

# Supplementary Appendix

## Table of Contents:

Table of Contents: .....	1
Supplementary Appendix 1 – CEAP Classification.....	2
Supplementary Appendix 2 – Inclusion and Exclusion Criteria.....	4
Supplementary Appendix 3 – Study Flow Diagram .....	5
Supplementary Appendix 4 – Quality of Life and Clinical Severity Scores: .....	6
Supplementary Appendix 5 – Limb Volume:.....	7
Supplementary Appendix 6 – Generic Quality of Life Measures:.....	8
Supplementary Appendix 7 – Venous Duplex Findings: .....	9

## Supplementary Appendix 1 – CEAP Classification

### CEAP Classification

C Clinical signs, (Grade 0-6) ed by (A) for asymptomatic and (S) for symptomatic presentation

E For a(E)tiological classification (congenital, primary, secondary)

A For Anatomical distribution (superficial, deep or perforator, alone or in combination)

P For Pathophysiological dysfunction (reflux or obstruction, alone or in combination)

### Clinical Classification

Grade 0 No visible, or palpable signs of venous disease

Grade 1 Telangiectases or reticular veins

Grade 2 Varicose veins

Grade 3 Oedema

Grade 4a Pigmentation and/or eczema

Grade 4b Lipodermatosclerosis and/or atrophie blanche

Grade 5 Healed venous ulcer

Grade 6 Active venous ulcer

### A(E)tiological Classification

Ec Congenital

Ep Primary

Es Secondary

En No venous aetiology identified

### Anatomical Classification

As Superficial veins

Ad Deep veins

Ap            Perforating veins  
An            No venous location identified

**Pathyphysiological classification**

Pr            Reflux  
Pr            Obstruction  
Pr,o          Reflux and obstruction  
Pn            No venous pathophysiology

## Supplementary Appendix 2 – Inclusion and Exclusion Criteria

### Inclusion Criteria

Patients with chronic venous insufficiency who have the following are eligible for the study:

- Able to understand the study and provide meaningful written informed consent for the study.
- Willing, able, and committed to participate in the procedures for the full length of the study.
- All ethnic groups, male or female above the age of 18 years.
- Diagnosis of chronic venous insufficiency (C3-C5 CEAP Classification)
- Blood pressure currently under moderate control (< 160/100mmHg)
- No current foot ulceration

### 4.3 Exclusion Criteria

Patients meeting any of the following criteria are to be excluded:

- Has an unstable condition (eg, psychiatric disorder, a recent history of substance abuse) that would affect compliance with protocol
- Pregnant
- Has a cardiac pacemaker, AICD or other implanted electrical device
- Has an Existing DVT.
- Has recent lower limb injury or lower back pain
- Has current foot ulceration or other skin ulcers
- Has any disorder that, in the opinion of the Investigator, might interfere with the conduct of the study.
- Has an ABPI < 0.8

