymph collector
Break		1 h	Piece of foam is placed on the injection points Elastic bandage (Mollelast L&R) is placed around the hand to increase the pressure on the injection points Subject performs exercises: alternatively 5 min of squeezing with hand, 10 min of rest, 5 min of circumduction with hand, 10 min of rest, etc.	
Late phase	3.1 Scan with camera	20 s	See step 1.4	
	3.2 Drawing on skin and body diagram	+/−10 min	Clinician draws, under fluorescence feedback, the main lymph collectors and regions with dermal rerouting on the skin of the subject	Reporting at the end of late phase:
			Pictures are taken of ventral, dorsal and lateral side of arm and trunk	See step 1.4
			Lymph collectors and dermal rerouting (splash, stardust and diffuse) is designed on a body diagram	
	3.3 Measuring		Length of each lymph collector is measured Assessment document to score the lymphatic transport is filled out Recommendations for manual lymphatic drainage are made	Length of each lymph collector

hand. A second primary outcome measure is the change of stagnation of lymph at the level of the shoulder or trunk. Table 2 gives an overview of the measurement method and the procedure to determine the outcome and the measurement method is shown in Fig. 3.

Secondary outcomes

Secondary outcome measures are: change of extracellular fluid in the arm and trunk; change of thickness and reflectivity of cutis and subcutis at the level of hand, arm, shoulder and trunk; change of elasticity of skin and subcutaneous tissue at the level of hand, arm, shoulder and trunk; change of problems in functioning related to the lymphoedema; change of quality of life; change of lymphatic architecture and function; change in number of episodes of erysipelas and direct costs related to the lymphoedema and its treatment. Additionally, treatment adherence during the intensive and maintenance phase as well as during and after the follow-up period is investigated. At the last clinical evaluation, at 6 months follow-up, overall outcome satisfaction and prediction of group allocation is assessed by means of a survey.

Interventions

The treatments in both phases are shown in the study flow chart (see Fig. 1) and different treatment modalities are described in Table 4.

Treatments are provided by three different physical therapists in the University Hospitals of Leuven (RVH, LB, LV), two in Saint-Pierre University Hospital in Brussels as well as in General Hospital Groeninge in Kortrijk (LV, TDV) and one in Antwerp University Hospital (TDV), all experienced in the treatment of BCRL. Same therapists give the standard therapy as well as the MLD, but to limit any subjective influences of the therapist, a standardised

Table 2
Overview of measurement method and procedure of the primary outcomes.

