Protocol study about 'effectiveness of fluoroscopy-guided manual lymph drainage (MLD) for the treatment of breast cancer-related lymphoedema (BCRL)'

Protocol EFForT BCRL trial

Version and date of final protocol: V13 03.09.2018

Trial identifiers

EudraCT Number: 2015-004822-33
NCT (clinicaltrials.gov): NCT02609724

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Table of Contents

1. Study Synopsis

Title of clinical trial	The effectiveness of fluoroscopy-guided manual lymph drainage (MLD) for the treatment of breast cancer-related lymphoedema (BCRL)
Protocol Short Title/Acronym	EFForT BCRL trial
Study Phase if not mentioned in title	Phase III trial
Sponsor name	UZ Leuven
Principal Investigator	Prof. Dr. Nele Devoogdt
Eudract number	2015-004822-33
Medical condition or disease under investigation	Lymphoedema
Purpose of clinical trial	To investigate the effectiveness of fluoroscopy-guided MLD for the treatment of BCRL
Primary objective	The main scientific objective entails examining the effectiveness of fluoroscopy-guided MLD versus traditional MLD or versus placebo MLD, applied as part of the intensive and maintenance phase of Decongestive Lymphatic Therapy, for the treatment of BCRL
Secondary objective (s)	Secondary scientific objectives entail: - examining the relationship between different variables of lymphoedema at baseline - examining reliability and validity of Lymph-ICF (Dutch version and French version) with NRS scale
Trial Design	Multi-centre double-blind randomised controlled trial
Endpoints	Primary end points: - Change of lymphoedema volume of arm/ hand - Change of stagnation of fluid (measured with tissue dielectric constant and bio-impedance analyses) at the level of shoulder/ trunk

	Secondary end points: - Number of responders after intensive treatment (>30% decrease of lymphoedema volume) and after maintenance treatment (<10% increase of lymphoedema volume) - Change of extracellular fluid in the arm - Change of tissue dielectric constant in cutis of arm - Change of thickness and reflectivity of cutis and subcutis of arm/ shoulder/ trunk - Change of lymphatic architecture and function - Change of problems in functioning related to the development of BCRL. - Change of quality of life - Number of episodes of erysipelas - Number of adverse events to MLD - Cost associated with the disease and its treatment
Sample Size	201 pts (67 pts/group)
Summary of eligibility criteria	Patient with unilateral breast cancer-related lymphoedema Chronic lymphoedema, stage I, IIa, IIb At least 5% difference between both arms and/ or hands, adjusted for dominance No active metastases
IMP, dosage and route of administration	Indocyanine Green 25mg/25 ml aqua, 2x intradermal injection of 0.2 ml ICG/ aqua (first webspace and fourth webspace)
Active comparator product(s)	NA
Maximum duration of treatment of a subject	6 months (+6 months follow-up)
Version and date of final protocol	V13 03-09-2018
Version and date of protocol amendments	Approval original protocol V4: 10-2-2016 V5 Amendement 20.4.2016 (Extra site UMC Sint-Pieter) V6 Amendement 22.12.2016 (Follow-up) V7 Amendement 28.4.2017 (Extra patients)

	V8 Amendement 19.05.2017 (Advertisements) V9 Amendement 14.08.2017 (Advertisements) with changes V10 Amendement 23.08.2017 (Extra site AZ Groeninge + treatments for participants in UMC St-Pierre can be provided in private practise in Luik) V11 Amendement 28.09.2017 (Extra site AZ Groeninge treatments for participants in UMC St-Pierre can be provided in private practise in Luik) with changes V12 Amendement 20.12.2017 (Extra site UZ Gent) with changes V13 Amendement 03.09.2018 (Extra patients in CHU UCL Namur site Mont-Godinne for realizing subtrial secondary objective)

2. Background and rationale

For many women, lymphoedema is an embarrassing and dreaded morbidity after the treatment of breast cancer. It induces not only functional impairments (problems with performing household chores, with mobility during activities), but also psychosocial problems such as depression, sexual dysfunction, social avoidance and a decrease in self-confidence (1).

According to the International Society of Lymphology, lymphoedema needs to be treated with Decongestive Lymphatic Therapy (2). This is a two-stage treatment programme. During the first or intensive phase, lymphoedema has to be 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 elastic sleeve, exercises and lymph drainage. Skin care, multi-layer bandaging, elastic sleeve and exercises are treatment modalities that (after instructing the patient) can be performed by the patient herself. MLD has to be applied by a physical therapist and hence entails a big financial cost for the patient and the Health Care (3). The effectiveness of MLD applied during the intensive phase has been investigated by 5 randomised controlled trials, but there is conflicting evidence. So, further investigation is warranted to determine the relative benefit of MLD. The effectiveness of MLD applied during the maintenance phase has never been investigated (3-6).

A possible explanation why MLD is not obviously proven to be effective, is that MLD is applied in an inefficient way: during MLD, hand manoeuvres are applied on all lymph nodes and lymphatics that may be anatomically present. After axillary dissection and/ or radiotherapy (for the treatment of breast cancer), the lymphatic system is damaged: lymph nodes are removed and often fibrosis of the superficial lymphatic system occurs. As a result, rerouting of the lymphatic drainage occurs. Rerouting is patient-specific, consequently, it is possible that the traditional MLD needs be abandoned and a tailored approach needs to be established. Lymphofluoroscopy can aid to apply a more efficient MLD. During lymphofluoroscopy, a fluorescent substance is injected subcutaneously in the hand and

it visualizes the transport of lymph from the hand up to the axilla and it demonstrates alternative pathways towards other lymph nodes.