## Supplementary Appendix 3 – Study Flow Diagram

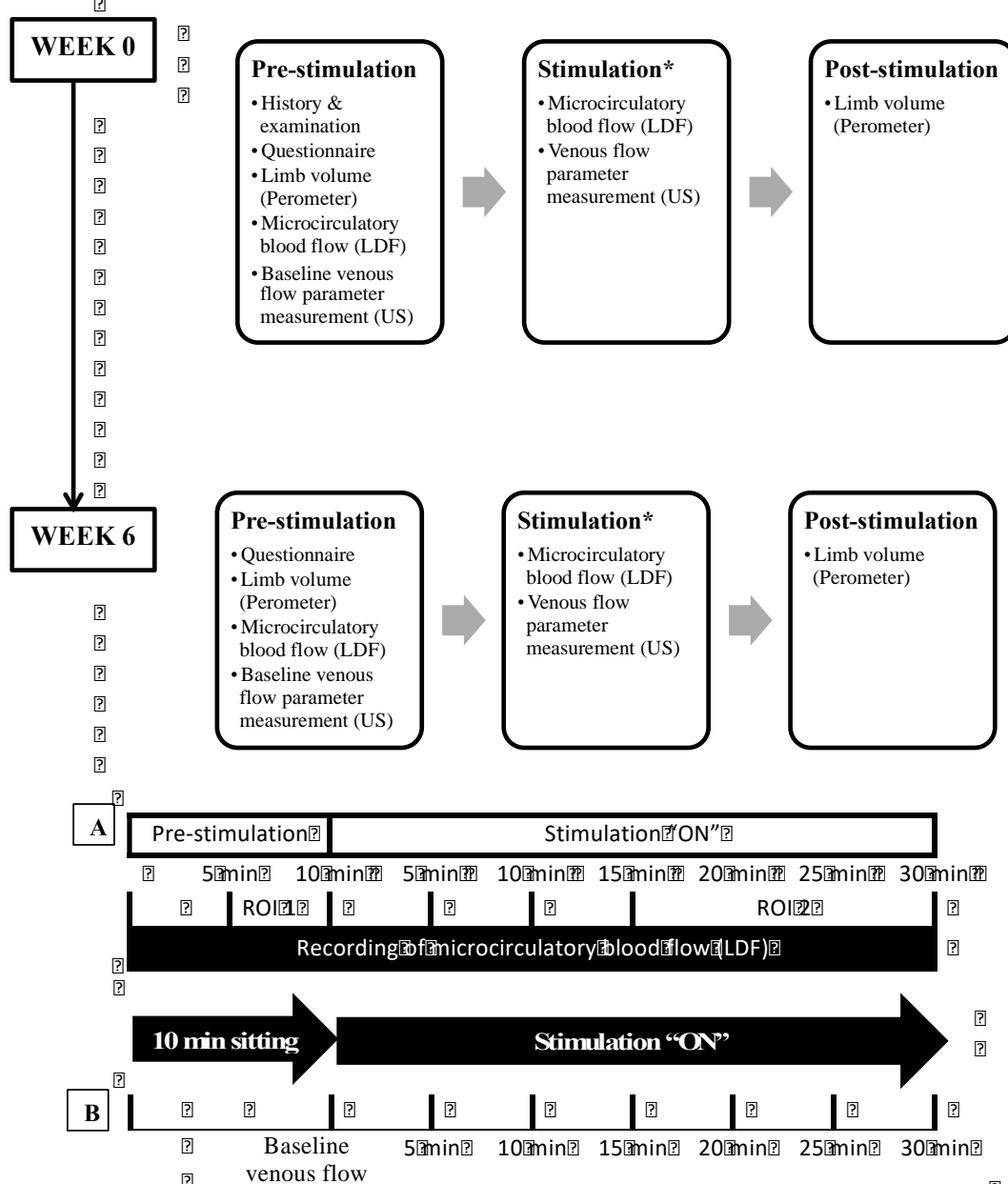


Illustration of timings of microcirculatory blood flow (laser Doppler fluximetry) and venous flow parameter (ultrasound) measurements. Stimulation "ON" applies to Group B and Group C. Group A underwent a period of quiet sitting during this period.

A) Microcirculatory blood flow was recorded as % change from baseline  $[(ROI2 - ROI1) / ROI1 \times 100]$ .

B) Venous flow parameters were calculated as  $[(\text{average of 6 measurements during stimulation "on"}) / \text{baseline venous flow} \times 100]$

(LDF laser doppler fluximeter, min minutes, ROI region of interest.)

## Supplementary Appendix 4 – Quality of Life and Clinical Severity Scores:

<b>AVVQ</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	24	25	25	24	23	20
Minimum	5.270	4.510	3.560	4.710	4.510	5.830
25% Percentile	10.13	16.34	11.91	11.30	14.99	11.04
Median	18.62	21.07	21.30	19.72	18.86	15.01
75% Percentile	26.83	29.47	31.33	25.38	28.52	21.31
Maximum	40.33	37.55	49.18	67.21	44.45	46.68
Mean	19.27	22.40	23.19	21.07	21.13	17.04
Std. Deviation	9.985	8.969	12.19	13.46	9.425	9.203
Std. Error of Mean	2.038	1.794	2.437	2.747	1.965	2.058
Lower 95% CI of mean	15.06	18.69	18.16	15.39	17.06	12.73
Upper 95% CI of mean	23.49	26.10	28.23	26.75	25.21	21.35

