

THE UNIVERSITY OF HULL

An RCT to determine an effective skin regime  
aimed at improving skin barrier function and  
quality of life in those with podoconiosis in Ethiopia

being a Thesis submitted for the Degree of PhD

in the University of Hull

by

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# CONTENTS

<b>ACKNOWLEDGEMENTS.</b>	<b>11</b>
<b>CHAPTER 1. INTRODUCTION.</b>	<b>13</b>
1.1. SIGNIFICANCE OF THE STUDY.	13
1.2. ORGANISATION OF THE THESIS.	16
<b>CHAPTER 2. LITERATURE REVIEW.</b>	<b>18</b>
2.1. INTRODUCTION.	18
2.2. SKIN DISEASE IN RESOURCE-POOR COUNTRIES.	18
2.3. PODOCONIOSIS.	20
2.3.1. NATURE AND SIGNIFICANCE OF PODOCONIOSIS.	21
2.3.2. PREVALENCE OF PODOCONIOSIS.	23
2.3.2.1. PREVALENCE OF PODOCONIOSIS IN ETHIOPIA, PATIENT'S AGE AND GENDER.	24
2.3.3. DIAGNOSIS AND STAGES OF PODOCONIOSIS.	26
2.3.4. EFFECTS OF PODOCONIOSIS ON THE SKIN AND LYMPHATIC SYSTEM.	28
2.3.5. ACUTE ADENOLYMPHANGITIS IN PODOCONIOSIS.	36
2.3.6. ADENO-LYMPHANGITIS IN LYMPHATIC FILARIASIS.	37
2.3.7. PREVENTION AND MANAGEMENT OF PODOCONIOSIS.	38
2.3.8. EFFECT OF DIFFERENT CARE/MANAGEMENT SERVICES.	48
2.3.8.1. REASONS FOR NON-ATTENDANCE AT PODOCONIOSIS CLINICS.	49
2.3.9. ECONOMIC CONSEQUENCES OF SKIN DISEASE AND PODOCONIOSIS.	50
2.3.10. PATIENT'S KNOWLEDGE OF ADENOLYMPHANGITIS IN PODOCONIOSIS.	51
2.3.11. KNOWLEDGE AND ATTITUDES OF HEALTH EXTENSION WORKERS, PATIENTS AND THE COMMUNITY TOWARDS PODOCONIOSIS.	51
2.3.11.1. HEALTH EXTENSION WORKER'S KNOWLEDGE.	52
2.3.11.2. COMMUNITY KNOWLEDGE.	52
2.3.11.3. PATIENT'S KNOWLEDGE OF PODOCONIOSIS AND PREVENTION.	53
2.3.12. PSYCHO-SOCIAL IMPACT OF PODOCONIOSIS.	59
2.3.13. QUALITY OF LIFE OF THOSE WITH PODOCONIOSIS.	62
2.3.14. CHALLENGES OF PROVIDING SKIN CARE IN RESOURCE-POOR COUNTRIES.	64
2.3.15. CLEANING SKIN IN RESOURCE-POOR COUNTRIES.	64
2.3.15.1. ACCESSING SKIN CLEANSERS, DRYING CLOTHS AND EMOLLIENTS.	66
2.3.16. KEY GAPS IN KNOWLEDGE ON THE TREATMENT OF PODOCONIOSIS	66
2.3.17. SUMMARY OF SECTION 2.3.	67

<b>2.4. ASSESSMENT AND MEASUREMENT OF SKIN BARRIER FUNCTION.</b>	<b>69</b>
2.4.1. THE IMPACT OF ETHNICITY ON SKIN BARRIER FUNCTION.	71
2.4.2. ETHNIC DIFFERENCES RELATED TO TRANS-EPIDERMAL WATER LOSS, STRATUM CORNEUM HYDRATION AND pH.	72
2.4.2.1. OTHER STUDIES OF ETHNICITY AND SKIN.	74
2.4.3. THE IMPACT OF GENDER DIFFERENCES ON SKIN BARRIER FUNCTION.	74
2.4.3.1. GENDER DIFFERENCES RELATED TO TRANS-EPIDERMAL WATER LOSS AND STRATUM CORNEUM HYDRATION.	74
2.4.4. THE EFFECT OF SKIN DISEASE ON BARRIER FUNCTION.	75
2.4.5. EFFECTS OF PSYCHOLOGICAL STRESS ON SKIN BARRIER FUNCTION.	77
<b>2.5. THE PSYCHO-SOCIAL IMPACT OF SKIN DISEASE.</b>	<b>79</b>
<b>2.6. IMPROVING AND MAINTAINING HEALTHY SKIN BARRIER FUNCTION.</b>	<b>81</b>
2.6.1. MAINTAINING OPTIMUM STRATUM CORNEUM HYDRATION AND TRANS-EPIDERMAL WATER LOSS.	82
2.6.1.1. WATER FOR CLEANING THE SKIN.	82
2.6.1.2. SOAP FOR CLEANING THE SKIN.	84
2.6.2. EFFECT ON SKIN OF THE COMBINATION OF DIFFERENT WASHING AND DRYING TECHNIQUES.	87
2.6.3. EFFECTS ON SKIN OF DIFFERENT DRYING PRACTICES.	87
2.6.4. EMOLLIENTS.	88
2.6.4.1. 'LEAVE-ON' EMOLLIENTS.	88
2.6.4.2. GLYCERINE.	89
2.6.4.3. FATS/OILS IN EMOLLIENTS.	92
2.6.4.4. POTENTIAL ALLERGENS AND SENSITIZERS IN EMOLLIENTS.	94
2.6.4.5. APPLYING EMOLLIENTS TO THE SKIN.	95
2.6.4.6. WHEN AND HOW TO APPLY AN EMOLLIENT.	95
2.6.4.7. HOW MUCH EMOLLIENT TO APPLY.	96
2.6.5. SUMMARY OF SECTION 2.6.	97
<b>2.7. SUMMARY OF CHAPTER 2.</b>	<b>98</b>
<b>CHAPTER 3. PILOT STUDY</b>	<b>100</b>
<b>3.1 INTRODUCTION.</b>	<b>100</b>
<b>3.2. AIM AND OBJECTIVES OF THE PILOT STUDY.</b>	<b>101</b>
<b>3.3. METHOD</b>	<b>101</b>
3.3.1 STUDY DESIGN	101
3.3.2. SAMPLE SIZE AND SELECTION	101
3.3.3. INCLUSION AND EXCLUSION CRITERIA.	102
3.3.4. TIME PERIOD.	102

<b>3.3.5. PERMISSION AND ETHICAL APPROVAL.</b>	<b>102</b>
3.3.6. INTERVENTIONS AND RATIONALE.	103
3.3.7. PREPARING PILOT INTERVENTIONS.	106
3.3.7.1. SOAPY WATER.	106
3.3.7.2. WATER.	106
3.3.7.3. GLYCERINE.	106
3.3.7.4. VASELINE <sup>®</sup> (PETROLEUM JELLY).	106
3.3.8. BODY SITES.	107
3.3.9. MEASUREMENTS OF SKIN BARRIER FUNCTION.	108
3.3.9.1. TRANS-EPIDERMAL WATER LOSS.	108
3.3.9.2. STRATUM CORNEUM HYDRATION.	108
3.3.10. INDEPENDENT AND DEPENDENT VARIABLES.	109
3.3.11. POSSIBLE ADVERSE EFFECTS OF THE PILOT STUDY.	109
<b>3.4. DATA ANALYSIS OF PILOT STUDY.</b>	<b>109</b>
3.4.1. STATISTICAL METHOD.	110
<b>3.5. RESULTS.</b>	<b>110</b>
<b>3.5. DISCUSSION.</b>	<b>113</b>
<b>3.6. CONCLUSION.</b>	<b>114</b>
<b>CHAPTER 4. METHOD.</b>	<b>115</b>
<b>4.1. INTRODUCTION.</b>	<b>115</b>
<b>4.2. THE RESEARCH AIM, OBJECTIVES AND NULL HYPOTHESIS.</b>	<b>115</b>
4.2.1. AIM.	115
4.2.2. OBJECTIVES.	115
4.2.3. NULL HYPOTHESIS.	116
<b>4.3. RESEARCH DESIGN AND METHODOLOGY.</b>	<b>116</b>
4.3.1. RESEARCH DESIGN.	116
4.3.1.1. VALIDITY AND RELIABILITY OF RESEARCH DESIGN.	117
4.3.1.2. ETHICAL APPROVAL.	117
4.3.1.3. STUDY POPULATION.	117
4.3.1.4. INCLUSION/EXCLUSION CRITERIA.	118
4.3.1.5. CONTROL GROUP.	118
4.3.1.6. EXPERIMENTAL GROUP.	119
4.3.1.7. SUSTAINABILITY OF PRODUCTS USED IN THE RESEARCH.	121
4.3.1.8. STUDY SAMPLE SIZE.	122
4.3.1.9. EDUCATIONAL PROGRAMME PROVIDED FOR Clinic STAFF.	123
4.3.2. RECRUITING PATIENTS ONTO THE STUDY.	123

4.3.2.1. PARTICIPANT CONSENT.	124
4.3.2.2. ALLOCATION TO GROUPS.	124
4.3.2.3. EDUCATION OF PARTICIPANTS.	124
4.3.2.4. FREQUENCY OF DATA COLLECTION AND STUDY PERIOD.	125
4.3.2.5. DATA RECORDED, RATIONALE AND METHOD.	125
4.3.2.6. MEASUREMENT SITES.	129
4.3.2.6.1. MoistureMeterSC® AND VapoMeter®.	129
4.3.2.6.2. PODOCONIOSIS STAGING TOOL.	130
<b>4.4. TREATMENT FIDELITY.</b>	<b>131</b>
<b>4.5. DATA COLLECTION AND FOLLOW-UP CLINIC VISITS.</b>	<b>132</b>
<b>4.6. DATA ANALYSIS.</b>	<b>133</b>
4.6.1. MEASURES OF THE RELATIONSHIP BETWEEN NUMBER OF WOUNDS AND NUMBER OF WORK DAYS LOST.	133
4.6.2. OUTCOME MEASURES OF TRANS-EPIDERMAL WATER LOSS, STRATUM CORNEUM HYDRATION, LEG AND FOOT CIRCUMFERENCE AND DERMATOLOGY LIFE QUALITY INDEX.	134
4.6.3. OUTCOME MEASURES OF THE NUMBER OF WORK DAYS LOST DUE TO ADENOLYMPHANGITIS, STAGE OF PODOCONIOSIS, MOSSY CHANGES, LEG ODOUR AND THE NUMBER OF LOWER LEG/FOOT WOUNDS.	134
<b>CHAPTER 5. RESULTS.</b>	<b>136</b>
<b>5.1. OVERVIEW OF RESULTS.</b>	<b>136</b>
5.1.1. STRATIFICATION OF CLINIC, GENDER AND DISEASE SEVERITY .	136
<b>5.2. DEMOGRAPHIC PROFILE OF PARTICIPANTS.</b>	<b>137</b>
5.2.1. STUDY PARTICIPANTS.	137
5.2.2. AGE OF PARTICIPANTS.	138
5.2.3. GENDER OF PARTICIPANTS.	138
5.2.4. OCCUPATION OF PARTICIPANTS	139
5.2.5. TIME TO ONSET OF CLINICAL SIGNS OF PODOCONIOSIS.	139
5.2.6. TYPE OF SHOES WORN.	140
<b>5.3. SKIN BARRIER FUNCTION.</b>	<b>142</b>
5.3.1. TRANS-EPIDERMAL WATER LOSS.	142
5.3.1.1. MEAN TRANS-EPIDERMAL WATER LOSS AT SPECIFIC POINTS ON THE LEG/FOOT OF ALL PARTICIPANTS AT BASELINE.	143
5.3.1.2. TRANS-EPIDERMAL WATER LOSS AT TOP OF LOWER LEGS.	143
5.3.1.3. TRANS-EPIDERMAL WATER LOSS AT MID-POINT ON THE LOWER LEGS.	145
5.3.1.4. TRANS-EPIDERMAL WATER LOSS AT BASE OF LOWER LEGS.	147
5.3.1.5. TRANS-EPIDERMAL WATER LOSS ON THE TOP OF THE FOOT.	149

5.3.2. STRATUM CORNEUM HYDRATION.	151
5.3.2.1. MEAN SC HYDRATION AT DIFFERENT POINTS ON THE LEGS/FEET OF ALL PARTICIPANTS AT BASELINE.	151
5.3.2.2. STRATUM CORNEUM HYDRATION AT TOP OF LOWER LEGS.	151
5.3.2.3. STRATUM CORNEUM HYDRATION AT THE MID-POINT ON LOWER LEGS.	154
5.3.2.4. STRATUM CORNEUM HYDRATION AT BASE OF LOWER LEGS.	156
5.3.2.5. STRATUM CORNEUM HYDRATION ON THE TOP OF FEET.	158
<b>5.4. GENERAL CLINICAL PROFILE OF LEGS/FEET.</b>	<b>160</b>
5.4.1. STAGE OF PODOCONIOSIS.	160
5.4.2. MOSSY SKIN CHANGES.	161
5.4.3. LEG/FOOT ODOUR.	161
5.4.4. NUMBER OF LEG/FOOT WOUNDS.	162
5.4.5. LOWER LEG CIRCUMFERENCE.	163
5.4.6. FOOT CIRCUMFERENCE.	165
5.4.7. NUMBER OF WORK DAYS LOST IN PREVIOUS MONTH DUE TO ADENOLYMPHANGITIS.	166
5.4.8. CORRELATION BETWEEN DAYS LOST DUE TO ADENOLYMPHANGITIS AND NUMBER OF WOUNDS.	170
<b>5.5. QUALITY OF LIFE.</b>	<b>170</b>
<b>CHAPTER 6. DISCUSSION.</b>	<b>172</b>
<b>6.1. OVERVIEW OF RESULTS.</b>	<b>172</b>
<b>6.2. STUDY RESULTS.</b>	<b>173</b>
6.2.1. SOCIAL AND DEMOGRAPHIC PROFILE OF PARTICIPANTS.	174
6.2.1.1. AGE OF PARTICIPANTS.	174
6.2.1.2. OCCUPATION AND GENDER OF PARTICIPANTS.	174
6.2.1.3. TIME FROM ONSET OF CLINICAL SIGNS OF PODOCONIOSIS TO CLINIC ATTENDANCE.	175
6.2.1.4. TYPE OF SHOES WORN.	177
6.2.2. SKIN BARRIER FUNCTION.	180
6.2.2.1. TRANS-EPIDERMAL WATER LOSS.	180
6.2.2.3. STRATUM CORNEUM HYDRATION.	182
6.2.3. GENERAL CLINICAL PROFILE OF LEGS/FEET.	185
6.2.3.1. STAGE OF PODOCONIOSIS.	185
6.2.3.2. MOSSY CHANGES.	185
6.2.3.3. THE NUMBER OF WOUNDS AND ODOUR ON THE LOWER LEGS/FEET.	186
6.2.3.4. DAYS OF WORK LOST DUE TO ADENOLYMPHANGITIS.	187
6.2.3.5. CORRELATION BETWEEN WORK DAYS LOST DUE TO ADENOLYMPHANGITIS, NUMBER OF WOUNDS AND STAGE OF PODOCONIOSIS.	188

6.2.3.6. LEG/FOOT CIRCUMFERENCE.	189
6.2.4. QUALITY OF LIFE.	190
6.2.5. STUDY CHALLENGES AND CHALLENGES OF ENSURING TREATMENT FIDELITY.	191
6.2.5.1. USE OF THE PROBES IN ETHIOPIA TO MEASURE TRANS-EPIDERMAL WATER LOSS AND SC HYDRATION.	192
6.2.5.2. COST OF GLYCERINE.	192
6.2.5.3. DISTANCE AND LANGUAGE	192
6.2.5.4. CLINIC ATTENDANCE AND LITERACY OF PARTICIPANTS.	193
<b>6.3. VALIDITY AND RELIABILITY OF THE STUDY.</b>	<b>196</b>
6.3.1. ACCURACY OF DATA RECORDING.	197
6.3.2. ADHERENCE OF PARTICIPANTS TO TREATMENT REGIME.	197
6.3.3. AMBIENT TEMPERATURE AND HUMIDITY.	198
<b>CHAPTER 7. CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS.</b>	<b>200</b>
<b>7.1. KEY CONCLUSIONS.</b>	<b>200</b>
7.1.1. HYPOTHESIS TESTING.	200
7.1.2. PILOT STUDY.	201
<b>7.2. KEY LIMITATIONS OF STUDY.</b>	<b>202</b>
<b>7.3. SIGNIFICANCE OF FINDINGS AND CONTRIBUTION TO THE FIELD.</b>	<b>204</b>
7.3.1. PRACTICE, RESEARCH AND EDUCATIONAL IMPLICATIONS.	204
<b>7.4. DISSEMINATING THE RESEARCH FINDINGS INTO CLINICAL PRACTICE.</b>	<b>206</b>
<b>7.5. SUMMARY OF MAIN POINTS.</b>	<b>207</b>

## ***TABLES.***

Table 2.1. Studies of the prevalence of podoconiosis in Ethiopia	25
Table 2.2. Differences between podoconiosis and lymphatic filariasis	37
Table 2.3. Current regimens used for treating podoconiosis in APA and Mossy Foot clinics, their rationale and issues	40
Table 2.4. Studies of ethnic differences related to trans-epidermal water loss	72
Table 2.5. Typical composition of soap bars	85
Table 2.6. Comparison of vegetable oils and mineral oil for a series of skin parameters	93
Table 2.7. Potential sensitizers found in emollients	94
Table 2.6. Guidance on the quantities of emollient that should be applied	97
Table 3.1. Pilot study interventions and their rationale	104
Table 3.2. Sites on the outer lower leg	107
Table 3.3. Sequential intervention system for the outer lower legs on sites 1-6.	107
Table 3.4. Summary of changes in trans-epidermal water loss (gm <sup>2</sup> h)	110
Table 3.5. Summary of changes in stratum corneum hydration	111
Table 3.6. Skin hydration - difference in changes between the treatment combination containing glycerine compared to control, soap and water soak.	111
Table 4.1. Experimental group intervention and rationale	119
Table 4.2. Sustainability of products used in control/experimental group	121
Table 4.3. Comparative cost of 3 months treatment for the control/experimental groups in UK pounds	122
Table 4.4. Educational programme of nurse and social worker delivered by principal investigator	123
Table 4.5. Data collected from participants, time, outcome measures, rationale and collection method.	126
Table 4.6. Methods used to improve treatment fidelity	132
Table 4.7. Variables analysed and units of analysis	133
Table 5.1. Number and code number of participants in each clinic by gender, stage of podoconiosis	137
Table 5.2. Mean TEWL at each specific point of leg/foot of all participants at baseline	143
Table 5.3. Trans-epidermal water loss (gm <sup>2</sup> h) at top of lower leg - changes from baseline by side and group at each visit	143
Table 5.4. Trans-epidermal water loss (gm <sup>2</sup> h) at mid-point lower leg - changes over time by side and group	145
Table 5.5. Trans-epidermal water loss (gm <sup>2</sup> h) at base of lower leg - changes over time by side and group	147
Table 5.6. Trans-epidermal water loss (gm <sup>2</sup> h) at top of feet - changes over time by side and group	149
Table 5.7. Mean difference in stratum corneum hydration at specific points on the leg/foot of all participants at baseline	151
Table 5.8. Stratum corneum hydration at top of lower legs - changes over time by side and group	152
Table 5.9. Stratum corneum hydration mid-point lower leg - changes over time by side and group	154
Table 5.10. Stratum corneum hydration at base of lower leg - changes over time by side and group	156
Table 5.11. Stratum corneum hydration on top of the feet - change over time by side and group	158

Table 5.12. Stage of podoconiosis in each leg of all participants at baseline and 4 <sup>th</sup> visit	
Table 5.13. Largest lower leg circumference in both legs by group and leg from baseline	163
Table 5.14. Largest foot circumference - changes from baseline by side and group	165
Table 5.15. Mean number of days work lost in previous month by group and side at each visit due to adenolymphangitis by group	169

## ***FIGURES.***

Figure 1.1. Countries where podoconiosis is endemic or reported	14
Figure 2.1. Development and cycle of progression of lymphoedema in podoconiosis	31
Figure 2.2. The Dry Skin Cycle	77
Figure 3.1. Individual plots of trans-epidermal water loss	112
Figure 3.2. Individual plots of stratum corneum hydration levels	113
Figure 5.1. Difference in age of participants between groups	138
Figure 5.2. Occupation of participants by group	139
Figures 5.3. and 5.4. Type of shoe worn by each group in the previous week at baseline and fourth visit	141
Figure 5.5. Change from baseline in mean trans-epidermal water loss at the top of the lower legs by side and group	144
Figure 5.6. Change from baseline in mean trans-epidermal water loss at mid-point lower legs by side and group	146
Figure 5.7. Change from baseline in mean trans-epidermal water loss at the base of lower legs by side and group	148
Figure 5.8. Change from baseline in mean trans-epidermal water loss at the top of the feet by side and group	150
Figure 5.9. Change from baseline in mean SC hydration at the top of the lower leg by side and group	153
Figure 5.10. Change from baseline in mean SC hydration at mid-point lower leg by side and group	155
Figure 5.11. Change from baseline in mean SC hydration at base of lower leg by side and group	157
Figure 5.12. Change from baseline in mean SC hydration on top of feet by group and side	159
Figure 5.13. Change in mean lower leg circumference between side and group	164
Figure 5.14. Change in mean foot circumference by side and group	166
Figures 5.15., Figure 5.16. Number of work days lost in previous month due to adenolymphangitis by each group at baseline	168

## **PHOTOGRAPHS.**

Photograph 2.1. An Ethiopian farmer ploughing barefoot	21
Photograph 2.2. Patient with podoconiosis exhibiting foot/leg oedema and hyperkeratosis	34
Photograph 2.3. Feet of podoconiosis patient displaying oedema of the foot, mossy changes, fibrosis and fused toes	34
Photograph 2.4. Feet of patients presenting with oedema, hyperkeratosis, nodules, fused toes, mossy changes and ulceration due to ill-fitting shoes	35
Photograph 2.5. Podoconiosis patient exhibiting oedema, fused toes, hyperkeratotic changes, deep fissures, mossy changes, fungal infection, inflammation and ulceration due to ill fitting shoes	35
Photographs 2.6, 2.7 and 2.8. Examples of the sandals worn by patients attending APA clinics	56
Photograph 4.1. Clinic nurse measuring the SC hydration of a participant with a <i>MoistureMeterSC</i> <sup>®</sup> after 3 months treatment	131

## **REFERENCES**

209

## **APPENDICES**

229

1. Literature search.	229
2. Probes used to measure skin hydration and trans-epidermal water loss.	230
3. Studies of the effects of glycerol (glycerine) on human skin. A summary of experimental data and clinical trials.	231
4. Podoconiosis staging sheet (podoconiosis-endemic areas).	235
5. Analysis of soap and Vaseline®.	237
6. Podoconiosis stigma score.	239
7. Pilot Ethics application.	243
8. Pilot - checklist for reviewers.	250
9. Approval for pilot study.	253
10. Care home owner consent.	254
11. Participant letter.	255
12. Participant Information Sheet.	256
13. Pilot Consent Form.	258
14. Pilot GP letter.	259
15. Pilot study data collection forms.	259
16. Consort (2010) checklist of information to include when reporting a randomised trial.	262
16B Consort Flow Chart.	264
17. E mail from Delfin Instruments.	265
18. Research ethics application.	266
19. Reviewer checklist for main research ethics application.	276
20. Research ethics approval.	279
21. Data management plan.	280
22. Ethical approval Sodo University, Ethiopia.	295
23. Protocol for using probes.	296
24. Dermatology life quality index (DLQI).	298
24B. DLQI instructions for use.	299
25. E mails requesting and approving use of DLQ.	301
26. Participant information sheet.	302

27. Consent form.	304
28. Coding for main study.	305
29. Experimental group instructions.	307
30. Data collection forms for main research.	308
31. Abbreviations.	312
32. Glossary.	312

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## **ABSTRACT.**

Podoconiosis is a neglected tropical skin disease caused by a fault in skin barrier function (SBF) combined with a genetic predisposition. Irritant minerals and pathogens entering breaches in plantar skin cause an inflammatory reaction and lower leg lymphoedema. This has a considerable negative impact on the quality of life and economic status of some of the poorest people in 20 countries. Podoconiosis is preventable and treatable but not curable.

No previous pre/post controlled intervention studies on skin treatment for the disease have been published. The aim of this randomised control trial (RCT) was to evaluate the effectiveness of a low-cost evidence-based skin care intervention to improve the SBF in the legs/feet and enhance disease related quality of life. A pilot study (n=10) indicated that adding 2% glycerine to the existing skin management regime used in Ethiopia could have a positive effect on stratum corneum (SC) hydration levels and trans-epidermal water loss (TEWL). The study recruited participants from two Ethiopian clinics (n=193). The control group used the existing treatment regime: washing legs/feet with soap, soaking in 6 litres of water with disinfectant added and applying *Vaseline*<sup>®</sup>. The experimental group added a 2% dilution of glycerine to 1/6 of the amount of soaking water and 0.0045% less disinfectant. After 3 months the experimental intervention had a highly significant positive effect on TEWL ( $p < 0.001$ ) and SC hydration ( $p < 0.002$ ) compared to the control. The reduction in foot circumference was highly significant ( $p < 0.001$ ). There was no significant group difference in Dermatology Life Quality Index ( $p = 0.907$ ).

The study indicates the very positive effect on SBF of adding 2% glycerine and less disinfectant to the current treatment. This finding offers a significant contribution to the body of knowledge on the management of the disease. The addition of 2% glycerine to treatment regimens may also have positive effects on other skin diseases with compromised SBF.

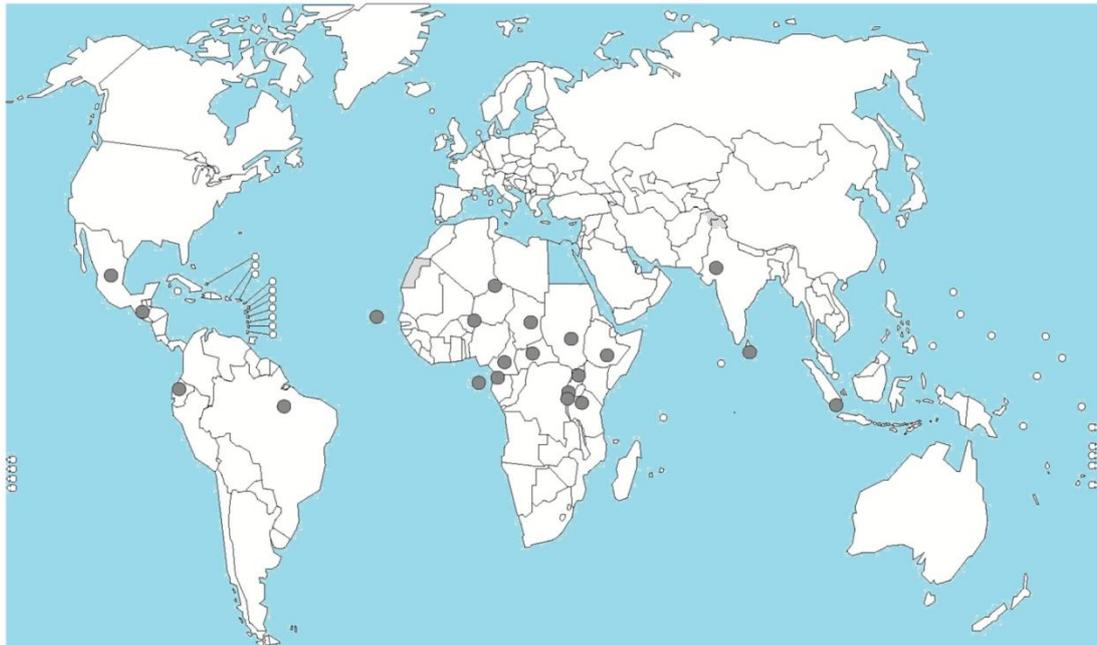
# *CHAPTER 1. INTRODUCTION.*

As a nurse I have always had a particular interest in wounds and skin. In my role as a district nurse assessing and dressing various wounds was significant part of my job. Prior to management posts I was, at one time Head of Tissue Viability Services in my county. In that post I completed a Master of Philosophy degree on the prevention of leg ulcer recurrence in the community. Following a holiday in Tanzania and learning about health care in Africa I undertook a course at the London School of Hygiene and Tropical Medicine. I then worked in a leprosy hospital in Ethiopia for a short while. This was followed by working for 3 months a year over several years as a voluntary nurse in the trauma and surgical ward of a rural hospital in Uganda. Most of my work was dealing with large neglected and infected wounds. I also taught wound care. During this time I became interested in undertaking a research project on skin disease in a resource-poor country and was fortunate in finding a University and a sponsor for the research. After a further trip to Ethiopia and witnessing the mental and physical suffering caused by podoconiosis I became intent in finding out if the current treatment provided for those with this devastating disease was optimum. The following section indicates the significance of this podoconiosis study and its organisation.

## ***1.1. SIGNIFICANCE OF THE STUDY.***

Podoconiosis was first recognised as a type of non-filarial elephantiasis in the 1930's (Price 1976a). It is now acknowledged by the World Health Organisation as a neglected tropical disease affecting millions of the poorest people in the world (Davey, Bockarie et al. 2012). It is not contagious or curable but it is treatable. Podoconiosis is endemic or has been reported in more than 20 countries where areas of high rainfall and high altitude coexist with volcanic soil and poverty including: Mexico, Guatemala, Costa Rica, Brazil, Honduras, El Salvador, Nicaragua, Panama, Columbia, Ecuador, Venezuela, India, Sri Lanka, Indonesia, Cape Verde, Equatorial Guinea, Sao Tome and Principe, Kenya, Ruanda, Burundi, Tanzania, Uganda, Sudan and Ethiopia (Figure1.1).

**Figure 1.1. Countries where podoconiosis is endemic or reported (Deribe, Tomczyk et al. 2013).**



Renewed interest in the disease began in 2002 when Dr. Gail Davey, a UK consultant dermatologist led a multi-disciplinary team into the disease and its impact in Ethiopia (Deribe, Tomczyk et al. 2013). Subsequently most of the research on podoconiosis has been conducted in Ethiopia. The disease is caused by a fault in skin barrier function (SBF). Particles of minerals found in alkaline, volcanic soil and pathogens enter via breaches in plantar skin causing an inflammatory reaction; those affected by the disease are mainly those who walk bare foot or with shoes providing insufficient protection against soil.

The inflammatory reaction caused by the minerals and pathogens entering skin results in skin swelling with subsequent damage to the superficial lymphatics. This causes lymphoedema of the lower leg, venous hypertension and further capillary leakage. Without intervention the condition deteriorates. Recent research has indicated that a specific cytokine and oxidative stress may have a role in the disease (Addisu, El-Metwally et al. 2010). Skin changes occur such as dryness, thickening, deposits of adipose tissue, and nodules. Fungal infections which are often malodorous are common; this odour plus the visible changes in the lower limbs results in widespread social stigma. The stigma is compounded by a general lack of

knowledge about the disease among patients, health workers and the general population.

Currently most outreach clinics treating those with podoconiosis in Ethiopia are funded by non-government organisations (NGOs) such as Action on Podoconiosis and Mossy Foot UK (Action on Podoconiosis Association 2014, Mossy Foot UK 2015). At the clinics patients are initially assessed and data collected including the severity of the disease in terms of the disease stage and lower limb circumference. Patients are taught the causes and treatment of the disease. Current treatment consists of a daily programme of leg/foot hygiene. It involves washing the legs/feet in soapy water, soaking them in water with dilute bleach (sodium hypochlorite, NaOCl) added as a disinfectant, drying, applying an emollient and if required an antifungal cream. Patients are given a month's supply of soap, emollient, NaOCl and if necessary an antifungal. Patients return to the clinic monthly to collect their supplies and to enable clinic staff to monitor their disease progression. A pair of custom made leather shoes is supplied to those with grossly swollen feet by both Mossy Foot and Action on Podoconiosis.

The International Podoconiosis Initiative launched in March 2012 aims at bringing together all those involved in the prevention and treatment of podoconiosis (Davey, Bockarie et al. 2012). It focused attention on the disease resulting in increased research activity. In February 2012 the NGO Action on Podoconiosis Association (APA) agreed a 3 year project for Southern Ethiopia (Action on Podoconiosis Association 2012). The aims included developing better treatment regimens. The PI linked with APA to undertake this research which, although funded by Procter and Gamble was independent.

The current skin regimen used in the clinics is effective at improving the stage of the disease and lower leg circumference (Sikorski, Ashine et al. 2010). The effect on skin barrier function has however, not been formally evaluated. To discover the effectiveness of each of the components currently used to manage the disease the published literature was searched. Searches were also undertaken to identify the most effective emollient

required to improve SBF. The emollient needed to be clinically effective, low cost, skin safe and readily available in Ethiopia.

## **1.2. ORGANISATION OF THE THESIS.**

The thesis is divided into six further chapters as follows:

Chapter 2 reviews the research on skin, skin disease, treatments used to clean and improve the condition of skin. The current research on the causes of podoconiosis, its prevalence and its profound affects both socially and economically are examined. The current treatments used are then discussed.

Chapter 3 focuses on the pilot study. This took place in the UK on a small number of participants with xerosis of their lower legs using the current skin care materials used in podoconiosis clinics plus a 2% dilution of glycerine. It provided evidence for the use of glycerine in the research study and statistical power calculations for the main study.

Chapter 4 details the research design. This includes the study population, recruitment of participants, the interventions used, staff educational programme and data recorded. The methods used for the data analysis are also detailed.

Chapter 5 details the results of the analysis. The demographic profile of the participants is reported including age, gender, occupation, time that they have had the disease and type of shoe worn. The results over time of the analysis of skin barrier function primarily trans-epidermal loss and stratum corneum hydration at the specific points on the lower leg/foot are then presented. This is followed by the results over time of the secondary analysis of disease stage, mossy changes, presence of odour, number of leg/foot wounds, lower leg/foot circumference number of work days lost due to ADL, the relationship between the number of wounds and days lost due to ADL and the quality of life of participants.

Chapter 6 introduces and discusses the study results. These are interpreted and compared with other published studies. The validity and reliability of the study is also discussed.

Chapter 7 provides the key conclusions of the pilot study and the randomised control trial (RCT) which are summarised. Limitations and

recommendations from the study are identified. Consideration is given to how the findings will be disseminated and the implications for education, research and clinical practice.

# ***CHAPTER 2. LITERATURE REVIEW.***

## ***2.1. INTRODUCTION.***

This chapter is a focused review of the published literature. The literature search strategy is presented in Appendix 1. The purpose of this was to review previous relevant studies. The section provides a broad overview of the impact of skin diseases in resource-poor countries. Next the current research on the skin disease podoconiosis is presented including its nature, prevalence, diagnosis, stages of the disease and the effects. The similarities and differences between lymphatic filariasis and podoconiosis are then discussed. This is followed by sections on the current knowledge of podoconiosis prevention, current treatment, economic consequences, and psycho-social impact. The challenges of providing skin care in resource-poor countries are presented next.

Skin barrier function (SBF) is the most important factor in podoconiosis; because of this a review of the current knowledge of SBF is then presented and discussed. This includes related ethnic and gender issues, the effects of skin diseases on SBF and strategies required for maintaining a healthy SBF. The associated psychological stress and dermatology quality of life impact is also discussed. Finally the key points of the literature review are summarised and gaps in knowledge regarding skin treatments for those with podoconiosis identified.

Podoconiosis is one of many skin diseases which occur in resource-poor countries. The problem and significance of these diseases are discussed next. The section is included in order to place podoconiosis in a global context.

## ***2.2. SKIN DISEASE IN RESOURCE-POOR COUNTRIES.***

Skin disease represents one of the commonest causes of morbidity in resource-poor countries but there is minimal knowledge concerning the

dermatological needs of their populations. It is estimated that approximately 3 billion people living in the rural areas of 127 resource-poor countries are denied the most basic skin care consisting of washing with soapy water and drying (Hay, Fuller 2011). This is due to poverty, poor and often overcrowded living conditions and the difficulty obtaining water. Skin disease places a huge burden on health services; it may cause loss of work time with a subsequent loss of income and can also result in social stigma and a deteriorating quality of life. As well as being prone to the general skin diseases afflicting people in the developed world those in the resource-poor countries are also liable to specific tropical skin diseases. The situation is exacerbated by a general lack of understanding regarding skin disease and a shortage of trained health care professionals able to identify and treat skin conditions.