A second explanation why the traditional method of MLD is not proven to be effective, is that research has shown that MLD with high pressure (vs low pressure) is more effective to improve lymph transport, as well as gliding (vs no gliding). During the new method of MLD (or fluoroscopy-guided MLD), the therapist only performs hand movements on functional lymphatics and lymph nodes. In addition, the hand movements are applied with higher pressure and lymph transport through the lymph collaterals is stimulated by applying strikes across the skin.

Belgrado(7) demonstrated by lymphofluoroscopy a temporary physiological effect of MLD on lymphatic transport. All patients with BCRL (N=30) had after application of one session (during 20 minutes) of lymph drainage an increase of lymph transport from the hand to the axilla. Also Tan et al(8) showed in patients with BCRL (N=10) after one session of MLD an improvement of lymph transport. Whether the application of different sessions of fluoroscopy-guided MLD has in fact a clinical and long-lasting effect on the lymphoedema, is yet to be established.

3. Trial objectives and Design

3.1 Trial objectives

The main scientific objective entails examining the effectiveness of fluoroscopy-guided MLD versus traditional MLD or versus placebo MLD, applied as part of the intensive and maintenance phase of Decongestive Lymphatic Therapy, for the treatment of BCRL

Secondary scientific objectives entail examining the relationship between different variables of lymphoedema at baseline and examining reliability and validity of Lymph-ICF (Dutch and French version) with NRS scale.

3.2 Primary endpoints

- Change of lymphoedema volume of arm/ hand
- Change of stagnation of fluid at the level of shoulder/ trunk

3.3 Secondary endpoints

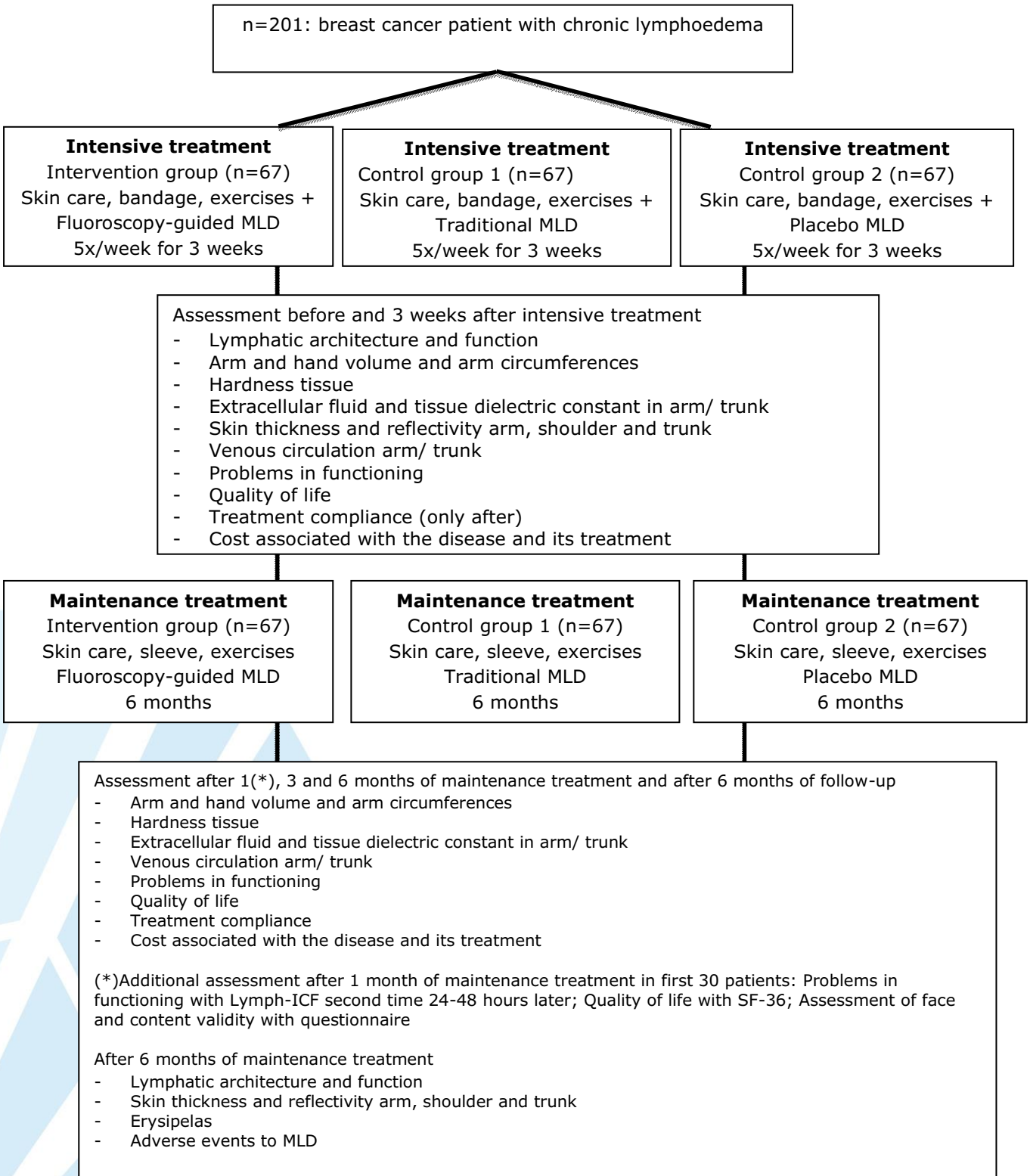
- Number of responders after intensive treatment (>30% decrease of lymphoedema volume) and after maintenance treatment (<10% increase of lymphoedema volume)
- Change of extracellular fluid in the arm
- Change of water content in the arm
- Change of thickness and reflectivity of cutis and subcutis of arm/ shoulder/ trunk
- Change of lymphatic architecture and function
- Change of venous circulation in arm and thorax
- Change of problems in functioning related to the development of BCRL.
- Change of quality of life
- Number of episodes of erysipelas.