Outcome	Measurement method	Procedure
Change of lymphoedema volume of whole arm/hand/distal lower arm/proximal lower arm/upper arm	Water displacement method (ICC 0.99; SEM% 0.7%)[22] (see Fig. 3)	Volume whole arm = volume up to point on upper arm
	Material	Volume of hand = volume up to point at wrist
	Cylinder filled with water of 20–30 °C, placed on weighing balance with 0.1 g accuracy (KERN 572); both are placed on top of a platform of 25 cm height	Volume of distal lower arm = volume up to midpoint lower arm − volume of hand
	Weighing balance is connected with software programme on laptop; software programme performs 10 vol measurements and calculates mean volume (Volume of upward displaced water = Mass of water/density of water, density of water with T° between 20 and 30 °C is 1); a signal is given if mean volume or its standard deviation is outside of preset range	Volume of proximal lower arm = volume up to point at elbow − volume hand − volume distal lower arm
	Reference points	Volume of upper arm = volume up to point on upper arm − volume hand − volume distal lower arm − volume proximal lower arm
	Lower ventral fold at level of wrist; middle between reference point at wrist and elbow; middle of elbow crease; at upper arm 10 cm above the elbow reference point	Relative lymphoedema volume of whole arm/hand/distal lower arm/proximal lower arm/upper arm = [(volume on affected side − volume on healthy side)/volume on healthy side] × 100
	Method	Relative lymphoedema volume of whole arm/hand/distal lower arm/proximal lower arm/upper arm is corrected with −3.3% for subjects with surgery on dominant side and with +3.3% for subjects operated on non-dominant side [23]
	Jewellery at level of hand or arm is removed	Change of (relative) lymphoedema volume of whole arm/hand/distal lower arm/proximal lower arm/upper arm = Relative lymphoedema volume time 2 − relative lymphoedema volume time 1
	Subject is positioned in standing beside the cylinder	
	Subject is drawn attention not to touch the border of the cylinder	
	Arm is put in the cylinder with axis perpendicular to water surface; first up to the most distal reference point at the wrist, thereafter up to the midpoint of lower arm, than up to point at elbow crease and finally up to reference point at upper arm;	
	Once the subject holds the arm stable, the assessor clicks on the assessment button on the programme and the volume is determined	
Change of lymphoedema volume of whole arm	Circumference measurements (ICC 0.99; SEM% 1.2%) [20,22] (see Fig. 3)	Volume of whole arm = sum of volumes of all segments of arm
	Material	Volume of arm segment = $4 \times (C_1^2 + C_1C_2 + C_2^2)/12\pi$, where C_1 is the upper circumference and C_2 is the lower circumference of each segment
	Perimeter, which is a flexible stainless steel bar with a tapeline fixed every 4 cm and a weight of 20 g at the end	Relative lymphoedema volume whole arm = cfr. supra
	Reference points	Change of (relative) lymphoedema volume of whole arm = cfr. supra
	Upper border of olecranon	
	Method	
	Jewellery at level of hand or arm is removed	
	Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table	
	Arm circumferences measured at olecranon and at 4, 8, 12, 16 and 20 cm proximal and distal of olecranon	
Change of stagnation of lymph at level of shoulder and trunk	Measurement of% water content (PWC) (ICC 0.92)[22] (see Fig. 3)	Ratio PWC = PWC healthy side/PWC affected side
	Material	Change of stagnation of lymph at level of shoulder and trunk = Ratio PWC time 2 − Ratio PWC time 1
	MoistureMeter D Compact (Delfin Technologies) [24–26]	
	Reference points	
	Deltoid, 5 cm below lateral border of acromion	
	Side of trunk, 5 cm below axillary crease	
	Method	
	If skin is recently hydrated, dehydrate skin	
	Sensor is placed perpendicular on the reference points with a pressure that is indicated by the device	
	High electromagnetic wave is sent through the skin which will only be absorbed by water	
	Degree of reflection/water content can be read on the display of MoistureMeter D	

ICC = Intraclass Correlation Coefficient, SEM = Standard Error of Measurement, PWC = Percentage of Water Content.

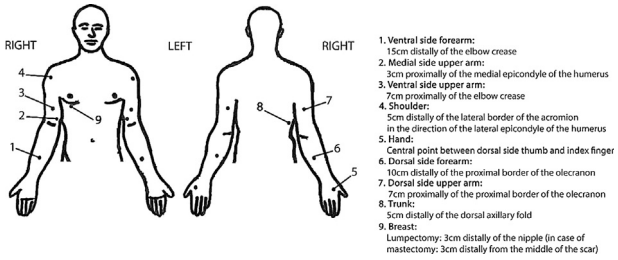
Table 3
Overview of measurement method and procedure of the secondary outcomes.