The World Health Organisation published their first report on 'Neglected Tropical Diseases' in 2010. These are a group of chronic disabling and disfiguring conditions mainly occurring in conditions of extreme poverty among the rural poor (WHO 2010). Over 50% of the 17 diseases identified in the report affect the skin. They include Buruli ulcer, Chagas disease (American trypanosomiasis), leishmaniasis, Hansen's disease (leprosy), lymphatic filariasis, onchocerciasis, trachoma and yaws. All these diseases cause immense suffering but do not attract the level of funding given to AIDS, tuberculosis and malaria. This is because they generally affect those living in poverty in remote areas. They are often treatable but social stigma, lack of access to health care facilities and a lack of financial resources results in those with skin disease not seeking treatment. This leads to a lack of prevalence data (WHO 2007). Due to the inaccurate data and because there is frequently disability but little mortality in those with skin conditions they are not prioritized within health systems. For example an Ethiopian study of all 827 households in two communities stated the numbers with self-reported skin disease was between 47% and 59%. A subsequent examination by dermatologists of randomly selected households reported far greater numbers. They stated that 67% of householders reporting no disease had in fact significant skin disease (Figuroa, Fuller et al. 1998). This lack of accurate information results in a lack of prominence at national

and international level. Podoconiosis is a skin disease which has only comparatively recently become prominent and it is the focus of the next section. Its nature, significance and prevalence are discussed followed by a section on its diagnosis, its effects and management, its prevention and the knowledge of health workers, patients and communities on the disease. The psycho-social impact of the disease and its effect on quality of life are then reviewed.

### **2.3. PODOCONIOSIS.**

Podoconiosis is a non-infectious form of elephantiasis (Molla, Le Blond et al. 2013). It is an entirely preventable disease which is sometimes called 'mossy foot' because of the visual presentation of moss like eruptions on the skin of the feet. It was common in many countries in past centuries including France, Ireland and Scotland (Price 1990). Due to improved hygiene levels and the wearing of shoes it is no longer found in these areas but still exists in some areas of tropical Africa, Central America, and northern India. These are areas where red volcanic clay soils coexist with high altitude (above 1,000 m), high rainfall (above 1,000 mm annually) and low income (Price, Bailey 1984). The alkaline clay contains irritant minerals such as silica. Because of poverty or for traditional reasons farmers and other occupations in these areas often do not wear shoes or wear those that provide little protection against the mud in the rainy season and dust in the dry season (Photograph 2.1).

**Photograph 2.1. An Ethiopian farmer ploughing barefoot.**



As a result the feet to become dry, cracked and fissured allowing soil particles and bacteria to enter the skin. There have been a number of recent initiatives in the field of podoconiosis. These and the nature and significance of podoconiosis are discussed in the next section. This is followed by a discussion on the prevalence of the disease.

### **2.3.1. NATURE AND SIGNIFICANCE OF PODOCONIOSIS.**

The word podoconiosis comes from the Greek word *podos* (foot) and *kunos* (dust/earth). It was identified relatively recently by Ernest Price, a doctor who in the 1970s realized that the earlier diagnosis of infectious elephantiasis was incorrect. He recognised the cause as the exposure of bare feet to mineral particles in irritant red clay soils derived from volcanic deposits (Price 1976a). A published review identified 19 published peer reviewed research articles with podoconiosis as their main topic in the period 1970 to 1990 and 10 from 1990 to 2007 (Davey, Tekola et al. 2007). A further 35 peer reviewed published articles were identified between 2007 and December 2014 with podoconiosis as the main topic. The 19 articles

published in 2015 up to 15<sup>th</sup> December which included information about podoconiosis indicate a renewed interest in the disease.

In recent years many NGOs have become involved in helping those with the disease including the Action on Podoconiosis Association, Footwork and Mossy Foot UK (Action on Podoconiosis Association 2014, Footwork 2015, Mossy Foot UK 2015). In 2011 podoconiosis was included in the World Health Organisation (WHO) list of Neglected Tropical Diseases (Davey, Bockarie et al. 2012). In late 2011 the first General Assembly of the Ethiopian National Podoconiosis Action Network was held. This brought together researchers, policy makers, clinicians and groups providing care for those with podoconiosis. The network aims to share expertise and put research into practice. It also aims to provide access to treatment for all patients and prevent new cases of the disease via the provision of adequately protective shoes. The Action on Podoconiosis Association (APA) an NGO was established in 2012. It aimed at creating treatment sites in three regions, treating 38,100 patients, providing vocational training, providing micro-credit (small loans to allow business start-ups), increasing awareness and transferring the projects to local government at the end of the 3 years. One of the key activities to ensure these aims were met is 'to actively network and collaborate with national and international partners in scientific research (e.g., identifying gene environment interaction, the role of SBF) and the development of new and better treatment regimes (including low cost water purifying technology and alternative cheaper emollients, etc.)' (Action on Podoconiosis Association 2012). In 2012 due to the progress of podoconiosis research in the previous 5 years 'Footwork' the International Podoconiosis Initiative was launched aimed at bringing together all those involved in the prevention and treatment of podoconiosis (Davey, Bockarie et al. 2012). These initiatives have focused world attention on the disease resulting in increased research activity. Discovering the prevalence of podoconiosis is of key importance as it is vital to know the size of the problem in order to focus finite resources. This is discussed next.

### **2.3.2. PREVALENCE OF PODOCONIOSIS.**

It was estimated that in 2010, 34.9 million people (43.8%) of Ethiopia's national population lived in areas environmentally suitable for the occurrence of podoconiosis (Deribe, Cano et al. 2015). Three million people are estimated to have the disease and 19 million to be at risk (22-24% of the population) (Yimer, Hailu et al. 2015).

Three published prevalence studies were found which were undertaken outside Ethiopia. The first was in Rwanda and Burundi, areas of high rainfall, high altitude and volcanic soil where 26,606 adults were observed in 23 markets, nine of which were in Burundi. Of the 264 patients seen in clinics 131 were in Burundi and the remainder in Rwanda. A further 77 adults were seen while travelling. Prevalence rates were 0.6% in Rwanda and 10% in Burundi (Price 1976b). The second study was in Mount Elgon, Uganda an area of high altitude (over 1500 metres above sea level), volcanic soil and the absence of filarial infection. The overall prevalence in three villages was 4.5% with prevalence in those aged over 20 years of age of 8.2% (Opana, Simonsen et al. 2001). The third was a cross sectional study undertaken in the highland area of north western Cameroon, an area with high annual rainfall. The study reported that 66 (8.1%) of 843 participants examined had lymphoedema of the lower limb. Tests for microfilaria on the blood of 792 of these participants were negative, indicating that the lymphoedema was of non-filarial origin. Due to the high rainfall and high altitude of the area the disease was presumed to be podoconiosis (Wanji, Tendongfor et al. 2008).

The World Health Organisation states that population-based surveys imply a prevalence of 5-10% in barefoot populations living on irritant soil (WHO 2012). But, obtaining data on the numbers of those with skin disease is very difficult due to a number of factors. Firstly there is a general lack of knowledge in the community as well as a lack of qualified staff able to identify the different skin diseases. Secondly the distances involved travelling to health care services which are mostly on foot, and are often long and difficult because of a lack of roads. Finally due to poverty there is a lack of money to pay for diagnosis and treatment (Hay, Fuller 2011). An

Ethiopian study reported that only 15% of those identified by a health care worker with podoconiosis had received any treatment. The majority (446) of those identified were from high or medium endemic areas (n=460) (Molla, Le Blond et al. 2013). Therefore prevalence data are probably considerably under-estimated. Studies of the prevalence of podoconiosis in Ethiopia are reported next. These include the age and gender of those affected.

#### *2.3.2.1. PREVALENCE OF PODOCONIOSIS IN ETHIOPIA, PATIENT'S AGE AND GENDER.*

Eleven published prevalence studies were undertaken 1969-2013. The highest prevalence was 9.1% (Kloos, Bedri Kello et al. 1992) and the lowest an average of 2.13% (Oomen 1969). Four of the six studies where gender was recorded noted more females had the disease compared to males. Details are in Table 2.1.

**Table 2.1. Studies of the prevalence of podoconiosis in Ethiopia.**

Area	Population	Prevalence	Age (years)	Gender	Study authors
Ethiopian markets	Attendees at 56 markets	0.42%-3.73% Average 2.13%	-	-	(Oomen 1969).
Wollamo District, Southern Ethiopia	Attendees at 5 markets	5.38%	-	-	(Oomen 1969).
Nation-wide in 14 provinces	115 rural schools	2.77%	-	-	(Price 1974).
Ocholo village, Southern Ethiopia	Village long term residents	5.1%	-	-	(Mengistu, Humber et al. 1987).
Ilubabor, Western Ethiopia	Village long-term residents n=222	9.1%	11- >60	Higher prevalence in males (no details)	(Kloos, Bedri Kello et al. 1992).
Pawe, Northwest Ethiopia	3 villages n =1,900	7%	-	-	(Birrie, Balsha et al. 1997).
Wolaita region, Southern Ethiopia	Population based survey of 4120 households n=33,678 from an estimated population 1.6 million	5.4%	64% 16-64	Ratio of 1. males to 0.98 female (reflected the gender ratio of the region)	(Destas, Ashine et al. 2003).
Gulliso District, Western Ethiopia	Household survey of 26 villages. n=1,935	2.8%	90.3% 15-64 Mean age 40.7	Ratio of 1male to 2.6 females	(Alemu, Tekola Ayele et al. 2011).
Midaken District, Central Ethiopia	Two villages n=5,590	7.4%	Average age of onset 25.8	1:1	(Getala, Fasil-Tekola et al. 2012).
East and West Gojam regions, Northern Ethiopia	Survey of 17,553 households in 20 kebeles in two districts with 51,017 of population >15 years of age. Structured interview of 1,704 participants with podoconiosis.	3.3%	87% in economically active age group 15-64	Podoconiosis patients interviewed (n=1,319), 649 females, 670 males	(Molla, Tomczyk et al. 2012a).
Bedele Zuria district, Western Ethiopia	House to house survey of 2285 households in 5 randomly selected villages	5.6%	76% in economically active age group 15-64	6.6% females, 4.7% males	(Tekola Ayele, Alemu et al. 2013).
Survey of 659 of the 817 <i>worda</i> (districts) in Ethiopia	Cross sectional community based study using cluster sampling. Identified 5,253 people with podoconiosis	4%	85.8% in economically active age group 15-65	58% females, 42% males	(Deribe, Brooker et al. 2015b).

There is conflicting evidence on whether or not podoconiosis is gender related (Table 2.1). In the Destas study 10% of women were not willing to be examined because of modesty resulting in an under-estimate of the numbers of women affected (Destas, Ashine et al. 2003). This may also have been a factor in other prevalence studies.

The low prevalence of 2.8% in the Gulliso district was thought to be due to only those with overtly swollen legs being reported by the head of the household. The stigma surrounding the disease may also have prevented patients identifying themselves (Alemu, Tekola Ayele et al. 2011). The different study results may also be due to different shoe wearing practices or to other as yet unknown factors. All the major community-based studies reported the onset of symptoms before 20 years of age with a progressive increase in podoconiosis prevalence up to 60 years of age. The diagnosis of podoconiosis including the differential diagnosis and various clinical stages of the disease are discussed next.

### ***2.3.3. DIAGNOSIS AND STAGES OF PODOCONIOSIS.***

The diagnosis of podoconiosis is based on the location, history, clinical findings and the absence of microfilaria on an antigen immunological card test. The disease starts in the foot and progresses up the leg to the knee rarely involving the groin. This helps to differentiate podoconiosis from lymphatic filariasis. It is also distinguishable from the lymphoedema found in leprosy by the presence of sensation in the feet, the lack of thickened nerves and involvement of the hands (Davey, Newport 2007). Common symptoms in the early stages of the disease are:

1. Intermittent intense burning or itching of the one lower leg/foot at night. This may follow a long walk and/or alcohol ingestion. Pain extending into the thigh possibly associated with tender femoral lymph nodes or fever (ADL). The attacks resolve spontaneously or after a few days of rest and limb elevation. Subsequent episodes typically affect the same limb which gradually increases in size. Onset in the other leg may not occur for months or years.
2. Itching of the dorsum of the foot with continuous or intermittent itching often over first two web spaces. Repeated scratching leads to skin thickening and

may also cause skin breaches allowing entry of pathogens causing secondary infection.

3. Knocking together of the big toes during walking due to spreading of the forefoot is an early sign of foot lymphoedema (Fuller 2013).

In advanced disease there is soft fluid ('water bag') or hard fibrotic (leathery) swelling often associated with multiple hard skin nodules. The patient's legs/feet are often malodorous because of infected lesions from trauma and fungal infections between the toes and in skin folds.

In order to determine disease severity a staging system is used. This has been adapted from the seven stage system which was developed for use on those with filarial lymphoedema (Dreyer, Addis et al. 2002). Because its use in those with podoconiosis was found to be inaccurate a simpler five stage system was developed specifically for those with podoconiosis (Tekola, Ayele et al. 2008). Four field tests were performed with 119-146 patients examined during each field test. Between field tests the staging system was reviewed by two international experts. Stage 1 is identified as foot swelling which is reversible during the night with progression increasing at stages 2, 3 and 4. At stage 5 there is joint fixation of ankle or toes and swelling at any place in the foot or leg. The staging also allows for the recording of mossy changes and the greatest below knee circumference. The final version of the staging system which has good inter-observer agreement and repeatability is presented in Appendix 4.

A study of skin tissue examined ten nodular specimens from each of ten people with stages 2-5 of the disease (Wendemagegn, Tirumalae et al. 2015). Five of the tissue samples were from the dorsum of the foot, four from the dorsum of the toe and one from the plantar surface of the toe. All showed thickening of the skin, warty lesions and papillomatosis with collagen bundles thickened and elastic fibres drastically reduced. Eccrine ducts were hyperplastic (increased amount of organic tissue) with hyperkeratotic nodules or plaques involving the extremities of eccrine origin and miliaria (sweat rash). The blood vessels were dilated and enlarged and often sclerotic lymphatics were reduced but generally not dilated.

The inflammation which occurs in podoconiosis as a result of minerals and pathogens entering the skin affects both the skin and the lymphatic system. The impact of this is discussed in the next section.

#### **2.3.4. EFFECTS OF PODOCONIOSIS ON THE SKIN AND LYMPHATIC SYSTEM.**

The minerals smectite, mica and quartz (crystalline silica) within the soil are associated with areas of podoconiosis prevalence (Molla, Wardrop et al. 2014). Silica particles have been found in the femoral lymph nodes of those with podoconiosis as well as those who do not have the disease (Price 1977, Price, Bailey 1984, Price, Henderson 1978). Silica and bacteria are both particles which can enter skin through defects in the SBF caused by dry cracked skin or trauma. The entry of these foreign bodies causes macrophages and neutrophils to be activated as a defence mechanism. T lymphocytes attack these antigens directly and release chemicals, known as cytokines which control the immune response. Some cytokines can increase up to 1,000-fold during trauma or infection (Cannon 2000). Silica particles are also known to interact with the cell membranes of many mammalian cells, including erythrocytes causing haemolysis (Gerashchenko, Gun'ko et al. 2002, Thomassen, Rabolli et al. 2011, Pavan, Tomatis et al. 2013). As part of the body's defence mechanism the damaged cells release chemicals including histamine, bradykinin, and prostaglandins. Histamine is produced by basophils and mast cells found in connective tissue. Mast cells are found in close vicinity to epidermal and hair follicle keratinocytes, blood vessels and sensory nerves (Metz, Ständer 2010). They are concentrated in areas that interface with the external environment and are especially numerous at sites of potential injury such as the feet (Prussin, Metcalfe 2003). Histamine increases the permeability of the capillaries to white blood cells and some proteins allowing them to move into the tissues and engage with pathogens. This increased permeability also allows fluid to leak into the tissues causes swelling and pain. The swelling disrupts the normal lymph flow in the epidermis which also collects in the tissues causing further swelling. Some of this lymph finds alternative deeper lymph pathways in the dermis which eventually connect to larger lymph vessels. This secondary system however; will fail if overloaded and protein rich interstitial fluids which are unable to

drain cause feet and legs to swell with fluid even further (Vaqas, Ryan 2001). The subsequent rise in interstitial osmotic pressure pulls more fluid from the capillaries into the tissues resulting in lymphoedema. The high protein content in the lymphatic fluid in the tissues leads to trophic skin changes. These include loss of hair, dryness, hyperkeratosis (thickening of the skin), deposits of adipose tissue, and papillomatiasis (nodules containing dilated lymphatics and fibrous tissue) (Lymphoedema Framework 2006).

Venous hypertension is present in those with lymphoedema and inflammatory skin disease due to infections (Vaqas, Ryan 2001). The swollen feet/legs in those with podoconiosis restrict ankle movements and walking may become difficult. This exacerbates the problem of venous hypertension because normally veins in the legs are emptied during normal walking. During normal walking dorsi-flexion and plantar flexion occurs causing the muscles in the legs to compress. This pushes blood upwards from the leg/feet back towards the heart reducing venous pressure. When this mechanism is compromised, high volumes of blood remain in the veins causing further venous hypertension and swelling (Vaqas, Ryan 2003).

Standard treatment for lymphoedema in the developed world is likely to consist of compression hosiery with advice on skin care and exercise (Preston, Seers et al. 2008). Lymphatic massage is another therapy that may be used. In the treatment of lymphoedema in podoconiosis Ryan suggests that 'restoring SBF and venous function is the top priority and lymphatic massage and/or pressure bandaging is probably not that important in the early stages' (Ryan 2012). To ensure their safe application pressure bandages require expertise and the exclusion of hypertension and arterial disease. As neither of these is routinely assessed in podoconiosis clinics, pressure bandages are not routinely used. They are also expensive and require frequent washing and replacing on a regular basis.

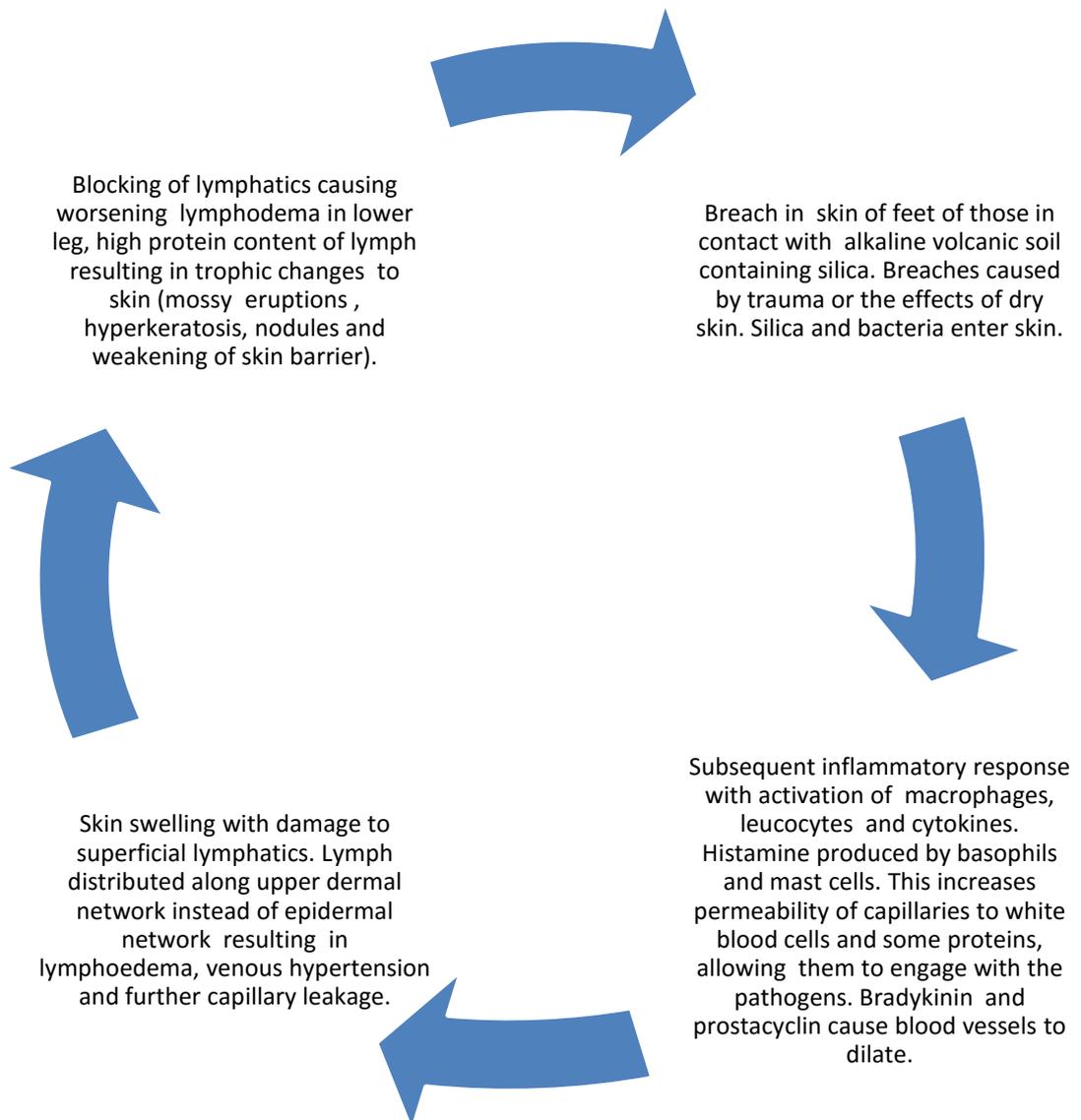
Lymphoedema results in enlarged feet and legs so measuring leg/foot circumference is an important method of determining disease severity. In a study in Ethiopia the leg/foot circumference of podoconiosis patients (n=53) was quantitatively measured and compared to controls (n=16) (Ferguson,

Yeshanehe et al. 2013). The average foot/leg ratio of those with podoconiosis was 0.89 and that of the controls 0.75. The foot/leg ratio of those with podoconiosis compared to controls was 1.19, 95% CI (1.11 to 1.28),  $p=0.001$ . This indicated a significant increase in the ratio of the mean foot/leg circumference of those with podoconiosis compared with controls. Essentially those with podoconiosis had very swollen feet compared with the size of the rest of their lower leg when compared with the control group. The low numbers in the control arm of the study may have affected results.

Foot/toe oedema causes the toes to be in very close proximity and difficult to move. The areas between the toes, the tightly packed nodules and the skin folds which are often present create niches which provide the warm, wet conditions where micro-organisms especially fungi and yeasts can thrive. Without attention to hygiene, local infections and/or cellulitis may result with consequential further oedema and exacerbation of the disease. In Tigray, Northern Ethiopia 14 males and 4 females (mean age 42 years) with podoconiosis were observed over a five years period. On presentation six of these (1/3) had superimposed bacterial and fungal infections ( $n=18$ ) (Morrone, Padovese et al. 2011). A further northern Ethiopian household survey reported the presence of open wounds in at least one leg in 53% of patients ( $n= 1319$ ) (Molla, Tomczyk et al. 2012a). No specific details on the definition of an 'open wound' the sites or extent were given. In a further recent study of patients reported lost to follow-up, 34 (17.8%) of participants had wounds on their feet at the time of interview ( $n=191$ ) (Campion, Tamiru et al. 2015).

Scarification marks have been frequently noted at the Mossy Foot clinics in Sodo, Southern Ethiopia (Ryan, Fuller et al. 2011). These are the result of traditional healers cutting the skin to let the 'badness' out. This cutting causes damage to the superficial lymphatic system and may lead to infection and disease progression. The progression of lymphoedema in podoconiosis is illustrated in Figure 2.1.

**Figure 2.1. Development and cycle of progression of lymphoedema in podoconiosis.**



Without therapeutic intervention this cycle is unrelenting with increasing lymphoedema and skin changes. New research evidence suggests that podoconiosis is the result of a genetically determined abnormal inflammatory reaction (WHO 2012). In the study molecular pathogenetic events were explored in 50 patients with early clinical stage podoconiosis and 43 patients with advanced stage disease. They were compared with 35 local healthy controls (Addisu, El-Metwally et al. 2010). Stages of the disease were identified using the 5 stage system (Tekola Ayele *et al.* 2008). Compared with healthy controls, patients with early stage disease showed higher mean levels of oxidative stress ( $p < 0.01$ ) and lower mean concentrations of transforming growth factor beta 1 (TGF- $\beta$ 1) ( $p < 0.001$ ). Mean levels of TGF-

$\beta$ 1 were even lower among patients with advanced stage disease ( $p < 0.001$ ). Mean total antioxidant levels were also significantly lower among patients with advanced disease than either other group ( $p < 0.001$ ). Oxidative stress is the name given to the cumulative results of significant damage to cell structures, such as lipids, proteins and DNA by free radicals (Devasagayam, Tilak et al. 2004). Some anti-oxidants are produced by the body (anti-oxidant enzymes) while others are obtained from the diet (Vitamins E, C and  $\beta$ carotene). The study suggests that the development of podoconiosis is due to a faulty immune system and that TGF- $\beta$ 1 may have a pathogenetic role in both early (stages 1-3) and late stage disease (stages 4-5) with oxidative stress having a lesser role in early stages of the disease. TGF- $\beta$ 1 which is secreted by most leucocytes is a polypeptide member of the TGF family of cytokines. It plays an important role in controlling the immune system and a large role in the control of autoimmunity (Jin, Almehed et al. 2012).

A later genome-wide association study in southern Ethiopia of 194 patients with podoconiosis and 203 controls showed a familial clustering with high heritability (63%) (Tekola, Adeyemo et al. 2012). The sibling recurrence risk ratio was 5.07 signifying that an affected person's siblings have an increased risk of podoconiosis five times that of a randomly selected person from the general population. The researchers concluded that the disease might be a T cell-mediated inflammatory disease. T cells (T lymphocytes) are a category of lymphocytes that play a central role in cell-mediated immunity. Cell-mediated skin diseases are chronic disorders with high-social impact. They include psoriasis, contact dermatitis and atopic dermatitis (Pastore, Korkina 2010). A Northern Ethiopian study reported that nearly half of cases (54.8% of men, 52.1% of women) had a family member with podoconiosis ( $n=480$ ) (Molla, Le Blond et al. 2013). However, the precise cause of the immune response in podoconiosis patients remain unknown requiring further research.

The first published study on SBF in those with podoconiosis was an Ethiopian study which compared the SBF of those with podoconiosis ( $n=55$ ) to controls ( $n=20$ ) (Ferguson, Yeshanehe et al. 2013). SC hydration was

measured with a corneometer and TEWL with an evaporimeter. At the thigh the average TEWL ratio of podoconiosis v control was 0.92, 95% CI (0.73 to 1.16),  $p=0.49$ . At the shin the average ratio of podoconiosis v control was 1.01, 95% CI (0.83 to 1.23),  $p=0.93$ . At the foot the average ratio of podoconiosis v control was 0.84, 95% CI (0.65 to 1.09),  $p=0.18$ . These results indicate no group difference in TEWL at any of the measurement sites.

At the thigh the average SC hydration ratio of podoconiosis v control was 0.83, 95% CI (0.66 to 1.04),  $p=0.11$ . At the shin the average SC hydration ratio of podoconiosis v control was 0.75, 95% CI (0.57 to 0.99),  $p=0.046$ . At the foot the average SC hydration ratio of podoconiosis v control was 0.61, 95% CI (0.44 to 0.84),  $p=0.004$ . This indicates significant differences between the two groups in SC hydration at the shin which were even more marked in the foot. The differences lessened moving up the leg. This reduced SC hydration in the feet/legs of podoconiosis patients compared with controls may well lead to skin cracking and splitting increasing the risk of infection and exacerbation of lymphoedema. The numbers were different in each arm which may have affected results and larger numbers may have detected a greater difference. The following photographs 2.2, 2.3, 2.4, 2.5 taken in Ethiopia indicate the effects of podoconiosis on the lower legs/feet. The first three photographs are by kind permission of the Action on Podoconiosis Association

**Photograph 2.2. Patient in Ethiopia podoconiosis exhibiting foot/leg oedema and hyperkeratosis.**



**Photograph 2.3. Feet of podoconiosis patient in Ethiopia displaying oedema of the foot, mossy changes, fibrosis and fused toes.**



**Photograph 2.4. Feet of patients in Ethiopia presenting with oedema, hyperkeratosis, nodules, fused toes, mossy changes and ulceration due to ill-fitting shoes.**



**Photograph 2.5. Podoconiosis patient exhibiting oedema, fused toes, hyperkerototic changes, deep fissures, mossy changes, fungal infection, inflammation and ulceration due to ill fitting shoes.**



Those with podoconiosis may be affected by episodes of acute adenolymphangitis (ADL). This manifests itself as recurring acute episodes of leg pain, fever and inguinal swelling. During the attacks patients are bedridden and unable to walk or work for several days. ADL prevalence, its causes and consequences are the focus of the next section.

### **2.3.5. ACUTE ADENOLYMPHANGITIS IN PODOCONIOSIS.**

A prevalence study in western Ethiopia reported ADL at least once in the previous year in 97% of patients with an average of 5.5 episodes annually. Open wounds were present in 7.2% of patients. On average 24 working days were lost due of ADL per year (n=335) (Alemu, Tekola Ayele et al. 2011). In a northern Ethiopian prevalence study ADL was present in 49.8% of those with podoconiosis at the time of interview. The leg was hot (49.8%), tender (60.2%) with swelling and inguinal lymphadenopathy (62.1%). On observation 13.9% of feet were both cracked and dirty. An average of five episodes of ADL per year confined patients to bed an average of 90 days. ADL episodes were reported to be related to walking long distances (72.2%) and 54.5% of participants stated that they occurred more often in hot dry seasons while 20% said that they were not season specific (n=1319) (Molla, Tomczyk et al. 2012a). A later Ethiopian study of the reasons for loss to follow-up stated that 26 participants (13.6%) reported weekly ADL attacks, 33 (17.3%) 2 weekly, 68 (35.6%) every month, 22 (11.5%) every 3 months and 6 (3.1%) every 6 months. Wounds were visible on 17.8% of feet (n=191) (Campion, Tamiru et al. 2015). The numbers reporting episodes every one or two weeks was 101 (52.9%) seems very high compared to the other studies. The reason for this is unclear. The only published study found on the relationship between open wounds and ADL reported high correlations with (t=2.6, p=0.009) and without (t=-2.1, p=0.037) adjustment for clinical stage (n=460) (Molla, Le Blond et al. 2013). The definition of a 'wound' was not reported in any of the studies and may or may not have included areas of fungal infection. This may have affected the number of 'wounds' reported and also contributed to the variation in the relationship between the number of 'wounds' and episodes of ADL. Currently a greater amount of research has been undertaken on the association between wounds and ADL in those

with lymphatic filariasis (LF) than on those with podoconiosis. The studies are reported in the succeeding section.

### **2.3.6. ADENO-LYMPHANGITIS IN LYMPHATIC FILARIASIS.**

LF is caused by filarial parasites transmitted by mosquito bites. The filaria cause inflammation and block the lymph channels in the feet and legs. The following Table 2.2 identifies the characteristic differences between podoconiosis and LF.

**Table 2.2. Differences between podoconiosis and lymphatic filariasis** (Amberbir, Tamiru et al. 2014).

<b>Characteristic</b>	<b>Podoconiosis</b>	<b>Lymphatic filariasis</b>
Area of residence	>1500 m above sea level	<1000 m above sea level
Mean age of onset	10–20 years	25–30 years
Relation to natural history	Initial symptom	Late complication
Site of first symptom	Toes and foot	Any part of limb except foot
Local lymphadenitis	Follows swelling of limb	Precedes swelling of limb
Typical site of swelling	Distal, below knee	Above and below knee

In patients with LF a significant relationship has been identified between the number of ADL attacks, the grade of oedema and the focus of infection in the affected limb (Shenoy, Sandhya et al. 1995). Infections were identified in 28 of the 65 patients with ADL. Patients were randomly allocated to one of four treatment regimens. These were: symptomatic alone, symptomatic plus antibiotics, symptomatic plus diethylcarbamazine (DEC) an anti-filarial drug, symptomatic plus DEC and antibiotic. Neither antibiotics nor DEC altered the frequency of ADL occurrence. It was also noted that ADL contributed to disease progression and that simple hygiene, foot care and topical antibiotics/antifungals given when required were effective in reducing ADL. A prospective analysis of patients with LF reviewed two treatments (n=600) (Dreyer, Medeiros et al. 1999). ADL was present in 97% of patients. ADL did not improve with DEC but did improve with good hygiene which reduced leg oedema and softened the skin. A further study noted that none of the patients (n=47) without entry lesions had ADL but 75/80 patients (93.8%) who had one or more entry sites on the affected limb also had ADL. Most of the lesions were minor injuries (57.3%) but all skin breaches were included (n=127) (Suma, Shenoy et al. 2002). A case controlled study of interdigital

lesions in those with lymphoedema due to LF reported that the number of lesions was the highest predictor of ADL (n=73). The mean number of episodes of ADL in the previous year increased from a mean of 0.7 in those with no lesions to a mean of 3.6 in those with eight lesions (McPherson, Persaud et al. 2006). In a double blind placebo controlled study those who had previously had ADL were studied over a two year period. Patients were randomly allocated to receive 12 monthly doses of Ivermectin or DEC (the usual treatment for filariasis) or a placebo in addition to local treatment over twelve months. There was no significant difference in frequency of ADL attacks in the three groups (n=120) (Shenoy 2008). Bacteria can be cultured from the tissues, lymph and lymph nodes of those with ADL and each episode of ADL results in a worsening of lymphoedema (Mortimer 2000). All the studies indicate that bacteria gaining entry via skin breaches are related to ADL attacks in LF and that oral medication with filarial drugs is not effective in preventing or treating ADL despite killing the nematode. A daily regimen of foot/leg hygiene is therefore the most important therapy in preventing and treating ADL. The following section reviews in more detail the daily foot/leg hygiene treatment used for the prevention and management of podoconiosis.

### **2.3.7. PREVENTION AND MANAGEMENT OF PODOCONIOSIS.**

Research indicates that podoconiosis results in high social and economic cost but can be prevented, controlled and treated with low cost interventions (Tekola, Mariam et al. 2006, Henok, Davey 2008, Morrone, Padovese et al. 2011). The early stages of the disease can be reversed by simple foot hygiene and wearing shoes (Tekola, Mariam et al. 2006). To avoid progression of the disease patients must adhere to the regime for the rest of their lives (Davey, Tekola et al. 2007). For those with advanced disease their legs and feet have been shown to improve significantly if a daily treatment regime is followed but it may not be possible to regain completely normal-looking legs and feet. In Ethiopia podoconiosis is treated with a daily regimen of: washing of the feet and legs with soap, water and dilute bleach, the application of *Whitfield's ointment* for fungal infections and the application of an emollient. Compression bandaging is used in some clinics

for selected patients and elevation of the legs at night and wearing shoes and socks encouraged (Henok, Davey 2008, Yakob, Deribe et al. 2009, Sikorski, Ashine et al. 2010, Morrone, Padovese et al. 2011). The succeeding Table 2.3 provides information and a critique on the current practices in APA clinics and Mossy foot clinics. These are the predominant clinics treating podoconiosis patients in Ethiopia.

**Table 2.3. Current regimens used for treating podoconiosis in APA and Mossy Foot clinics, their rationale and issues**

(Lienhart, Ashine et al. 2010) and the principal investigator's observations of APA and Mossy Foot clinics in 2012).

<b>Regimen</b>	<b>Rationale</b>	<b>APA regimens</b>	<b>Mossy Foot regimens</b>	<b>Issues and discussion</b>
Baseline assessment form completed	To identify:-burden of disease, clinical stage of disease, changes over time, monitor behaviour.	Record stage of disease, mossy changes.	Record stage of disease, mossy changes and presence of wounds.	The quality of the information collected may vary depending on the accuracy of the person giving the information and that of the data collector in recording the information.
Monthly clinic attendance	To monitor disease progress, obtain supplies and support.	Monthly clinics available.	Monthly clinics available. Home visits available by treated patients who have undergone training.	Long distances to walk resulted in clinic non-attendance (Tora, Davey et al. 2011). Long walks related to ADL (Molla, Tomczyk et al. 2012a).
Educational programme	To improve patients understanding of treatment and causes of podoconiosis.	Nurse provides 15-20 minute educational/practical session to patients on 1st visit. Sessions repeated at subsequent visits. Patients taught to follow the regime every evening.	The educational programme is taught by other podoconiosis patients who have undergone training.	A meta-analysis of 153 published studies 1977-1994 noted that combinations of strategies including education, behavioural and affective strategies were the most effective at improving adherence (Roter, Hall et al. 1998). A systematic review of adherence in long term conditions to self-administered medication reported interventions that were most effective included patient information, reinforcement and support (Nieuwlaat, Wliczynski et al. 2014).