3.4 Trial Design

Multi-center double-blind placebo-controlled randomised controlled trial

- Multi-center: cooperation between KU Leuven/ UZ Leuven, UAntwerp, UZ Antwerp. UMC Sint-Pieter, ULB, AZ Groeninge Kortrijk, UZ Gent
- Double-blind: patients and assessor are blinded for the intervention
- Placebo-controlled: the effect of the intervention fluoroscopy-guided MLD is controlled with traditional MLD and with placebo MLD

3.5 Study diagram



3.6 Trial Flowchart

		Intensive treatment	Maintenance treatment			Follow-up
	Baseline	After 3 weeks	After 1 month	After 3 months	After 6 months	After 6 months
Informed consent	X					
Clinical evaluation - Arm and hand volume - Extracellular fluid at level of shoulder/ trunk - Tissue dielectric constant at level of shoulder/ trunk - Tissue elasticity at level of arm/ shoulder/ trunk - Extracellular fluid arm - Tissue dielectric constant arm - Quality of life - Problems in functioning - Erysipelas	X	X	X	X	X	x
Lymphofluoroscopy (lymph architecture and lymph transport)	X	X			X	
Echography (thickness and echogenicity of skin and subcutis)	X	X			X	x
Treatment compliance		X	X	X	X	x
Costs associated with the treatment		X	X	X	X	

4. Trial Medication

4.1 Investigational Medicinal product and dosing regimen

At baseline, each included patient receives a lymphofluoroscopy of the arm and shoulder/ trunk to visualise the patient-specific lymphatic architecture and transport. The lymphofluoroscopy is repeated after 3 weeks of intensive treatment and after 6 months of maintenance treatment.

Indocyanine Green (ICG), a fluorescent molecule, is injected subcutaneously in the hand/ arm/ shoulder 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) system. The lymphatic architecture of the patient is designed on the body of the patient. Afterwards, a photo is taken from the design.

We will use the packaging and labeling provided by the manufacturer of the products, i.e. Pulsion. 25 mg ICG powder is diluted with 25 ml water. 0.2ml of this mixture is injected intradermally in the first and fourth webspace of the hand of the patient. ICG, aqua, syringe and plasters are bought by the KU Leuven. For description of the product, see appendix.

Before the injection, landmarks (that are visible on the PDE camera) are drawn on the dorsal side of the forearm and biceps side of the upper arm. These landmarks are necessary to measure lymph propagation velocity in the superficial lymphatic vessels. After the measurement, video sequences are analyzed using the ICG dedicated software IC-CALC 2.0. This programme counts the number of pixels in function of time, reaching a target threshold of grey scale in a region of interest (ROI) delimitated by a selected surface drawn on the image (9).

4.2 Drug accountability

Patients receive 3 times (baseline, after 3 weeks and after 6 months) intradermal injection of 0.2 ml ICG/ aqua in first and fourth webspace.

The purpose of the baseline lymphofluoroscopy is to have knowledge about the lymphatic transport at baseline. This is important to investigate whether fluoroscopy-guided MLD result in a better improvement of lymphatic transport than traditional MLD or placebo MLD, after the intensive phase of Decongestive Lymphatic Therapy and/ or the maintenance phase of Decongestive Lymphatic Therapy. In the group receiving fluoroscopy-guided MLD, de baseline lymphofluoroscopy is also necessary to investigate the superficial lymphatic architecture.

4.3 Subject compliance

Not applicable. No specific procedures to determine subject compliance with the medication are necessary, since the injections will be performed by the vascular surgeon after informed consent.

4.4 Concomitant medication (non-IMP)

Not applicable. In the present study, the application of medication (ICG) is not the intervention. It is applied in order to be able to perform the intervention, i.e. fluoroscopy-guided MLD. Patients of both control groups also receive an injection because change of lymphatic architecture and lymphatic transport is one of our secondary outcomes that we aim to compare between the 3 groups and this after 3 weeks of intensive treatment and after 6 months of treatment.