Outcome	Measurement method
Change of extracellular fluid in arm/shoulder/trunk	Bio-impedance Spectroscopy (ICC 0.95) [22,27,28] 1. Bio-impedance Spectroscopy determining L-Dex value Material Impedimed L-Dex U400 Reference points On each hand, one double electrode is placed on the dorsum of the hand On the right foot, one double electrode is placed on the dorsum of the foot Method Subject is in lying position; arms and legs spread Measurements are generated by a low frequency electrical signal transmitted to the patient (3–1000 kHz frequency range) Subject's gender, side at risk and dominant side are entered into the L-Dex software; according to this information, patient-specific instructions concerning the attachment of the color-coded leads are provided by the software program One measurement at each side is performed 2. Bio-impedance Spectroscopy determining phase angle, impedance (5 kHz, 50 kHz, 100 kHz, 200 kHz), resistance (50 kHz), reactance (50 kHz) Material BodyStat Quadscan 4000 Reference points On each hand, two electrodes are placed on the dorsum of the hand On each foot, two electrodes are placed on the dorsum of the foot On the trunk, two electrodes are placed on the sternum Method Subject is in lying position; arms and legs spread Two measurements according to two different measurement procedures (including the whole body versus only the arm) of both sides are performed
Change of thickness and reflectivity of cutis and subcutis of arm/shoulder/trunk	Measurement of thickness and reflectivity of cutis and subcutis Material Sonoscape S8 Portable ultrasound device Reference points See infra (annex I) Method Subject is seated according to which reference point is being evaluated (see annex I) A high frequency linear probe (10–5 MHz) is used Probe is placed perpendicular to the skin; reference point is located in the middle of the probe Minimal amount of pressure needs to be given Thickness of the cutis and subcutis is determined in mm Images of every reference point are saved with its indicated thicknesses at both sides using a patient-specific code Afterwards, assessment of reflectivity is made based upon the saved images
Change of elasticity of skin and subcutaneous tissue of arm/shoulder/trunk	Measurement of induration of skin and subcutaneous tissue Material SkinFibrometer (Delfin Technologies) Device consists of a 1-mm-long intender and records the resistance to 50 g of pressure using its reference plate and related built-in force sensors Reference points See infra (annex I) Method First, the grey button is pressed to activate the device; if the display shows 'ready', the measurement can start Sensor is placed perpendicular on 1 of the 9 indicated points, in order to obtain maximal skin contact a light vertical pressure is applied; the device gives immediately feedback about the pressure and velocity Each measurement is repeated 5 times at each reference point The skin and subcutis resist deformation and induration and the induration force in Newton is determined by calculating the average resistance of 5 measurements A lower value indicates less resistance or softer tissue
Change of problems in functioning	Investigation of% of problems in functioning related to the development of arm lymphoedema (ICC Total score: 0.93, SEM Total score: 4.8) [29] Material Lymph-ICF- Questionnaire with Numeric Rating Scale (Dutch and French version) Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire consists of 29 questions, divided into 5 domains: physical function, mental function, household activities, mobility activities, and life and social activities A numeric rating scale with 11 possibilities (0–10) is used onto a visual analogue scale Each of the 29 questions corresponds to a score between 0 and 100; a total score and 5 different domain scores are calculated A lower score indicates less problems in functioning
Change of Quality of Life (QoL)	Investigation of Quality of Life of patients with a chronic disease (ICC Total score: 0.93, SEM Total score: 0.44) [30] Material McGill-Quality of Life Questionnaire (Dutch version)

Table 3 (*Continued*)

Outcome	Measurement method
	Method At the end of each assessment, subjects are asked to fill in the questionnaire individually Questionnaire counts 16 + 1 questions, which relate to the following 5 domains: physical symptoms; physical wellbeing, psychological symptoms; existential wellbeing and support A Likert scale with 11 possibilities (0–10) is used for the 16 questions and part D is an open question Each question corresponds to a score between 0 (very bad) and 10 (excellent); a total score and 5 different domain scores are calculated A lower score indicates a lower Quality of Life
Change of lymphatic architecture and function	Near-infrared fluorescence imaging or lymphofluoroscopy for investigation of superficial lymphatic system ($\leq$2 cm) [31–33] Material Near-infrared fluorescence imaging device with PDE camera Indocyanine Green (IGC) Method Subject is in sitting position with 90° anteflexion of the arm, straight elbow and hand supported on table A tracer (ICG) is injected in the subject's hand into the 1st and the 4th webspace Tracer is excited by near-infrared light and disseminates a fluorescent photon which makes observation of the lymphatic architecture and function possible by visualising fluorescence of near-infrared light of the injected tracer For a detailed description of the procedure and protocol, see Table 1
Number of episodes of erysipelas	Investigation of the number of episodes of erysipelas in between two assessments Method The number of episodes of erysipelas is directly asked to the patient and noted down at the beginning of every clinical evaluation
Costs	Investigation of direct costs related to the treatment of (side effects of) lymphoedema Material Self-developed questionnaire Method Investigation of the amount of direct costs is conducted in all subjects regarding following levels: • Compression material (i.e. bandaging material, stockings, gloves, accessories, . . .) • Medication related to the treatment of (the acquired side effects of) lymphoedema (i.e. diuretics, antibiotics, . . .) • Diagnostics: imaging procedures related to the disease, blood examination (i.e. infection, . . .) • Human recourses: -Admissions to the hospital/surgery -Consultation(s) with a general practitioner or medical doctor/physiotherapist/psychologist/nutrition specialist/ nurse/other due to the disease, inside or outside the hospital. -...