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
Support from other patients	To lessen stigma, feeling of isolation and learn from each other. Seeing the effectiveness of treatment in others (Bandura 1997, Bandura, Locke 2003).	Available	Available	Social support provides knowledge and is likely to encourage self-efficacy. Seeing others manage their disease and achieve improvements gives confidence that they too can succeed in improving their condition (Bandura 2004).
Importance of daily washing of feet and legs with soapy water taught during educational programme. Patients are given a month's supply of soap at each visit.	Removes soil and organic material. Soap acts as an emulsifier allowing oil and water to mix so that oily grime can be removed during rinsing. Skin care is recommended in lymphoedema to optimize skin condition, treat complications caused by lymphoedema and minimize infections (Preston, Seers et al. 2008).	Demonstration at 1 <sup>st</sup> and subsequent clinic visits. Feet are washed with soap for up to 10 minutes depending on the degree of soil contamination. In the clinics a small piece of gauze was used to wash between toes and skin folds. Soap originally used had pH 10 and contained silica rich particles, ~ 1% glycerine and 50% fatty acids as C16 and iron rich particles (Procter and Gamble laboratory analysis 2013 (Appendix 5). C16 is a vegetable or animal fat. In this instance it is an animal fat derived from tallow. Following this analysis and prior to the study the soap used in the clinics was changed to a more refined 'beauty soap' containing palm and coconut oil with pH 8.5.	Demonstrations -feet/legs are washed with local soap and rinsed in fresh water. pH of soap variable depending on local availability.	Prolonged water soaks dehydrate skin. Soaks should be less than 30 minutes daily (Ramsing 1997). The water used should be near body temperature (Beradesca, Vignoli et al. 1995). To avoid the introduction of infections via skin breaches water should be of drinkable quality (Fernandez, Griffiths 2008). In LF patient 93.8% of those with ADL had lesions on the legs (Suma, Shenoy et al. 2002). Hygiene has been shown to significantly reduce ADL in LF patients (Shenoy, Sandhya et al. 1995, Shenoy 2008). Soap is currently the most commonly used cleansing agent. It removes dirt and oils (Ananthapadmanabhan, Subramanyan et al. 2013). All tests of soap indicate that frequent exposure induces barrier damage and skin dryness followed by inflammation (Wolf, Parish 2012). Most soap has a pH of 7-10 which alters skin pH making it more susceptible to pathogens and is detrimental to SBF. Further details on the use of soaps for skin cleansing are in Section 2.6.1.2.

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
<p>Bleach (5% sodium hypochlorite, NaOCl) is added to the soaking water. Patients are given a month's supply at each visit</p>	<p>Water not of drinkable quality and contains pathogens. NaOCl is added for bactericidal properties.</p>	<p>After washing feet soaked in another bowl containing 15mls of 5% NaOCl diluted in approximately 6 litres (not accurately measured) of local water (~0.0125% dilution, pH = 8) for approximately 30 minutes to remove pathogens. The solution is frequently splashed onto the whole leg below the knee with the hands.</p> <p>The amount of NaOCl is measured with the bleach cap which contains 10mls.</p>	<p>After washing and rinsing feet/ legs soaked for 15 minutes in 2 litres local water containing 5 mls of 5% NaOCl (0.0125% dilution). The solution is frequently splashed onto the whole leg below the knee with the hands.</p> <p>The quantity of water is measured with a jug.</p>	<p><i>In vitro</i> tests on solutions of 0.5% NaOCl had a total bactericidal effect on <i>Staphylococcus Aureus</i>, <i>Pseudomonas aeruginosa</i>, <i>Escherichia coli</i> and <i>Streptococcus faecalis</i> while solutions of 0.00025%-0.5% had a partial effect, 24% of fibroblasts were viable after exposure to a 0.025% solution and 98.9% after exposure to a 0.003% solution (Hidalgo, Bartolome et al. 2002). Fibroblasts are necessary for tissue repair so adding NaOCl inhibits wound healing. In another study the lowest NaOCl concentration at which <i>Pseudomonas aeruginosa</i> was killed was 0.003%, for <i>Staphylococcus aureus</i> it was 0.006% and for <i>Staphylococcus pyogenes</i> 0.0015% (Coetzee, Whitelaw et al. 2012).</p>

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
<p><i>Vaseline</i>® applied after washing, soaking and drying.</p>	<p>SC hydration and improving TEWL and SBF.</p>	<p><i>Vaseline</i>® applied in a thin layer to legs below the knee. 100g supplied monthly.</p>		<p><i>Vaseline</i>® is an occlusive which when applied after an emollient acts as sealant locking moisture in the skin. It has been found to be 100% effective as a skin barrier reducing TEWL when applied at a rate of 3mg/cm<sup>2</sup> (Teichmann, Jacobi et al. 2006). An investigation of forearms noted TEWL lower on the sites using <i>Vaseline</i>® at a rate of 2mg/cm<sup>2</sup> than in the control site (p≥0.05) (n=10) (Marques, Basso et al. 2007). In tests of three barrier creams on 2 areas of the forearms of 6 men only <i>Vaseline</i>® was shown to be a 100% barrier when measured by laser scanning microscopy, laser doppler flowmetry and tape stripping (Rieger, Teichmann et al. 2007). <i>Vaseline</i>® at a rate of 2mg/cm<sup>2</sup> was used as the control in a study of the skin penetration of oil. The area covered with <i>Vaseline</i>® showed the highest decrease in TEWL (p=0.05) (Patzelt, Lademann et al. 2012). Clothing may remove the layer <i>Vaseline</i>®.</p>

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
<p><i>Whitfield's ointment</i> (3% salicylic acid and 6% benzoic acid in a base of petroleum)</p>	<p>Fungal infections are common in moist areas between nodules and skin folds and cause skin breakdown and an entry point for other infections. Benzoic acid is an antifungal and salicylic acid helps the body shed rough or dead skin cells (keratolytic action). It is recommended to be applied at a depth of 1/8 inch twice a day.</p>	<p>Use <i>Whitfield's ointment</i> daily only on areas with a fungal infection so the amount given monthly varies depending on number and size of areas affected.</p>	<p>Apply <i>Whitfield's ointment</i> daily to whole lower leg, 40 gm tube supplied monthly.</p>	<p>A double blind trial in Malawi (n=153) compared <i>Whitfield's</i> with <i>clotrimazole</i>. Patients (75) with fungal infections were treated for six weeks with <i>clotrimazole</i> and the remainder with <i>Whitfield's</i>. These included HIV patients. Cure rates ranged from 80% to over 90% depending on the definition a cure. <i>Whitfield's</i> and <i>clotrimazole</i> were both very effective. A Cochrane Review noted that there was insufficient evidence to determine if <i>Whitfield's ointment</i> is effective (El-Gohary, van Zuuren et al. 2014). Despite this it is still used and preferred to other antifungals as it is low cost (Gooskens, Pönnighaus et al. 1994).</p>

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
Elevation of the legs at night	Reduces oedema.	Teach the importance of raising the feet at night above heart level (25°) on a cushion or bundle of clothing.	Suggest raising the foot of the bed on a brick or other object to raise legs above heart level at night and placing the leg on a stool while sitting.	Venous pressures in the lower leg vary depending on whether the person is in an erect or supine position. When the body is erect gravitational forces are exerted (hydrostatic pressure). In a person 1.83 metres tall these pressure will be approximately 100 mm Hg. This will result in a total pressure in the foot veins of an erect person of this height of 115 mm Hg. (Browse, Burnand et al. 1988). The pressure in the foot veins in the supine position is approximately 15mm Hg. When the legs are above heart level the venous pressure falls to zero and tissue fluid is absorbed, reducing any swelling (Browse, Burnand et al. 1988). For oedema in podoconiosis to be reduced the legs need to be elevated to heart level or above for at least 8 hours per day (Davey, Tekola et al. 2007). Swollen legs are cumbersome and prone to trauma which may result in ulceration.

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
Bandaging	Short stretch compression bandaging bandages used to treat lymphoedema. This bandage provides muscles with a firm resistance to work against thus increasing lymphatic drainage.	Do not routinely use compression bandages.	Teach bandaging to those with stage 3 and above and give patients 4-6 short stretch bandages per year. They are removed overnight.	Short stretch bandages are expensive and require expertise to apply. Arterial disease, DVT, severe cardiac failure and infections need to be excluded before application. They may be used with caution in patients with hypertension and diabetes. The leg should be padded with a wool bandage to ensure it is a normal shape before applying short stretch. Several layers are required for gross oedema (Todd 2000, Pike 2011).
Exercise	Exercise of the ankle reduces lymphoedema and venous hypertension (Vaqas, Ryan 2003).	Teach ankle exercises and the importance of movement.	Teach ankle exercises and the importance of movement.	The calf pump in the lower leg performs two vital functions. It ensures venous return during exercise and reduces superficial venous pressure thereby relieving the damaging effect of hydrostatic pressure, which results from a person's upright posture (Browse <i>et al.</i> 1988). The resting standing venous pressure is ≈80 to 90 mm Hg. This falls with calf exercise to ≈20 to 30 mm Hg a >50% decrease.

Regimen	Rationale	APA regimens	Mossy Foot regimens	Issues and discussion
Wearing shoes and socks	Keeping the feet clean. Maintaining intact and healthy SC preventing further silica entering the lymphatics via skin beaches.	Importance of shoe wearing taught but patients are poor. They often cannot afford suitable shoes. Custom made shoes supplied to patients with Stage 3 disease and over at low cost. Socks not provided.	Importance taught. Custom made shoes provided free or at low cost (10 Birr = 30p). One pair of socks is provided for each pair of shoes. Replaced twice a year.	Plastic sandals are often used by patients. They provide little protection to dirt, are hot and do not absorb sweat. This may increase the occurrence of fungal infections. Socks are not often used unless supplied.
Wound care advice	To prevent and treat wounds.	Deep wounds referred to health centre.	Patients with wounds are given a roll of gauze to use as a dressing. Deep wounds referred to health centre.	Wounds have been related to ADL and increased lymphoedema in LF patients (Dreyer, Medeiros et al. 1999, Suma, Shenoy et al. 2002, Shenoy 2008). High correlations also recorded between the number of wounds and ADL in those with podoconiosis (Molla, Le Blond et al. 2013).
Debulking surgery and removal of prominent nodules is sometimes undertaken.	Comfort	Patients referred for surgery required.	Patients referred for surgery if required.	More radical surgery is no longer recommended since patients unable to scrupulously avoid contact with soil experience recurrent swelling which is more painful than the original disease because of scarring (WHO 2012).

There are many similarities and a few discrepancies between regimens taught in APA and Mossy Foot Clinics. The majority of podoconiosis treatment is provided in these clinics but there are issues of non-attendance. Different care settings and management approaches have been examined. Details of these and their effects are the next topic.

### ***2.3.8. EFFECT OF DIFFERENT CARE/MANAGEMENT SERVICES.***

A 12 month non-comparative, longitudinal evaluation of 33 patients newly presented to a Mossy Foot clinic in the Wolaita region, Southern Ethiopia used the regime reported in Table 2.3 (Sikorski, Ashine et al. 2010). During the study six patients moved out of the area so their results were not included in the final analysis. The study tested the effectiveness of a community based, patient led treatment regime. Initially 80% of patients presented with stage 2 of the disease. Information about podoconiosis was given at monthly meetings including prevention and treatment. Social and spiritual support was also offered. At 12 months there was significant improvement in the clinical progression of the disease with 63% of patients recorded as having stage 1 disease. Lower leg circumference decreased significantly from a mean of 26.22 cms to a mean of 24.22 cms, a mean difference of -2cm, 95% CI (-1.26 to 2.74),  $p=0.001$  ( $n=27$ ). Only one fifth of the patients (22.2%) still had mossy changes but this change was not significant ( $p=0.375$ ). Although there was no comparative control group the authors noted that lymphoedema related to podoconiosis has never been reported as improving without intervention. The results of the study indicate the considerable impact of the regimen on the clinical progression of the disease. No other follow-up studies on podoconiosis have been reported. Further larger pre and post intervention studies are needed to provide further evidence of treatment effects. A study of LF in a poor area of North-eastern Nigeria compared three systems of hygiene management. The first was community care, the second patient care and the third health facility care. In the community care arm of the study, communities selected one of their members as the care giver. In the patient care group, patients were allocated into groups under a leader with a responsibility for providing care to group members. In the health facility group care was given by the nearest health

facility. Care givers in the three arms were all trained. At six months 325 patients had been recruited to the study. After 12 months those in the community care arm increased compliance to the hygiene practices from 29.4% to 62.6% and episodes of adenolymphangitis (ADL) fell from 43.1% to 4.4%. In the patient and the health facility arms of the study compliance was poor. Access to supplies was affected by poor coordination and delays in collection. This resulted in minimal effect on lesions, odour, frequency of ADL and duration. Participants abandoned the health facility after the second visit (Akogun, Badaki 2011). The study indicates that patient preference in Nigeria is for community treatment.

In Ethiopia out-reach clinics provide most of the care to those with podoconiosis. This is because they appear to be the most cost effective and easiest system to deliver. Until research on cost/outcome comparisons provides evidence to the contrary this system may continue. Studies have reported a more normal looking leg, a reduction in limb size, and an improvement in quality of life when the regime taught in Mossy Foot clinics is followed (Henok, Davey 2008, Yakob, Deribe et al. 2009, Sikorski, Ashine et al. 2010, Morrone, Padovese et al. 2011). To date there have been no studies published into the effects of APA clinics on podoconiosis.

Some patients in clinics have reported difficulties in attending clinics on a monthly basis. There are many reasons for this which are discussed next however, distance and the time taken travelling to and from clinics seems to be the main issue.

#### *2.3.8.1. REASONS FOR NON-ATTENDANCE AT PODOCONIOSIS CLINICS.*

Three articles were found which focused on non-attendance at podoconiosis clinics. The first was undertaken in Mossy Foot clinics in southern Ethiopia. A qualitative study of the reason patients discontinued their attendance was undertaken at four of fifteen clinic sites. Focus group discussions and interviews were undertaken on 44 of the patients (n=88) (Tora, Davey et al. 2012). The following factors were identified: remoteness from clinic site, expectations of 'special support' such as financial or material benefit, worries about increasing stigma, illness and misconceptions about treatment for

example the failure to have an immediate improvement. The second was a qualitative study which undertook in-depth interviews with 28 patients and three project leaders to identify barriers to those with podoconiosis attending treatment centres. Three focus group discussions were carried out with 22 patients, patient association leaders and project staff members. The barriers identified were as follows: beliefs about the cause and nature of podoconiosis, occupation, geographical and financial issues, stigma and conflicting expectations of treatment (Tsegay, Wubie et al. 2014). The third study was at clinics with high drop-out rates in Northern Ethiopia (n=191) (Campion, Tamiru et al. 2015). The following reasons were given by patients in descending order of importance: distance (51:26.7%), acute attacks (33:18.8%), illness (31:16.2%) and too busy (25:13.1%). Fewer patients said non-attendance was due to financial constraints, lack of material support, ineffective treatment or worries about stigma. Some of the reasons for non-attendance might be overcome by improving patients understanding of the disease, increasing the number of clinics and/or providing a home visiting service. But increasing services to the enormous numbers involved would be a huge challenge.

### ***2.3.9. ECONOMIC CONSEQUENCES OF SKIN DISEASE AND PODOCONIOSIS.***

In the Wolaita region in Southern Ethiopia a matched comparative cross sectional study estimated productivity losses caused by podoconiosis as 45% of the total working days per year per patient (Tekola, Mariam et al. 2006). The estimated cost of this in a population of 1.5 million across the region was US\$ 16 million (current value £10.4 million) a year. Interviews with 335 people with podoconiosis in western Ethiopia noted that 97% had ADL in the previous year (Alemu, Tekola Ayele et al. 2011). They were mostly uneducated poor farmers who lost an average of 24 working days a year due to adenolymphangitis. A study in Northern Ethiopia reported that those with podoconiosis (n=460) spent approximately 60 days less on farming activities than those without (n=707) (t=-4.6, p<0.001). When comparing the incomes of those with podoconiosis to those without, those with the disease earned on average 62 Birr (~3 \$) (current value ~£2) a month less (t=4.4, p<0.001). Affected women earned less than the men

( $t=3.2$ ,  $p=0.001$ ) (Molla, Le Blond et al. 2013). The working days lost due to skin diseases including podoconiosis have a major effect on the patient's capability to produce food for their family and an income. It is therefore, important for patients and their families to understand the causes, prevention and treatment of ADL in podoconiosis. This is the focus of the next section.

#### **2.3.10. PATIENT'S KNOWLEDGE OF ADENOLYMPHANGITIS IN PODOCONIOSIS.**

Only one study was found on patient's knowledge of ADL in podoconiosis. This was a cross sectional household survey of 17,553 households (Molla, Tomczyk et al. 2012a). A structured interview took place with 1319 of those identified with podoconiosis. In the study 55.4% of those interviewed said that ADL occurred more in the hot dry seasons, 25.7% that it occurred in the rainy seasons and 20% that it was not season specific. The overall response to the precipitating factors included: long walks (72.2%), *mitch* (the sun causing inflammation) (52.1%), laborious work (28.9%) and dust (13.2%). The overall response to coping mechanisms for ADL reported were: staying in bed (55.6%), changing to less laborious work (44.2%), use of antibiotics (25.8%), use of *Hereg Resa* a local herb which is boiled and the steam inhaled by patients thought to have *mitch* 20.5%, sleeping/nothing (16.1%) and washing (7.8%).

Because of the lack of understanding of the cause and treatment of the disease patients sometimes seek treatments from traditional healers thereby paying for infective or harmful treatments (Ryan, Fuller et al. 2011). Studies have been undertaken on the knowledge and attitudes of patients and of the population towards the causes and prevention of podoconiosis. They are discussed next.

#### **2.3.11. KNOWLEDGE AND ATTITUDES OF HEALTH EXTENSION WORKERS, PATIENTS AND THE COMMUNITY TOWARDS PODOCONIOSIS.**

Several published studies were found relating to the knowledge and attitudes towards podoconiosis. The first section relates to the knowledge of HEWs, the second to community knowledge and the third to patient knowledge.

#### *2.3.11.1. HEALTH EXTENSION WORKER'S KNOWLEDGE.*

Health extension workers (HEWs) were introduced by the Ethiopian government in 2003 to provide access to primary health care. They are trained for one year in disease prevention and health promotion. There are two HEWs in each kebele (smallest administrative district) which comprises about 5,000 people. More than 35,000 HEWs are employed by the Ethiopian Government (Mangham-Jefferies, Mathewos et al. 2014).

A quantitative cross sectional study was conducted in the Gamo Gofa region of Southern Ethiopia to determine HEWs knowledge of podoconiosis. Structured questionnaires were completed by 384 HEWs. Most, 350 (91%) had received no education on podoconiosis during their training (Mengistu, Berhane et al. 2013). The study indicated that 244 (63.5%) had a poor knowledge of podoconiosis and only 140 (36.5%) a good knowledge. The definition of 'good' or 'poor' knowledge was based on whether their score was below or above the mean of the responses. Although the definition of knowledge is imprecise the study indicates that HEWs knowledge of podoconiosis requires improvement.

#### *2.3.11.2. COMMUNITY KNOWLEDGE.*

A cross-sectional study recruited 438 members of a community in a highly endemic area of southern Ethiopia (Yakob, Deribe et al. 2009). The age range was 18-71 years. Participants were selected by multi-stage probability sampling. Most of the respondents (93.5%) had seen a person with podoconiosis. The proportion of respondents with at least one misconception about the cause was 93.4%, 95% CI (91.1-95.75%). Over 55% thought that podoconiosis was transmitted via contact with someone who already had the disease and 30.5% thought it was the result of a curse, 71.7% knew that good hygiene could prevent the disease, 64.4% thought it was due to heredity to familial causes, 63.6% that it was the result of stepping on dead animals, 62.9% that it was the result stepping on a snake and 56.4% knew that wearing shoes could prevent the disease. In response to questions on the risk of podoconiosis 49% felt they were at risk, 48.4% thought their society was doing enough for those with the disease, 44.1% knew that it

could not be transmitted from person to person and 41.4% knew that podoconiosis was treatable. In response to questions about attitudes to the disease 55.8% showed stigmatising attitudes towards social interactions, 63.8% had unfavourable attitudes to the condition, 35.9% would not purchase items from a person with podoconiosis, 53.4% would not eat with someone with the disease and 48.8% felt that those with podoconiosis were less productive. Those with a high knowledge score were more than twice as likely to have a positive attitude compared with those with a low knowledge score (AOR 2.23, 95% CI (1.32-3.98)). Respondents with a high knowledge score were also twice as likely to wear shoes compared to those with a low score (AOR 2.18, 95% CI (1.32-4.48)). This study indicates low levels of knowledge within the community about the causes and prevention of the disease and the high degree of social stigmatization. It also indicates the positive effects of educating communities on the causes, prevention and treatment of podoconiosis.

#### *2.3.11.3. PATIENT'S KNOWLEDGE OF PODOCONIOSIS AND PREVENTION.*

Patient's knowledge of the disease has also been reported as poor. A cross sectional household survey of 17,553 households in Northern Ethiopia asked patients what they thought were the causes podoconiosis 41.3% said they did not know the cause, 18% said walking barefoot and 7% that it was inherited. Other responses included the curse of God, the action of a witch, injury and *mitch* (n=1319) (Molla, Tomczyk et al. 2012b). Patients were next asked whether they thought podoconiosis could be prevented and controlled. Some patients (37.5%) believed podoconiosis was preventable and 40.4% that disease progression could be controlled. The remaining respondents said they either 'knew' or 'thought that' podoconiosis could not be prevented (22.2% and 40.3%, respectively) or controlled (27.3% and 32.3%, respectively). Preventative methods reported in studies included wearing shoes (82.1%) and washing feet (19.1%) (Molla, Tomczyk et al. 2012b).

A cross sectional study reported 55.5% wearing shoes at the time of interview. The commonest reasons for not wearing shoes was unaffordability (69.3%) with 96.4% stating that they were willing to wear shoes if provided (n=337) (Yakob, Deribe et al. 2008). Another study reported that 96% of

patients had worn shoes once in their life with the mean time for starting to wear them as 23 years (+/- 15.9). It was noted that this coincides with the age of onset of the signs and symptoms of podoconiosis (Alemu, Tekola Ayele et al. 2011).

There also appears to be a difference in the shoe wearing behaviour of males compared with females. In one study the male/female shoe wearing ratio was equal but more males were reported to be wearing better quality more expensive leather shoes (Alemu, Tekola Ayele et al. 2011). A further study reported that at interview 23.6% of participants were barefoot of which 65.3% were women (n=1319) (Molla, Tomczyk et al. 2012a). Although 40% stated they had a pair of shoes, more of these were males (61.1 % v 50.5%). The types of shoe worn at interview by participants were: covered hard plastic (33.3%), canvas (20.9%) and open sandals made from tyres (13.2%). The majority were not considered protective against podoconiosis. A later study exploring barriers to shoe wearing in Southern Ethiopia recorded information from 242 respondents (69 were receiving podoconiosis treatment, 129 were unaffected and 444 were community leaders, or religious leaders. Focus groups, semi-structured interviews and extended case studies were used to gain information. Not wearing shoes was regarded as shameful (Ayode, McBride et al. 2013). The higher quality and greater number of shoes owned by men compared to women in the studies maybe due to the differing status of men in Ethiopian society. This difference may result in more women developing podoconiosis. As Ethiopia becomes more prosperous the attitude to shoe wearing is likely to change and shoe wearing increase.

The instances that shoes are worn have been reported in several studies. Shoes were more likely to be worn at social events or for school attendance and not while working in the fields, gathering water or when children were playing (Alemu, Tekola Ayele et al. 2011). The occasions that those with podoconiosis walked barefoot were: in fields (18%), during the rainy season (13%) and at home (11%) (n=335). The reason given for not wearing shoes while farming in the rainy season was that they quickly became thick with mud making them heavy and failing to grip, while during the dry season soil

particles fell inside shoes making them uncomfortable to wear (Ayode, McBride et al. 2013). A Northern Ethiopian study of those with podoconiosis noted a high number (332, 72%) not wearing shoes at interview (n=460) (Molla, Le Blond et al. 2013). Although the season was not specified this high number may have been related to the season. A later Northern Ethiopian study reported that 59 (30.9%) of those questioned said they did not wear shoes (n=191) (Campion, Tamiru et al. 2015).

The look of shoes has also been deemed important. A qualitative study noted a difference between the shoes provided by the Mossy Foot Treatment and Prevention Association and those available in markets. This difference prevented some people from wearing shoes provided by clinics as they felt labelled and subjected to stigma (n=242) (Ayode, McBride et al. 2013). The studies also reported that wearing shoes seems to be dependent on the season, the activity, possibly different shoe wearing customs in different areas, peer pressure, income and the effects of stigma. The following pictures 2.6, 2.7, 2.8 are of shoes worn by patients at APACs.

**Photographs 2.6, 2.7 and 2.8.** Examples of the sandals worn by patients attending APA clinics (November 2012).





To help prevent podoconiosis the charitable arm of an American shoe company has started providing thick canvas shoes free of charge to barefoot school children in some parts of Southern Ethiopia. Eighty six thousand pairs were distributed via APA mid-2014 and the same number again six months later (Action on Podoconiosis Association 2014).

As well as wearing shoes, washing of feet/legs daily to remove soil is an essential part of podoconiosis prevention. A study in Western Ethiopia questioned patients about their attitudes and knowledge towards hygiene and footwear. Two-thirds stated that they washed their feet at least daily and 58% that they used soap to wash their feet daily (Alemu, Tekola Ayele et al. 2011). The percentage may have been higher than in actuality as patients may have wished to please the interviewer, a recognised problem with questionnaires (Holtgraves 2004). Two studies reported foot cleanliness at the time of interview. The first reported that 46.8% of those with podoconiosis had clean feet, 21.1% dirty feet, 13.9% had cracked feet and 13.9% dirty and cracked feet (n=1319) (Molla, Tomczyk et al. 2012a). Definitions of 'clean' and 'dirty' were not given so were subjective. They reported that on average feet were washed as seven times a week. Molla also noted that patients prioritized water for drinking and cooking before

washing their feet so again patients may have exaggerated the amount of their foot washing (Molla, Tomczyk et al. 2012a). The second study reported 38.5% with clean and intact feet, 22.5% with dirty feet and 14.9% with cracked feet. The odds ratio of subjects having podoconiosis were twice among those with dirty feet OR=1.9, 95% CI (1.4 to 2.5),  $p < 0.0001$ , four times greater in those with cracked feet OR=4.2, 95% CI (2.7 to 6.4),  $p < 0.0001$  and four times greater in those with both dirty and cracked feet OR=4.2, 95% CI (2.9 to 6.0),  $p < 0.0001$  (n=460) (Molla, Le Blond et al. 2013). However, yet again the frequency of reported foot washing may have been overstated to please the interviewer. The significant relationships remained after adjusting for age, gender, 'ever' owning shoes and frequency of foot washing.

Regardless of shoe type adherent soil was present on nearly all the feet of children 7-15 years of age (n=168) (Watanabe, McBride et al. 2014). In the study half of those who reported wearing enclosed shoes had adherent soil present and 74% of those wearing open-toed shoes had adherent soil present ( $p < 0.001$ ). While wearing closed-toed shoes was associated with a significant reduction in adherent soil on the feet there was no difference by shoe type in heel cracks and foot trauma.

The studies confirm that in order to minimize the risk of podoconiosis shoe wearing alone is not sufficient. To remove soil and prevent feet becoming dry and cracked thus allowing the entry of foreign particles a daily regimen of foot hygiene and moisturization is also required. It seems that further education of both the public and health workers is required on all aspects of podoconiosis. HEWs have the potential to play a major role in this by increasing public awareness of the disease, encouraging good foot hygiene and the wearing of shoes, reducing stigma and encouraging clinic attendance for those with the disease. Lack of knowledge concerning the disease causes stigmatization. This affects both those with the disease and their families psycho-socially and economically. This is the focus of the following section.

### **2.3.12. PSYCHO-SOCIAL IMPACT OF PODOCONIOSIS.**

A WHO bulletin stated that skin diseases in resource-poor countries had a serious impact on people's quality of life (WHO 2005). The quality of life encompasses many aspects such as physical and psychological health, social relationships and relationships to the environment. Podoconiosis results in lost productivity at work and school and discrimination due to the obvious manifestations of the disease such as swollen legs/feet, malodour from infections and/or disfigurement. Stigma is also more likely where imperfections are very visual as in podoconiosis. It can result in children being excluded from school and may limit chances of marrying in some circumstances. In some circumstances it may result in them having to leave their family or village and become beggars. Stigma and loss of self-esteem is exacerbated where people are less educated on the causes of skin disease.

A qualitative study on social stigma was attached to the recruitment into a genetic research study of participants with podoconiosis. In depth interviews were undertaken (n=25) and group discussions (n=4). Overall 46 individuals participated (27 male and 19 female). Patients were afraid to take part in the study because of fears that this might increase stigmatization by advertising the familial nature of the disease. As a result patients felt guilty and isolated themselves (Tekola, Bull et al. 2009). Although the study was concerned with participation in genetic research it could be concluded that participation in any podoconiosis study might highlight to the rest of the community that the person has the disease. The types of stigma reported by patients were as follows: unable to marry, others avoided patients and family members, exclusion from social events, classmates not willing to sit at the same desk and others pinched their noses as they walked past. Those with the disease were also spat at. Even unaffected family members were not willing to be near an affected member (Tekola, Bull et al. 2009). A qualitative study on stigma and coping strategies undertaken in Southern Ethiopia (n=88) noted that many participants used avoidance as a coping mechanism (Tora, Davey et al. 2011).

Health professionals in the Wolaita region have also shown a tendency to stigmatize those with podoconiosis (n=275) (Yakob, Deribe et al. 2009). At the time of the study 1.6 million people lived in this region 99.2% of them in rural areas. Podoconiosis was highly endemic in the area with an estimated prevalence of 5.5%. All 460 health professionals in the area were contacted but some of these were no longer delivering care or were in training outside the area. Of the 334 eligible 293 (87.7%) agreed to participate. Eighteen responses were incomplete and excluded from analysis. Of the 275 participants remaining 68.4% were nurses, 15.4% health assistants and 13.6% laboratory or pharmacy technicians. Of these 36.4% had not treated a person with podoconiosis but prescribed medicines or laboratory investigations or referred them to another facility. The majority (88.7%) had seen someone with podoconiosis. A structured self-administered questionnaire based on stigma in HIV/AIDS and on earlier qualitative research on podoconiosis was developed. This identified their knowledge of podoconiosis as follows: 86.4% felt that they had inadequate knowledge and skills to treat the disease, 68.7% would not eat with a person with the disease, 58.2% knew that not wearing shoes and poor foot hygiene were risk factors, 55.6% thought the disease was transmitted by flies or mosquitoes, 50.9% thought podoconiosis was infectious and 38.8% were afraid of acquiring the disease while providing care. Their attitude to patients was as follows: 50% stated that patient's feet had a bad smell, 48.2% would not purchase an item from a person with the disease, 42% felt that patients were not willing to accept the care offered and 17% stated that few patients visited their health facility. When asked about the provision of care 72.4% showed a favorable attitude to providing care for those with podoconiosis, 70% said that the drugs and supplies were inadequate and 52.2% felt the community was unwilling to care for those affected. From these results it would seem reducing stigma via the education of health care staff, patients and communities on the disease and its treatment is of prime importance.

A scale for measuring podoconiosis related stigma has been developed and tested in Southern Ethiopia (Franklin, Tora et al. 2013) (Appendix 6). Questionnaires were used to survey 150 podoconiosis patients and 500

unaffected members of the community. Questionnaires were interview based because of low literacy rates. Four scales were developed:

1. podoconiosis patients felt stigma scale -15 questions
2. podoconiosis patients enacted stigma scale -17 questions
3. community felt stigma scale -24 questions
4. community enacted stigma scale -23 questions

Enacted stigma refers to the actual experience and felt or perceived stigma to the fear of stigma. Multi-stage random sampling was used for selection. Seventeen of the 500 were incomplete and excluded from analysis.

Respondents were asked to answer each question with 'yes', 'possibly, uncertain or 'no'. Scores were given to each answer, three for 'yes', two for 'possibly' one for 'uncertain' and nil for 'no'. The reliability of the scales was calculated using Cronbach's alpha; all scales indicated good consistency.

The content and construct validity of the scales were satisfactory with modest correlation between items. There was significant correlation between the 'felt' and 'enacted' stigma scales among patients (Spearman's  $r=0.892$ ;  $p<0.001$ ) and within the community (Spearman's  $r=0.794$ ;  $p<0.001$ ).

The same stigma score was used in a study in the Wolaita region of Southern Ethiopia of the stigma of those with the disease remembered over the previous 12 months ( $n=150$ ). In the enacted stigma score 98 (65%) said friends spent less time with them because of their condition, 82 (54.7%) that they received insults about their foot, 80 (60%) that they were mistreated at work and 89 (59.4%) that they were isolated from social events. In the felt stigma score 81 (54%) said they had tried to kill themselves and the same number that they had tried to change their place of residence, 77 (52.3%) thought others felt uncomfortable working with them, 77 (50%) that it affected their chances of marrying and 82 (54.3%) avoided public places. For total stigma (enacted and felt) the mean score of those with stage 2 and below was 37 (29.3%) with stage 3 and above it was 49.8 (32.4%) (Tora, Franklin et al. 2014). This indicates that social stigma is greater in those with more severe and thus more obvious podoconiosis.

From the evidence it would seem that podoconiosis has a profoundly negative effect on the lives of those with the disease and that the effect

increases as their condition becomes more obvious. Additional research evidence is required to further validate the scoring system. Education of the community, health care workers and field workers into the disease including its prevention and treatment is required to avoid this stigmatization. The high level of stigma related to podoconiosis affects the quality of life of those with the disease and provides the focus of the following section.

### **2.3.13. QUALITY OF LIFE OF THOSE WITH PODOCONIOSIS.**

The Amharic version of Dermatology Life Quality Index (DLQI) was used in a comparative cross sectional study of 74 new patients and 74 patients treated for minimum of 3 months at outreach clinics of the Mossy Foot Treatment and Prevention Association. The highest score is 30 signifying a high impact on quality of life. The mean score of all patients was 8.42 indicating a moderate effect on patient's lives. The highest score for new patients was 'Over the past week how itchy, sore, painful or stinging has your skin been?' The highest score was for the question 'Over the last week, how embarrassed or self-conscious have you been because of your skin?' (Henok, Davey 2008). The Amharic version of DLQI was also used in the small study undertaken over 12 months in Southern Ethiopia (Sikorski, Ashine et al. 2010). The study numbers were initially 33 reducing to 27 at 12 months. The mean DLQI score was 21.11 at the first visit reducing to 6.07 at 12 months (mean difference -15.04),  $p < 0.001$ ; indicating a very significant improvement in the quality of patient's lives as a result of the treatment regimen.

Franklin compared the quality of life of those with podoconiosis (n=150) and of those without the disease (controls) (n=483). The Amharic version of the WHO Quality of life (QOL), a questionnaire (26 questions), Kessler's psychological distress scale (10 questions) and the podoconiosis stigma scale (4 scales) were used (WHO 2004, Kessler, Barker et al. 2003). Questionnaires were interview based because of high illiteracy rates (98, 65.5%) for those with podoconiosis and 207, 42.9% for those without the disease). Those with podoconiosis had significantly lower QOL than controls 52.05 versus 64.39. This was the same in all four subgroups – physical,

psychological, environmental and social. High levels of stigma, being illiterate, being unmarried and living in an urban area were associated with lower QOL. Healthy adults were seven times more likely to have an above median QOL. Podoconiosis patients had lower mean QOL scores than those with lymphatic filariasis or leprosy (Franklin, Tora et al. 2013). The authors note that the interview based questionnaires may have resulted in social desirability bias.