5. Selection and withdrawal of subjects

5.1 Inclusion criteria

- Age >18y (since the treatment with MLD and the investigation using ICG is not dangerous for pregnant women, women with child bearing age are included)
- Women/ men with unilateral breast cancer related lymphedema.
- Chronic lymphoedema (>3 months present), stage I to IIb concomitantly with signs of pitting
- At least 5% difference between both arms and/ or hands, adjusted for dominance
- Written informed consent obtained

5.2 Exclusion criteria

- Allergy for iodine; sodiumiodine, ICG
- Increased activity of the thyroid gland; benign tumors of the thyroid gland
- Age <18y
- Oedema of the upper limb from other causes
- Surgery of the lymphatic system in the past (lymph node transplantation, lymphovenous shunt)
- Bilateral axillary lymph node dissection
- Cannot participate during the entire study period
- Mentally or physically unable to participate in the study

5.3 Selection of participants

Patients with breast cancer-related lymphoedema (BCRL) are recruited in the University Hospitals Leuven (lymphoedema center, multidisciplinary breast center, department of vascular surgery) (N=90), in the University Hospital Sint-Pieter (lymphoedema center) (N=10), in the Antwerp University Hospital (multidisciplinary breast center) (N=41), in AZ Groeninge Kortrijk (Center of Oncology) (N=35). Patients who are participating in Brussels, can choose whether they prefer to receive the treatments (14x during the intensive phase and 18x during the maintenance phase) in the hospital in Brussels or in a private practice for physiotherapy situated in Liège. However, all investigations will be performed in the hospital itself. Furthermore, we would like to include a fifth study center located in Flanders to improve recruitment, UZ Gent (department of Radiotherapy) (N=25). Note considering practical issue: in case of lack of sufficient space at the department of Radiotherapy to provide the treatments, the private cabinet of one of the project's researchers of UZ Gent (dr. Monten) can be used as well (location: Amand Casier de Terbekenlaan 43, 9030 Gent).

For an additional investigation within this project, regarding analysis of the validity and reliability of the Lymph-ICF questionnaire with NRS scale in patients with breast cancer-related lymphoedema, which is the questionnaire being used as assessment tool to evaluate the change of problems in functioning related to the development of BCRL (= one of the secondary endpoints), a total of 30 extra patients with breast cancer-related lymphoedema will be recruited in the Lymphovenous Center of UZ Leuven. To realize the same investigation for the French version of the questionnaire, a total of 30 patients with breast cancer-related lymphoedema (meeting the same inclusion criteria) will be recruited in the Centre for Lymphoedema of CHU UCL Namur, site Mont-Godinne.

To boost the recruitment of patients, we will submit a short communication about the existence of the study in waiting rooms for patients of the participating centres and in health-related websites and/or (weekly or monthly) newsletters/magazines distributed in Flanders (i.e. Think Pink, Vlaamse kanker liga, Kom Op Tegen Kanker, Stichting tegen kanker, Visie CM, METRO, Deze Week, De Zondag, Goed Gevoel, Libelle, Flair).

5.4 Randomisation procedure/Code Break

After baseline assessment, patients are randomised in one of the three treatment groups. Randomisation is performed by someone different form the assessors or therapists of the study. Before randomization, the patient receives an ID. Randomisation is performed using an excel-file and the order of the randomization is determined by the ID number.

5.5 Withdrawal of subjects

Patients have the right to withdraw from the study at any point in time at its own request. This has no effect on the patient. The patient will not be replaced but will be asked to participate in the follow-up measurements (3 weeks after the intensive treatment and 1, 3 and 6 months after the start of the maintenance treatment and at the end of the follow-up phase, this is 6 months after the end of the maintenance phase).

When patients withdraw from the study as the result of (serious) adverse events (which we do not expect) they will be followed on a regular base by the department of Vascular Surgery of UZ Leuven, in the Lymphoedema Clinic of University Hospital Sint-Pieter, by the Multidisciplinary Breast Clinic of Antwerp University Hospital, by the Centre of Oncology of AZ Groeninge Kortrijk and by the Department of Radiotherapy of UZ Gent (depending where the patient was included). Patients are not withdrawn from the study when they fail to come to the physical therapy sessions, since we apply the intention-to-treat principle.

5.6 Expected duration of trial

Month 1: 1st of December 2015: start of trial

Month 3-38: recruiting and inclusion of 201 patients and baseline assessment

We estimate that around one patient with arm lymphoedema is included each week in UH Leuven (0.75/week), one patient is included in UH Sint-Pieter each two weeks (0.5/week) and one patient is included in UH Antwerp each 3 weeks (0.3/week). So the inclusion period will reach month 38 of the project. If we reach this frequency of inclusion, at the end of month 12 of the project, 81 patients will be included (32 patients in UH Leuven, 16 patients in UH Antwerp and 26 patients in UH Sint-Pieter).

Go/ no go: if the assumed frequency of inclusion is not reached the first 6 months of the inclusion period (16 patients in UH Leuven, 8 patients in UH Antwerp and 13 patients in UH Sint-Pieter), we have to change the strategy of recruitment (through other hospitals, patient groups, physical therapists, …).

Month 22: September 2017: By the end of this month, the sub-investigation about reliability and validity of the Lymph-ICF questionnaire, which is the questionnaire being used to determine the change of problems in functioning related to the development of BCRL as secondary endpoint, needs to be fulfilled (2nd aim of PhD Tessa De Vrieze). This means that by the end of this month, data concerning this aim needs to be analysed from at least 30 patients. To speed up this recruitment, 30 patients who are 1) visiting the Lymphovenous Center UZ Leuven, 2) are meeting the inclusion criteria, and 3) have given written informed consent, will

be recruited in the Lymphovenous Center UZ Leuven, additional to the patients who are participating the EFforT-trial.