Annex I
Reference points



Measurement position
- Ventral side forearm (1), medial side upper arm (2), ventral side upper arm (3):
● Sitting position with forearm partly supported on the table
● Elbow slightly flexed, supination of forearm, arm slightly abducted
- Shoulder (4), hand (5), dorsal side forearm (6), dorsal side upper arm (7):
● Sitting position with forearm partly supported on the table
● Pronation of forearm
● Fingers slightly abducted
- Trunk (8): Standing position, arms relaxed beside the body
Breast (9): Supine position

ICC = Intraclass Correlation Coefficient, SEM = Standard Error of Measurement.

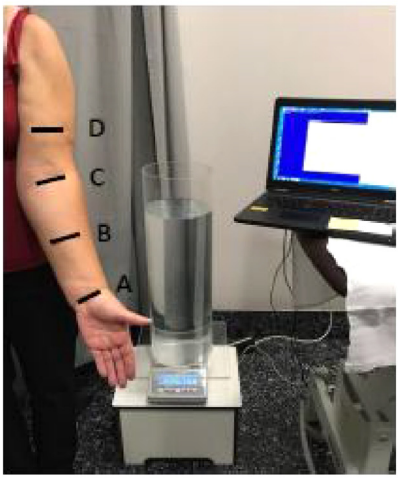
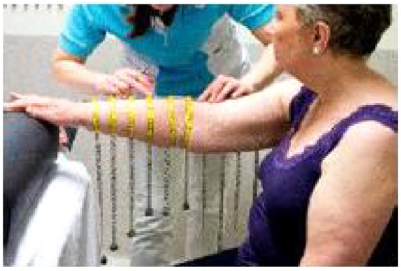
Primary outcome	Picture
Change of lymphoedema volume of whole arm/ hand/ distal lower arm/ proximal lower arm/ upper arm	Water displacement method  Reference points A: Ventral side wrist/ distal crease, B: Middle between reference point A and C, C: Middle elbow crease, D: 10 cm proximal of elbow crease
Change of lymphoedema volume of whole arm	Circumference measurements  Reference points Proximal border olecranon
Change of stagnation of lymph at level of shoulder and trunk	Measurement of % water content (PWC)  Reference points See Table 3 annex I

Fig. 3. Illustration of primary outcome measurement devices.

treatment protocol has been developed. Multiple training and evaluation sessions are performed to make the therapists familiar with the procedure and to ensure that the treatments given by each therapist are identical. Therapists are blinded to the participant's data collected during clinical evaluations.

All participants receive a standard treatment for lymphoedema consisting of information, skin care, compression therapy (bandage/compression stocking) and exercise; referred to as decongestive lymphatic therapy [4]. The only treatment modality that differs among the three groups is the application of MLD (fluoroscopy-guided MLD versus traditional MLD versus placebo MLD). Participants receive 14 sessions during the three weeks of intensive treatment for lymphoedema. Thereafter they receive during 6 months a maintenance treatment with 18 sessions in decreasing frequency (i.e. 2 weekly sessions during month 1; 1 weekly session during month 2; 2 two-weekly sessions during months 3–4; 1 monthly session during months 5–6).