A questionnaire based comparative cross-sectional study of mental distress and podoconiosis in northern Ethiopia compared 346 adults with podoconiosis to 349 healthy adults in one district (Mousley, Deribe et al. 2013). Those with podoconiosis were less likely to be married than healthy controls 198 (57.2%) v 265 (75.9%) and more likely to be divorced 63 (18.2%) v 34 (8.0%). A validated Amharic translation of the Kessler-10 scale (K10) questionnaire was used to measure the level of distress. It is based on questions about anxiety and depressive symptoms that a person has experienced in the previous four week period. The mean Kessler score was 15.92, 95% CI (15.27 to 16.57) in people with podoconiosis and 14.49, (95% CI (13.85 to 15.12) in controls with average scores 1.43 points higher, 95% CI (0.52 to 2.34). The differences remained significant when adjusted for gender, income, alcohol use, age, place of residence and family history of mental illness. In the adjusted model, those with podoconiosis had scores 1.37 points higher than controls, 95% CI (0.64 to 2.18). Females had scores 1.41 points higher than males, 95% CI (0.63 to 2.18) and those with family history of mental illness had scores 3.56 points higher than those without, 95% CI (0.55 to 6.56). The difference in scores between those with and without podoconiosis was not clinically significant ( $p \geq 0.05$ ). In conclusion podoconiosis has a highly negative impact on the quality of life of those with the disease. This is in conjunction with high levels of stigma.

In order to reduce stigma and improve the quality of life of those with podoconiosis a regimen of skin daily management is required to reduce the visual manifestations of the disease. This is difficult in a resource-poor country where there are numerous challenges. Literacy, access to clean water, the financial cost of soap, cloths and emollients for washing, drying

and hydrating the skin are all problematic. They are discussed in the next section.

#### ***2.3.14. CHALLENGES OF PROVIDING SKIN CARE IN RESOURCE-POOR COUNTRIES.***

Being poor in a hot dusty environment, living in cramped poor quality housing with inadequate nutrition and no piped water is not conducive to healthy skin. Accessing health care is not easy either because of poor road systems and the long distances to travel which are costly in time and money. Health facilities usually charge for treatment too so many people use local healers for treatment in the first instance. Their preparations may be ineffective, possibly harmful and often expensive. Low literacy rates are also an issue as written information on health care cannot for many people be understood and verbal instructions may not be remembered. In 2012 the estimated population of Ethiopia was 91.73 million (WHO (c) 2012). Total adult literacy 2008-2012 was estimated at 39% with literacy rates are often lower in rural areas (UNICEF 2012).

#### ***2.3.15. CLEANING SKIN IN RESOURCE-POOR COUNTRIES.***

Cleaning skin to remove dirt, dead skin and pathogens is necessary to keep it in optimum condition. Water is the basic prerequisite for washing but obtaining it is a major challenge in much of the world. Globally water from unprotected dug wells, rivers, lakes and ponds is used by 187 million people. Most of these are the rural inhabitants of sub Saharan Africa (WHO/UNICEF 2012). Approximately 1/3 of the diseases in Africa are due to environmental hazards such as lack of access to safe drinking water, lack of sanitation and hygiene and indoor air pollution. Around 1.1 billion people globally do not have access to improved water supply sources (WHO (b) 2012). Countries that have less than 50% coverage of water supply are almost all in sub Saharan Africa where the majority of the population (70-80%) are rural. In Ethiopia in 2008 only 38% of the population had access to improved drinking water sources (WHO (b) 2012). An improved water facility is one in which water is piped from a stand pipe or protected well or a protected spring or rain water. But being protected does not necessarily mean is it free from all pathogens (WHO 2010). Almost 884 million people in resource-poor

countries live without access to safe drinking water and 37% of these live in Sub-Saharan Africa (UNICEF 2011). As a result water grossly polluted by animal and human waste and/or by chemicals and heavy metals is used for cleaning the skin often resulting in skin infections. In rural areas scarce water is primarily used for drinking and cooking. Using water for washing is a low priority which results in poor foot hygiene (Molla, Tomczyk et al. 2012a).

Boiling polluted water to kill bacteria may use expensive fuels such a gas or electricity but for the majority of the population these fuels may not be available or affordable. Even charcoal is beyond the reach of most poor people and wood has to be collected which is time consuming and may result in environmental damage. Regardless of whether or not collected household water is initially of acceptable microbiological quality, it often becomes contaminated with pathogens of faecal origin during transport and storage due to unhygienic storage and handling practices. Investigations have shown sodium hypochlorite (NaOCl) to be an effective disinfectant having broad applications. It is low cost, easy to use and safe. It is recommend that drinking water contains 0.0002% - 0.0001% NaOCl (Centers for Disease Control and Prevention 2014).

The World Health Organisation defines 'access to drinking water' as the availability of at least 20 litres of water per person per day within a walking round trip of 30 minutes (WHO 2010). A Western Ethiopian study noted that the majority of patients had no issues finding enough water taking an average 10 minute walk to reach the water source (Alemu, Tekola Ayele et al. 2011). A later household survey in Northern Ethiopia reported that a return journey of 40 minutes was required to collect water (Molla, Tomczyk et al. 2012a). A third study also in Northern Ethiopia reported the average one way time to walk to the nearest water source as 19 minutes (Molla, Tomczyk et al. 2012a). There was no indication in the studies of water quality, the amount collected or the frequency with which it was collected.

The United Nations Millennium Development Target 7.C is 'to halve by 2015 the proportion of people without sustainable access to safe drinking water and basic sanitation.' In 2010 they reported that efforts needed to be

targeted and increased to bring drinking water to all rural households and that the 2015 target appears to be out of reach (United Nations 2010). Until this goal is reached those in the poorest countries will continue to have difficulty accessing even polluted water. As a result skin cleaning will remain low on the list of priorities for its use. Water alone however is not sufficient for cleaning dirty skin and treating dry skin. Soap, drying cloths and emollients are also required.

#### *2.3.15.1. ACCESSING SKIN CLEANSERS, DRYING CLOTHS AND EMOLLIENTS.*

Soaps are the main form of cleanser used in resource-poor countries. But they are not a priority purchase for the very poor and may not be easily accessible in very rural areas. Many of the block soaps which are available are highly alkaline which will disrupt the skin's normal flora and dry the skin. For example pre 2014, the soap used and supplied to patients with podoconiosis in APA clinics for washing their feet/legs had a pH of 10 and contained silicates (Section 3.3.7.1 and Appendix 5). The provision of clean cloths for washing and drying skin are beyond the budgets of very poor people. Clean separate bowls for washing their bodies are often not possible either. Emollients are not generally used as they are unaffordable and not available in the smaller villages. In the PI's observation they are not used even when the feet/legs are dry and cracked which is common when people walk barefoot.

From the literature search key gaps were found in the knowledge of the effects of the current skin treatment for those with podoconiosis. No RCTs have been published on therapeutic skin treatment for the disease. It is these gaps which are presented in the next section that the research intends to fill.

#### **2.3.16. KEY GAPS IN KNOWLEDGE ON THE TREATMENT OF PODOCONIOSIS**

No published articles were found on podoconiosis which:-

- quantitatively measured improvements in SBF via SC hydration and TEWL in those with podoconiosis before or after therapeutic interventions
- identified the most effective moisturizer to use, the quantity and how to use it

- provided an evidence based podoconiosis treatment intervention
- measured and compared the dermatology quality of life of those with podoconiosis pre and 3 months post therapeutic skin interventions.

This study will focus on these key gaps in the literature in order to provide evidence based treatments which can be measured and improve the dermatology quality of life of those with the disease.

### **2.3.17. SUMMARY OF SECTION 2.3.**

There are several billion people living in the rural areas of resource-poor countries mainly in Africa who for numerous reasons lack even the most basic skin care (Hay, Fuller 2011). The numbers are estimated because skin disease is under-reported and for a number of reasons not adequately treated. Podoconiosis is one of these diseases and in 2011 it was recognised as a neglected tropical skin disease (Davey, Bockarie et al. 2012). It affects about 3 million of the poorest people in Ethiopia and largely unknown numbers in a least 20 other countries that walk barefoot in areas of volcanic soil at high altitude with high rainfall. It is caused by skin breaches in the feet through which silica and bacteria enter. These cause an inflammatory reaction which impacts on skin and the lymphatic system in the legs. Although the exact cause is unknown its development appears due to a faulty immune system (Addisu, El-Metwally et al. 2010). Indications are that there is a familial component and it is thought the disease might be a T cell-mediated inflammatory disease (Tekola Ayele, Adeyemo et al. 2012). It results in lymphoedema, pain, lost working days and stigma. It has a major effect on quality of life and mental health. Most of those who have the disease are in the economically active age group. Episodes of ADL result in work days being lost due to pain causing economic distress which impacts on the individual and society.

Although podoconiosis is preventable it is not curable and will progress unless a lifetime skin management regime is followed. To improve SBF, reduce oedema and prevent ADL the SC needs to be kept clean and hydrated. This can be achieved by washing the skin in soap and water, careful drying and applying moisturisers, barrier ointments with the addition

antifungal creams where necessary. Shoes and socks should be encouraged but may not be possible for patients to provide due to cost. Elevation of the effected limbs at night and exercise of the ankle should be encouraged to reduce lymphoedema. Compression bandaging may be appropriate but is expensive and requires the exclusion of co-morbidities and expertise to apply. Improving the symptoms of the disease improves quality of life. The skin condition, social stigma and consequently the quality of life of those with the disease have been shown to significantly improve using the current skin treatments. Although effective they are based on custom and practise and not evidence based.

Regular attendance at clinics enables staff to educate patients, monitor and support their progress and provide supplies but non-attendance is an issue. A lack of knowledge about the disease by health professionals and local populations results in those with the disease not being treated. Although simple skin care is the main treatment providing this in resource-poor countries is challenging. Any interventions should be low cost, easy to use and sustainable. Ryan (2006) notes the huge poverty stricken rural areas in resource-poor countries are 'crying out' for skin care at low cost. To address the key gaps found in the current skin treatment for those with podoconiosis further literature searches were undertaken. These were to provide information on the SBF, its assessment and the effects of skin disease. It was also to provide evidence for the use of each of the components current used in the skin hygiene regime in podoconiosis clinics. Literature searches were also carried out to provide information on the optimal yet cost effective emollient to improve SBF. No research studies on maintaining a healthy SBF were found which were undertaken in Africa, most were carried out in the developed world as described in Section 2.6.

Podoconiosis is a disease caused primarily by an impaired skin barrier function (SBF). For this reason the many functions of the skin, the components and functions of the SC and measurements required to determine the condition of SBF are discussed next.

## **2.4. ASSESSMENT AND MEASUREMENT OF SKIN BARRIER FUNCTION.**

Skin performs many vital functions including forming a barrier to physical agents and preventing loss of body fluid thus avoiding desiccation and death in a terrestrial environment. It also helps protect the body against potential pathogenic organisms and aids the regulation of body temperature by radiation, convection, conduction and evaporation. It contains both sensory and autonomic nerves and several types of sensory receptors which detect the stimuli of vibration, touch, changes of temperature, pressure pain and itch. Skin also reduces the penetration of ultra violet radiation and synthesises Vitamin D which is necessary for the absorption of calcium and calcification. Additionally it is an important means of socio-sexual communication.

The stratum corneum (SC) which is the outermost layer of the skin is thickest on the soles of the feet and palms of the hands. Although it constitutes only 10% of the entire skin it contributes to over 80% of the SBF (Pouillot, Dayan et al. 2008). The inner cell layers of the SC are more hydrated (about 70%) compared to the outer layers suggesting a water gradient. The water acts as a plasticizer keeping the SC flexible and helping prevent cracks due to physical forces (Chrit, Bastien et al. 2006).

Natural moisturizing factors (NMFs) are present in high concentrations within the cells of the SC (corneocytes) making up approximately 15-20% of their dry weight (Rawlings, Harding 2004). NMFs are essential for SC hydration, barrier homeostasis, desquamation and plasticity. They absorb water from the atmosphere combining it with their own water content thus allowing the outermost layers of the stratum corneum to stay hydrated despite exposure to the elements. NMFs include free amino acids or their derivatives, urea, hyaluronic acid and glycerol (Choi, Maibach 2005, Meyer, Thyssen 2012, Rawlings, Harding 2004). Endogenous glycerol (glycerine) is produced in the pilo-sebaceous units of skin and transported to the epidermis by the water/glycerol channels (aquaporin-3) (Verdier-Sévrain, Bonté 2007). These channels are discussed further in section 2.6.3.2. Generally the SC is semi-permeable only allowing a small amount of water loss in order to hydrate its

outer layers and maintain flexibility. Normal skin loses approximately 100-150 mls of water per day per square metre of skin surface (Marks 2004). In normal skin the relationship between hydration and the skin's permeability results in a TEWL which is virtually constant over a wide range of ambient relative humidity (Sparr, Millecamps et al. 2012). In inflammatory skin diseases because the SC is disrupted the water loss increases.

A systematic review and meta-analysis of English and German primary studies of *in vivo* measurements of TEWL in normal adult human skin identified 167 studies with adequate and clear reporting. This provided data on 50 skin areas. The lowest TEWL recorded was 2.3 grams per metre squared per hour ( $\text{g/m}^2\text{h}$ ) on breast skin and the highest 44.0  $\text{g/m}^2\text{h}$  in the axilla (Kottner, Lichterfeld et al. 2013). The high scores in the axilla may have been related to the number of apocrine glands in that area.

The level of SC hydration influences all the interconnected constituents and activities within the SC which lead to an effective moisture barrier (Rawlings, Harding 2004). In order to fulfil its function of preventing dehydration and maintaining its flexibility the SC needs to contain at least 10% water (Warner, Lilly 1994). It has three essential mechanisms for achieving this. Firstly the lamellar lipids provide a tight and semi-permeable barrier to water passing through the tissue. Secondly fully mature corneocytes bound by corneodesmosomes provide convoluted and lengthy pathways which inhibit water loss. Thirdly NMFs absorb water from the atmosphere and combine it with their own water content. Together these allow the outer layers of the SC to remain hydrated despite exposure to the elements allowing enzyme reactions to aid SC maturation, corneodesmolysis and finally desquamation (Rawlings and Matts 2004).

Influential factors in the capacity of skin to retain water and therefore a satisfactory SBF are a person's age and gender, the skin's pH, NMFs, antimicrobial peptides, the arrangement of the corneocytes, the structure of the intercellular lipids and the calcium gradient. Low calcium levels in the lower epidermal layers increase progressively towards the outer stratum granulosum and declines again in the SC (Elias, Ahn et al. 2002). This

gradient facilitates keratinocyte differentiation and helps regulate the formation of the epidermal layers (Proksch, Brandner et al. 2008). Some of the intrinsic and extrinsic factors influencing measures of TEWL and SC hydration were identified by the International Guidelines (du Plessis, Stefaniak et al. 2013). The variables effecting both TEWL and SC hydration included anatomical site, skin temperature, sweating, air convection, ambient temperature, humidity and season. Gender seemed to have no influence on either TEWL or SC hydration. There was conflicting evidence on the effect of age of TEWL and no data on the effect of direct sunlight on SC hydration.

SBF may be assessed by measuring trans-epidermal water loss (TEWL) and stratum corneum (SC) hydration. TEWL is the water lost through the skin and its appendages under non-sweating conditions. It is the major indicator of healthy skin. TEWL can be measured quantitatively with non-invasive probes which are placed on the skin (Appendix 2). The international standard TEWL measurement is  $g/m^2h$  (du Plessis, Stefaniak et al. 2013). SC hydration can also be measured quantitatively in arbitrary units with non-invasive probes by measuring skin capacitance, conductance, impedance and resistance. The measurement devices used and methods are discussed in Section 3.3.9. TEWL varies depending on the specific body site at which it is recorded, because of this there is no agreed definition of a 'normal' TEWL. An expert working group reviewed the evidence and produced International Guidelines for the *in vivo* assessment of skin properties. This recommends reporting difference or percentage change in TEWL and SC hydration rather than absolute values (du Plessis, Stefaniak et al. 2013).

Because the study is being undertaken on Ethiopian people with black skin, the differences in SBF between racial groups are the focus of the next section. They have been investigated in several studies.

#### **2.4.1. THE IMPACT OF ETHNICITY ON SKIN BARRIER FUNCTION.**

TEWL, SC hydration and skin pH are very important elements in maintaining SBF. Studies of these in relation to ethnicity are the focus of the following section.

**2.4.2. ETHNIC DIFFERENCES RELATED TO TRANS-EPIDERMAL WATER LOSS,  
STRATUM CORNEUM HYDRATION AND pH.**

Ethnic differences in TEWL, SC hydration and pH have been the focus of many studies. Published studies found on TEWL related to ethnicity are presented in Table 2.4. The studies are difficult to compare because of the variation in the anatomical sites used, the difference in pH of different sites, the different study conditions and disparity in the numbers in each ethnic group. Because of this the results are inconclusive.

**Table 2.4. Studies of ethnic differences related to trans-epidermal water loss.**

Type of study	Method	Numbers	Body sites	Results	Reference
Review of 10 studies from 1988-2002.	Nine <i>in vivo</i> , one <i>in vitro</i>	Numbers (16-60). Numbers not specified in the <i>in vivo</i> study.	Five studies on volar forearm, one on inner thigh, two on back, one on left and right cheeks, lower legs and volar forearms. Sites not reported in the <i>in vivo</i> study.	Six studies indicated TEWL greater in black skin compared to Caucasian skin. Three were the same when using forearm, back and inner thigh. One study indicated TEWL lower in black skin.	Wesley, Maibach 2003.
Comparative biometrical evaluations.	<i>In vivo</i> TEWL measured.	18 African/American women, 19 Caucasian women 35-65 years.	Volar forearms.	No difference in TEWL.	Grimes, Edison et al. 2004.
	In subset TEWL measured after application of 5% lauryl sulphate under occlusion 6 hours, 30 minutes (mins), 24 hours, 48 hours after patch removal.	Subset of three African/American and five Caucasians.	Volar forearms.	After 30 mins TEWL was 21.9 g/m <sup>2</sup> h in African/American skin and 32.3 g/m <sup>2</sup> h in Caucasian skin. After 24hrs TEWL was similar in both groups and the same after 48hrs.	

Comparative biometrical evaluations	<i>In vivo</i> study over 4 weeks in spring. Approximately 8 age matched sub-Saharan black, African/Caribbean mixed race /Caucasian subjects matched each week. Total of 25 in each of the three groups. All living in France for at least six months.	75 women aged 18-32 years with healthy skin.	Forehead and volar forearm.	No differences in TEWL.	Fotoh, Elkhyat et al. 2008.
Comparative biometric evaluation	<i>In vivo</i> testing in controlled temperature (20°C- 21°C) and humidity (25% relative). TEWL baseline data measured skin then disrupted using tape. TEWL re-measured.	73 African/Americans, 119 Caucasians and 149 east Asians all healthy with no skin disease aged 18-45 years.	Both cheeks.	Baseline TEWL significantly different in the three groups (p=0.001). Lowest in African/Americans signifying an intact, functioning SBF and highest in Caucasians with SBF of Asians between the two.	Muizzuddin, Hellemans et al. 2010.

Ethnic differences in skin pH have also been explored since an optimal pH is crucial for maintaining SBF. A review reporting on two small studies implied some difference in pH between black and Caucasian skin but they were inconclusive requiring further investigation (Wesley, Maibach 2003). Grimes found no difference between skin pH on the faces of African/American (n=18) and Caucasian (n=19) females (Grimes, Edison et al. 2004). The result may have been different if pH had been measured on other body sites. A further study was undertaken on the skin pH of women of different ethnicity aged 20-32 years with twenty-five in each ethnic group (n=75) (Fotoh, Elkhyat et al. 2008). Skin pH was measured three times on the forehead and volar forearm during a four week period. A higher pH was noted in sub Saharan black skin as opposed to the Caucasian and African/mixed African ethnicity groups. The authors suggest this highlights the acidic effect of their greater sweat and/or sebaceous secretions. A greater age range and the inclusion of males may have affected results.

#### ***2.4.2.1. OTHER STUDIES OF ETHNICITY AND SKIN.***

A review of the differences in SBF between ethnic skin types reported a greater number of melanosomes in those with black skin (Rawlings 2006). The SBF was reported as more effective in darker skin when subjected to chemical or mechanical assault. Apocrine and eccrine glands which both produce sweat were more abundant in black skin with larger gland size, greater sebum production and more skin micro-flora compared to other skin types. The review provided no details of the review period or search methods.

In summary the SC is a complex dynamic physiological system which is essential to human life. Intrinsic factors influencing TEWL and SC hydration include age, anatomical site, skin temperature and sweating. Extrinsic factors include air convection, ambient temperature and humidity. Existing studies on ethnicity and SBF are generally on small numbers. From available evidence it would appear that compared to Caucasian and Asian skin black skin has greater cohesion of corneocytes but the same skin thickness. Black skin has greater sebum production and appears to be more acidic with higher quantities of micro-flora. Skin shedding is also higher. Studies of TEWL and SC hydration are inconclusive. Because of the lack of published studies on TEWL, SC hydration and skin pH related to ethnicity further research evidence is required.

There is conflicting information on whether podoconiosis prevalence is higher in males or females (Table 2.1). Because podoconiosis is primarily due to a fault in SBF the next section discusses gender issues related to SBF.

#### ***2.4.3. THE IMPACT OF GENDER DIFFERENCES ON SKIN BARRIER FUNCTION.***

Studies on TEWL and SC hydration in healthy skin related to gender are discussed next. This section includes the International Guideline consensus on gender and skin.

#### **2.4.3.1. GENDER DIFFERENCES RELATED TO TRANS-EPIDERMAL WATER LOSS AND STRATUM CORNEUM HYDRATION.**

There have been several studies on gender difference related to TEWL and SC hydration (Chilcott, Farrar 2000, Man, Xin et al. 2009, Firooz, Sadr et al. 2012, Mizukoshi, Akamatsu 2013). They were all conducted on different age groups, different parts of the body with different study numbers and subsequently produced inconsistent results. The International Guideline for the *in vivo* assessment of skin properties has concluded that there is insufficient evidence to determine gender effects on TEWL and skin hydration (du Plessis, Stefaniak et al. 2013).

Skin diseases including podoconiosis have a detrimental effect on SBF causing dryness, a roughened skin surface, reducing SC hydration and increasing TEWL. There is also a consequential inflammatory reaction which exacerbates the condition. This is discussed next.

#### **2.4.4. THE EFFECT OF SKIN DISEASE ON BARRIER FUNCTION.**

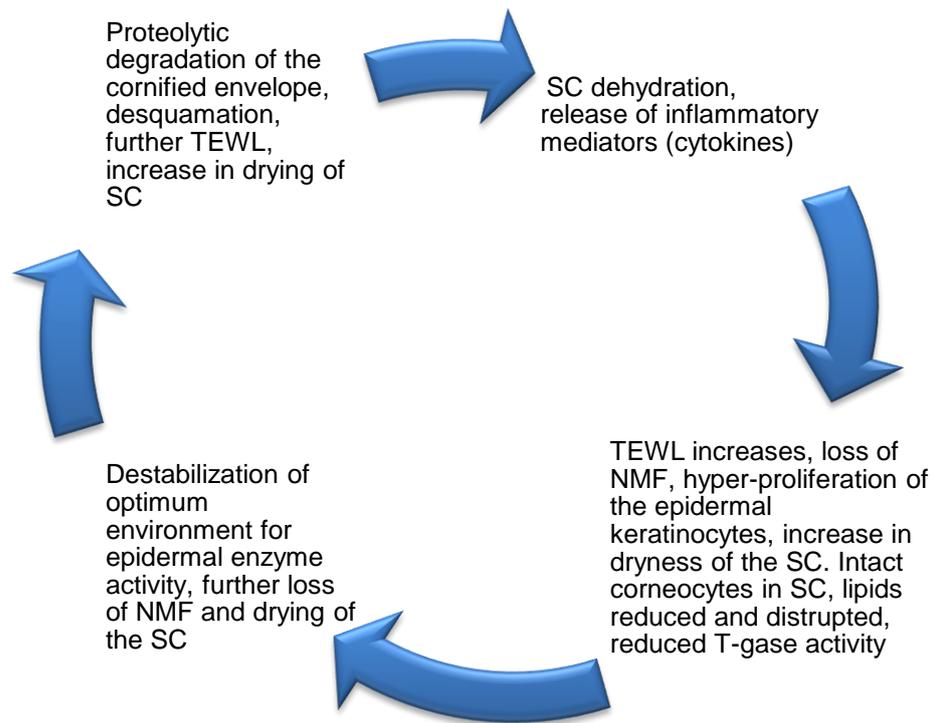
Healthy skin may be defined as skin which is unblemished, with a consistent tone and colour which has a soft firm texture, is not dry or itchy and fulfils all its functions. Dry skin is a common feature of skin diseases characterized by a disruption of the skin barrier and a consequential excess loss of skin moisture.

The common characteristics of dry skin have been reported. These related to the visual changes of redness, lack lustre surface, dry patches, flakes, possible fissures and fine lines and possible thickening and the sensory changes of feeling dry and tight, uncomfortable, itchy, painful, stinging and tingly. The reported tactile changes were a rough and uneven skin surface and chemical changes were reduced water content, reduced NMF, changed lipid composition and functional changes of increased permeability, increased TEWL and less resistance (Lodén 2005).

Within the inner layers of the SC in healthy skin, corneodesmosomes activated by enzymes, begin to degrade and encapsulate with barrier lipids. This transforms the fragile corneocytes into ones that are more resilient. This

normal functioning of the SC is disturbed in dry flaky skin conditions which occur in skin disease resulting in a deteriorating cycle of events. Superficial dehydration of the SC causes an inflammatory reaction and the release of cytokines. These are non-antibody proteins which act as inflammatory mediators. This results in hyper-proliferation of epidermal keratinocytes and the production of smaller immature corneocyte envelopes. It also leads to lipid disruption, reduced filaggrin synthesis and reduced T-gase activity. The reduction in T-gase activity causes the cornified envelopes surrounding the corneocytes to be less resistant to proteolytic degradation. Because the corneocytes are weakened they are prone to further insults from activities such as washing. This results in an excessive loss of NMFs from the fragile corneocytes and subsequent loss of SBF (Rawlings, Matts 2004). Desquamation at the surface of the SC results in scaling and thickening. The water gradient across this thickened SC becomes steeper leading to further increases in water lost via evaporation. The next Figure 2.2 illustrates the continuing cycle of progression resulting from dry skin.

**Figure 2.2. The Dry Skin Cycle** (based on Rawlings, Matts 2004).



Without intervention this cycle of events perpetuates itself. In order to break the cycle the symptoms need to be treated, the SC repaired and SC barrier function improved.

The visual manifestations of skin disease such as flakiness, redness and thickening may have profound effects on a person's psychological health and social interactions. This may in turn exacerbate the severity of the disease. These topics are the focus of the next section.

#### **2.4.5. EFFECTS OF PSYCHOLOGICAL STRESS ON SKIN BARRIER FUNCTION.**

A review of the defensive functions of the SC noted that psychological stress exerts a negative effect on permeability barrier homeostasis (Elias 2005). It increases endogenous glucocorticoids, suppresses lamellar body production and epidermal lipid synthesis resulting in altered barrier function and the integrity/cohesion of the SC. The review was based on three human studies (Altemus, Rao et al. 2001, Garg, Chren et al. 2001, Kao, Fluhr et al. 2003).

An investigation was undertaken into the relationship between stress and epidermal permeability barrier in 27 medical, dental and pharmacy students without any skin disease. Their psychological state was measured by the Perceived Stress Scale (PSS) and the Profile Mood States (PMS). SBF was measured during one period of perceived high stress, during final examinations and on two lower stress occasions, return from winter holidays and four weeks after the exam. The entire group had a statistically significant reduction in the permeability barrier recovery after tape stripping related to increases in perceived stress. Improved barrier recovery function was noted in all participants at times of lower stress ( $p=0.001$ ) (Garg, Chren et al. 2001).

Another study was undertaken into the effects of stress on SBF women ( $n=46$ ). Of these 25 participated in a laboratory psychological interview, 11 were deprived of sleep for one night and 10 undertook an exercise protocol (Altemus, Rao et al. 2001). Measurements were taken before and after the stress factors. They were: TEWL, SC hydration and SBF recovery after skin stripping. The interview resulted in an increased TEWL, no effect on SC hydration and delayed skin barrier recovery ( $p<0.04$ ). Deprivation of sleep had no effect on either TEWL or SC hydration but it did delay skin barrier recovery ( $p<0.04$ ). Exercise had no effect on any of the measures. The participants were all female, this and the different numbers in each arm of the study may have affected outcomes. A double blind study of three male and four females with no skin disease (aged 20-59) applied clobetasol propionate (potent topical corticosteroid) to one volar forearm and a vehicle to the other forearm once a day for three days. TEWL was measured at baseline, 3 and 24 hours after disruption by tape stripping (Kao *et al.* 2003). The application of stress hormones resulted in delayed barrier recovery after stripping and abnormal SC integrity and cohesion ( $p=0.05$ ). Numbers on the study were small so further evidence is required.

A six month longitudinal study of patients in the Netherlands with psoriasis measured serum cortisol, Psoriasis Area Severity Index and self-reported measures of daily stressors over six months ( $n=62$ , 73% male, 27% female). The result was that peak levels of daily stressors predicted an increase in

disease severity four weeks later (Evers, Verhoeven et al. 2010). The unequal male/female ratio may have affected results.

In summary evidence suggests that psychological factors such as stress, increases glucocorticoid levels which negatively affects SBF by delaying skin barrier recovery and SC cohesion/integrity. No published studies were found on the effects of stress on the skin of indigenous people in resource-poor countries. This is an area requiring further research.

It is increasingly recognised that skin disease can significantly impact on psychological health, social functioning and daily activities of patients and their families (Schofield, Grindlay et al. 2009). These issues related to pododermatitis were previously discussed in Section 2.3.12. The psycho-social effects of other skin diseases are discussed next.

## ***2.5. THE PSYCHO-SOCIAL IMPACT OF SKIN DISEASE.***

Skin is the individual's interface with their environment. Judgements on a person's age, ethnicity, health status, hygiene levels and attractiveness are made by others observing the condition of their skin. Any skin disfigurement may result in ridicule, depression, lack of self-esteem, social isolation, loss of income, reduction in a person's chance of marriage and stigmatisation. Imperfections may be interpreted as unhealthy, ugly and likely to be a source of infection. An enquiry by The All Party Parliamentary Group on Skin into the impact on people's lives of skin disease highlighted the prejudice and discrimination they experience (All Party Parliamentary Group on Skin 2003). Those with skin disease avoided activities in which it might be necessary to expose their skin such as sporting activities, being photographed and meeting new people. This limited their social lives. The authors stated that the effects of skin disease are considerable and undervalued affecting lives psychologically comparable to the effects of those with arthritis or other disabling illnesses (Barankin, DeKoven 2002). Several studies have noted the psychological and social issues related to skin disease. The psychological issues include stress, anger, anxiety, depression, embarrassment, helplessness, guilt, irritability, low confidence, loneliness

and low self-esteem. Social issues include performance and relationship issues, sexual problems, social isolation, increased alcohol intake, bullying, loneliness, sleep deprivation and victimization (Barankin, DeKoven 2002, Schofield, Grindlay et al. 2009, Millard, Millard 2010).

There are a number of tools for measuring the impact of skin disease on quality of life. They include: Dermatology-Specific Quality of Life (DSQL), Dermatology Quality of Life Scales (DQOLS), Health Related Quality of Life (HRQOL), Nottingham Health Profile (NHP), Short-Form-36 (SF-36), Sickness Impact Profile (SIP) and World Health Organization Quality of Life (WHOQOL) and Dermatology Life Quality Index (DLQI). DLQI in those with podoconiosis was discussed further in Section 2.3.13. No systematic reviews were found on the psychological effects of skin disease in general or on those in developed or resource-poor countries; therefore the following selection of larger published studies on different aspects of quality of life of those with different skin diseases in both the developed and resource-poor countries were included.

Skin disease was reported to have a significant impact on the quality of life of American patients with psoriasis who completed a non-disease specific, health related quality of life (HRQOL) questionnaire. This was then compared to those of patients with other chronic health conditions such as cancer, heart disease, diabetes, depression and arthritis. The impact on HRQOL was found to be similar to the other chronic diseases some of which are potentially fatal (n=318) (Rapp, Feldman et al. 1999). The impact of two skin diseases on the domestic and social lives of patients was the focus of a cross sectional study in India which compared patients with vitiligo (n=150, mean age 35.11 years) to those with psoriasis (n=150, mean age 42.13 years) (Pichaimuthu, Ramaswamy et al. 2011). Problems in participating in work, education and employment as well as in community and civic life were significantly greater than in the vitiligo patients (p=0.027). This difference may have been due to those with psoriasis having more of their skin and more parts of their body affected. No differences were noted in minor psychological morbidity, self-consciousness and neuroticism between those with different skin diseases (acne, psoriasis and atopic eczema) (n= 180) in

a cross sectional study in Australia (Magin, Pond et al. 2008). Higher levels of moderate to severe depression and personality disorders in those with skin disease were reported in an Iranian study of 144 dermatology patients and 100 controls (Rasouljan, Ebrahimi et al. 2010). Some suffered with moderate to severe depression (77 (70%) patients versus 26 (20%) controls) and some from personality disorders (22 (15.27%) patients and five (5%) controls). They concluded that skin disease is associated with deep emotional suffering. A questionnaire study of anxiety and depression in an Italian dermatology out patients (n=567) revealed 149 (26.2%) of participants, scored positive for anxiety, and 52 (9.2%) scored positive for depression (Mazzotti, Mastroeni et al. 2012). They suggested that stress management and psychological support should be incorporated into the treatment of these diseases.

Despite the use of different outcome measures and in some of the control studies which had different numbers in each arm, all the studies all indicate that skin disease can have a profoundly negative effect on the mental and emotional health and quality of life. This effect is consistent across different age groups, racial groups and cultures and in both the developed and resource-poor countries. In order to reduce its psycho-social impact those with skin disease need to improve the condition of their skin. Improving and maintaining SBF ensures that the appearance of skin improves and that it is able to fulfil all its functions. This is discussed in the next section with particular reference to the skin management regime currently used for those with podocniosis.

## ***2.6. IMPROVING AND MAINTAINING HEALTHY SKIN BARRIER***

### ***FUNCTION.***

Cleaning the skin is an essential skin management therapy generally achieved by washing in water but the quality and temperature of the water is important and this is discussed in 2.6.1.1 and 2.6.1.2. Soap may be added to help remove dirt but this may adversely affect SBF. These issues and the use of emollients to improve SBF are discussed next.

### ***2.6.1. MAINTAINING OPTIMUM STRATUM CORNEUM HYDRATION AND TRANS-EPIDERMAL WATER LOSS.***

Under normal conditions the surface of the skin is continually losing water to the atmosphere. This is replenished from the epidermis beneath creating a water gradient which decreases towards the surface of the skin. The water gradient affects SBF and the enzymes which control desquamation. Any alteration in the optimum levels of this gradient may result in 'dry skin' (Crowther, Matts et al. 2012). Prolonged exposure of skin to water, exposure to variable temperatures and humidity, the application of cleansers and skin disease can all upset normal SC hydration leading to dryness and increased desquamation. These issues are discussed further in the following sections.

#### ***2.6.1.1. WATER FOR CLEANING THE SKIN.***

To maintain its functions skin needs to be kept clean, surface dirt and excessive grease removed and the build-up of micro-organisms on its surface prevented. The cleaning process also rejuvenates skin by assisting exfoliation. Bathing or showering in water alone cleans the skin by mechanical means but, prolonged or too frequent contact with water actually makes skin drier. This is because NMF components in the SC are water soluble and easily leached from cells during water contact. Studies suggest that exposure to water of less than 1 hour even if repeated over a day or several days had no damaging effects on the intercellular lipids (Ramsing 1997, Warner, Stone et al. 2003).