Month 37: December 2018: By the end of this month, the sub-investigation about reliability and validity of the French version Lymph-ICF questionnaire, which is the questionnaire being used to determine the change of problems in functioning related to the development of BCRL as secondary endpoint, needs to be fulfilled (3rd aim of PhD Tessa De Vrieze). This means that by the end of this month, data concerning this aim needs to be analysed from at least 30 French-speaking patients. To speed up this recruitment, 30 patients who are 1) visiting the Centre for Lymphoedema CHU UCL Namur site Mont-Godinne, 2) are meeting the inclusion criteria, and 3) have given written informed consent, will be recruited in the Centre for Lymphoedema CHU UCL Namur site Mont-Godinne, however these patients are not participating in the interventional EFfoRT-BCRL trial.

Month 38: January 2019: end of inclusion period = milestone 1: analysing and interpreting data concerning relation between the different baseline measurements

Month 1-45 baseline and follow-up assessments

Month 45: August 2019: last treatment = milestone 2: start analyses and interpretation (cfr infra)

March 2020: last measurements of follow-up period

Month 45-48: statistical analyses and interpretation of data concerning effect of fluoroscopy-guided MLD compared to traditional MLD or placebo MLD for the treatment of BCRL.

Month 48: November 2019: end of statistical analyses and interpretations = milestone 3

Month 45-48: utilisation period.

Month 48: November 2019: end of the project = milestone 4

6. Trial Procedures

6.1 By visit

All treatments are performed in the lymphoedema centre of the University Hospitals Leuven, in the lymphoedema centre of the University Hospital Sint-Pieter, in the Multidisciplinary Breast Clinic of the Antwerp University Hospital, in the Centre of Oncology of AZ Groeninge Kortrijk or in the Department of Radiotherapy of UZ Gent.

Patients who are participating in Brussels, can choose whether they prefer to receive the treatments in the hospital in Brussels itself or in a private practice for physiotherapy situated in Liège if the distance between domicile and the hospital seems too significant. However, all investigations will be performed in the hospital in Brussels. Practice for physiotherapy situated in Liège:

Le Centre Paramédical "Les Prés d'Or"
Chaussée des Prés 33
4020 Liège

All patients receive during 3 weeks 15 sessions of intensive treatment for the lymphoedema. Thereafter they receive during 6 months (18 sessions) maintenance treatment.

Intensive treatment

All groups receive information, skin care, multi-layer bandaging and exercises.

Additionally the three groups receive MLD. The intervention group receives additionally fluoroscopy-guided MLD, the first control group receives traditional MLD and the second control group receives placebo MLD.

The content and duration of the treatment in the three groups is based on the current reimbursement of physical therapy applied in patients with lymphoedema of at least 5% difference.

The patients receive each week 5 sessions of treatment. The session with skin care, bandaging and exercises last for 30 minutes. The session with MLD also last for 30 minutes. So, the total duration of both sessions is 60 minutes and they receive 15 sessions of standard treatment and 15 sessions of MLD in total. All treatments are performed by physical therapists experienced in treatment of patients with lymphoedema.

Content of each treatment modality:

Information: the patient receive a leaflet with information about the lymphatic system and lymphoedema, clinical evaluation and conservative treatment of lymphoedema

Skin care: The skin is hydrated during the session. If wounds are present, the wound is cared for.

Multi-layer bandaging: This 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. The bandage is applied after hydrating the skin, the

patient performs than exercises. After exercising, MLD is applied on the shoulder and trunk. After MLD, the bandage is applied again. 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 herself.

Exercise therapy: 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.

Fluoroscopy-guided MLD: The lymphatic system is stimulated optimally with the new method of MLD. The therapist applies hand movements of higher pressure (up to 80 mmHg) which consist of following techniques:

- Cleaning techniques to empty the lymph nodes at the level of the clavicular, axilla, humerus and elbow
- Resorption technique to create resorption of lymph by the lymph capillaries
- Gliding technique alongside the skin to stimulate transport of lymph through the lymph collectors or to stimulate transport of lymph through the interstitium.

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 lymphatic transport, obtained by the lymphofluoroscopy.

Traditional MLD: MLD with drainage of the jugular and occipital region, emptying retroclavicular lymph nodes, axillary lymph nodes, humeral lymph nodes and cubital lymph nodes, stimulating lymph collectors on the trunk, shoulder, arm and hand, without knowledge of the patient-specific lymphatic architecture. A pressure with the hands up to 40 mmHg is applied and to stimulate lymphatic transport through the lymph collaterals, the therapist's hands perform 'pump-movements' while stretching the skin.

Placebo MLD: deep massage by performing relaxing transverse movements on the muscles of the ipsilateral neck, shoulder, arm and belly. We give following explanation to the patients about the effect of the treatment: '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.'

Patients are taught to stimulate their lymphatic transport and are asked to repeat the self-drainage daily at home.

Maintenance treatment

Immediately after the intensive treatment, the maintenance treatment is started for 6 months.