<b>VCSS</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	25	25	26	25	23	25
Minimum	2.000	2.000	0.000	2.000	2.000	0.000
25% Percentile	4.500	5.000	4.750	5.000	4.000	2.000
Median	6.000	6.000	7.000	7.000	5.000	3.000
75% Percentile	8.000	8.000	9.250	9.500	8.000	6.500
Maximum	12.00	13.00	15.00	13.00	14.00	9.000
Mean	6.320	6.880	7.462	7.320	6.087	4.000
Std. Deviation	2.410	2.728	3.797	2.996	2.937	3.028
Std. Error of Mean	0.4821	0.5456	0.7447	0.5992	0.6125	0.6055
Lower 95% CI of mean	5.325	5.754	5.928	6.083	4.817	2.750
Upper 95% CI of mean	7.315	8.006	8.995	8.557	7.357	5.250

<b>VDS</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	25	25	25	25	23	20
Minimum	1.000	1.000	1.000	1.000	1.000	1.000
25% Percentile	1.000	1.000	1.000	1.000	1.000	1.000
Median	1.000	2.000	1.000	1.000	1.000	1.000
75% Percentile	2.000	2.000	2.000	2.000	2.000	1.750
Maximum	3.000	3.000	3.000	3.000	3.000	3.000
Mean	1.520	1.800	1.560	1.400	1.609	1.350
Std. Deviation	0.6532	0.7638	0.6506	0.5774	0.7827	0.6708
Std. Error of Mean	0.1306	0.1528	0.1301	0.1155	0.1632	0.1500
Lower 95% CI of mean	1.250	1.485	1.291	1.162	1.270	1.036
Upper 95% CI of mean	1.790	2.115	1.829	1.638	1.947	1.664

## Supplementary Appendix 5 – Limb Volume:

	0	0	0	0	0	0	6	6	6	6	6	6
	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks
	A	A	B	B	C	C	A	A	B	B	C	C
<b>Limb Volume</b>	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
Number of values	25	25	24	24	25	25	25	25	22	22	21	20
Minimum	2467	3039	2875	2941	2754	2733	3033	3063	3006	2987	2860	2846
25% Percentile	3929	3991	4038	4059	4090	4125	3978	4020	3900	3888	4127	4031
Median	4464	4537	4618	4600	4674	4685	4599	4645	4631	4646	4749	4704
75% Percentile	6651	6656	5479	5539	5476	5490	6541	6599	5377	5437	5789	5502
Maximum	7186	7276	11707	11797	9097	9148	7944	8017	11158	11320	9366	8748
Mean	4966	5039	5092	5117	5029	5048	5051	5091	4969	4982	5129	4901
Std. Deviation	1415	1394	1891	1904	1535	1551	1448	1463	1765	1795	1616	1311
Std. Error of Mean	282.9	278.7	385.9	388.6	307.0	310.2	289.5	292.7	376.3	382.6	352.6	293.0
Lower 95% CI of mean	4382	4464	4294	4313	4395	4407	4453	4487	4186	4186	4394	4287
Upper 95% CI of mean	5550	5614	5891	5921	5663	5688	5648	5696	5751	5778	5865	5514
95% CI of median	95.67	95.67	97.73	97.73	95.67	95.67	95.67	95.67	98.31	98.31	97.34	95.86
Actual confidence level	%	%	%	%	%	%	%	%	%	%	%	%
Lower confidence limit	4004	4012	4108	4165	4206	4203	4123	4133	3915	3897	4230	4223
Upper confidence limit	6178	6305	5220	5305	5399	5391	6001	6059	5301	5393	5497	5289