A literature search found the following three small published studies. In the first the effect of water on experimentally irritated skin was investigated on 21 volunteers. One hand was exposed to water for 15 minutes twice a day for two weeks. The other hand served as a control. TEWL and skin hydration were measured and it was reported that immersion in water did not significantly alter TEWL. The conclusion was that exposure to water for 30 minutes daily does not disrupt the SC barrier of previously sub-clinically irritated skin (Ramsing 1997). A further small study placed water on the volar forearms of two healthy males, aged 38 years and 54 years. This was sealed under an occlusive dressing. The control site was a third area on the same

forearm. After four and 24 hours shave biopsies were taken. The skin exposed to water for four hours and 24 hours showed a three or four fold expansion in the thickness the stratum corneum respectively. The corneocytes swelled and large pools of water were found in the intercellular spaces. These increased in size over time. Their conclusion was that when the skin is exposed to water for over 1 hour it causes significant swelling of corneocytes (Warner, Stone et al. 2003). The third study on normal skin on the back and shin noted that endogenous glycerol levels significantly reduced following a <5 minute soap-less shower ( $p=0.002$ ). The study also assessed SC hydration in sites on the forearms after a 20 minutes water soak. The decline in SC hydration ( $p=<0.01$ ) was matched by a significant decrease in SC glycerol ( $p=0.034$ ) ( $n=8$ ) (Choi, Mao-Qiang et al. 2005). Although the study was small it suggests that endogenous glycerol influences SC hydration. From the studies it seems that immersion of skin in water should be kept to a minimum to maintain endogenous glycerol levels, hydration and TEWL. Additional larger studies are required to provide further evidence.

The quality of washing water is important for maintaining skin health. A Cochrane review analysed 11 randomized and quasi-randomised into the effects on wounds of drinkable quality tap water compared to other wound cleansing solutions (Fernandez, Griffiths 2008). The studies were of variable quality. Trials on burns and dental procedures were excluded. The other solutions used were normal saline, procaine spirit, distilled water and boiled water. The studies were undertaken in various settings including hospitals and the community. Patient's ages ranged from 2-95 years. The review concluded that using tap water to cleanse acute wounds in adults did not increase infection rates. The reviewers concluded that where tap water is of drinkable quality it may be as good as other methods such as sterile water or saline and more cost-effective. It is now extensively used in the UK for managing wounds. Drinkable quality water should therefore be suitable for washing the skin of those with skin disease. This is because the reduction in SC barrier function in their skin makes it more susceptible to infection.

The temperature of washing water is also important as it can affect SBF. Only two studies were found related to this both with small numbers. A study on surfactant-induced skin irritation focused on the effect of water temperature (n=10) (Berardesca, Vignoli et al. 1995). Four random areas on the volar forearm of were treated daily with 5% lauryl sulphate for four days. The solutions were at three temperatures: 4<sup>0</sup>C, 20<sup>0</sup>C and 40<sup>0</sup>C. One site was the control. On the fifth day skin irritation was assessed using TEWL measurement, erythema, skin reflectance, SC hydration and desquamation. Skin damage was higher on sites treated with higher temperatures. Results indicated a highly significant effect of the solution's temperature on skin irritation (p=<0.001). Another study compared the effects of blood flow in the foot following immersion in a warm bath (100°F/37.8°C) to contrast baths (Petrofsky, Lohman III et al. 2007). Measurements were made by laser Doppler flow meter on dorsal and plantar aspects. Feet were immersed in the warm bath or for three minutes followed by 1 minute cold 60°F/15.6°C. The cycle was repeated for 16 minutes. Fourteen participants, average age of 55.1 years were compared to 12 people, average age 23.9 years. The blood flow increased in both groups with the warm bath. There is a lack papers published on the most effective water temperature for washing but hot water essentially removes more lipids from skin. Warm water immersion increases blood flow in feet and barrier function recovery. It would appear that to avoid skin damage washing water should be at or near the normal body temperature of 37.2°C. In a guide on protecting skin and preventing its breakdown it is recommend that very hot water should be avoided as it increases evaporation and removes skin lipids (Ersser 2010).

Water alone cannot remove oily, organic soiling. It requires a cleansing agent. There are three major categories of cleansing agents: soaps (detergents), syndets, and lipid-free cleansing agents. Although there are three categories, soap will be the focus of the next section as it the only cleanser used extensively in Ethiopia where the study will be based.

#### *2.6.1.2. SOAP FOR CLEANING THE SKIN.*

The following table 2.5 identifies some of the constituents of typical soap bars.

**Table 2.5. Typical composition of soap bars** adapted from (Ananthapadmanabhan, Moore et al. 2004).

Soap bar (ordinary)	Soap bar (super-fatted)
Sodium tallowate	Sodium tallowate
Sodium cocoate	Glycerin
	Sodium cocoate
	Sorbitol
	Palm kernelate
	Types Sodium chloride
	Sodium palmitate
	Pentasodium pentetate
	Water
	Tetrasodium etidronate
	PEG-6 methyl ether
	Butyl hydroxy toluene (BHT)
	Palm acid or tallow acid
	Titanium dioxide

Soaps clean by acting as an emulsifier allowing oil and water to mix in order that oily substances and dirt can be removed during rinsing. They are obtained by treating vegetable or animal oils and fats with a strong alkaline solution. Fats and oils are composed of triglycerides: three molecules of fatty acids attached to a single molecule of glycerol. The alkaline solution brings about a chemical reaction known as saponification. In saponification, the fats are first hydrolysed into free fatty acids, which combine with the alkali to form a basic soap. The glycerol (glycerine) which is liberated is either left in the soap or washed out and recovered as a useful by-product. Super-fatted soaps contain extra fats such as glycerine and palm oil.

Soaps may leave a residue on skin that can be irritating. All testing methods of soaps indicate that frequent exposure induces barrier damage and skin dryness followed by inflammation (Wolf, Parish 2012). An expert dermatology symposium report noted that most soap has a pH of over 7 with some as high as 10 (Ananthapadmanabhan, Subramanyan et al. 2013). A high pH affects the acid mantle of the skin changing it from one which is slightly acid into one which is more alkaline and decreasing the fat content. This causes an increase in surface micro-organisms, colonisation and possible infections by pathogenic bacteria.

The effects on skin micro-flora of washing with soap and water versus washing with a no-rinse cleanser were compared in healthy adult volunteers

(n=45) (Rönner, Berland et al. 2010). A solution of test bacteria, either *Escherichia coli* or *Staphylococcus aureus*, was applied to participant's forearms. After 15 minutes incubation one arm was cleaned using soap and water and the other arm was cleaned with the no-rinse cleanser. Both cleaning methods resulted in 4-5 fold log reductions in bacterial count. A 4 fold log reduction means the number of pathogens is 10,000 times smaller and a 5 log reduction that the number of is 100,000 times smaller. A randomised controlled study of faecal hand contamination recruited 20 volunteers who deliberately contaminated their hands by touching door handles and railings in public places. They were then randomly allocated to either hand washing with water or hand washing with non-antibacterial soap or no hand washing. Each performed the procedure 24 times resulting in 480 samples. Bacteria of potential faecal origin (mostly *Enterococcus* and *Enterobacter spp.*) were found after no hand washing in 44% of samples. Hand washing with water alone reduced the presence of bacteria to 23% ( $p < 0.001$ ). Hand washing with soap and water reduced the presence of bacteria to 8% (comparison of both hand washing arms:  $p < 0.001$ ). The effect did not appear to depend on the bacteria species (Burton, Cobb et al. 2011). The results of this small study indicates that washing with non-antibacterial soap is more effective in removing faecal bacteria than washing with water alone or no washing.

In conclusion conventional soaps remove natural oils from skin so are not suitable for those with dry skin conditions. The surface pH value (acid mantle) in healthy skin is normally acidic with a pH value of 4-6 (Ali, Yosipovitch 2013). Most soap is alkaline and therefore alters the skin's normal acid mantle and normal skin flora making it more susceptible to pathogens. Soaps which are super-fatted and have a pH nearer the normal skin surface pH values are therefore preferable. After washing careful drying of the skin is important as it may cause disruption to the skin surface, this discussed next.

### **2.6.2.EFFECT ON SKIN OF THE COMBINATION OF DIFFERENT WASHING AND DRYING TECHNIQUES.**

An experimental cohort design study of healthy volunteers had six different washing and drying techniques applied to their volar forearms (n=15). Participants underwent three washing and drying procedures on each arm. Each technique was repeated twice, separated by a two hour rest period. The skin was assessed by measuring TEWL, SC hydration, skin pH, and erythema. Comparisons were made between washing with soap or water alone, and drying using a towel (rubbing and patting) or by evaporation. TEWL increased after each type of washing process and increased further with repeated washing. There was an increase in skin pH with all washing and drying techniques, especially when soap was used. No significant changes were observed in SC hydration when measured with a corneometer, although there was a tendency for the values to decrease with washing (Voegeli 2008a). The study was small and soap pH was not reported but the data suggests that washing with soap and water and towel drying had a significant disrupting effect on the skin's barrier function. A cumulative effect of increasing damage may occur as washing and drying frequency increases.

### **2.6.3. EFFECTS ON SKIN OF DIFFERENT DRYING PRACTICES.**

Only two published research articles were found on this topic. A small South Korean study enrolled females aged 19-34 years to investigate the acute effects on forearm skin of weekly rubbing with a rough towel (n=10) (Huh, Seo et al. 2002). Rubbing was undertaken after soaking the skin for 5 minutes in warm water (36°C). A further 32 women aged 19-49 years were enrolled to investigate any chronic effects. None of the women had dermatological problems. The skin was rubbed 0, 5, 10 and 15 times, although the degree of rubbing was not controlled. All of the measurements were performed at a constant room temperature of 20-22°C and a relative humidity of 30%-32%. There was a decrease in the water holding capacity of the SC six hours after treatment. This decreased further until after day three when it returned to normal levels. TEWL also peaked at day two and

declined thereafter. There were no changes noted in the SBF or the water holding capacity but the stratum corneum turnover time was shortened. This would indicate that the SC in those with normal skin is able to return to normal within a few days of rubbing with a towel. However more frequent washing and rough drying would not have allowed the SC to recover before another episode of the treatment. An experimental cohort study indicated that drying the skin by patting with a towel increased TEWL and did not offer any advantage over conventional gentle rubbing (n=15) (Voegeli 2008b). This he suggests was because it left the skin significantly wetter and at greater risk of frictional damage. The definition of gentle rubbing was not given. From very limited evidence of these two small studies it would seem that in order to avoid damage to the SC, drying is best undertaken by gentle rubbing with a towel.

Emollients are increasingly used to hydrate and improve the appearance of skin. They are discussed in the next section. Emollients are particularly important in those with podoconiosis a disease caused by a defect in SBF as they have the ability to improve SBF.

#### **2.6.4. EMOLLIENTS.**

Emollients are topical products used to hydrate the SC. They are designed to make the external layers of the skin softer and more pliable. They may be composed of naturally occurring skin lipids and sterols as well as artificial or natural oils and lubricants. Occlusive emollients form a thin film on the skin's surface filling the spaces common in dry skin conditions between the desquamating corneocytes, smoothing the SC surface and increasing the skin's ability to hold water (Levi, Weber et al. 2010). They may be found in bath additives, skin cleansers or in 'leave on' products. Only 'leave on' products will be discussed as bath additives and skin cleansers are generally not available in Ethiopia where the study will be conducted.

##### **2.6.4.1. 'LEAVE-ON' EMOLLIENTS.**

'Leave-on' emollients are available in the form of:-

- Lotions which contain high levels of water and are easily absorbed by the skin.
- Creams which contain oil and water but are thicker and greasier than lotions. They contain preservatives and emulsifiers which are potential sensitizers. Because of this they are not recommended for those with damaged skin (Penzer 2012).
- Ointments which are heavy and greasy and so are often not acceptable to patients (British National Formulary March 2015). They do not contain any water or preservatives and so are less likely to cause sensitization. Other products may be added to ointments to increase their effectiveness but could cause sensitization.
- Gels contain oil and water. The gelling agent dissolves when applied to the skin. This allows the oil to stay on the skin longer and is less vulnerable to being washed off.

'Leave on' emollients often contain humectants which absorb water from the air increasing the water content in the SC. Glycerine (glycerol, glycerin) is widely used in pharmaceutical formulations as an humectant. Because of its non-toxicity, low cost, readily availability in Ethiopia and has many beneficial effects on skin it is worthy of focussed attention.

#### 2.6.4.2. GLYCERINE.

Glycerine is a NMF produced endogenously but it may also be manufactured. It is a sweet-tasting, colourless, odourless, viscous liquid that dissolves easily in water. It attracts water from its surroundings by absorption and adsorption slowing or preventing excessive drying and evaporation. Glycerine is non-toxic and non-irritating when applied to the skin (Atrux-Tallau, Romagny et al. 2010, Roussel, Atrux-Tallau et al. 2012).

There have been many studies on the effects of glycerine on the SBF used alone or in combination with other substances. Studies range from randomised double blind studies to comparative biometric skin tests. Effects studied include: SBF, skin barrier repair, anti-irritant effect, penetration enhancing properties, skin mechanical properties and quality of life (Appendix 3). A review of five double blind randomized clinical studies was

undertaken on patients with severe winter dry skin from 1991-1996 (n=394) (Appa, Orth 1997). Two high glycerine moisturizers were compared with 16 other moisturizers. One g ( $\approx 0.0353$  ounce) of the test material was applied to the test site (lower leg or back of both hands) 8 hours apart twice a day for 3 weeks. In the first 5 minutes following the application of glycerine to dry skin there was a flood of moisture to the skin followed by decrease to a constant level after 10-20 minutes. The constant level was higher in skin treated with moisturizers containing higher glycerine levels of  $>25\%$  than in skin treated with  $<10\%$  glycerine. The areas treated with  $>25\%$  glycerine restored the SC to normal hydration levels during the treatment. Evaluation was by self-assessment using a grading system, skin conductance and TEWL. The effects of glycerine on skin moisturization were reported as: moisture maintenance, providing constant osmotic pressure and by regulating water and salt concentrations in the intracellular environment. It also maintained the fluidity of cell membranes and intercellular lipids and normalized the regulation of desquamation by hydrating enzymes. Glycerine is noted to be one of the best natural skin moisturizers (Chrit, Bastien et al. 2006). It is used in skin care products because of its moisturizing and plasticizing effects on the SC which prevent and treat dryness. The effects of glycerine on SC hydration have been reported to last for 1 week and 2 weeks post treatment (Fluhr, Gloor et al. 1999, Breternitz, Kowatzki et al. 2008). A review of the literature summarizes the effect of glycerine as: improving SC hydration, inhibiting SC lipid phase transmission, improving SBF, enhancing desmosomal degradation, improving skin mechanical properties, accelerating wound healing and protecting against irritating stimuli (Fluhr, Cavallotti et al. 2008).

Glycerine also has virucidal and antimicrobial effects. The virucidal effects of glycerine were noted in a study of allograft skin preservation in which 85% glycerine destroyed or inactivated viruses (van Baare, Buitenwerf et al. 1994). The antimicrobial effects on allograft skin incubated with *pseudomonas aeruginosa*, *staphylococci aureus* and *bacillus subtilis* at temperatures of  $4^{\circ}\text{C}$ ,  $24^{\circ}\text{C}$  and  $36^{\circ}\text{C}$  have also been studied. Cell populations declined faster in those treated with 85% glycerol compared to the control. The antimicrobial effects of glycerine were more evident at  $36^{\circ}\text{C}$ .

Gram-negative species (e.g. *Escherichia coli*, *salmonella* and *pseudomonas aeruginosa*) were more susceptible than Gram-positives (e.g. *staphylococci* and *streptococci*) perhaps due to the difference in the bacterial wall structure between the groups (Saegeman, De Vos et al. 2007). Further long term tests indicated that 85% glycerine had an antimicrobial effect on eleven bacteria with mean survival time ranging from 2.6 to 29 days (Saegeman, Ectors et al. 2008).

Glycerine activates transglutaminase in the SC accelerating maturation of corneocytes and reducing scaling in xerotic skin (Anderson, Dinulos 2009). It is also able to sustain its moisturizing effect after it is no longer detected on skin by modulating water channels (aquaporin-3) within the skin (Draelos 2010). Aquaporins are a family of trans-membrane proteins that form water channels across cell membranes. Aquaporin-3 transports water, glycerol and small solutes across the plasma membrane (Jungersted, Bomholt et al. 2013). A report from a global expert dermatology symposium notes that using glycerine to hydrate the SC corrects the effects of cleanser induced skin damage (Ananthapadmanabhan, Subramanyan et al. 2013). A Korean study investigated the moisturizing effects on healthy skin of 41 components of oil in water emulsions (O/W) on SC hydration (n=177). From these 106 different single oils, and combinations of oil with oil, wax, humectants and surfactant were formulated and tested on volar forearms. Capacitance tests 30 minutes after application found that only the humectants urea and glycerine had significant positive effects on SC hydration compared to other humectants (Jeong, Han et al. 2013).

In summary the effects of glycerine on skin and its barrier function have been extensively studied and found to be positive. Glycerine effects are dose dependant with higher levels producing the most positive effects. However, low concentrations of glycerine between 0.02% - 5% have also had a positive effect on SBF. Glycerine is low cost and widely available making it an ideal treatment for dry or compromised skin especially in resource-poor countries. Choi et al (2005) suggested that glycerol containing therapeutic moisturizers should be developed. But despite this the British National Formulary lists only one emollient and one wash preparation containing

glycerine (at 10% and 15%) in the 'Emollients and barrier preparations' section (British National Formulary March 2015). The fat and oils used in emollients are a subgroup of lipids known as triglycerides and are the topic of the next section.

#### 2.6.4.3. FATS/OILS IN EMOLLIENTS.

The common fats in moisturizers are animal fats, mineral oils and vegetable oils. They are all occlusive to some degree. Because they are greasy they may rub off on clothes and be unacceptable to some people. In order to avoid folliculitis they should be applied following the direction of hair growth (Penzer 2012). Lanolin is the most commonly used animal fat in emollients. It is secreted by the sebaceous glands of wool-bearing animals. Most lanolin used by humans comes from domesticated sheep. It is occlusive and used extensively in products designed for the protection and treatment of dry skin. Paraffin and soft white paraffin which are highly refined mineral oils are also occlusive. They are hydrophobic (water-repelling) forming a barrier on the surface of the skin protecting against water loss. *Vaseline*<sup>®</sup> is 100% white petrolatum. It is able to penetrate the upper layers of the SC maintaining its water content and create the environment for fibroblast migration resulting in restoration of SBF (Draelos 2010). By blocking evaporation it helps keep skin moist and supple. An *in vivo* evaluation of three barrier creams placed on the volar forearms on healthy men found only *Vaseline*<sup>®</sup> to be 100% effective when applied at a rate of 3mg/cm<sup>2</sup>. Measurements were laser scanning microscopy, laser Doppler flowmetry, and the tape-stripping procedure. An extension of the same study investigated the penetration of a hydrophilic dye using the tape stripping technique and histological investigations. Only beeswax and *Vaseline*<sup>®</sup> showed 100% protection against the dye (n=6) (Teichmann, Jacobi et al. 2006). A study of skin hydration measured via the reflection of millimetre (mm) wavelength electromagnetic waves. It found that a thin layer (about 0.2-0.5mm) of *Vaseline*<sup>®</sup> entirely blocked the water loss from the SC (n=12). An additional study measured TEWL on 3 sites on each forearm (n=10). TEWL measurements were taken 15 min, 1, 2, 3 and 4 hours after product application. TEWL was lower in the sites using *Vaseline*<sup>®</sup> applied at rate of 2mg/cm<sup>2</sup> than in the control site to which nothing was applied signifying

*Vaseline*'s<sup>®</sup> occlusive properties ( $p \geq 0.05$ ) (Marques, Basso et al. 2007). Another small study investigated the penetration of five oils after 30 minutes on skin and their influence on SBF ( $n=6$ ). *Vaseline*<sup>®</sup> was applied at a rate of  $2\text{mg}/\text{cm}^2$  as the control because of its occlusive properties. The area covered with *Vaseline*<sup>®</sup> showed the highest decrease in TEWL ( $p=0.05$ ) (Patzelt, Lademann et al. 2012). Occlusives such as *Vaseline*<sup>®</sup> applied to skin in combination with a humectant such as glycerine have been shown to significantly reduce TEWL (Draelos 2010). When *Vaseline*<sup>®</sup> was applied to skin already treated with other moisturizers, SC hydration remained at the maximum level achieved with these moisturizers for longer than the areas where *Vaseline*<sup>®</sup> was not applied ( $n=12$ ) (Alekseev, Szabo et al. 2008). A review compared the skin benefits of mineral oils such as *Vaseline*<sup>®</sup> to vegetable oils (Rawlings, Lombard 2012). The results appear in Table 2.6.

**Table 2.6. Comparison of vegetable oils and mineral oil for a series of skin parameters** (Rawlings, Lombard 2012).

Parameter	Vegetable oils (average) - derivative of various plants	Mineral oil - derivative of petroleum
Occlusivity	Medium at most because of chemical diversity	High (because of alignment of straight alkyl chains)
Emolliency (the degree to which the oil provides softness to the skin)	Variable	High
Blocking pores (acne inducing)	Rarely	Not (based on experimental findings)
Moisturizing (increasing moisture content of skin)	Variable, mainly medium, but biologically active ingredients can deliver improved moisturising with time (after weeks of treatment)	Medium
Skin elasticity (increasing flexibility of skin)	Low	Low
Substantivity (extent to which a chemical remains on the skin)	Extremely variable, from very low to very high	Medium
Skin penetrability	Variable, but on average some penetration because of smaller chemical structures than mineral oil	Low to extremely low because of molecular size of alkyl chains

Only ranges were given for vegetable oils as they are an extremely diverse group. Care was taken to list the 'average'. Details of the review period and articles surveyed were not given. From this limited evidence it would seem that on average mineral oils such as *Vaseline*<sup>®</sup> are more beneficial to skin than vegetable oils. Although all trials on *Vaseline*<sup>®</sup> were on small numbers they all indicated high levels of occlusion when measured quantitatively.

*Vaseline*<sup>®</sup> is currently used in podoconiosis clinics and applied after washing the legs/feet with soap and air drying. The studies reported in 2.6.4.3 suggest that its effect might be further enhanced by the prior use of a moisturizer. Yet moisturizers may not be without harms as some moisturizers contain potential allergens and sensitizers in the form of perfumes, preservatives, antimicrobial agents, fungicides, thickeners, synthetic moisturizers, antioxidants and emulsifiers. These are particularly liable to affect damaged or diseased skin and are the focus of the following section.

#### 2.6.4.4. POTENTIAL ALLERGENS AND SENSITIZERS IN EMOLLIENTS.

Emollients should be used with care because of their possible detrimental effects it is therefore advisable to choose one containing the least or if possible no sensitizers. The possible sensitizers found in moisturizers are shown in the Table 2.7.

**Table 2.7. Potential sensitizers found in emollients** (British National Formulary March 2015).

Beeswax	Imidurea
Benzyl alcohol	Isopropyl palmitate
Butylated hydroxyanisole	N-(3-Chloroallyl) hexaminium chloride (quaternium 15)
Butylated hydroxytoluene	Polysorbates
Cetostearyl alcohol including cetyl and stearyl alcohol	Propylene glycol
Chlorocresol	Sodium metabisulphite
Editic acid (EDTA)	Sorbic Acid
Ethylene diamine	Wool fat related substances including lanolin
Fragrances	Hydroxybenzoates (parabens)

Despite the fact that emollients have been used for many years there is an almost complete lack of experimental data on how they should be applied for

maximum therapeutic effect (Penzer 2010b). The following section focuses on when, how and how much emollient to apply.

#### *2.6.4.5. APPLYING EMOLLIENTS TO THE SKIN.*

Due to a lack of evidence on the current use of emollients current use is often based on 'custom and practice'. Emollients can be applied 'as often as necessary' but it is generally recommended to apply 'liberally' and 'frequently' to keep skin well moisturised and in good condition.

#### *2.6.4.6. WHEN AND HOW TO APPLY AN EMOLLIENT.*

Various regimens are currently used to apply emollients including application to dry skin, application after bathing or washing and adding them to bathing water. Published research on the topic is limited. A quantitative assessment of a combination of bathing and moisturizing regimens on SC hydration was undertaken on those with atopic dermatitis and five with healthy skin (n=10) (Chiang, Eichenfield 2009). Four bathing/moisturizing regimens were evaluated. The moisturizer used was *Cetaphil Cream*<sup>TM</sup> which contains glycerine as its second ingredient and water as the first. The regimens were:

- ten minute bath alone, ten minute bath with immediate emollient application, ten minute bath with delayed emollient application (thirty minutes post bath) or emollient application alone.

Each regime was evaluated in all subjects. SC hydration was measured using standard skin capacitance measurements. In atopic patients the result was that the emollient cream alone resulted in greater mean hydration ( $p=0.05$ ) over 90 minutes (206.2% baseline hydration) than bathing. Bathing followed by immediate moisturizer application provided modest hydration benefit (141.6 % baseline hydration). Bathing alone was the least effective with 91.4% of baseline hydration. In this study application of the moisturising cream to the skin without prior bathing provided the most beneficial results. However the trial was small, the numbers in each arm were different and there was no comparison with any other emollients. Japanese studies investigated the effects on skin conditions and the prevention of skin disorders of bathing in warm water (Iiyama, Kawahira 2008). The first study was non-randomly divided into two (n=18). One group had baths in water only and the other with 0.02% glycerine added. Subjects all bathed twice weekly immersed in the water at

40<sup>0</sup> to 41<sup>0</sup> for 2-3 minutes for 6 months. The second study was retrospective (n=78). Patients bathed in water with added glycerine as mentioned previously, over the same period and with the same frequency. After six months of the glycerine bath regime SC moisture levels at the forearm and forehead measured quantitatively improved significantly in the glycerine group ( $p<0.05$ ). The moisture level was higher in other skin areas in the glycerine group too but without significance. Skin sebum level at the forehead improved significantly in the glycerine group ( $p=0.05$ ) (Iiyama, Kawahira 2008). The number of diagnosis, drugs and areas of skin disease were significantly lower in the glycerine group. The researchers concluded that the glycerine baths maintained the skin's moisture and sebum preventing skin disorders. Although the dilution of glycerine used in this study was small it was still effective.

In the guidelines 'Advised best practice on the use of emollients in eczema and other dry skin conditions' it is suggested that emollients are best applied when the skin is moist as it is after bathing or washing when the skin has a high water content and that they should ideally be applied to the skin at least three or four times a day (Holden, English et al. 2002). The guidelines are supported by the National Eczema Society and accredited by the British Skin Foundation.

#### *2.6.4.7. HOW MUCH EMOLLIENT TO APPLY.*

The amount of emollient required to have a beneficial effect will depend on the extent of the area affected and the level of dryness. Because of this health care workers have to make an informed judgement and give precise instructions on the amount required to individual patients. General guidance on quantities is given in Table 2.8.

**Table 2.8. Guidance on the quantities of emollient that should be applied** (British National Formulary March 2015).

Area of the body	Creams and ointments (grams)	Lotions (ml)
Face	15-30	100
Both hands	25-50	200
Scalp	50-100	200
Both arm or both legs	100-200	200
Trunk	400	500
Groins and genitalia	15-25	100

5 grams is equivalent to a teaspoon and 20 grams to a tablespoonful

These amounts are usually suitable for an adult for twice daily application for 1 week. Custom and practice is that an adult with a dry skin condition should use around 500g per week and a child half that amount.

#### **2.6.5. SUMMARY OF SECTION 2.6.**

From the available evidence it would seem that washing the skin should be undertaken to remove skin flakes and micro-organisms. Water alone is sufficient if there is no oil or soil contamination. Soaps may be necessary to remove dirt, oil and grease from skin but may contain surfactants. These are best avoided as they are a skin irritant. Cleansing products with a neutral or near neutral pH are preferable and skin should be immersed in warm drinkable quality water for less than 30 minutes per day to avoid altering the skin's natural balance. To achieve drinkable quality water dilute sodium hypochlorite may be used as a disinfectant. The water should be as near to body temperature as possible (37.2<sup>0</sup>C). Drying should be carried out by gentle rubbing. Emollients are useful for SC hydration and maintaining SBF. They are best added to washing water or used immediately afterwards. For severe skin disease applications twice daily or more are recommended. Glycerine is a non-toxic and non-irritant emollient. It is very effective at improving SBF. It is comparatively inexpensive, skin safe and easily accessible making it ideal for use especially in resource- poor countries. It is effective in increasing SC hydration in dilutions of 0.02% but is dose dependant with maximum positive effects to the SC being achieved with dilutions over 20%. It should be used at least daily.

The following section summarizes the key information found in the literature search. This provided the research evidence for an improved skin regimen for use in those with podoconiosis. It also provided information on the measurements and data required to demonstrate an improvement in SBF and the quality of life of those with podoconiosis.

## **2.7. SUMMARY OF CHAPTER 2.**

Podoconiosis affects some of the poorest people in more than 20 countries across the world. It is found in areas with the combination of volcanic soil, high rainfall, high altitude and low incomes. In Ethiopia 3 million people are estimated to have the disease and 19 million more are at risk. It is a treatable non-infectious disease caused by a breach in SBF which allows particles of soil and pathogens to enter the skin causing an abnormal inflammatory reaction. This atypical reaction is due to a genetic defect in the immune system involving TGF-  $\beta$ 1 and oxidative stress. Podoconiosis results in high levels of social stigma. Due to frequent episodes of ADL causing severe pain work days are lost significantly affecting the economic status of individuals, societies and consequently countries.

Wearing protective shoes is important but because soil and pathogens may still be in contact with plantar skin improving the SBF of those with podoconiosis is vital in order to successfully treat the disease. Current treatment is effective but may not be optimum. Glycerine is a very effective humectant/emollient which increases SC hydration and reduces TEWL. Emollients are most effective when added to soaking water or applied to damp skin. A thin layer of *Vaseline*<sup>®</sup> significantly reduces TEWL and when applied to skin following the application of a humectant such as glycerine SC hydration remained at the maximum level achieved with the glycerine (Alekseev, Szabo et al. 2008). Measuring the SBF using non-invasive probes is a reliable quantitative method of determining its health. The severity of podoconiosis may be reliably determined using the five stage system developed specifically for those with podoconiosis. The Amharic DLQI is a valid and reliable tool for measuring the quality of life of those with podoconiosis. Measuring the largest leg and foot circumference is helpful in

determining disease improvement or progression. The current skin treatment regimen for podoconiosis is effective but not evidence based and may not be the optimum treatment. It consists of washing with soap, soaking the leg/feet for approximately 30 minutes in water with added NaOCl, air drying and the application of *Vaseline*<sup>®</sup>. Antifungals are used if required. No pre/post intervention studies of podoconiosis were found in the literature search.

Prior to the research a pilot study was undertaken. This was to test the effects of the various skin regimen elements used in APA clinics on SBF. The effects of these have not previously been studied. Details of the pilot study, the analysis and results are provided in the following Chapter 3.

# **CHAPTER 3. PILOT STUDY**

## **3.1 INTRODUCTION.**

Podoconiosis is the result of an inflammatory reaction. To test the various components used to treat the SBF in the Actions on Podoconiosis Clinics (APCs) in Ethiopia a pilot study was undertaken. Due to the practical difficulties and increased financial cost of undertaking a pilot study in Ethiopia the decision was made to base it in the UK. A common skin condition in the UK which is also caused by an inflammatory reaction is xerosis. This is estimated to affect 75% of those over 75 years of age (Barco, Giménez-Arnau 2008). This is because as skin ages sweat glands atrophy and sebum production decreases. Stratum corneum lipids also reduce decreasing the ability of the skin to retain water. This results in dry, thickened, flaky, reddened skin (xerosis) which initiates an inflammatory response. The lower leg is one of the places most likely to be effected (Balaskas, Szepietowski et al. 2011). The inflammatory response worsens without intervention. To break the cycle of progression there is a need to treat the symptoms, repair the SC and enhance the SC barrier function (Rawlings, Matts 2004). As previously mentioned xerosis generally affects older people so a residential care home and the local Women's Institute where older people were likely to be found were contacted for possible participants.

Glycerine was added to the pilot interventions because 20 published research studies from 1984-2010 indicate its very positive effect on human skin (Appendix 3). Emollients such as glycerine have also been shown to decrease TEWL when applied to the skin before the application of the occlusive *Vaseline*<sup>®</sup> (Alekseev, Szabo et al. 2008, Patzelt, Lademann et al. 2012). The other interventions used in the pilot were as close as possible those used to treat people with podoconiosis in APCs in Ethiopia. The method used for the pilot study is detailed in the following section.

### **3.2. AIM AND OBJECTIVES OF THE PILOT STUDY.**

The aim of the pilot study was to test the effects the current skin treatments used for those with podoconiosis in APCs in Ethiopia. The current treatment regime was broken into its component parts testing components separately and in combination. The study also tested the effects of adding a 2% dilution of glycerine into the current regime.

The objectives were to:

- determine the quantitative effects of water, soapy water, *Vaseline*<sup>®</sup> (petroleum jelly) used singly and in combination on skin hydration levels and TEWL of the lower legs of those with xerosis in the UK.
- determine the effect of adding 2% glycerine to the water soak of the lower legs of those with xerosis in the UK
- help to make a power calculation for the research study
- allow the principal investigator to become familiar with the measuring tools

### **3.3. METHOD**

#### **3.3.1 STUDY DESIGN**

A quasi-experimental design study was employed. The study included healthy volunteers living in private accommodation.

#### **3.3.2. SAMPLE SIZE AND SELECTION**

Participant numbers for the pilot were 10. This number was pragmatic and based on previous pilot studies calculated to produce useful data. Pilot studies are generally not powered and numbers usually small. Studies on the effect of glycerine on SBF have previously indicated positive effects with participant numbers of 4-197 (Appendix 3).

Potential participants were identified by the owner/manager and staff at a private residential care home. As participant numbers were lower than required the University of Hull Ethics Committee were asked to extend the study to members of the local Women's Institute who lived in their own homes. This was

granted (9). Women's Institute participants were self-selecting following an E mail requesting participants sent to the local branch. All possible participants were made aware of the inclusion/exclusion criteria by the PI.

### ***3.3.3. INCLUSION AND EXCLUSION CRITERIA.***

The inclusion criteria for the participants were as follows: aged >60 years, able to give informed consent, xerosis on both lower legs determined by clinical judgement of the PI and the presence of skin thickening, redness, flaking skin, itching, no current leg ulcers and willingness to forgo showering and immersion bathing for the duration of the study. The exclusion criteria were: aged <60 years, unable to give informed consent, absence of lower leg xerosis, diagnosed with skin disease, with a current leg ulcer and unwilling to forgo showering and immersion bathing for the duration of the study.

### ***3.3.4. TIME PERIOD.***

The study took place in the UK over 6 consecutive days in May 2013. Baseline measurements were taken on day 1. Final measurements were taken on day 6 after 5 days of interventions. The time period was chosen as previous studies have reported a positive effect of glycerine on SBF when applied for periods between 10 minutes (Overgaard Olsen, Jemec 1993) to 49 days (Balaskas, Szepletowski et al. 2011). Details of the time periods of all the studies are in Appendix 3.

### ***3.3.5. PERMISSION AND ETHICAL APPROVAL.***

Application was made to the University of Hull, Faculty of Health and Social Care Research Ethics Committee (7, 8). Ethical approval was granted after minor clarification (Appendix 9). A letter giving permission for the study to take place in a private care home was obtained from the owner/manager of the home (Appendix 10). Potential participants were given a letter and information sheet explaining the research a minimum of four days before the study (11, 12). Informed consent was obtained and participants signed a consent form (Appendix 13). If requested by the participant the participants' general practitioner was informed of their participation in the study (Appendix 14). No personal data were recorded.

### **3.3.6. INTERVENTIONS AND RATIONALE.**

All interventions and recordings were carried out by the PI to ensure intervention fidelity. The gauze swabs used were 8 ply and 5cms x 5cms. All interventions except *Vaseline*<sup>®</sup> were covered in cling film to keep the substance next to the skin as an alternative to soaking. The cling film was cut larger than 5cms x 5cms and of sufficient quantity to allow the gauze to be in contact with the skin. It was usually wrapped around the limb to secure it in place. The amount of solution placed on the gauze was 1½ mls. This was sufficient to wet the gauze without leakage. TEWL and conductance was measured at baseline on day 1 and on day 6. Table 3.1 identifies the pilot interventions and their rationale and compares them to the current practices in APCs.