All patients (intervention and control 1 and 2 group) have to:

- continue skin care
- wear a custom-made compression sleeve
- perform twice a day exercises at home (same as during intensive treatment)
- follow two informational sessions: one session about self-management and one session about compression sleeves and other compression material.

The intervention group receives additionally fluoroscopy-guided MLD, the control 1 group receives traditional MLD and the control 2 group receives placebo MLD. Each session lasts for 30 minutes, with a frequency decreasing from 2 times a week to one each two weeks (M1: 2x/week, M2: 1x/week, M3-4: 1x/2 weeks, M5-6 1x/ month, 18 sessions in total). Patients are asked to continue the self-MLD once a day at home.

6.2 Laboratory tests

Not applicable.

6.3 Other investigations

Ultrasonography at the level of the shoulder and trunk to detect stagnation of lymph at the level of the shoulder and trunk.

7. Assessment of efficacy

All assessments are performed in the Lymphoedema Centre of UZ Leuven, in the Lymphoedema Clinic of UZ Sint-Pieter, in the Multidisciplinary Breast Clinic of UZA, in the Centre of Oncology of AZ Groeninge Kortrijk or in the Department of Radiotherapy of UZ Gent. All assessments are performed by someone who is blinded for the allocation to the treatment groups.

Primary outcome parameters are:

- Change of lymphoedema volume of arm and hand
- Change of stagnation (measured with tissue dielectric constant and with bio-impedance analyses) of fluid at the level of shoulder/ trunk

Secondary outcome parameters are:

- Number of responders after intensive treatment (>30% decrease of lymphoedema volume) and after maintenance treatment (<10% increase of lymphoedema volume)
- Change of tissue elasticity at level of arm/ shoulder/ trunk
- Change of extracellular fluid in the arm
- Change of tissue dielectric constant at the level of the arm
- Change of thickness and reflectivity of cutis and subcutis of arm/ shoulder/ trunk
- Change of lymphatic architecture and function

- Change of problems in functioning related to the development of BCRL.
- Change of quality of life
- Number of episodes of erysipelas
- Adverse events associated from MLD
- Cost associated with the disease (lymphoedema) and its treatment

Following clinical outcome parameters are measured before and after 3 weeks of intensive treatment, after 1, 3 and 6 months of maintenance treatment and after 6 months of follow-up: arm and hand volume and arm circumferences of both arms, extracellular fluid in the arm, problems in functioning related to the development of lymphedema, health-related quality of life and treatment compliance are measured.

Lymphatic architecture and function, thickness and consistency of cutis and subcutis and venous blood circulation in arm and trunk are measured before and after the intensive treatment and after 6 months of maintenance treatment.

The first 30 patients are measured twice to check test-retest reliability of the clinical measurements (except lymphofluoroscopy). To correct for changes outside of lymphoedema, all clinical assessments are performed on the affected side and on the healthy side as well.

Arm volume (10 min): measured with an arm volumeter: the first 30 patients receive an arm volume measurement with the volumeter of Belgrado (in publication), with the volumeter of Gebruers (10) and with the volumeter of Damstra (11); based on comparison of test-retest reliability and time-efficiency of the different techniques, measurement of arm volume is chosen

Hand volume (10 min): measured with a hand volumeter (12)

Arm circumferences (10 min): measured with a circumference measurement device (perimeter) (13)

Tissue elasticity (5 min): measured with the tonometer (14) and SkinFibrometer

Water content in the arm/ shoulder/ trunk (5 min): measured with MoistureMeter (15)

Water content in the arm/ shoulder/ trunk (10 min): measured with BioImpedance Spectroscopy (16)

Problems in functioning related to development of arm lymphoedema (15 min): measured with the Functioning Disability and Health questionnaire (Lymph-ICF) (17)
*An additional sub-investigation is linked to this questionnaire by analysing the validity and reliability of the Dutch as well as the French versions of this questionnaire. In order to realise this analysis in time (regarding one of the PhD's pre-planned time schedule), 30 additional

patients, who 1) are meeting the inclusion criteria, and 2) have given written informed consent, will be recruited in the Lymphovenous Center UZ Leuven regarding the investigation of the Dutch version, and 30 additional patients who 1) are meeting the inclusion criteria, and 2) have given written informed consent, will be recruited in the Centre for Lympholoedema of CHU UCL Namur site Mont-Godinne regarding the investigation of the French version. To determine reliability and validity, all patients are asked to complete following documents/questionnaires during (ICF) and after their consultation:

1) Informed Consent document
2) Lymph-ICF Questionnaire with Numeric Rating Scale (this questionnaire has to be filled in twice to analyse test-retest reliability; once at the hospital and a second time at home, 24h hours after completing the first one (for this second "blanco" questionnaire an addressed and stamped envelope will be provided)
3) SF-36 Questionnaire (a general questionnaire regarding "general Quality of Life" (investigation of validity of the Lymph-ICF questionnaire)
4) Questionnaire regarding content validity of the Lymph-ICF ((1) Was each question of the Lymph-ICF understandable? (2) Was the scoring system clear? and (3) Were all complaints related to your lymphoedema mentioned in the Lymph-ICF?)
5) Questionnaire regarding medical and socio-demographic data of the participants in order to determine the characteristics of the study sample.