## Supplementary Appendix 6 – Generic Quality of Life Measures:

<b>EQ-5D QOL</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	24	25	25	25	23	20
Minimum	0.2060	-0.08700	0.01900	0.1110	-0.1420	0.1120
25% Percentile	0.6268	0.2355	0.5500	0.5860	0.4580	0.4880
Median	0.6840	0.6420	0.7250	0.7350	0.6910	0.7535
75% Percentile	0.7670	0.7440	0.8230	0.7670	0.7670	0.8368
Maximum	0.9060	1.000	1.000	1.000	1.000	1.000
Mean	0.6720	0.5406	0.6676	0.6566	0.5994	0.6611
Std. Deviation	0.1504	0.3031	0.2225	0.2126	0.2763	0.2742
Std. Error of Mean	0.03069	0.06061	0.04450	0.04253	0.05761	0.06131
Lower 95% CI of mean	0.6086	0.4155	0.5757	0.5688	0.4799	0.5327
Upper 95% CI of mean	0.7355	0.6657	0.7594	0.7444	0.7189	0.7894

<b>EQ-5D VAS</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	25	25	25	25	23	20
Minimum	30.00	20.00	25.00	30.00	7.000	38.00
25% Percentile	57.50	50.00	54.00	52.50	50.00	50.75
Median	70.00	70.00	70.00	70.00	65.00	75.00
75% Percentile	80.00	80.00	80.00	77.50	85.00	85.00
Maximum	95.00	99.00	100.0	95.00	95.00	100.0
Mean	67.72	64.68	67.08	66.28	63.61	71.20
Std. Deviation	16.33	20.62	19.85	18.45	24.30	18.48
Std. Error of Mean	3.266	4.124	3.969	3.691	5.067	4.131
Lower 95% CI of mean	60.98	56.17	58.89	58.66	53.10	62.55
Upper 95% CI of mean	74.46	73.19	75.27	73.90	74.12	79.85

<b>SF12 - PCS</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	25	24	24	24	23	20
Minimum	15.39	21.58	26.77	18.17	22.19	32.56
25% Percentile	35.91	33.34	41.10	31.89	33.59	43.45
Median	41.98	40.61	48.95	47.68	45.10	51.82
75% Percentile	52.69	52.63	55.52	54.31	53.34	55.99
Maximum	58.38	60.11	59.59	59.23	58.17	65.90
Mean	42.03	42.02	47.30	43.73	43.32	49.89
Std. Deviation	11.42	12.06	8.543	12.00	10.88	8.277
Std. Error of Mean	2.283	2.461	1.744	2.450	2.268	1.851
Lower 95% CI of mean	37.32	36.93	43.69	38.66	38.61	46.02
Upper 95% CI of mean	46.74	47.11	50.90	48.80	48.02	53.77

<b>SF12 - MCS</b>	0 weeks Group A	0 weeks Group B	0 weeks Group C	6 weeks Group A	6 weeks Group B	6 weeks Group C
Number of values	25	24	24	24	23	20
Minimum	26.54	25.31	23.97	28.29	25.16	17.10
25% Percentile	49.41	43.16	42.41	48.24	41.26	41.01
Median	55.11	52.38	47.96	53.93	50.37	50.03
75% Percentile	59.47	56.75	55.76	57.16	55.47	55.18
Maximum	69.47	64.41	67.20	65.16	61.57	62.91
Mean	53.26	50.26	48.01	51.13	48.49	48.17
Std. Deviation	10.27	9.455	10.06	9.560	9.332	10.54
Std. Error of Mean	2.053	1.930	2.054	1.951	1.946	2.357
Lower 95% CI of mean	49.02	46.26	43.76	47.10	44.45	43.24
Upper 95% CI of mean	57.49	54.25	52.26	55.17	52.52	53.10



## Supplementary Appendix 7 – Venous Duplex Findings:

	GSV SVI	SSV SVI	ATV SVI	VV SVI	Iliac DVI	SFV DVI	PFV DVI	Calf DVI	Disease Segment Count	Superficial territories	Deep territories	Mixed?	Obstruction
Sum	23	13	7	39	18	47	11	30	172	81	91	34	16