**Table 3.1. Pilot study interventions and their rationale.**

Interventions on right and left lower outer legs	Rationale for use in pilot study	Comparison to current practice in APCs
<p><b>Intervention 1.</b> This was untreated.</p>	<p>This was the control.</p>	
<p><b>Intervention 2.</b> Gauze wetted with 1½ mls soapy water applied and covered with cling film (thin plastic wrap) for 10 minutes.</p>	<p>Soap is currently the most commonly used cleansing agent. It removes dirt and oils. Most soap has a pH of 7-10 (Ananthapadmanabhan, Subramanyan et al. 2013). All testing methods of soaps indicate that frequent exposure induces barrier damage and skin dryness followed by inflammation (Wolf, Parish 2012).</p>	<p>The soap used in the pilot study was sourced in Ethiopia and was the same soap used in the APCs which has a pH of 10. APCs currently wash patient's legs in soapy water for up to 10 minutes. The soapy water was an approximation of the solution used in APCs based on the PIs observations.</p>
<p><b>Intervention 3.</b> Boiled tap water 1½ mls on gauze covered with cling film for 30 minutes.</p>	<p>The water for the pilot was boiled as an extra precaution against possible infection but this was not strictly necessary as tap water in the UK is already of drinkable quality. It had a pH of 7. Drinking quality water is suitable for use on compromised skin. Further details are in Section 2.6.1.1. Soaking skin in water for longer than 30 minutes daily damages the SC (Ramsing 1997).</p>	<p>The pH of the soak used in APCs is 8 as it has added NaOCl. This is a slightly higher pH than water in the UK possibly due to the water in the area already being affected by the highly alkaline soil.</p>
<p><b>Intervention 4.</b> <i>Vaseline</i><sup>®</sup> applied to the area in a thin layer.</p>	<p>This was to test the effect of <i>Vaseline</i><sup>®</sup> when used alone. Details of the occlusive effects of <i>Vaseline</i><sup>®</sup> are in Section 2.6.4.3.</p>	<p><i>Vaseline</i><sup>®</sup> is currently applied in a thin layer to the feet/ legs of those with podoconiosis in APCs after washing, soaking and drying.</p>
<p><b>Intervention 5.</b> Gauze wetted with 1½ mls soapy water applied and covered with cling film for 10 minutes. This was followed by 1½mls boiled tap water on gauze covered with cling film for 30mins. After patting dry and a thin film of <i>Vaseline</i><sup>®</sup> was applied.</p>		<p>This is the equivalent of the current combination of treatments in the APCs.</p>

Interventions on right and left lower outer legs	Rationale for use in pilot study	Comparison to current practice in APCs
<p><b>Intervention 6.</b> Gauze wetted with 1½ mls soapy water applied and covered with cling film for 10 minutes. This was followed by 1½ mls boiled tap water on gauze with 2% glycerine added covered with cling film for 30 minutes. This was patted dry and a thin film of <i>Vaseline</i>® applied.</p>	<p>Glycerine has a dose dependant positive effect on TEWL and SC hydration. Studies have reported positive effects of a glycerine dilution below 2% (Section 2.6.3.2). Glycerine is low-cost and easily available in Ethiopia. A further consideration was participant's ability to carry quantities of glycerine home from clinics as well as soap, bottles of NaOCl and <i>Vaseline</i>®. When all these factors were considered it seemed that a 2% glycerine dilution was the most pragmatic Emollients are best applied when skin is moist as it is after bathing or washing when the skin has a high water content (Holden, English et al. 2002, Ersser, Maguire et al. 2012).</p>	<p>This combination was the proposed intervention for the experimental group in the main study.</p>

### **3.3.7. PREPARING PILOT INTERVENTIONS.**

Details of the preparation of the interventions are in the following four sections. The interventions were: soapy water, water, a dilution of glycerine and *Vaseline*<sup>®</sup>.

#### **3.3.7.1. SOAPY WATER.**

The soap used was manufactured in Ethiopia and the pH was 10. It was the same as the soap used in APCs and given to patients monthly at their clinic attendance to wash their feet/legs with at home. An analysis of the soap was undertaken by Chris Nunn, Chemist, Procter and Gamble's Research Centre, Surrey, UK (Appendix 5). It was made from tallow (C16 fatty acid) and contained silica throughout its mass thought to be due to contamination during manufacture. Soapy water was prepared daily as follows:

1. gloved hands wetted with warm cooled boiled tap water for 5 seconds
2. soap wetted with warm cooled boiled tap water 10 seconds
3. soap lathered in gloved hands for 30 seconds using a firm, slow massaging procedure
4. 1½ mls of the resulting lather measured with a syringe was transferred onto the gauze before application to the skin.

#### **3.3.7.2. WATER.**

Warm cooled boiled tap water was prepared daily. It was measured with a syringe and transferred to the gauze before application to the skin.

#### **3.3.7.3. GLYCERINE.**

This was prepared daily as follows:

1. 2mls glycerine was added to 100 mls of cooled boiled tap water.
2. 1½ mls of the resulting liquid was measured with a syringe and transferred onto the gauze before application to the skin.

#### **3.3.7.4. VASELINE<sup>®</sup> (PETROLEUM JELLY).**

This was supplied in 20g containers for each participant's sole use. It was applied with a gloved hand directly onto damp skin. The gloves were used once only. The amount applied provided a thin occlusive layer.

### 3.3.8. BODY SITES.

The lower leg was chosen as it is an area likely to be affected by xerosis (Balaskas, Szepietowski et al. 2011). It is also the area affected by podoconiosis. The lateral aspect was used as this is easily accessible, and preserved participant's dignity. Three sites on each leg between the knee and outer malleolus were used as the measurement sites. They were each 5cm x 5 cm. Because no previous studies were found which included specific measurement sites on legs a pragmatic approach was employed. Sites on the leg were numbered as reported in Table 3.2.

**Table 3.2. Sites on the outer lower leg.**

Site on lower outer leg	Number of site right leg	Number of site on left leg
8cms below the head of fibula,	1	4
8cms above the external malleolus	2	5
Mid-way between these two sites	3	6

Sites were marked with a dot in each corner with a water proof felt pen. Interventions were allocated sequentially to ensure that different sites of the lower leg were used for each intervention. This was because different skin areas will have differences in, for example blood supply and skin dryness. Table 3.3 below identifies the sequential system used.

**Table 3.3. Sequential intervention system for the outer lower legs on sites 1-6.**

Participant number	Intervention on site 1	Intervention on site 2	Intervention on site 3	Intervention on site 4	Intervention on site 5	Intervention on site 6
1	1	2	3	4	5	6
2	6	1	2	3	4	5
3	5	6	1	2	3	4
4	4	5	6	1	2	3
5	3	4	5	6	1	2
6	2	3	4	5	6	1
7	1	2	3	4	5	6
8	6	1	2	3	4	5
9	5	6	1	2	3	4
10	4	5	6	1	2	3

No emollients were applied to the lower legs for three days before or during the pilot study and no water was applied during the study. This was to

ensure that applications of emollients or water on the skin would not confound study results.

### **3.3.9. MEASUREMENTS OF SKIN BARRIER FUNCTION.**

The non-invasive probes used for measuring skin hydration and TEWL are sensitive to changes in ambient temperature and relative humidity. They may be affected by sweat on the skin. To allow for this the ambient relative humidity (%) and ambient temperature (°C) were recorded. Participants were seated with their lower legs uncrossed and exposed for 20 minutes prior to readings being taken. No hot drinks were given during this time which could have altered TEWL.

#### **3.3.9.1. TRANS-EPIDERMAL WATER LOSS.**

TEWL is a robust indicator of the skin barrier function efficiency. If it rises too high, the skin can become dehydrated, disrupting its form and function and potentially leading to infection or the trans-epidermal passage of harmful agents. An evaporimeter measures TEWL. It consists of a sensor placed above the surface of the skin. The apparatus measures the amount of water lost by evaporation. It also re-measures the ambient temperature and relative humidity each time it is used. Elkeeb states that both closed and open chamber evaporimeters have been validated in the measurement of TEWL (Elkeeb, Hui et al. 2010). In this study a closed chamber *VapoMeter*<sup>®</sup> was used. It was manufactured by Delfin Technologies Ltd, Kuipio, Finland (Delfin Technologies Ltd. 2013). Single TEWL measures were taken at each site as per manufacturer's instructions (Appendix 2).

#### **3.3.9.2. STRATUM CORNEUM HYDRATION.**

Stratum corneum hydration levels were measured with a corneometer. It measures the skin's capacitance which is the total electrical resistance of the skin to an applied alternating current. Corneometers are used to measure the SC hydration level in the outer layer of the skin and the ability of the skin to retain moisture. The corneometer has high reproducibility, is easy to handle and have a short measuring time. A study by O'Goshi and Serup compared three corneometers on six body sites of 53 subjects (median age 54 years). All of the corneometers produced similar measurements and were

closely correlated (O'Goshi, Serup 2005). Hair on the skin may affect corneometer readings so this needs to be considered when assessing the SC hydration. A study comparing readings at the volar forearm with the dorsal forearm indicated significantly lower levels on the dorsal aspect. ( $p=0.05$ ) indicating less hydrated skin. After shaving the readings were comparable (Lodén, Hagforsen et al. 1995). Shaving would have removed some SC layers and affected results. Hair was not present on any of the legs of those in the pilot study. A *MoistureMeterSC*<sup>®</sup> was used to record SC hydration measurements. Three measurements were taken at slightly different areas on each site and the mean of these recorded as per the manufacturer's instructions. The manufacturer of both probes was Delfin Technologies Ltd, Kuipio, Finland (Appendix 2).

#### **3.3.10. INDEPENDENT AND DEPENDENT VARIABLES.**

The independent study variables were the experimental intervention and the control. The dependent study variables were the measures on TEWL and SC hydration.

#### **3.3.11. POSSIBLE ADVERSE EFFECTS OF THE PILOT STUDY.**

Participants were required to be available for 45 minutes every morning for five days. They were not able to have an immersion bath or shower during the 6 days without using leg protectors which were given if requested. The soap used had a high pH and silica which may have caused irritation and further dryness or irritation. As the skin all participants' legs was intact with no skin breaches the silica was not considered to pose any risk. Any skin changes on the treated areas were noted by the PI. Changes noted by staff were reported to the PI.

#### **3.4. DATA ANALYSIS OF PILOT STUDY.**

Only the PI was involved in the pilot visiting all participants to build a relationship of trust. This also ensured continuity of recording. All ten participants were female because only females agreed to participate. All of them completed the study. The mean age was 76.1 years. The age range

was 65-95 years. During the study the relative humidity of the environment was between 34-54% and ambient temperature between 19-22°C.

### 3.4.1. STATISTICAL METHOD.

Changes (post-intervention minus pre-intervention values) in skin hydration and TEWL were computed for all treatments and participants. Descriptive statistics (means and standard deviations) were calculated and profile plots constructed.

Friedman's test was used to test whether the changes differed significantly between the six treatments. If statistically significant, then Friedman's test was followed by a post-hoc Nemenyi test to establish which treatment pairs differed significantly. R for Windows Version 3.0.0 was used for the statistical analysis.

### 3.5. RESULTS.

All participants confirmed that they had not had a shower or immersion bath during the trial or used any other emollients for three days before or during the trial. The interventions were well tolerated by the participants and all completed the study. No adverse effects were reported. Descriptive statistics for changes in TEWL and SC hydration levels are reported in Tables 3.4, 3.5.

**Table 3.4. Summary of changes in trans-epidermal water loss (gm<sup>2</sup>h) (n=10).**

Treatment	Mean (SD)	Minimum	Maximum
Control	-0.66 (2.12)	-3.20	3.40
Soapy water	0.29 (1.29)	-2.70	2.10
Water soak	-0.12 (1.41)	-2.10	1.60
<i>Vaseline</i> <sup>®</sup>	-0.38 (1.11)	-2.00	1.00
Soapy water, water soak and <i>Vaseline</i> <sup>®</sup>	-0.09 (1.18)	-2.30	1.10
Soapy water, 2% glycerine soak and <i>Vaseline</i> <sup>®</sup>	-1.14 (1.47)	-4.30	0.10

**Table 3.5. Summary of changes in stratum corneum hydration (n=10).**

Treatment	Mean (SD)	Minimum	Maximum
Control	0.14 (2.89)	-5.94	3.20
Soapy water	0.56 (2.44)	-2.06	6.30
Water soak	0.81 (4.32)	-5.37	6.84
<i>Vaseline</i> <sup>®</sup>	2.42 (3.12)	-1.50	7.47
Soapy water, water soak and <i>Vaseline</i> <sup>®</sup>	3.11 (2.21)	-0.66	5.66
Soapy water, 2% glycerine soak and <i>Vaseline</i> <sup>®</sup>	7.92 (3.93)	1.47	12.93

The greatest improvement in SBF as measured by the mean decrease in TEWL was observed for the soapy water, glycerine and *Vaseline*<sup>®</sup> regimen (mean -1.14, SD 1.47). This was a small improvement on that observed for the control treatment which is apparent in the profile plots (Figure 3.2).

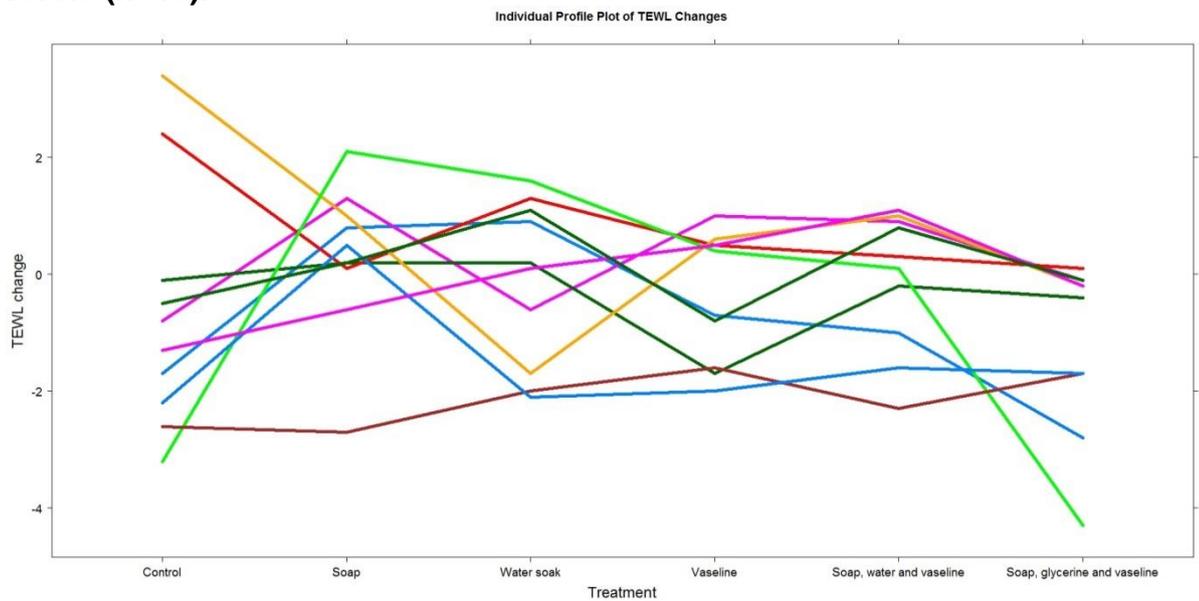
The greatest mean increase in SC hydration level at day 6 was observed for the regimen combining soapy water, 2% glycerine soak and *Vaseline*<sup>®</sup> (mean 7.92, SD 3.93). From Friedman's test it was found that there were statistically significant treatment differences for changes in skin hydration levels but not for TEWL ( $p=0.002$  and  $0.185$  respectively). The  $p$ -values are for the overall comparison between all six treatments. The post-hoc Nemenyi test for skin hydration level changes indicated that three treatment pairs differed significantly. The test indicates the positive effects on SC hydration of soapy water, 2% glycerine soak and *Vaseline*<sup>®</sup> compared to the control, soapy water and the water soak of applying 2% glycerine to the skin for 30 minutes a day over five days. The results are reported in Table 3.6.

**Table 3.6. Skin hydration - difference in changes between the treatment combination containing glycerine compared to control, soap and water soak (n=10).**

Intervention	p value
Control vs soapy water, 2% glycerine soak and <i>Vaseline</i> <sup>®</sup>	0.011
Soap vs soapy water, 2% glycerine soak and <i>Vaseline</i> <sup>®</sup>	0.050
Water soak vs soapy water, 2% glycerine soak and <i>Vaseline</i> <sup>®</sup>	0.011

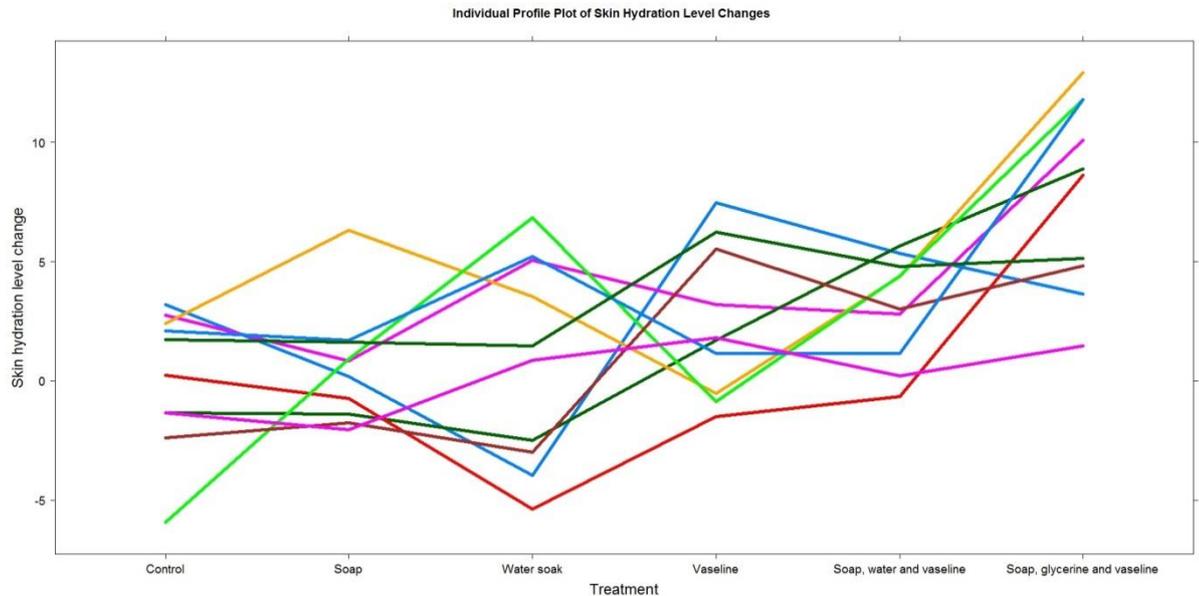
The greatest mean decrease in TEWL was for the intervention containing 2% glycerine but this was not significantly different to changes observed for other interventions. The following two figures 3.1 and 3.2 plot the effects of the six interventions effects on TEWL and SC hydration of each participant.

**Figure 3.1. Individual plots of the change in trans-epidermal water loss levels (n=10).**



Key: The 6 interventions shown on the horizontal axis were: control, soapy water, water soak, *Vaseline*<sup>®</sup>, a combination of soapy/water soak/*Vaseline*<sup>®</sup> and a combination of soapy water/2% glycerine soak/*Vaseline*<sup>®</sup>. Each of the different line colours represents the change in SC hydration in each participant following 5 days treatment with the different interventions.

**Figure 3.2. Individual plots of stratum corneum hydration levels (n=10).**



Key: The 6 interventions shown on the horizontal axis were: control, soapy water, water soak, *Vaseline*<sup>®</sup>, a combination of soapy/water soak/*Vaseline*<sup>®</sup> and a combination of soapy water/2% glycerine soak/*Vaseline*<sup>®</sup>. Each of the different line colours represents the change in SC hydration in each participant following 5 days treatment with the different interventions.

### **3.5. DISCUSSION.**

The pilot study tested the interventions used and taught in the APACs both alone and in combination. A further combination of soapy water, soaking in a dilution of 2% glycerine followed by the application *Vaseline*<sup>®</sup> was added. No other studies were found which measured TEWL and SC hydration in those with xerosis before and after these single or combined interventions over 5 days. The results may have been affected by the small and all female sample size. There were no adverse skin effects reported or noted by the PI during the study.

The water used in the pilot was of drinkable quality with a pH of 7. It was not the same as the water used in APCs which is polluted and not of drinkable quality. Because of this it has 0.0125% NaOCl added as an antiseptic with a resulting pH of 8. This difference may affect results in the main study. Soap is known to dry the skin but is necessary to reduce skin pathogens and remove soil and dirt. For this reason it will be used in both arms of the main study. All three of the combination of interventions using *Vaseline*<sup>®</sup> had a highly significant positive effect on SC hydration. For this reason it too will be

used in the main study. Both soap and *Vaseline*<sup>®</sup> are easily sourced in resource-poor countries at low cost. One study suggested that TEWL was a less sensitive test than SC hydration (n=15) (Goffin, Pierard et al. 1997). An Expert Review of moisturizers in dry or eczematous skin also stated that increasing hydration does not necessarily results in a reduction in TEWL (Lodén 2008). The effectiveness of glycerine in decreasing TEWL may have been improved using higher concentrations or have been identified with higher study numbers.

### **3.6. CONCLUSION.**

The objectives of the pilot study were achieved. The effects of the components of the skin management regimen used in APCs were determined, and the effects of the adding 2% glycerine to the water soak. It also helped clarify the numbers required for the research study (Section 4.2.18) and enabled the PI to become familiar with using the measuring devices.

The study confirms earlier findings on the positive effects of glycerine and of *Vaseline*<sup>®</sup> increasing SC hydration and reducing TEWL (Bissett, McBride 1984, Fluhr, Gloor et al. 1999 (b), Fluhr, Vrzak et al. 1998, Bettinger, Gloor et al. 1999, Gloor, Gabard et al. 2001, Lodén, Andersson et al. 2001, Lodén, Andersson et al. 2002, Andersen, Hedegaard et al. 2006 (2), Chrit, Bastien et al. 2006, Breternitz, Kowatzki et al. 2008). It was hypothesised that a treatment regime which improved the SC hydration and SBF in those with xerosis should be equally beneficial to the SBF of those with podoconiosis which is also caused by an inflammatory reaction. For the research study the PI worked with Action on Podoconiosis an NGO with clinics based in Southern Ethiopia. One of their stated key activities is to collaborate with national and international partners in scientific research. The research they identified included the role of SBF in podoconiosis and the development of new and better treatment regimens (Action on Podoconiosis Association 2012). The author linked with them to help achieve some of these important aims. The research study is presented in the succeeding Chapter 4.

# **CHAPTER 4. METHOD.**

## **4.1. INTRODUCTION.**

The current podoconiosis treatment regimen used in Ethiopia is effective at reducing oedema and disease stage (Sikorski, Ashine et al. 2010). However it may not be the optimum treatment. The pilot study indicated that compared to the current regimen the addition of 2% glycerine had a significantly positive effect on skin hydration. SBF has not previously been measured in those with podoconiosis pre/post intervention and no previous controlled studies the skin treatment of podoconiosis were found in the published literature. This chapter includes the research aim, objectives and null hypothesis, research design, recruitment of participants, treatment fidelity, data collection and data analysis

## **4.2. THE RESEARCH AIM, OBJECTIVES AND NULL HYPOTHESIS.**

### **4.2.1. AIM.**

To evaluate the effectiveness of a low cost evidence-based skin care intervention to improve skin barrier function in the lower limbs and enhance the disease related quality of life of Ethiopian people with podoconiosis.

### **4.2.2. OBJECTIVES.**

1. To identify the current skin care interventions used on the lower limbs of those with podoconiosis attending APA and Mossy foot clinics in Ethiopia.
2. To evaluate the effectiveness of an evidence-based skin care intervention in terms of changes in skin barrier function in the affected area and disease related quality of life. The specific objectives were to determine if after 3 months intervention compared to the control group those in the experimental group had:-
  - less trans-epidermal loss and increased SC hydration at three specific points on the lower leg and on the top of the feet

- a reduced stage of the disease
- less mossy changes, wounds and odour on the lower leg/foot
- reduced circumference on the lower leg and foot
- less days of work lost due to ADL and if there was a correlation between the number of wounds and the days lost due to ADL.
- an improved quality of life

#### **4.2.3. NULL HYPOTHESIS.**

The null hypothesis was that an evidence-based skin care intervention with added glycerine does not improve skin barrier function in the legs/feet or enhance the disease related quality of life of Ethiopian people with podoconiosis when compared to the control group using the current skin care regimen.

#### **4.3. RESEARCH DESIGN AND METHODOLOGY.**

The research study involved the staff and those with podoconiosis attending Action on Podoconiosis Association outreach clinics (APCs) in Southern Ethiopia. The aim was to evaluate the effectiveness of a structured evidence-based skin care intervention aimed at improving SBF in the lower limbs and improving the disease related quality of life in those in Ethiopia living with podoconiosis.

##### **4.3.1. RESEARCH DESIGN.**

A randomised control trial (RCT) design was selected for the study which included the following significant features. Initially participants were randomly allocated to the experimental or control groups. Next intervention groups were treated identically except for the experimental treatments. Participants were then analysed within their allocated group, irrespective of whether they experienced the intended intervention (intention to treat analysis). Finally analysis was focused on estimating the size of the difference in the predefined outcomes between the groups.

The two clinics used were chosen from similar socio-economic populations in similar geographical areas. The choice was also pragmatic as they had to be within three hours each way from the PI's base. This was to ensure the PI and drivers safety by not driving in the dark (before 6 am and after 7pm) and yet allowing the PI about 6 hours daily at each clinic. Both clinics included both control and experimental groups. The sample was stratified by clinic, gender and disease severity to ensure similar numbers were recruited. This allowed any differences between them to be determined. Randomization to the different stratified groups was generated using computerized random block sizes.

#### *4.3.1.1. VALIDITY AND RELIABILITY OF RESEARCH DESIGN.*

To ensure the validity and reliability of the research the Consort Statement and flow chart (2010) was used to guide the study (Appendix 16, 16B). Their use helped to ensure adequate reporting and design, transparency and unbiased treatment effects (Moher, Hopewell et al. 2012). The University of Hull Data Management Plan was completed to ensure correct data management (Appendix 21). Ethical approval was also sought as it is a requirement for all research studies. It is the subject of the next section.

#### *4.3.1.2. ETHICAL APPROVAL.*

Ethical approval was requested and granted by the University of Hull, Faculty of Health and Social Care Research Ethics Committee (Appendix 18, 19, 20). Because the research was conducted in Ethiopia it was also requested and granted by the Ethics Committee at Sodo University, Wolaita Region, Ethiopia (Appendix 22).

#### *4.3.1.3. STUDY POPULATION.*

The study population comprised patients attending two Action on Podoconiosis outreach clinics in the Gamo Gofa region in south-central Ethiopia. The area has a population of 1.8 million and covers 12003.79km<sup>2</sup>. Both clinics are in highland areas with an elevation between 1,600 and 2,100 meters above sea level, volcanic soil and high rainfall. A demographic study to assess the burden of podoconiosis has not yet been conducted in the area. The clinical practice in each clinic was the same and each opened five

days a week. An English speaking nurse and social worker were based in each clinic. They also speak the local language. Numbers of new patients attending these clinics in the period January 2012 to July 2013 were as follows:-

Clinic A covering 32 kebele (the smallest administrative unit in Ethiopia consisting of a number of villages), new patients = 413 patients.

Clinic B covering 24 kebele, new patients = 396.

#### *4.3.1.4. INCLUSION/EXCLUSION CRITERIA.*

Specific inclusion criteria for the study were:-

- Patients in Ethiopia with a diagnosis of podoconiosis. That is those living above 1000 feet above sea level with high rainfall, above 1,00mm annually with foot or lower leg oedema which had started in the feet, with sensation present in the feet and no hand involvement (Price, Bailey 1984, Davey, Tekola et al. 2007). A lack of sensation in the feet and/or hands may be an indication of leprosy. The diagnosis was determined by the nurses at the outreach clinics.
- Patients who were able to understand instructions and give informed consent. This was determined by the nurses at the outreach clinics.
- Patients over 18 years of age.

Specific exclusion criteria for the study were:-

- Patients not diagnosed with podoconiosis as determined by nurses at the two outreach clinics.
- Patients who were unable to understand instructions or give informed consent as determined by nurses at the outreach clinics.
- Patients under 18 years of age.

#### *4.3.1.5. CONTROL GROUP.*

Participants in the control group continued with the usual treatment practice taught in APCs (Table 2.3). The PI checked at every visit the consistency of the treatment taught and demonstrated. The soap used in the pilot contained silica and had a pH of 10. Following the analysis of soap undertaken for the pilot study APA changed to a purer soap. This contains palm and coconut oil and has a pH of 8.5. It is now used in all APA clinics.

#### 4.3.1.6. EXPERIMENTAL GROUP.

Participants in the experimental group followed the practice detailed in Table 4.1.

**Table 4.1. Experimental group intervention and rationale.**

Intervention	Rationale
Educational programme provided to participants.	As in Table 2.3.
Legs/feet washed every evening in soapy water for up to 10 minutes daily paying particular attention to skin folds and between toes.	The soap used had pH of 8.5 which was a lower pH than that used in the pilot study. Soap is necessary to remove the dirt from skin (Corazza, Lauriola et al. 2009). Cleaning feet and legs after working on the land will result in less soil and pathogens on skin. Further information is in Table 2.3. A previous podoconiosis study indicated that following a leg/foot hygiene regimen including washing over 12 months improved clinical progression of the disease, significantly decreased lower leg circumference (p=0.001) and reduced with only of patients still having mossy changes to 22.2% (n=27) (Sikorski, Ashine et al. 2010).
<p>Legs/feet soaked every evening for approximately 30 minutes in 1 litre of non-drinkable quality water containing 1.6mls (0.008% NaOCl) and 2% glycerine (20 mls). The dilution of NaOCl was 0.0045% less than that used in the control group.</p> <p>Participants were unlikely to have access to a watch so they were instructed to soak their legs for the time it takes to make coffee. In Ethiopia this is approximately 30 minutes.</p> <p>The quantity of NaOCl was measured with a 2 ml syringe which was marked to show the 1.6 ml level. 20 mls of glycerine was measured using the bleach bottle top which has a capacity of 10 mls.</p> <p>Water was measured with a 1 litre jug. The soaking solution was frequently splashed with the hands onto the legs below the knee.</p>	<p>In the rural areas of resource-poor countries collecting water is heavy time consuming work. In order to reduce water consumption the experimental group used 1/6<sup>th</sup> of the water used in the control group. 42% of those in rural Ethiopia do not have access to improved drinking water sources (WHO (4) 2012). As a result polluted water is used for cleaning the skin often resulting in skin infections as pathogens enter skin breaches.</p> <p>As reported in Table 2.3 <i>in vitro</i> tests on solutions of 0.5% NaOCl had a total bactericidal effect on <i>Staphylococcus Aureus</i>, <i>Pseudomonas aeruginosa</i>, <i>Escherichia coli</i> and <i>Streptococcus faecalis</i> while solutions of 0.00025%-0.5% had a partial effect, 24% of fibroblasts were viable after exposure to a 0.025% solution and 98.9% after exposure to a 0.003% solution (Hidalgo, Bartolome et al. 2002). Fibroblasts are necessary for tissue repair so adding NaOCl inhibits wound healing. In a later study the lowest NaOCl concentration at which killed <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> and <i>Staphylococcus pyogenes</i> was 0.006% (Coetzee, Whitelaw et al. 2012). These pathogens are common causes of skin and soft tissue infections. A double blind study patch tested skin TEWL and SC hydration levels in 15 minute intervals for periods between 15 to 90 minutes with 4% NaOCl (n=15). TEWL and conductance were measured 72hours after patch removal. Indications were that 4% NaOCl decreased SC hydration without effecting TEWL (Goffin, Pierard et al. 1997).The study was small but indicates that TEWL is a less sensitive test than SC hydration.</p> <p>APACs normally add 15 mls (1½ capfuls of bleach to 6 litres of water (a dilution of 0.0125% NaOCl) making water slightly alkaline (pH 8). The dilution seems to be a pragmatic compromise between the antimicrobial effect on polluted water and the consequences of disrupting the skin's normal pH, effecting SC hydration, TEWL levels and wound healing. A lesser dilution of 0.008% (pH 8) was used in the experimental group. This is still effective against pathogens, does not destroy all fibroblasts and because of the difficulty</p>

	<p>measuring ½ a capful is more accurate and reduces cost. In emergency situations the Centre for Disease Control and Prevention recommends that household bleach is used as a drinking water disinfectant at a dilution of 0.165 mls in 1 litre (0.33 mls in 2 litres) of water to remove bacteria and viruses (Centers for Disease Control and Prevention 2009). Further research recommends household bleach is used in turbid water at a dilution of 0.62 mls per litre (1.24 mls per 2 litres) to produce emergency drinking water (Elmaksoud, Patel et al. 2014). These amounts are less than that used in both the control and experimental group. As reported in Table 2.3 drinkable quality is suitable for washing skin (Fernandez, Griffiths 2008).</p> <p>The water used was at the ambient temperature.</p> <p>Water does not affect intercellular lipid or cause significant swelling of the corneocytes if used for less than 1 hour per day (Ramsing 1997, Warner, Boisse et al. 1999).</p> <p>Glycerine is effective, low-cost and available in Ethiopia. It has antimicrobial, anti-inflammatory and many other positive effects on SBF (WHO (4) 2012). The pilot study indicated that the addition of 2% glycerine to the soak post washing with soapy water and pre application of <i>Vaseline</i>® significantly improved SC hydration and reduced TEWL when compared to current APC practice.</p>
Air drying of legs/feet.	<p>Air drying is current practice (Table 2.3). Occasionally patients were given a small piece of gauze to take home to dry between skin folds and toes. It was only sufficient to last one or two days. The PI considered this amount of gauze to be of little value. It was not known if participants used other pieces of cloth at home for drying purposes.</p> <p>Fungal infections are common where opposing skin surfaces are in close proximity. The friction in these folds may lead to a variety of complications such as secondary bacterial or fungal infections. Washing and careful thorough drying between folds will minimize these (Janniger, Schwartz et al. 2005). But in this very poor rural environment where water is difficult to obtain cloths are often dirty. Supplying rolls of cloth or gauze to dry between skin surfaces would be costly and currently not sustainable.</p> <p>Rough drying is detrimental to SBF. A study indicated that SC dehydrates 6 hours after and TEWL peaks 2 days after rough drying (n=42) (Huh, Seo et al. 2002).</p>
<i>Vaseline</i> ® applied after the soak in a thin occlusive layer.	<p><i>Vaseline</i>® applied at a rate of 3mg/cm<sup>2</sup> is 100% occlusive. Currently in APCs it is applied in a thin layer after washing, soaking and drying (Table 2.3). In the pilot study the combination of soapy water, soak in 2% glycerine, patting the area dry and the application of <i>Vaseline</i>® in a thin layer had a significant positive effect on skin moisture levels when used daily for 5 days.</p>
<i>Whitfield's ointment</i> (3% salicylic acid and 6% benzoic acid in a base of petroleum) applied to areas with a fungal infection.	<p>To treat fungal infections (Table 2.3).</p> <p>A common side effect following the application of <i>Whitfield's ointment</i> is a feeling of warmth or a burning sensation lasting a few minutes.</p>
Elevation of the legs at night to above heart level encouraged.	<p>This is already taught to patients in APACs (Table 2.3.) Elevation will be encouraged to reduce leg oedema.</p>
Wound care advice	<p>As in Table 2.3</p>
The importance of wearing shoes and socks taught in the educational programme.	<p>Already taught in APCs (Table 2.3). Wearing shoes and socks helps to prevent alkaline soil drying the skin causing drying, cracking and trauma of the skin. Improvements in skin barrier function prevent the entry of silica and bacteria.</p>

The difference between the two groups was that in the experimental group:

- only 1 litre of water was used for soaking the feet/splashing on the legs as opposed to 6 litres in the control
- 2/3 of the amount of NaOCl was used (0.008% v 0.0125% = 0.0045% less)
- 20mls of glycerine was added to the soaking water giving a 2% glycerine concentration.

It was important to ensure that all interventions used in the research were able to be sustained long term. If interventions indicated a significant improvement it would have been unethical if they were unavailable at either low or no cost in the future. Details of the sustainability of products used in the research are presented next.

#### 4.3.1.7. SUSTAINABILITY OF PRODUCTS USED IN THE RESEARCH.

Table 4.2 identifies the sustainability of products used in the control and experimental arms of the study. This is included given the African context where resources are often limited.

**Table 4.2. Sustainability of products used in control/experimental group.**

Intervention	Group	Sustainability
Soap	Experimental and control	Low cost and available locally. Currently supplied to those attending APA clinics. Easily stored.
Vaseline <sup>®</sup> (petroleum jelly)	Experimental and control	Low cost and available locally. Currently supplied to those attending APA clinics. Easily stored.
Sodium hypochlorite, NaOCl (bleach)	Experimental and control	Low cost and available locally. Currently supplied to those attending APA clinics. Easily stored.
Whitfield's ointment (3% salicylic acid and 6% benzoic acid in a base of petroleum).	Experimental and control	Low cost and available locally. Supplied to those with fungal infections attending in APA clinics. Easily stored.
1 litre jugs	Experimental and control	Available locally at low cost. Easily stored.
2% glycerine	Experimental	Available locally at low cost. Easily stored.
2 ml syringes to measure NaOCl	Experimental	Available locally at low cost.