Information regarding circumference measurements of the upper limb, received during the consultation will be used to calculate and analyze the amount of lymphoedema present in each patient at the time of completing the questionnaires.
***For patients participating the EFforT-trial, these questionnaires are completed during the assessment which takes place 1 month after the start of the maintenance phase (see 3.5 study diagram).*

Health-related quality of life (15 min): measured with McGill quality of life questionnaire (in publication)

Skin thickness and reflectivity at level of arm/ shoulder/ trunk (15 min): measured by ultrasonography (18)

Lymphatic architecture and function (2.5 hours): measured by lymphofluoroscopy (see above) (8, 19)

Treatment compliance (5 min): measured with a self-developed questionnaire.

Costs associated lymphoedema and its treatment (10 min): measured with a self-developed questionnaire.

Episodes of erysipelas: measured with a self-developed questionnaire

Adverse events from MLD: measured with a self-developed questionnaire

Patient-related data (such as age, body length and weight and physical activity level (with FPACQ)) (20), breast cancer treatment- related data (such as type of surgery, type of adjuvant treatment, number and level of axillary lymph nodes dissected) and lymphoedema related data (such as duration of the oedema and pitting) are collected before the start of the treatment programme.

Body weight is measured at each measurement session.

8. Assessment of Safety

8.1 Specification, timing and recording of safety parameters

We will involve an external safety board to determine subject safety during the study.

They will perform their first analyses after 6 months of inclusion of patients and again 6 months later. Thereafter, analyses are performed after 2 years, 3 years and 4 years.

They will analyse adverse events related to the assessment (especially with lymphofluoroscopy) and to the treatment of lymphoedema (especially the MLD).

8.2 Procedures for recording and reporting adverse events (AE)

8.2.1 Definitions in Law of May 7, 2004 concerning experiments on the human person

Adverse reaction (AR): all untoward and unintended responses to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered;

Adverse event (AE): any untoward medical occurrence in a patient or subject of the treated group during an experiment, and which does not necessarily have a causal relationship with this treatment

Unexpected adverse reaction (UAR): an adverse reaction, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical trial is concerned, with the applicable product information (e.g. investigator's brochure for an unauthorised investigational

product or the patient leaflet joined to the summary of product characteristics for an authorised product);

Serious adverse event (SAE) or serious adverse reaction (SAR): any untoward medical occurrence or effect that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, and this, when it is a clinical trial, at any dose;

Suspected unexpected serious adverse reaction (SUSAR): is an AR that is serious and unexpected (meaning that nature or severity of the AR is not consistent with the Investigational Medicinal Product reference safety information, which is the Investigator's Brochure) and is judged by either the investigator or the sponsor as having a reasonable suspected causal relationship with the investigational medicinal product.

8.2.2 Notification of adverse events

The investigator shall report all serious adverse events immediately, after first knowledge, to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the terms specified in the protocol

For reported deaths of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the minister if the experiment is being conducted in Belgium, if he so requests.

8.2.3 Notification of serious adverse reactions

The sponsor shall ensure that all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the minister, to the competent authorities in all the Member States concerned in the case of a trial, and to the competent ethics committee, and in any case no later than seven days after knowledge by the sponsor

of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected unexpected serious adverse reactions shall be reported to the minister, to the competent authorities of all Member States concerned in the case of a clinical trial and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

The sponsor shall also inform the other investigators.

Once a year throughout the experiment, the sponsor shall provide the minister and the ethics committee in Belgium and those of the member States in whose territory the trial is conducted in the case of a multicentre trial, with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

Regarding those adverse events and serious adverse reactions the Principal Investigator will take all reasonable measures, in consultation with Sponsor, to protect subjects at risk following the occurrence of such events.

8.2.4 Adverse events that do not require reporting

No AE's or SAE's are expected nor after the subcutaneous injection of ICG, neither associated with the treatment of lymphoedema.

AE will be reported during the entire trial period, i.e. 7 months (3 weeks intensive phase and 6 months maintenance phase)

8.3 Treatment stopping rules

Not applicable. **No AE's or SAE's are expected nor after the subcutaneous injection of ICG, neither associated with the treatment of lymphoedema.**

8.4 Data monitoring committee (DMC)

Not applicable.

There are no indications for setting up a data monitoring committee, such as:

- Life-threatening disease
- Patient population (e.g. pediatric population)
- Prior knowledge or strong suspicion that a treatment under consideration has the potential to harm patients
- Complex study design

9. Statistics

9.1 Sample size

The required sample size for the study is 192 subjects or 64 subjects per group to detect a difference of 15% in the reduction of lymphoedema volume at the level of the arm/ hand (first primary outcome) or at the level of the shoulder/ trunk (second primary outcome) between the three groups. This is based on an alpha of 0.0125 and a power of 80%. The effect size is determined from clinical results of the Leuven Lymphovenous Center and by consulting experts in the field of lymphology, with the estimated reduction of 35% (±25%) for the traditional MLD group and an estimated reduction of 50% (±25%) for the fluoroscopy guided MLD group, and of 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).

73 patients with unilateral BCRL were followed in the Leuven Lymphovenous Center between November 2011 and November 2013. Patients firstly received intensive decongestive lymphatic therapy with skin care, bandaging, exercises and traditional MLD. Thereafter they received maintenance decongestive lymphatic therapy with skin care, compression sleeve, exercises and traditional MLD. Lymphoedema volume of the arm reduced 36% (±28%) on average after intensive treatment on average.