Each intensive treatment session lasts for 60 min: 30 min of standard treatment (skin care, bandaging, exercises) and 30 min of MLD. Treatment starts with drainage of the shoulder and trunk, is followed by removal of the bandage and circumference measurements of the arm using a perimeter [20]. Afterwards, drainage of the arm (and hand), shoulder and trunk is continued. After MLD, skin care and bandaging is applied and the session ends with performing exercises. In the maintenance phase, therapeutic sessions last for 30 min as they only consist of skin care and manual lymph drainage. Additionally, participants perform exercises at home as they are wearing compression garment during daytime (sleeve and glove).

Sample size calculation

The required sample size for the study is 201 subjects or 67 subjects per group to detect a difference of 15% in the reduction of

Table 4
Treatment modalities.

	Modality	Duration	Intensive treatment		
Standard treatment	Information		Patient receives a leaflet with information about the lymphatic system and lymphoedema, clinical evaluation and conservative treatment of lymphoedema. During the treatments, this information is provided orally as well.		
	Skin care	5 min	Skin is hydrated during the session. If wounds are present, the wound is cared for.		
	Multi-layer bandaging	15 min	The bandage consists of different layers: a cotton tube embraces the limb and protects the skin; the cotton wool decreases the pressure under the bandage or protects the skin against injuries from the bandages; padding with structure creates a massage-effect under the bandage; inelastic (low-stretch) bandages, also applied from distal to proximal and in a criss-cross pattern, provide an axial rotation of the whole bandage and an improvement of the lymphatic transport. At the start of the treatment, MLD is applied on the shoulder/trunk in a first phase (with bandage), and on the arm/hand in a second phase (without bandage). After MLD, hydration of the skin is performed. The bandage is applied again after hydrating the skin; than the patient performs the exercises. Patients have to wear the multi-layer bandage daily during day and night. Patients are also taught to bandage themselves. In case of slipping down of the bandage or in case of pain, the patient has to change the bandage her-/himself.		
	Exercise therapy	10 min	Patients have to perform upper limb exercises while wearing the multi-layer bandage. They have to perform these exercises a second time at home and twice daily during the weekend. They are advised to use the arm as normal as possible. Exercises: Mobilising and stretching exercises Lymphatic transport-enhancing exercises Breathing exercises		
Experimental treatment	MLD	30 min	Fluoroscopy-guided MLD:	Traditional MLD:	Placebo MLD:
			Therapist applies hand movements of higher pressure (up to 80 mmHg) which consist of following techniques:	Therapist applies hand movements of lower pressure (up to 40 mmHg) which consists of following techniques:	Deep massage by performing relaxing transverse movements on the muscles of the ipsilateral neck, back, shoulder, arm and hand. Following explanation to the patient about the effect of the treatment is given to prevent suspicion for this irregular type of MLD: 'After axillary lymph node dissection, the superficial lymphatic network partially disappears (i.e. axillary web syndrome). Lymph transport mainly happens through the deep lymphatic network that is surrounded by the muscles. By relaxing the muscles lymphatic transport through the deep lymphatic network will improve.'
			Cleaning techniques to empty the lymph nodes at the level of the clavicula, axilla, humerus and elbow;	Cleaning techniques to empty the lymph nodes at the level of the clavicula, axilla, humerus and elbow;	
			Resorption technique with the thumb to create resorption of lymph by the lymph capillaries;	Drainage of the jugular and occipital region, stimulating lymph collectors on the trunk, shoulder, arm and hand;	
			Gliding technique alongside the skin to stimulate transport of lymph through the lymph collectors or to stimulate transport of lymph through the rerouting.	'Pumping' technique while stretching the skin to stimulate lymphatic transport through the lymph collaterals.	
			Above mentioned techniques are described in the same way to the patient in order to explain this irregular ('new') type of MLD.	Above mentioned techniques are in the same way described to the patient to support the purpose of this applied drainage.	
			MLD is also based on the assessment by fluoroscopy. During the drainage session, the therapist has to consider the photo of the patient =the lymph mapping) and her/him lymphatic transport obtained by the lymphofluoroscopy.	MLD is performed based on 'normal' anatomy of the lymphatic system, without knowledge of the patient-specific lymphatic architecture.	
	Modality	Duration	Maintenance treatment		
Standard treatment	Skin care	5 min	Skin is hydrated during the session. If wounds are present, the wound is cared for.		
	Compression garment	All day	Patients have to wear a custom-made compression sleeve and glove at daytime.		
	Exercise therapy	At home (2×10 min)	Patients have to perform upper limb exercises twice daily at home, while wearing the compression garment.		
Experimental treatment	MLD	30 min	Fluoroscopy-guided MLD	Traditional MLD	Placebo MLD
			Patients are taught to perform a self-drainage daily at home, except the days patients are visiting the therapist.		