The costs of treatment for each group over 3 months are detailed in Table 4.3.

**Table 4.3. Comparative cost of 3 months treatment for the control/experimental groups in UK pounds.**

Control group		Experimental group	
Product per month	Cost of 3 months' supply	Product per month	Cost of 3 months' supply
450ml bottle of NaOCl	19p x 3 = 57p	300 mls of NaOCl	19px2 = 38p
bars of soap	15p x 3 = 45p	650 ml bottle of glycerine	1.14p x3 = 3.42p
100 gram jar of <i>Vaseline</i> <sup>®</sup>	18p x 3 = 54p	bars of soap	15p x3 = 45p
1litre jug	39p	100 gram jar of <i>Vaseline</i> <sup>®</sup>	18p x3 = 54p
		1litre jug	39p
		2 ml syringe	2p
<b>TOTAL COST</b>	<b>£ 1.95</b>		<b>£ 5.10</b>

Tubes of *Whitfield's ointment* were given only to those with fungal infections. The number of tubes given per month depended on the extent of the infection. It was applied daily. The cost of a tube *Whitfield's ointment* in Ethiopia is equivalent to 38p.

#### 4.3.1.8. STUDY SAMPLE SIZE.

Based on the pilot results statistical calculations were used to determine the numbers needed to detect a statistically significant difference in SC hydration and in TEWL between the two treatments soapy wash + water soak + *Vaseline*<sup>®</sup> and the soapy wash + 2% glycerine soak + *Vaseline*<sup>®</sup>. For SC hydration a mean difference in SC hydration level of 4.81 between the control and experimental groups was expected after three months of treatment. The within-group standard deviation was expected to be around 3.93, leading to an expected large effect size of around 1.23. To detect this effect size with 80% using a two-sided t-test with a 5% significance level, 24 participants were required, divided equally between the two treatment groups. For TEWL a mean difference in TEWL of 1.05 gm<sup>2</sup> h between the control and experimental group was expected after three months treatment. The within-group standard deviation was expected to be around 1.47, leading to an expected effect size of around 0.72 to detect an effect size of 80% using a two-sided t-test with a 5% significance level 64 participants were required divided equally between the two groups. The data 3 months post intervention was considered the main point for comparing outcome measures. Because this was the first RCT on pododermatitis and the large number of variables to be analysed it was decided to increase the

numbers of participants on the study to approximately 200. This number was thought to be achievable based previous new patients at the clinics.

The study required the nurse and social worker at each clinic to fully understand the research, the importance of ethical recruitment, the importance of the consistent and correct application of treatments to both groups and the significance of accurate data recording. An educational programme was therefore provided for them at each clinic and is detailed below.

#### 4.3.1.9. EDUCATIONAL PROGRAMME PROVIDED FOR CLINIC STAFF.

The PI provided the educational programme to staff in both clinics before participants were recruited to the study. Table 4.4 indicates the programme provided.

**Table 4.4. Educational programme of nurse and social worker delivered by principal investigator.**

Time	Teaching and rationale
9-9.30.	Explain research aims and objectives, inclusion/exclusion criteria and patient consent. Difference in treatment between the experimental and control groups. Importance of accurate data collection. Criteria for extra payment of nurse and social worker for taking part in the research.
9.30-10.45	Measurements to be collected on data collection sheets. Explain rationale and demonstrate in practical session.
10.45-11.15	Explain rationale for using 2% glycerine. Demonstrate measuring amounts of water, NaOCl and glycerine.
Break	
11.30-12.15.	Explain rationale and demonstrate use of <i>VapoMeter®</i> , <i>MoistureMeterSC®</i> . Practice use and recording results. Advise on cleaning of probes between patients. Provide staff with the Protocol for using the <i>VapoMeter®</i> and <i>MoistureMeterSC®</i> (Appendix 23).
Break	
1.00-1.40	Completing forms - demonstration and practice. Encourage questions and provide answers.

Any unusual changes in the skin of the legs/feet noted by staff or participants during the study were to be reported were reported to the PI.

The next section details the system of recruiting participants from the clinics onto the study.

#### 4.3.2. RECRUITING PATIENTS ONTO THE STUDY.

All new patients at two APACs who fulfilled the criteria were approached regarding their possible inclusion in the study.

#### *4.3.2.1. PARTICIPANT CONSENT.*

The vast majority of potential participants were illiterate so the SW or nurse read the Patient Information Form to them (Appendix 26) and they were encouraged to ask questions. They were given 1/2 hour to consider their involvement in the study. The short time scale was because of the long difficult journeys taken on foot to travel to the clinic so a further delay would have resulted in an additional journey with the high possibility of non-return. If they agreed they were given a Consent Form (Appendix 27). Participants either signed the Consent Form or, if they were illiterate indicated consent via a cross or other mark or an ink mark from their index finger. Following informed consent participants were allocated to groups as detailed in the next section.

#### *4.3.2.2. ALLOCATION TO GROUPS.*

Eight file boxes were labelled, four boxes for each clinic (A or B). The four boxes in each clinic were labelled by gender and disease severity. For example in clinic B one box were labelled 'male/moderate/less severe disease', the second box 'male/severe disease', the third 'female/moderate/less severe disease' and the fourth female/severe disease. Within each box were sealed individually coded envelopes. An envelope from the appropriate container was opened sequentially. For example the fifth participant in clinic B who was female with severe disease was given the envelope was marked BFS5. The contents of the envelope revealed if she was in the experimental or the control group. Those in the control group were subject to the 'usual' treatment (Table 2.6) and the experimental group to the experimental treatment (Table 4.1). Participants were encouraged to attend clinics monthly for data collection and pick up supplies for the following month's treatment.

#### *4.3.2.3. EDUCATION OF PARTICIPANTS.*

Verbal instructions and demonstrations of the daily treatment regimen of the feet/legs were given to participants by the nurse and SW in both clinics at every visit. This consisted of washing the feet/legs every evening with soap until all dirt was removed paying special attention to folds in the skin and between the toes. All participants were taught how to measure the amount of water and the NaOCl for soaking the legs/feet. Those in in the experimental group were shown how to measure the glycerine and add it to the water soak. They were all

instructed to soak their feet/ankles for the time it takes to make an Ethiopia cup of coffee (about 30 minutes) frequently splashing the water up the lower legs. All were shown how to place their feet on clean cardboard or thick paper and wait for the air to dry them. Those with toes in close proximity and/or skin folds were shown how to dry between them with a piece of gauze. Although as previously mentioned the amount of clean gauze given to participants to take home was only sufficient to last a few days. This was followed by a demonstration on the amount and correct application of *Vaseline*<sup>®</sup> and of *Whitfield's ointment* to those with fungal infections. All participants were encouraged to ask questions. Table 2.3 details the current regime provided to the control group. Table 4.1 details the experimental group intervention. The only difference was that the experimental group used 1/6<sup>th</sup> less soaking water with a lower (0.008% v 0.0125%) dilution of NaOCl and added a 2% dilution of glycerine.

#### *4.3.2.4. FREQUENCY OF DATA COLLECTION AND STUDY PERIOD.*

The nurse and SW at each clinic collected data from participants for 3 months. The study took place over 7 months from late January to late August 2014.

#### *4.3.2.5. DATA RECORDED, RATIONALE AND METHOD.*

Data were collected from each participant by the nurse and SW using the Data Collection Forms (Appendix 30). The data were recorded on each participant at baseline and then every month for three months. Three months was chosen as the clinic nurses and SWs considered that, in their experience it was the time at which there were visible improvements in skin condition and leg/foot circumference. A previous study had also indicated that three months treatment resulted in physical improvements in legs/feet including decreased swelling and odour and improved mobility (Henok, Davey 2008). Table 4.5 identifies the type of data recorded the rationale and collection method.

**Table 4.5. Data collected from participants, time, outcome measures, rationale and collection method.**

Data collected	Time of data collection	Outcome measure	Rationale	Method of collection
Trans-epidermal water loss (TEWL) and stratum corneum hydration levels of each affected leg/foot	All visits	Primary	TEWL is the most important indicator of healthy skin. It is the prime outcome measure of this research. TEWL increases in inflammatory skin disease. It progresses if skin without a therapeutic intervention. SC hydration indicates the amount of moisture in the SC. Dehydration of the SC causes an inflammatory reaction to occur. This disrupts and decreases the lipids leading to an excessive loss of NMF and subsequent loss of SBF (Ferguson, Yeshanehe et al. 2013). The same instruments were used to measure TEWL and skin hydration as in the pilot study. The manufacturer was contacted to determine any specific issues regarding their use in Ethiopia. The reply is in Appendix 17. Both instruments had previously been used to measure SC hydration levels and TEWL (Ferguson, Yeshanehe et al. 2013). Details of their use and protocol for use are in Appendix 23.	TEWL was measured on each of the 4 sites at each visit (Section 4.2.2.6.). SC hydration levels were measured on the same 4 sites as TEWL (Section 4.2.2.6.). The mean of the 3 measurements were recorded for each site.
Dermatology Life Quality Index  Permission was obtained from Professor Finlay, Cardiff University to use the Amharic version of the DLQI in the study (Appendix 24).	All visits	Primary	The impact of disease can be assessed by measuring a person's skin specific quality of life. This seeks to measure a person's physical health, psychological status, level of independence, social relationships, beliefs and relationship with the environment (Halioua, Beumont et al. 2000). There are a number of these tools including the Dermatological Life Quality Index (DLQI) (Appendix 24, 24B). DLQI consists of ten questions answered by patients. They are grouped together in themes. They relate to how they felt over the previous week. The responses are 'very much', 'a lot', 'a little' or 'not at all'. There is an Amharic (official language of Ethiopia) version of the DLQI. Henok and Davey (2008) noted that this was quick and simple to use taking an average of four minutes to administer. It successfully distinguished between new and treated patients ( $p > 0.001$ ). It indicated high internal consistency, inter-item correlation averaged 0.44 and Cronbach's alpha was 0.9. It was concluded that the tool was feasible, reliable and valid to use among patients with podoconiosis even in remote urban and rural settings.	Information from participant

<b>Data collected</b>	<b>Time of data collection</b>	<b>Outcome measure</b>	<b>Rationale</b>	<b>Method of collection</b>
Age	1 <sup>st</sup> visit	Descriptive	To compare with other studies. Onset is in the first and second decades of life with progressive increase in prevalence up to 60 years (Davey, Tekola et al. 2007).	Information from participant
Gender	1 <sup>st</sup> visit	Descriptive	Two large studies reported more females with the disease which may be related to shoe wearing differences between males/females.	Observation of nurse/SW
Occupation	1 <sup>st</sup> visit	Descriptive	Barefoot farmers are particularly vulnerable to the disease. For example a study in Ethiopia stated that 69.1% of those with the disease were farmers and 13.9% housewives (n=437) (Molla, Le Blond et al. 2013).	Information from participant
Date of onset of podoconiosis	1 <sup>st</sup> visit	Secondary	Indication of disease progression	Information from participant
Stage of podoconiosis each affected leg	All visits	Secondary	Indication of disease progression using the five stage system (Tekola, Ayele et al. 2008). Further details are in Appendix 4.	Observation/ judgement by nurse/SW
Mossy changes present both legs	All visits	Secondary	Indication of disease progression	Observation and judgement by nurse/SW
Odour present both legs	All visits	Secondary	Indication of wound/skin infection. Odour may also relate to stigma and DLQI.	Observation and judgement by nurse/SW
Number of wounds on each leg/foot	All visits	Secondary	Related to skin integrity.	Observation and counting by nurse/SW
Time unable to work in previous month due to ADL	All visits	Secondary	Effects economic capacity.	Information from participant

Data collected	Time of data collection	Type of data collected	Rationale	Method of collection
Type of shoes worn in previous week	All visits	Secondary	The majority of those with the disease are barefoot. Shoes which cover the feet worn consistently shoes should reduce ADL and disease progression. Previous studies indicate women are less likely to wear shoes (Section 1.5.10.3.) and that shoe wearing decreases the probability of developing podoconiosis (Molla, Le Blond et al. 2013).	Information from participant and observation by nurse/SW
Circumference of each affected leg	All visits	Secondary	Changes in measurement indicate progression or improvement in the disease.	Measured at the area of greatest circumference by the nurse/SW using disposable tape measures
Circumference of each affected foot	All visits	Secondary	Changes in measurement indicate progression or improvement in the disease.	Measured at the area of greatest circumference by the nurse/SW using disposable tape measures

#### 4.3.2.6. MEASUREMENT SITES.

In those with podoconiosis skin changes and lymphoedema start at the foot and move up the leg not extending above the knee (Molla, Le Blond et al. 2013). In order to note this disease progression measurements were taken at the points indicated below. They were the same points as used in the pilot study.

Points used on the lateral lower leg were:

- 8cms below the head of the fibula
- 8cms above the external malleolus
- mid-way between these two sites

Measurements were also recorded on the mid top of the foot, the site used in the only other study of TEWL and skin hydration in those with podoconiosis (Ferguson, Yeshanehe et al. 2013). In their study recordings were made only at one point on the lower outer leg. However, the study gave no indication of the exact point of measurement. Sites used in this study were identified with a tape measure and marked with an indelible pen. Hairs in the area that may have resulted in false results in TEWL and SC hydration were carefully removed with scissors. This was done because shaving may have disrupted the skin's surface increasing TEWL. Sites with wounds or deep skin folds were avoided.

Measurements of leg and foot circumference were taken at the largest circumference point in centimetres (cms) with a disposable tape measure. Two different non-invasive probes used to measure SBF. One measures SC hydration and the other TEWL. The details of these devices are presented next.

##### **4.3.2.6.1. MoistureMeterSC® AND VapoMeter®.**

Staff followed the protocol given by the PI for using the *MoistureMeterSC*® and *VapoMeter*® (Appendix 23). Details of the measurement devices are given in Appendix 2. Spares of each device and spare batteries were available from the study supervisor if required. The manufacturer's guidelines were followed and the instruments previously calibrated.

Participants sat in the shade without shoes and socks and without crossing their legs for 20 minutes before any readings using the probes were undertaken. The nurse/SW held the probes with the index finger and thumb to avoid transferring their body temperature to the probes. One *VapoMeter*® reading was taken at each marked site and recorded. The ambient

temperature and humidity were also recorded. Three *MoistureMeterSC*<sup>®</sup> readings were taken in close proximity within the marked area and the mean of these three readings recorded. The manufacturers recommend that both probes are used in temperatures 10<sup>0</sup>C-30<sup>0</sup>C and it was found that the probes ceased to function correctly giving bizarre readings when the temperature reached over 32<sup>0</sup>C. In clinic B this was between approximately 11.30am and 2.30pm. Participants were encouraged to arrive at clinics early. If probes ceased to function because of high ambient temperature participants were invited to wait till the temperature dropped before recordings could be taken. Photograph 4.1 is the clinic nurse using the *MoistureMeterSC*<sup>®</sup>.

**Photographs 4.1. Clinic nurse measuring the SC hydration of a participant with a *MoistureMeterSC*<sup>®</sup> after 3 months treatment.**



#### **4.3.2.6.2. PODOCONIOSIS STAGING TOOL.**

The 5 stage podoconiosis tool (Appendix 4) was used for the research (Tekola, Ayele et al. 2008). It was reported to be simple to use, with good content reliability and inter-observer agreement and repeatability (Tekola, Ayele et al. 2008). It identified changes in the stage of disease between the control and experimental group pre and post intervention. The tool had been used previously in other Ethiopian studies thus allowing comparison of the

results with these previous studies (Sikorski, Ashine et al. 2010, Molla, Tomczyk et al. 2012a).

#### ***4.4. TREATMENT FIDELITY.***

Treatment fidelity is the degree to which interventions are conducted as planned (Horner, Rew et al. 2006). This is an essential element in study design and implementation as it maintains the credibility of research findings (Horner 2012). It is a means of ensuring the reliability and validity of interventions (Bellg, Borrelli et al. 2004). The Treatment Fidelity Workgroup of the National Institute of Behavioural Change Consortium suggested ways to improve intervention fidelity designed to ensure that interventions were delivered as intended when used in different populations in different sites (Bellg, Borrelli et al. 2004). They are summarised as follows:-

1. ensuring the intervention is the same for all participants
2. standardizing interventionist training
3. monitoring interventionist delivery
4. evaluating participants understanding of information provided
5. ensuring all participants use the skills taught in the intervention (Horner 2012)

To address these points the methods identified in Table 4.6 were implemented.

**Table 4.6. Methods used to improve treatment fidelity.**

Ensuring treatment fidelity	Methods undertaken to improve treatment fidelity
Ensuring the intervention is the same for all participants	The PI provided education on the research to the nurse and social worker (SW). To ensure their understanding and provide support the PI was available daily for the first week of the research at each clinic to answer any questions. She also checked data collection, measurements and data recording. A local nurse with a particular interest in podocoinosis and a Master in Public Health qualification was appointed as a supervisor. He monitored staff data collection and visited both clinic sites initially weekly reducing this to every 2/3 weeks. He reported back to the PI in the UK. He also accompanied the PI on all visits.
Standardizing interventionist training	All training to staff was provided by PI.
Monitoring interventionist delivery	The PI daily monitored patient education by staff by for the first 5 days and ensured accurate data collection and recording. The interventions of patients checked by staff after they have been taught and demonstrated at subsequent attendances at monthly clinics. The supervisor monitored the clinic staff and data collection in the PIs absence. Frequent updates on progress were provided to the PI. The PI directly monitored clinic staff, their teaching of participants and data collection at 1, 10, 17, and 24 weeks to ensure that their teaching was consistent and that their data recording and collection was carried out correctly.
Evaluating participants understanding of information provided	At the monthly attendance at clinic the staff in both groups checked patients understanding of the interventions.
Ensuring all participants use the skills taught in the intervention	It was difficult to monitor patients at home as they live in very poor rural areas with few roads and are often illiterate. Patients in the groups were asked to demonstrate the treatment regime they were using at their monthly clinic visits. Patients were re-educated and supported as necessary.

Data collection and clinic follow-up visits are discussed in the next section. It was important that data was collected and kept methodically. Due to issues with lack of local supplies all the equipment required for the study was taken to the clinics from the UK.

#### **4.5. DATA COLLECTION AND FOLLOW-UP CLINIC VISITS.**

All data were collected on paper forms which were supplied by the PI. Ball point pens, box files, disposable tape measures and staplers were also supplied. Due to the high cost of each of the probes clinic staff were given information on how to care and store them as well as how to use them

(Appendix 23). They also signed a form agreeing to take responsibility for caring for the probes and keeping them safe and in good order.

#### **4.6. DATA ANALYSIS.**

Data was entered into IBM SPSS statistical package version 22. It was checked for outliers, completeness and accuracy prior to analysis. The variables analysed in each group are specified in Table 4.7.

**Table 4.7. Variables analysed and units of analysis.**

<b>Variables</b>	<b>Unit of analysis</b>
Age	Categorised in units of 10 years
Gender	Male or female
Occupation	Open question subsequently then categorized
Time since onset of clinical signs of podoconiosis	Years
Stage of podoconiosis on each affected leg/foot	Disease stage 1-5
Mossy changes	Present in each leg yes or no
Leg odour	Present in each leg yes or no
Number of leg/foot wounds	Present in each leg yes or no
Type of shoes worn at baseline	Categorised
Number of work days lost due to adenolymphangitis	Days
Leg/foot circumference by group on each affected leg/foot	Centimetres (cms)
TEWL at all points on leg/foot on each affected leg/foot	Grams of water lost per metre squared per hour (gm <sup>2</sup> h)
Stratum corneum hydration at all points on each affected leg/foot	Units

Although the 4<sup>th</sup> visit was considered to be the main time point for comparison, data from all time points was included in the analysis of each outcome measure. The data analysed is presented in sections 4.6.1, 4.6.2 and 4.6.3. In each section the methods of analysis are presented.

##### **4.6.1. MEASURES OF THE RELATIONSHIP BETWEEN NUMBER OF WOUNDS AND NUMBER OF WORK DAYS LOST.**

Spearman's rank correlation coefficient was used to determine any statistical relationship between the number of wounds and the numbers of days participants were unable to work due to ADL.

#### **4.6.2. OUTCOME MEASURES OF TRANS-EPIDEMAL WATER LOSS, STRATUM**

##### **CORNEUM HYDRATION, LEG AND FOOT CIRCUMFERENCE AND DERMATOLOGY LIFE QUALITY INDEX.**

For outcome measures that were interval level and for which a normal distribution assumption would be realistic, mixed modelling analysis (MMA) was used. For each such measure, the change from baseline at Visits 2, 3 and 4 was calculated and used as the dependent variable in the model. The mixed modelling approach initially assumed an unstructured correlation for the six measurements (or three measurements in the case of DLQI) taken within a participant. A group by time interaction was included in the model to allow the group difference, if any, to vary with time. Clinic, gender, initial stage of podoconiosis, leg or foot side (when relevant) and the corresponding outcome measure at baseline (Visit 1) were controlled for in the modelling. MMA measured the change between groups and, except for DLQI (which applied to a person rather than a side of a person), the difference between the right and left legs/feet in: TEWL at 3 points on each lower leg, TEWL on the top of both feet, skin hydration at 3 points on each lower leg, skin hydration on the top of both feet, leg circumference on each lower leg, foot circumference of each foot and DLQI.

#### **4.6.3. OUTCOME MEASURES OF THE NUMBER OF WORK DAYS LOST DUE TO**

##### **ADENOLYMPHANGITIS, STAGE OF PODOCONIOSIS, MOSSY CHANGES, LEG ODOUR AND THE NUMBER OF LOWER LEG/FOOT WOUNDS.**

For outcome measures that were unlikely to be normally distributed, generalised estimating equations (GEEs) were used. For binary outcome measures (mossy changes and odour), a Bernoulli distribution with a logistic link function was used. For outcome measures taking the form of counts (days lost and number of leg/foot wounds), a Poisson distribution with a logarithmic link function was used. For ordinal outcome measures (stage of podoconiosis) a cumulative logistic link function was used. For each measure for which GEEs were used, the values at Visits 2, 3 and 4 were used as the dependent variable in the model. As in the mixed modelling, a

group by time interaction was included in the GEE procedure to allow the group difference, if any, to vary with time. Gender, initial stage of podoconiosis, leg or foot side (when relevant) and the corresponding outcome measure at baseline (Visit 1) were included as covariates in the GEE procedure. They provide details of central tendency, variation and shape. They were used to analyze, the number of work days lost due to ADL, the stage of podoconiosis, the presence of mossy changes, the presence of leg odour and the number of leg/foot wounds.

At the end of the study all data collection forms were brought back to the UK for computer input and analysis using SPSS version 22. Analysis of the study results are detailed in the following Chapter 5.

## ***CHAPTER 5. RESULTS.***

### ***5.1. OVERVIEW OF RESULTS.***

In this chapter the first section reports the stratification of participants by clinic, gender and disease severity and the rationale. The next section specifies the social and demographic profile of participants including the number of participants in each group and each clinic, their age, gender and occupation. The time to onset of podoconiosis is then presented followed by the type of shoes worn by participants in the previous week. A section on SBF follows which details the trans-epidermal water loss and SC hydration at the specific points on the leg/foot. A general clinical profile of the legs/feet is then presented. This includes the stage of podoconiosis, mossy changes, odour, wounds, leg and foot circumference, the number of days work lost due to ADL and the correlation between the numbers of days lost and ADL. The last section specifies the quality of life of participants as measured by the Dermatology Life Quality Index.

#### ***5.1.1. STRATIFICATION OF CLINIC, GENDER AND DISEASE SEVERITY .***

Stratification was undertaken to ensure virtually equal numbers by clinic, gender and disease severity. This was to allow any difference between them to be identified. The results of the stratification are presented in Table 5.1.

**Table 5.1. Number and code number of participants in each clinic by gender, stage of podoconiosis.**

<b>Clinic, gender and stage of podoconiosis</b>	<b>Code and number of participants</b>
Clinic A. Female participants with less severe podoconiosis	AFLS 1-24 (12 in each group)
Clinic A. Female participants with severe podoconiosis	AFS 1-24 (12 in each group)
Clinic A. Male participants with less severe podoconiosis	AMLS 1-22 (11 in each group)
Clinic A. Male participants with severe podoconiosis	AMS1-24 (12 in each group)
Clinic B. Female participants with less severe podoconiosis	BFLS 1-26 (13 each group)
Clinic B. Female participants with severe podoconiosis	BFS 1-24 (12 each group)
Clinic B. Male participants with less severe podoconiosis	BMLS 1-22 (11 each group)
Clinic B. Male participants with severe podoconiosis	BMS1-28 (14 each group)

Due to a counting error one male Clinic B participant with mild/moderate disease in the experimental group was not recruited to the study from Clinic B. A total 94 participants was recruited from Clinic A comprising 47 with less severe disease (stages 1, 2 and 3) and 47 with severe disease (stages 4 and 5). A total of 99 participants was recruited from Clinic B comprising 49 with less severe disease and 50 with severe disease. If legs had different stages of podoconiosis the leg with the highest stage was used to denote severity.

## **5.2. DEMOGRAPHIC PROFILE OF PARTICIPANTS.**

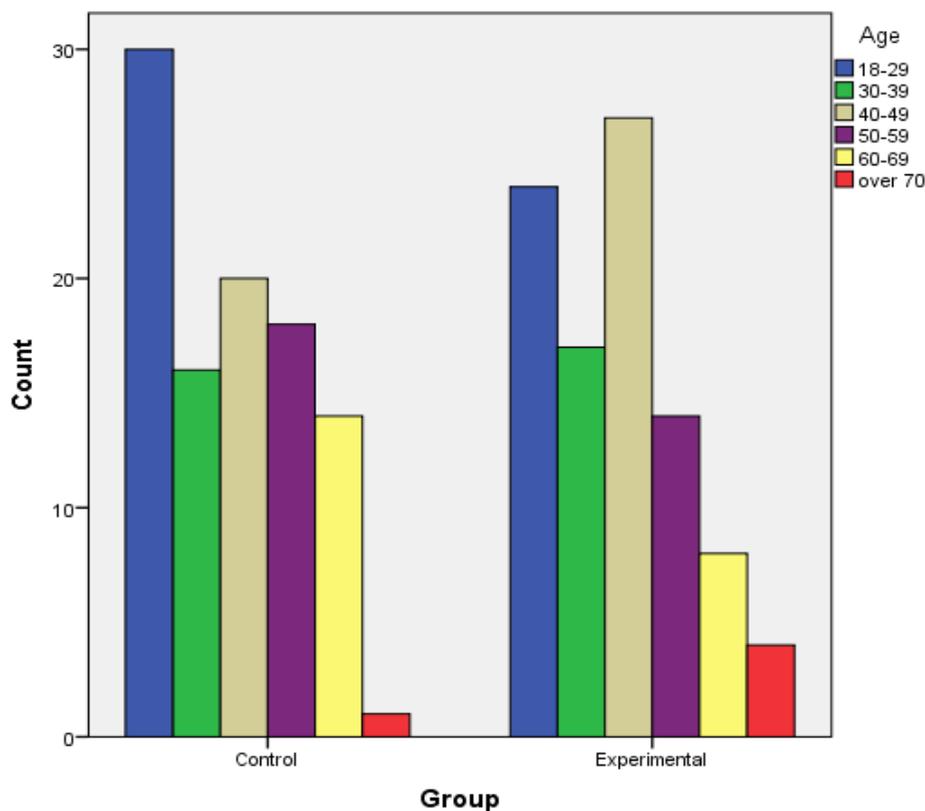
### **5.2.1. STUDY PARTICIPANTS.**

There were 193 newly presenting patients with podoconiosis recruited onto the study. There were 97 participants in the control group and 96 in the experimental group. Clinic A enrolled 94 (48.7%) participants and Clinic B 99 (51.3%). Three month post-intervention data was missing from one male Clinic B participant in the control group with mild/moderate disease. This was because he did not return to clinic for the fourth visit. The reason was not known. All legs with clinical signs of podoconiosis were used for the analysis. Three participants (1.55%) had only one of their legs/feet with clinical signs of podoconiosis. Twenty five participants (12.95%) had different stages of podoconiosis in each of their legs (severe disease versus moderate/less severe disease).

### 5.2.2. AGE OF PARTICIPANTS.

The majority of participants 188 (97.1%) were aged 18-69 years. Only 5 (2.6%) were over 70 years of age. Most participants were aged between 18-29 years (54, 28%). Thirty three were aged 30-39 (17.1%), 47 (24%) were aged 40-49 years, 32 (16.6%) were aged 50-59 and 22 (11.4%) were 60-69. As only age ranges were recorded there are no subsequent mean or median ages. Figure 5.1 indicates the difference in ages between groups.

**Figure 5.1. Difference in age of participants between groups.**



In the experimental group there were slightly fewer participants in the 18-29, 50-59, 60-69 age groups and slightly more in the 40-49 and 70 plus age groups compared to the control.

### 5.2.3. GENDER OF PARTICIPANTS.

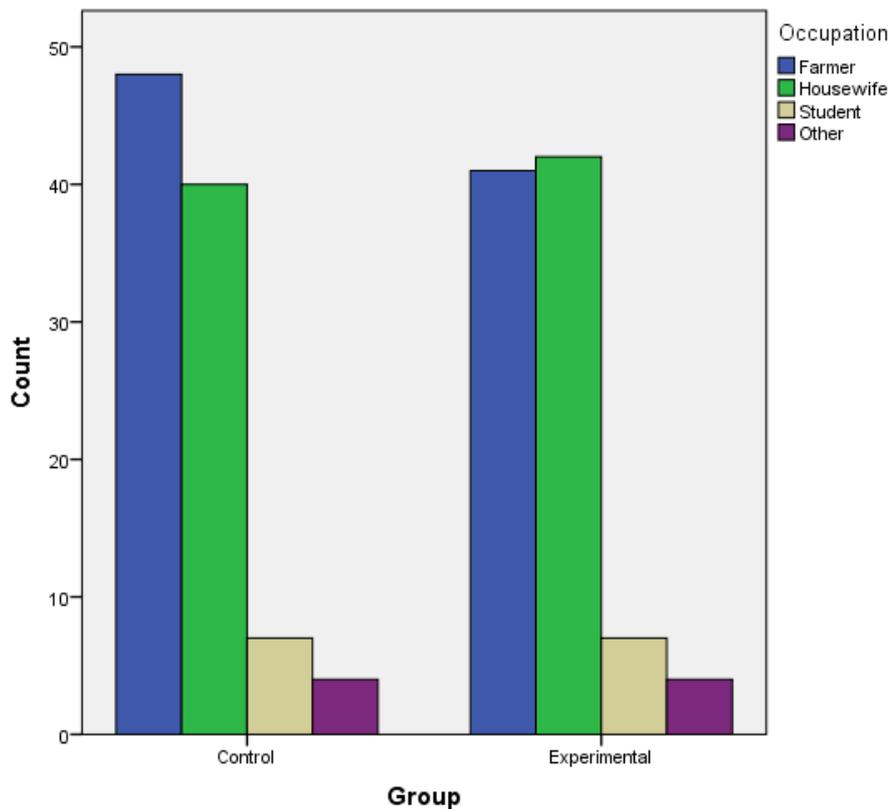
Participants were stratified to ensure numbers of males/females were fairly equal. Ninety five (49.2%) of participants were male and ninety eight (50.8%)

female. There were 49 females and 48 males in the control group. In the experimental group there were 49 females and 47 males.

#### **5.2.4. OCCUPATION OF PARTICIPANTS**

Figure 5.2 shows the occupations of participants by group.

**Figure 5.2. Occupation of participants by group.**



The majority of participants described themselves as farmers 89 (46.1%), 82 (42.5%) as housewives and 14 (7.3%) as students. There were approximately the same numbers of housewives in each group. More farmers were in the control group compared to the experimental group (48 versus 40). Those who were 'others' included those who described themselves as servants or merchants.

#### **5.2.5. TIME TO ONSET OF CLINICAL SIGNS OF PODOCONIOSIS.**

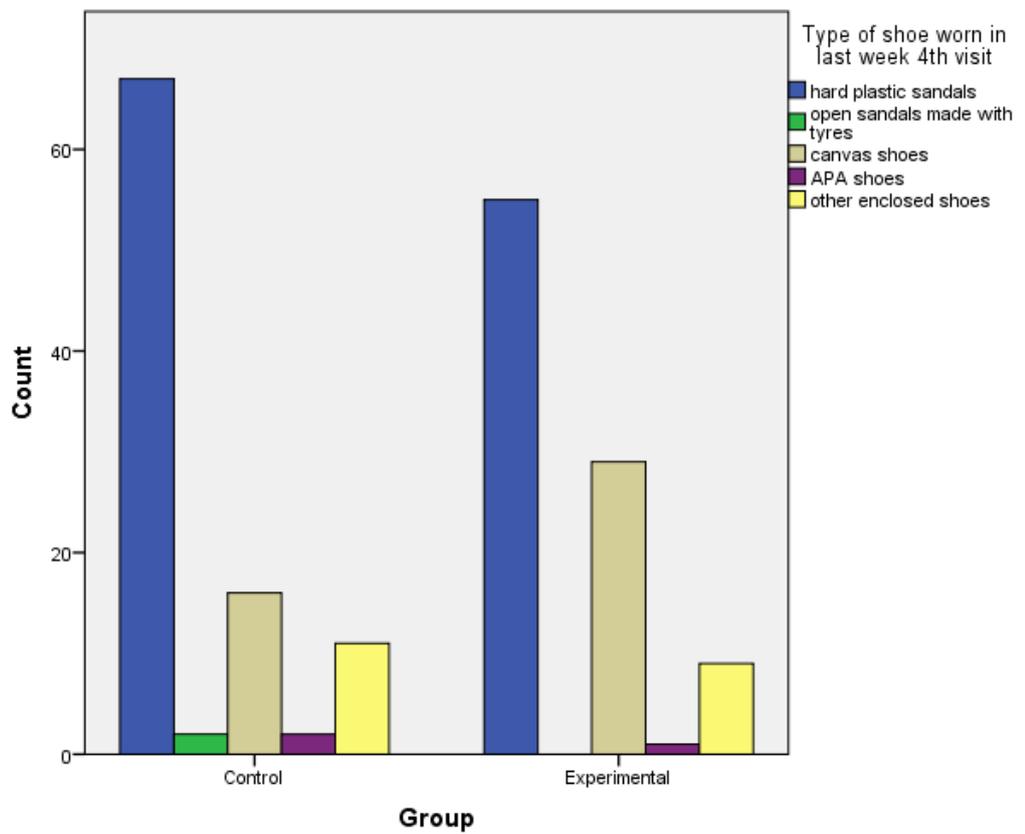
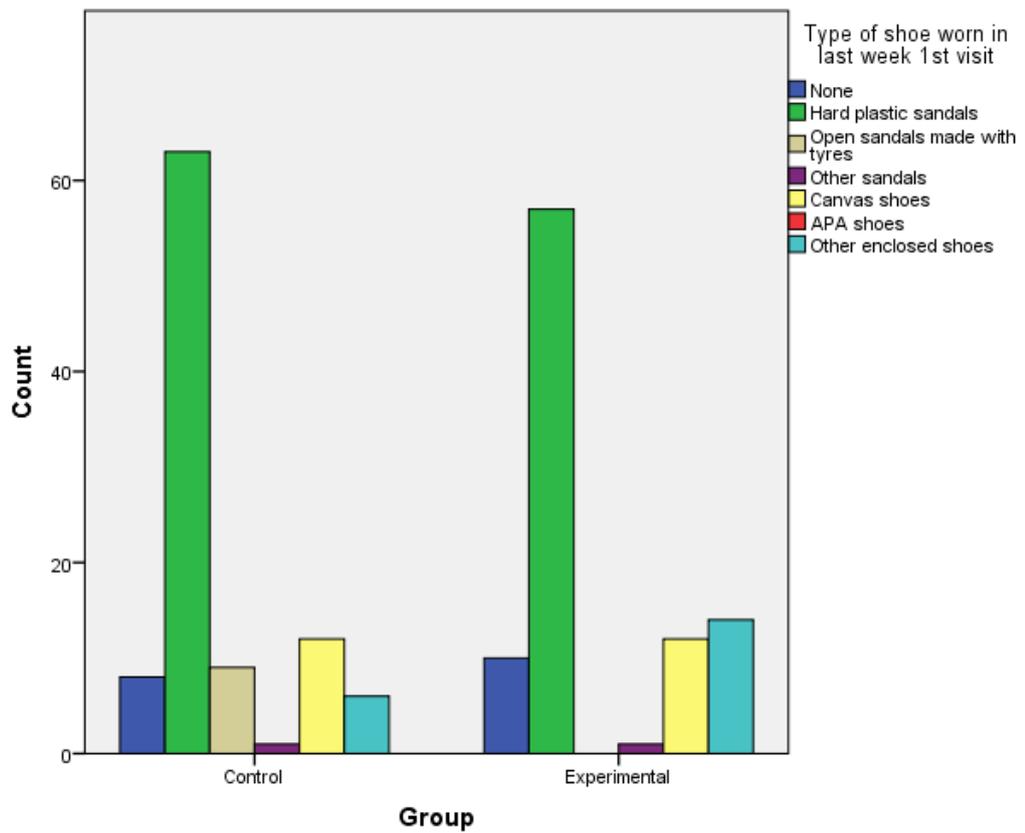
The majority (143, 74.2%) had clinical signs of the podocniosis for 1-6 years. The time to onset was as follows: less than 1 year 2 (1%), 1-2 years 47 (24.4%), 3-4 years 49 (25.4%), 5-6 years 47 (24.4%), 7-8 years 23

(11.9%), 9-10 years 18 (9.3%), 11-12 years 4 (2.1%). There were 188 (87.1%) who had the disease for less than 8 years. Only 3 (1.6%) had the disease for over 12 years. Compared to participants in the experimental group more in the control group had signs of the disease for 1-4 years. More of the participants in the experimental group had clinical signs of disease in excess of 9 years. The mean time since clinical onset of the disease was higher in the experimental group. The mean for the control group was 3.39 years and for the experimental group 3.94 years.