According to different experts in the field of lymphology (the principle and sub-investigators of this study), 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. 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 Bonferoni correction). In literature, data on change of lymphoedema volume at the level of the shoulder/ trunk is missing.

9.2 Randomisation

Patients in the intervention group will receive standard physical therapy + fluoroscopy-guided MLD

Patients in the control 1 group will receive standard physical therapy + traditional MLD

Patients in the control 2 group will receive standard physical therapy + placebo MLD

Randomisation is performed by someone different form the assessors or therapists of the study. Before randomization, the patient receives an ID. Randomisation is performed using an excel-file and the order of the randomization is determined by the ID number.

The assessments are performed by someone who is blinded to the allocation to the treatment groups.

Patients are also blinded to the allocation to the treatment group

9.3 Analysis

Month 45-48: statistical analyses and interpretation of data concerning effect of fluoroscopy-guided MLD compared to traditional MLD or placebo MLD for the treatment of BCRL.

Month 48: November 2019: end of statistical analyses and interpretations = milestone 3

The statistical department of KU Leuven is counselled about the statistical analyses.

Following hypotheses will be tested:

- Patients receiving fluoroscopy-guided MLD during the intensive or maintenance phase of decongestive lymphatic therapy will have a significantly:
    - greater reduction of lymphoedema volume at the level of the hand/ arm
    - less stagnation of lymph at the level of the shoulder/ trunk
    - greater response
    - greater reduction of extracellular fluid in the arm
    - greater reduction of tissue dielectric constant in the arm
    - greater improvement of tissue elasticity
    - greater reduction of problems in functioning related to lymphoedema
    - greater improvement of health related quality of life improvement of lymphatic function
    - greater change of cutis and subcutis consistency
    - greater decrease of cutis and subcutis thickness
    - more improvement of lymphatic transport

  than patients receiving traditional MLD or placebo MLD.

Data will be analyzed according the intention to treat principle. A 1.25% level of significance is applied.

10. Quality assurance

Experienced assessors will perform all lymphofluoroscopic evaluations after informed consent. Injections will be given under sterile conditions.

Physical therapy will be given by experienced physical therapists.

The safety board will collect all adverse events and will supervise the safety of the patients.

11. Direct access to source data and documents

It will be specified, (or reference is made to another written agreement) that the investigator(s) and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie patients' case sheets, blood test reports, X-ray reports, histology reports etc).

12. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee of the University Hospitals Leuven, University Hospital Antwerp, to UMC Sint-Pieter, to AZ Groeninge Kortrijk, to UZ Gent and to the Federal Agency for medicinal products for Clinical Trial Authorisation.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

Data are anonymous. The table with the data of the study do not contain information that can be linked to the patient (such as name, date of birth). All documents to collect patient-specific data for the study contain a patient-specific code (and not the name of the patient). The overview of

the different codes and related name and date of birth of the patient is kept by the principle investigator.

13.Data Handling

The data will be stored on a shared file (on UZ data). Only the principle investigator, sub-investigators and project co-workers (after permission from the principle investigator) have access to the file. The access is secured by a login and password.

14.Data Management

All documents concerning the organization of the project (such as documents concerning approval by the Ethical Committee), may be – after permission of the persons who has to sign - signed electronically. Each site will retain all study related documents according to storage and record retention principles of good clinical practices.

15.Translational research

Not applicable

16.Publication Policy

Possible publications are:

- Protocol study: Nele Devoogdt first author and Sarah Thomis last author
- PhD student 1
    - Effect intensive treatment: on clinical parameters
    - Effect intensive treatment: changing lymphatic architecture and lymph transport
    - Comparison of arm volume measured with 3 devices: Gebruers, Belgrado, Damstra
    - Responsiveness of Lymph-ICF
    - Economic analyses of current conservative treatment of lymphoedema analyse
- PhD student 2
    - Effect maintenance treatment: on clinical parameters
    - Effect maintenance treatment: changing lymphatic architecture and lymph transport
    - Reliability and validity of the French version of the Lymph-ICF
    - Comparison of extracellular fluid measured with 2 devices: Impedimed versus Bodystat Quadscan
    - Economic analyses old conservative treatment of lymphoedema versus new one

On every publication, PhD student is first author and Nele Devoogdt (principle investigator) is last author.
All sub-investigators are mentioned on every publication as co-authors.
Adding co-authors, change of the order of co-authors will be discussed with all investigators.

If an investigator wants to make an extra publication with existing data, he/ she has to discuss this with all investigators.

17.Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, UH Leuven shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

18.Financial Aspects

This study is financed by the Agency for Innovation by Science and Technology, applied Biomedical Research. In order to arrange such financing a separate collaboration agreement has been agreed between UH Leuven and the beneficiaries.

For patients, participating in the study will be cost free. Neither the assessment of the patient (clinically, echography, fluoroscopy) nor the treatment with MLD will be charged. The standard physical therapy sessions however are on doctor's prescription. One part will be reimbursed by the social services. The other part is paid by the patient. At the end of the study the patient will receive a compensation for participating in the study which is equivalent to the amount she/ he had to pay herself/ himself for the physical therapy sessions (by giving gift cards).

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