ID	GSV SVI	SSV SVI	ATV SVI	VV SVI	Iliac DVI	SFV DVI	PFV DVI	Calf DVI
RVD01	0	0	0	0	0	1	0	1
RVD02	0	0	0	0	0	0	1	1
RVD03	0	0	1	1	1	2	1	0
RVD04	0	0	0	1	0	0	0	0
RVD05	0	0	0	0	0	2	0	1
RVD06	0	1	0	0	2	2	0	1
RVD07	0	0	0	1	0	0	0	0
RVD08	0	0	0	1	1	1	1	0
RVD09	0	0	0	1	0	0	0	1
RVD10	0	0	0	0	0	0	0	0
RVD11	0	1	0	1	1	1	1	1
RVD12	0	0	0	1	0	0	0	1
RVD13								
RVD14	0	0	0	0	0	0	0	1
RVD15								
RVD16	1	0	1	1	0	0	0	1
RVD17	0	1	0	0	0	0	0	0
RVD18	0	0	0	1	0	1	1	1
RVD19	0	1	0	1	0	1	0	1
RVD20	0	0	0	0	0	1	0	1
RVD21	0	0	0	0	0	1	0	1
RVD22	0	0	0	1	0	1	0	0
RVD23	0	1	0	1	1	1	1	1
RVD24	0	0	0	1	0	0	0	0
RVD25	0	0	0	0	0	0	0	1
RVD26	0	0	0	0	0	1	0	0
RVD27	1	0	0	0	1	1	0	0
RVD28	1	1	0	0	0	2	0	0
RVD29	0	0	0	1	0	0	0	0
RVD30	0	0	0	0	2	2	0	0
RVD31	0	0	0	1	0	0	0	0
RVD32	1	0	0	0	0	1	0	1
RVD33	0	0	0	0	2	2	2	0
RVD34								
RVD35								
RVD36	0	0	0	1	0	0	0	0
RVD37	1	0	0	0	0	1	0	1
RVD38	0	0	0	0	0	1	0	1
RVD39								
RVD40	0	0	0	1	0	1	0	0
RVD41	0	0	0	0	1	1	1	1
RVD42	0	0	0	0	0	1	1	0
RVD43	0	0	0	1	0	1	0	0
RVD44	0	0	1	1	0	1	0	0
RVD45	1	0	0	0	0	1	1	0
RVD46	1	0	0	1	0	0	0	0
RVD47	1	0	0	1	0	0	0	0
RVD48	0	1	0	1	0	1	1	0
RVD49	0	0	0	1	0	0	0	0
RVD50	0	2	0	0	0	1	0	0
RVD51	0	0	0	1	0	0	0	1
RVD52	1	0	0	1	0	0	0	0
RVD53	1	0	0	1	0	1	0	0
RVD54	1	0	0	1	0	1	0	1
RVD55	1	0	0	0	0	2	0	0
RVD56	1	0	0	1	0	0	0	1
RVD57	0	0	0	0	0	0	0	1
RVD58	1	0	0	1	0	1	0	1
RVD59	1	0	0	0	2	1	0	0
RVD60	0	1	0	1	0	0	0	0
RVD61	0	0	0	0	0	2	0	1
RVD62	1	0	1	0	0	1	0	0
RVD63	1	0	0	1	0	1	0	0
RVD64	1	0	0	0	0	0	0	0
RVD65	1	0	0	0	0	0	0	1
RVD66	0	0	0	1	0	0	0	0
RVD67	1	0	1	1	0	0	0	1
RVD68	0	0	0	0	2	2	0	1
RVD69	0	1	0	0	1	1	0	0
RVD70	1	0	0	1	0	1	0	1
RVD71	0	1	0	0	0	0	0	0
RVD72	1	0	0	1	0	0	0	0
RVD73	1	0	0	1	0	0	0	0
RVD74	0	1	1	1	0	0	0	0
RVD75								
RVD76	0	0	1	1	0	0	0	0
RVD77	0	0	0	1	0	0	0	0

### Legend:

0 = no disease

1 = reflux disease

2 = obstructive disease