lymphoedema volume at the level of the arm or hand (primary outcome) or at the level of the shoulder or trunk (primary outcome) between the three groups. This is based on an alpha of 0.0125, a power of 80% and a two-way ANOVA for repeated measures analysis. The effect size is determined from clinical results of the Leuven Lymphovenous Centre and by consulting

experts in the field of lymphology. 73 patients with unilateral BCRL were followed in the Leuven Lymphovenous Centre between November 2011 and November 2013. All patients received decongestive lymphatic therapy. Lymphoedema volume of the arm reduced 36% (±28%) on average. According to different experts in the field of lymphology, an additional reduction of the lymphoedema volume of 15% is clinically relevant. This can be a reduction of the lymphoedema volume at the level of the arm/hand OR at the level of the shoulder/trunk. Consequently, the estimated reduction after the intensive phase is 35% (±25%) for the traditional MLD group, 50% (±25%) for the fluoroscopy guided MLD group, and 20% (±25%) for the placebo MLD group. Based on a previous longitudinal study with breast cancer patients [21], a dropout rate of 5% is estimated (or 9 patients). The group with fluoroscopy-guided MLD is compared to the group with traditional MLD, and the group with fluoroscopy-guided MLD is compared to placebo MLD. This explains why an alpha level of 1.25% was chosen (and not 5%) (=2 times Bonferroni correction). In literature, data on change of lymphoedema volume at the level of the shoulder/trunk is missing.

Statistical methods

The statistical analysis plan was developed under supervision of a statistician of Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat). Following hypotheses will be tested:

Patients receiving fluoroscopy-guided MLD additional to decongestive lymphatic therapy will have a significantly; 1) greater reduction of lymphoedema volume at the level of the hand or arm OR 2) less stagnation of lymph at the level of the shoulder or trunk; than patients receiving traditional MLD or placebo MLD. To test the hypotheses a two-way ANOVA for repeated measures will be applied, assisted with post hoc analyses for further evaluation. Data will be analysed according the intention-to-treat principle.

Discussion

This will be the first multicentre double-blind RCT to investigate the effectiveness of lymphofluoroscopy-guided MLD, in addition to the other parts of the decongestive lymphatic therapy, for the treatment of BCRL. If the current trial is able to demonstrate a significant improvement in change of lymphoedema volume at the level of the arm/hand or in stagnation of lymph at the level of the shoulder/trunk, due to the application of fluoroscopy-guided MLD, a clear answer to the question 'do we need to implement fluoroscopy-guided MLD in the conservative decongestive treatment of BCRL' can be stated. If the current study fails to prove an additional value of fluoroscopy-guided MLD or traditional MLD to placebo MLD, then MLD may be omitted from the decongestive lymphatic therapy. If MLD is omitted, a large reduction in therapy burden and a large reduction in social services costs can be achieved. If fluoroscopy-guided MLD is equally effective than traditional MLD and both are more effective than placebo MLD, traditional MLD has to be continued. Less expenses have to be made for the reimbursement of lymphofluoroscopic investigations.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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