#### ***5.2.6. TYPE OF SHOES WORN.***

The types of shoes worn by groups in the week prior to baseline and the fourth visit are illustrated in Figures 5.5, 5.4.

**Figures 5.3. and 5.4. Type of shoe worn by each group in the previous week at baseline and fourth visit.**



At baseline 18 (9.4%) participants were barefoot in the previous week. One hundred and twenty (62.2%) wore hard plastic sandals, 24 (12.4%) canvas shoes, 20 (10.4%) other enclosed shoes, 9 (4.7%) open sandals made with tyres and 2 (1%) other sandals. Post intervention no one reported being barefoot in the previous week. One hundred and twenty two (63.3%) had worn hard plastic sandals, 45 (23.3%) canvas shoes, 20 (10.4%) other enclosed shoes, 3 (1.6%) custom made APA shoes and 2 (1%) open sandals made with tyres. Those in the control group had worn more hard plastic sandals and fewer canvas shoes in the previous week compared to the experimental group.

The type of shoes worn by gender was as follows: no shoes - 5 (2.6%) males v 13 (6.7%) females, hard plastic sandals - 61 (31.6%) males v 59 (30.6%) females, open sandals made with tyres - 7 (3.6%) males v 2 (1%) females, other sandals males 0 (0%) v 2 (1%) females, canvas shoes - 11 (5.7%) males v 13 (6.7%) females and other enclosed shoes - 11 (5.7%) males v 9 (4.7%) females.

### ***5.3. SKIN BARRIER FUNCTION.***

This section presents the results of the analysis of the primary outcome measures TEWL and SC hydration. These were both measured quantitatively at specific anatomical points on the lower legs/feet. Group and gender differences and differences between the right and left legs are presented. The mean levels at different points on the leg were not strongly correlated because of this individual sites were used for the measurements.

#### ***5.3.1. TRANS-EPIDERMAL WATER LOSS.***

The mean TEWL was recorded at 3 specific points on the lower leg and also on the top of the foot. The mean TEWL of all participants at baseline is presented first. This is followed by the group differences in TEWL at each specific point on the lower leg/foot.

5.3.1.1. MEAN TRANS-EPIDERMAL WATER LOSS AT SPECIFIC POINTS ON THE LEG/FOOT OF ALL PARTICIPANTS AT BASELINE.

Table 5.2 indicates the mean TEWL at specific points on each leg/foot of all of the participants at baseline.

**Table 5.2. Mean TEWL at each specific point of leg/foot of all participants at baseline.**

Point on the lower leg	Mean TEWL right leg at baseline	Mean TEWL left leg at baseline
Top	13.08 gm <sup>2</sup> h	13.40 gm <sup>2</sup> h
Mid-point	14.29 gm <sup>2</sup> h	15.02 gm <sup>2</sup> h
Base	16.62 gm <sup>2</sup> h	17.17 gm <sup>2</sup> h
Top of Foot	22.41 gm <sup>2</sup> h	22.75 gm <sup>2</sup> h

The highest mean TEWL at baseline was at the top of the feet. It decreased considerably moving up the leg.

5.3.1.2. TRANS-EPIDERMAL WATER LOSS AT TOP OF LOWER LEGS.

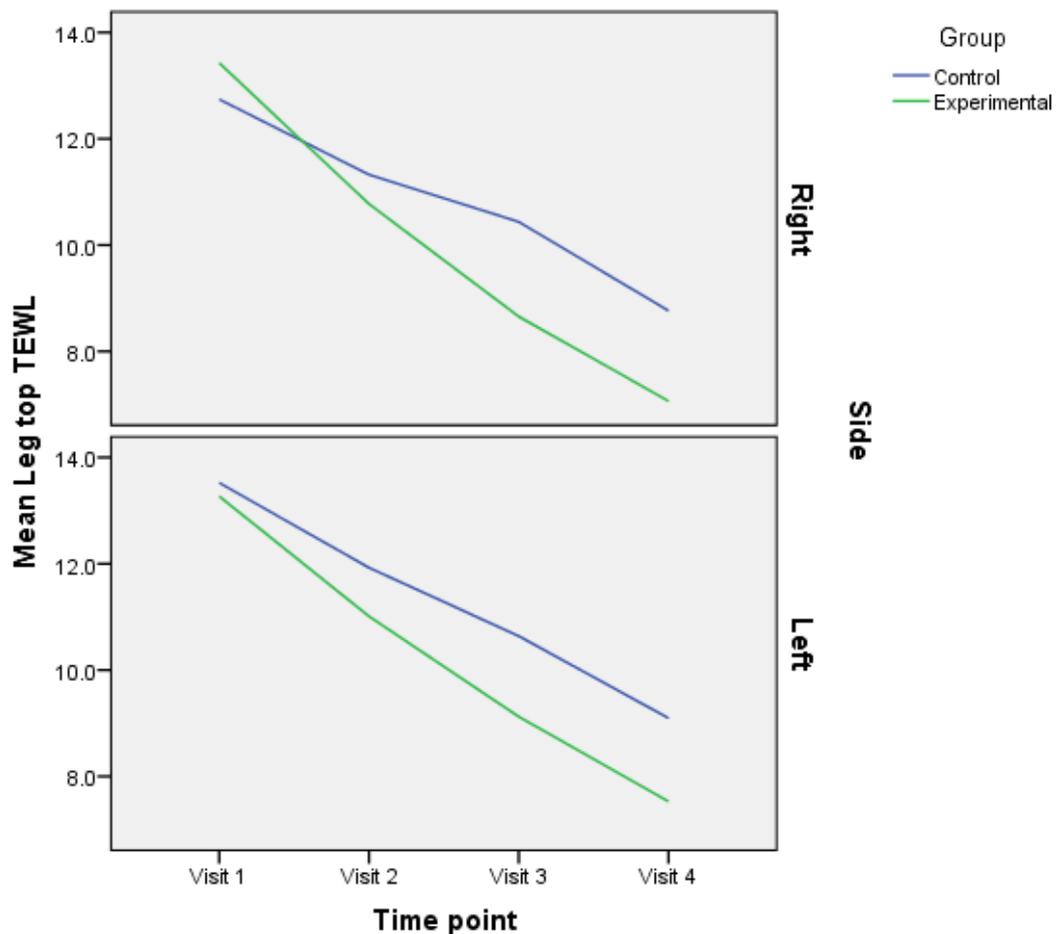
Table 5.3 presents the changes in TEWL at the top of the lower legs from baseline by side and group at each visit.

**Table 5.3. Trans-epidermal water loss (gm<sup>2</sup>h) at top of lower leg – changes from baseline by side and group at each visit.**

Leg top TEWL	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Mean	12.74	11.33	10.44	8.76	13.52	11.93	10.64	9.09	13.43	10.77	8.66	7.06	13.27	11.01	9.12	7.53
Median	11.80	10.55	9.95	8.80	12.60	11.40	10.10	8.50	12.20	10.00	8.40	6.90	12.00	10.10	8.90	7.10
Standard Deviation	4.73	3.32	3.96	2.63	5.61	4.09	3.19	2.63	5.61	3.60	2.70	1.96	4.91	3.89	2.60	2.12
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

Figure 5.5 shows the change in TEWL at top of the lower legs from baseline by side and group.

**Figure 5.5. Change from baseline in mean trans-epidermal water loss at the top of the lower legs by side and group.**



The mean TEWL reduced in both groups over the study period but the reduction was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was  $1.581 \text{ gm}^2\text{h}$  ( $\text{SE}=0.296$ ); this difference was highly significant ( $t=5.341$ ,  $\text{df}=89.347$ ,  $p<0.001$ ). The 95% CI for the group difference at this visit was (0.997 to 2.164).

The estimated gender difference at visits 2, 3 and 4 was  $0.539 \text{ gm}^2\text{h}$  ( $\text{SE}=0.286$ ). The reduction in TEWL was greater in females; this difference was approaching significance ( $t=1.883$ ,  $\text{df}=187.845$ ,  $p=0.061$ ). The 95% CI for the gender difference at these visits was (-0.026 to 1.104).

The estimated side difference at visits 2, 3 and 4 was  $-0.364 \text{ gm}^2\text{h}$  ( $\text{SE}=0.106$ ). The reduction in TEWL was greater in right legs; this difference was highly significant  $t=-3.415$ ,  $\text{df}=186.089$ ,  $p=0.001$ . The 95% CI for the leg difference at these visits was (-0.574 to -0.154).

5.3.1.3. TRANS-EPIDERMAL WATER LOSS AT MID-POINT ON THE LOWER LEGS.

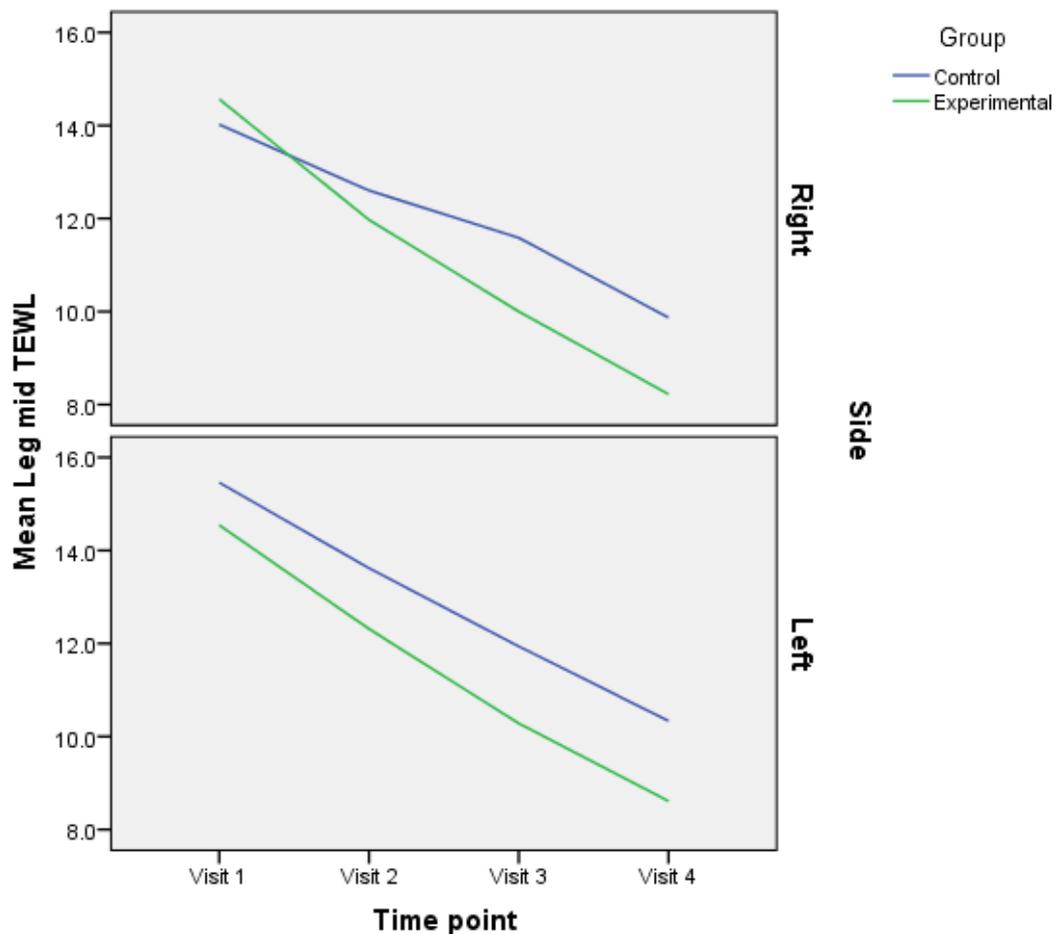
Table 5.4 presents the changes in TEWL at the mid-point of the lower legs from baseline by side and group.

**Table 5.4. Trans-epidermal water loss (gm<sup>2</sup>h) at mid-point lower leg - changes over time by side and group.**

Leg mid TEWL	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	14.02	12.60	11.59	9.87	15.46	13.62	11.94	10.34	14.57	11.97	10.00	8.22	14.55	12.31	10.28	8.61
Median	12.60	12.05	11.00	9.30	14.80	13.10	11.50	10.00	13.20	11.60	9.70	8.20	13.40	11.50	9.90	8.10
Standard Deviation	5.12	3.89	3.94	2.86	6.07	4.28	4.02	3.27	6.03	3.89	3.25	2.27	5.12	4.20	3.20	2.43
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	97.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

Figure 5.6 shows the change in mean TEWL at mid-point on the lower legs from baseline by side and group.

**Figure 5.6. Change from baseline in mean trans-epidermal water loss at mid-point lower legs by side and group.**



At the mid-point of the lower legs the mean TEWL reduced over time in both groups but the reduction was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was 1.684 gm<sup>2</sup>h (SE=0.346); this difference was highly significant (t=4.871, df=189.789, p=<0.001). The 95% CI for the group difference at this visit was (1.002 to 2.367).

The estimated gender difference at visits 2, 3 and 4 was 0.731 gm<sup>2</sup>h (SE=0.325). TEWL reduction was greater in females; this difference was significant (t=2.252, df=185.421, p=0.025). The 95% CI for the gender difference at these visits was (0.098 to 1.371).

The estimated side difference at visits 2, 3 and 4 was -0.366 gm<sup>2</sup>h (SE=0.141). TEWL reduction was greater in right legs; this difference was highly significant (t=-2.588, df=187.075, p=0.010). The 95% CI for the leg difference at these visits was (-0.645 to -0.087).

5.3.1.4. TRANS-EPIDERMAL WATER LOSS AT BASE OF LOWER LEGS.

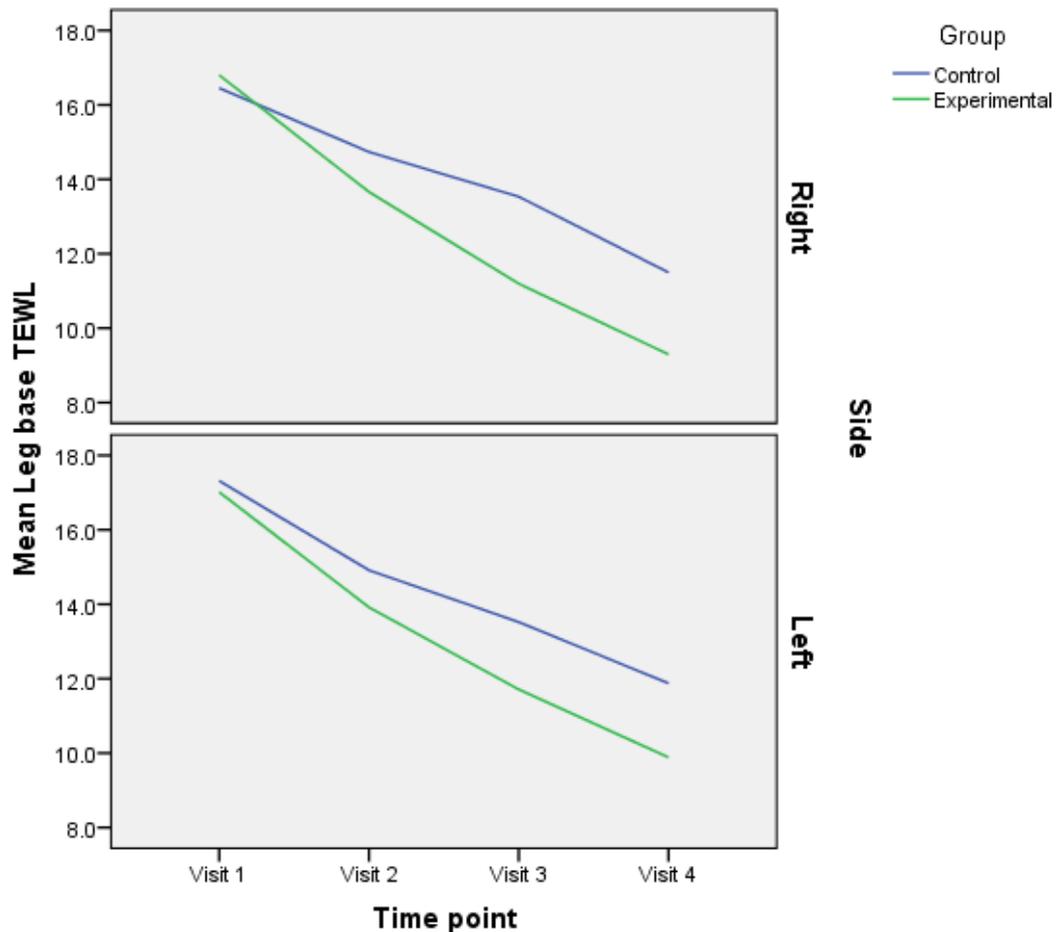
The table below presents the changes in TEWL at the base of the lower legs from baseline by side and group.

**Table 5.5. Trans-epidermal water loss (gm<sup>2</sup>h) at base of lower leg - changes by side and group.**

Leg base TEWL	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	16.45	14.74	13.53	11.50	17.32	14.92	13.52	11.87	16.80	13.66	11.19	9.30	17.02	13.92	11.71	9.88
Median	15.50	14.05	13.05	11.70	16.70	14.50	13.00	11.75	16.10	13.10	10.70	9.00	16.90	13.00	11.20	9.50
Standard Deviation	6.13	4.00	4.34	3.35	5.64	4.01	4.20	3.59	6.79	4.53	3.37	2.56	5.98	4.06	2.98	2.27
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

The following figure 5.7 indicates the change from baseline in the mean TEWL at the base of the lower legs by side and group.

**Figure 5.7. Change from baseline in mean trans-epidermal water loss at the base of lower legs by side and group.**



At the base of the lower legs the mean TEWL reduced in both groups over the study period but the reduction was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was  $1.970 \text{ gm}^2\text{h}$  ( $\text{SE}=0.386$ ); this difference was highly significant ( $t=5.111$ ,  $\text{df}=189.620$ ,  $p<0.001$ ). The 95% CI for the group difference at this visit was (1.210 to 2.731).

The estimated gender difference at visits 2, 3 and 4 was  $0.713 \text{ gm}^2\text{h}$  ( $\text{SE}=0.362$ ). The reduction in TEWL was in greater in females; this difference was significant ( $t=1.970$ ,  $\text{df}=190.302$ ,  $p=0.050$ ). The 95% CI for the gender difference at these visits was (-0.001 to 1.427).

The estimated side difference at visits 2, 3 and 4 was  $-0.340 \text{ gm}^2\text{h}$  ( $\text{SE}=0.130$ ). TEWL reduction was greater in right legs; this difference was highly significant ( $t=-2.616$ ,  $\text{df}=189.834$ ,  $p=0.010$ ). The 95% CI for the leg difference at these visits was (-0.595 to -0.083).

5.3.1.5. TRANS-EPIDERMAL WATER LOSS ON THE TOP OF THE FOOT.

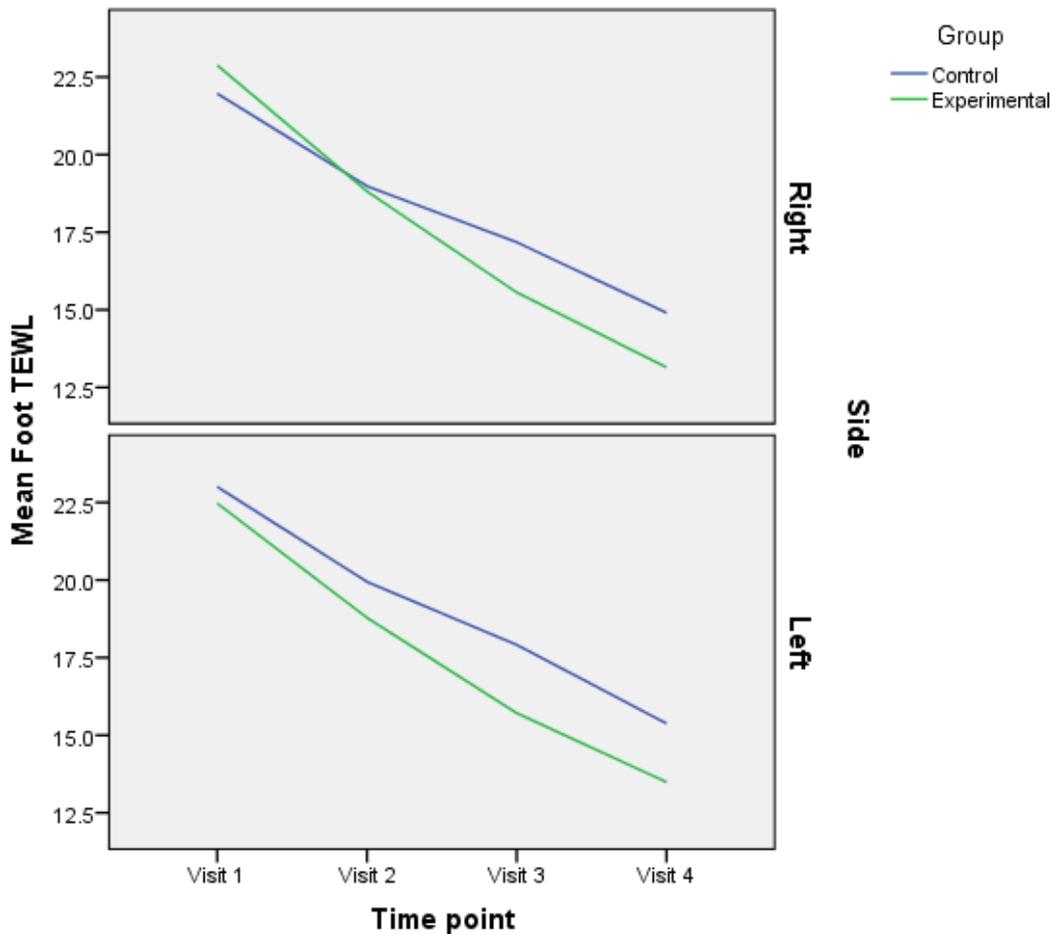
Table 5.6 presents the changes in TEWL at the top of the feet from baseline by side and group.

**Table 5.6. Trans-epidermal water loss (gm<sup>2</sup>h) at top of feet – changes over time by side and group.**

Foot TEWL	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	21.97	18.98	17.18	14.90	23.01	19.94	17.91	15.38	22.88	18.82	15.56	13.15	22.47	18.78	15.71	13.49
Median	21.40	19.45	17.10	14.50	22.70	20.00	17.80	14.80	22.80	18.30	15.10	13.30	22.20	18.50	15.60	13.00
Standard Deviation	5.46	4.21	4.35	4.36	5.06	4.45	4.77	4.09	6.74	4.05	3.61	3.87	6.79	4.19	3.61	3.77
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

Figure 5.8 shows the change in mean TEWL at top of the feet from baseline by side and group.

**Figure 5.8. Change from baseline in mean trans-epidermal water loss at the top of the feet by side and group.**



At the top of the foot the mean TEWL reduced in both groups over the study period but the reduction was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was 1.751 gm<sup>2</sup>h (SE=0.390); this difference was highly significant (t=3.154, df=189.580, p=0.002). The 95% CI for the group difference at this visit was (0.656 to 2.846).

The estimated gender difference at visits 2, 3 and 4 was 0.862 gm<sup>2</sup>h (SE=0.442). TEWL reduction was greater in females; the difference was nearing significance (t=1.953, df=188.868, p=0.052). The 95% CI for the gender difference at these visits was (-0.009 to 1.734).

The estimated difference between feet at visits 2, 3 and 4 was -0.353 gm<sup>2</sup>h (SE=0.138). TEWL reduction was greater in right feet; this difference was highly significant (t=-2.570, df=189.419, p=0.011). The 95% CI for the leg difference at these visits was (-0.625 to -0.082).

SC hydration is the topic of the next section. The mean SC hydration was recorded at 3 specific points on the lower leg and also on the top of the foot.

**5.3.2. STRATUM CORNEUM HYDRATION.**

The mean SC hydration of all participants at baseline is presented first. This is followed by the group differences in SC hydration at each of the specific points on the lower leg/foot. Gender and side differences were measured at visits 2, 3 and 4 as the model did not contain a side x time or gender x time interaction.

*5.3.2.1. MEAN SC HYDRATION AT DIFFERENT POINTS ON THE LEGS/FEET OF ALL PARTICIPANTS AT BASELINE.*

Table 5.7 presents the mean SC hydration at the different specific points on the leg/foot at baseline of all participants.

**Table 5.7. Mean difference in stratum corneum hydration at specific points on the leg/ foot of all participants at baseline.**

<b>Point on the lower leg</b>	<b>Mean SC hydration right lower leg</b>	<b>Mean SC hydration left lower leg</b>
Top	9.33	9.54
Mid-point	9.03	9.23
Base	8.51	8.55
Top of foot	8.49	8.62

The mean SC hydration in both groups was lower at the base of the leg and top of the feet at baseline compared to points higher on the lower leg.

*5.3.2.2. STRATUM CORNEUM HYDRATION AT TOP OF LOWER LEGS.*

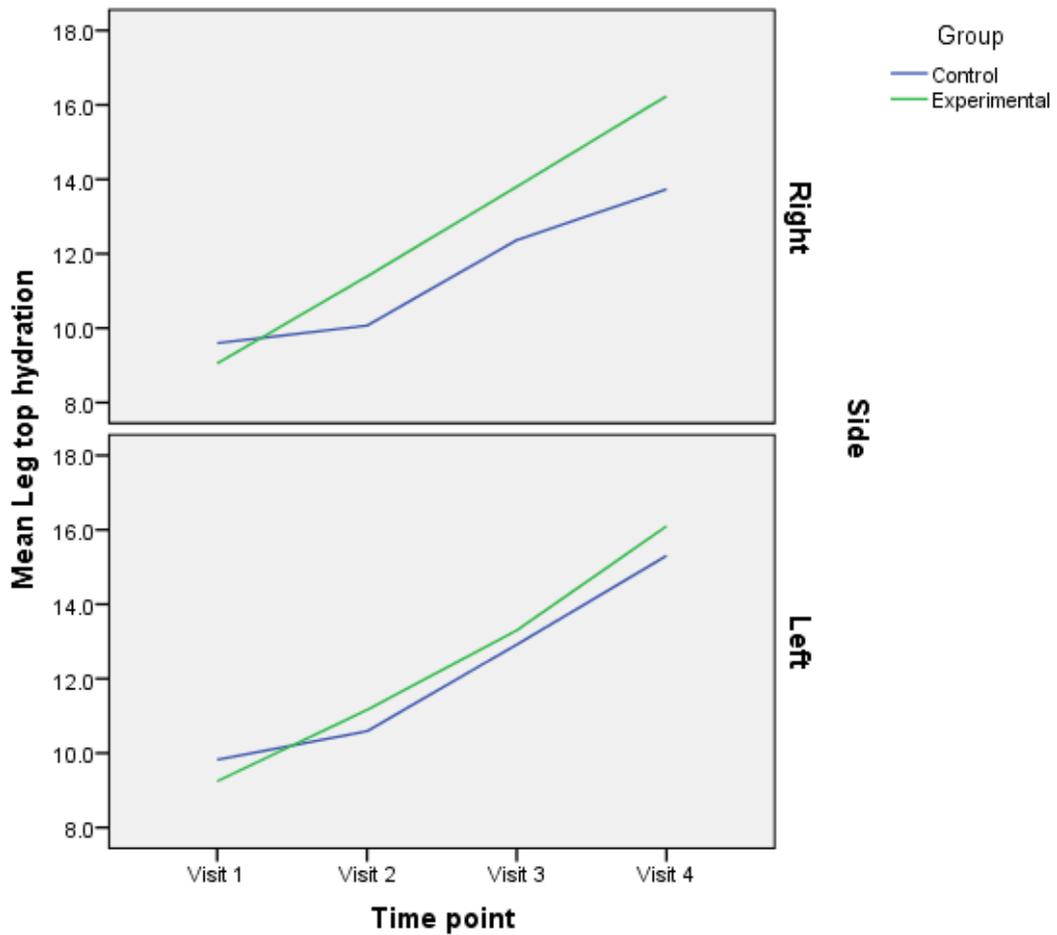
Table 5.8 presents the changes in SC hydration at the top of the lower legs from baseline by side and group.

**Table 5.8. Stratum corneum hydration at top of lower legs - changes over time by side and group.**

Leg top hydration	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	9.60	10.07	12.37	13.73	9.82	10.59	12.92	15.30	9.05	11.39	13.80	16.24	9.25	11.16	13.30	16.10
Median	8.50	10.30	11.85	13.50	8.70	9.70	12.60	14.15	8.40	10.70	13.70	15.50	8.40	10.40	13.30	15.60
Standard Deviation	3.98	3.30	4.63	3.59	4.54	3.61	4.79	11.19	3.98	3.84	3.46	3.72	4.09	4.12	3.88	4.15
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

The following Figure 5.9 illustrates the change in mean SC hydration at top of the lower leg from baseline by side and group.

**Figure 5.9. Change from baseline in mean SC hydration at the top of the lower leg by side and group.**



At the top of the lower leg the mean SC hydration increased in both groups during the study period but the increase was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was -2.075 (SE=0.515); this difference was highly significant ( $t=-4.236$ ,  $df=165.310$ ,  $p<0.001$ ). The 95% CI for the group difference at this visit was (-3.042 to -1.1078).

The estimated gender difference at visits 2, 3 and 4 was -0.371 (SE=0.368); this difference was not significant ( $t=-1.010$ ,  $df=183.371$ ,  $p=0.314$ ). The 95% CI for the gender difference at these visits was (-1.097 to 0.354).

The estimated leg difference at visits 2, 3 and 4 was -0.056 (SE=0.156); this difference was not significant ( $t=-0.056104$ ,  $df=186.959$ ,  $p=0.721$ ). The 95% CI for the leg difference at these visits was (-0.365 to 0.253).

5.3.2.3. STRATUM CORNEUM HYDRATION AT THE MID-POINT ON LOWER LEGS.

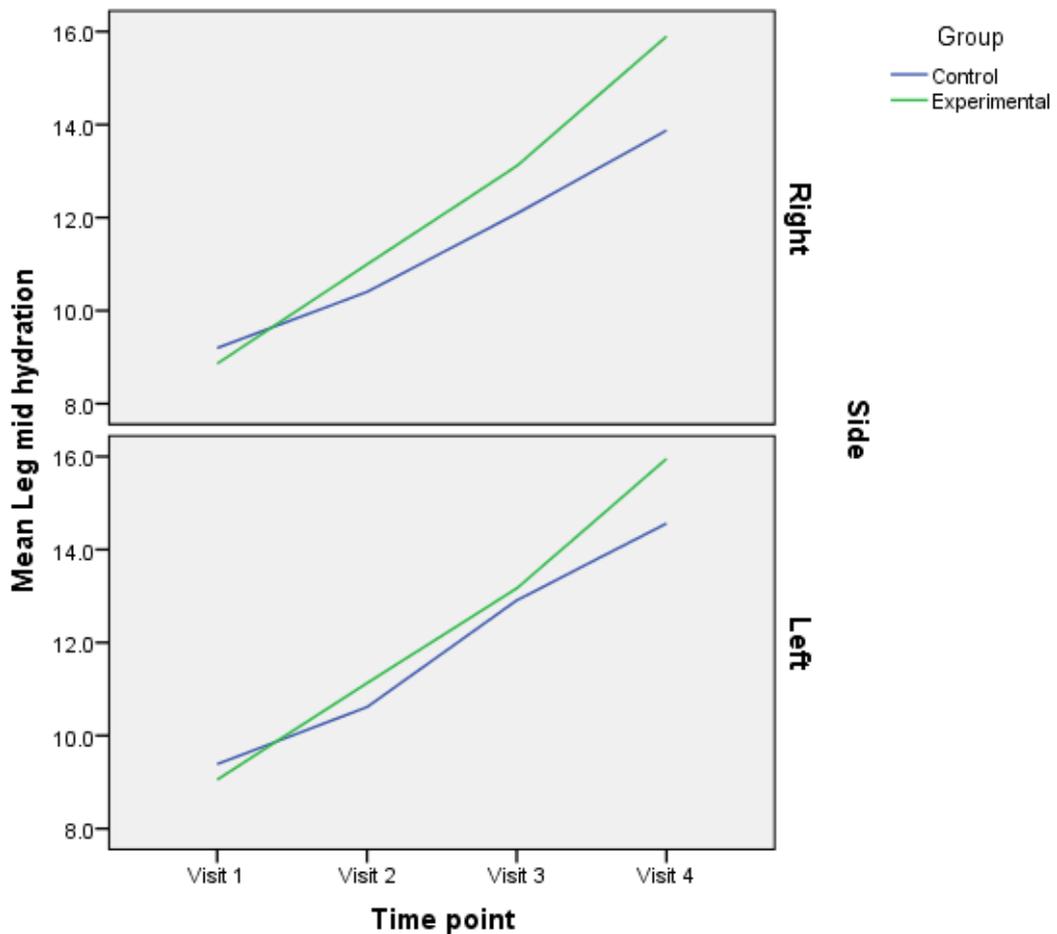
Table 5.9 presents the changes in SC hydration at mid-point of the lower legs from baseline by side and group.

**Table 5.9. Stratum corneum hydration mid-point lower leg - changes over time by side and group.**

Leg mid hydration	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	9.20	10.40	12.09	13.88	9.39	10.61	12.91	14.56	8.86	10.99	13.11	15.90	9.05	11.13	13.17	15.95
Median	8.50	10.15	11.70	13.50	8.40	10.00	13.00	14.30	8.30	10.20	12.70	15.20	8.30	11.40	13.50	15.80
Standard Deviation	3.29	3.81	4.31	3.78	3.83	3.71	4.38	3.90	4.08	3.94	3.82	3.77	3.78	3.98	3.62	3.19
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

The following Figure 5.10 shows the change in mean SC hydration at mid-point lower leg from baseline by side and group.

**Figure 5.10. Change from baseline in mean SC hydration at mid-point lower leg by side and group.**



At the mid-point of the lower legs the mean SC hydration increased in both legs over the study period but the increase was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was -1.658 (SE=0.467); this difference was highly significant ( $t=-3.549$ ,  $df=180.923$ ,  $p<0.001$ ). The 95% CI for the group difference at this visit was (-2.581 to -0.736).

The estimated gender difference at visits 2, 3 and 4 was -0.272 (SE=0.361); this difference was not significant ( $t=-0.754$ ,  $df=175.854$ ,  $p=0.452$ ). The 95% CI for the gender difference at these visits was (-0.984 to 0.440).

The estimated side difference at visits 2, 3 and 4 was -0.226 (SE=0.1481); this difference was not significant ( $t=-1.521$ ,  $df=179.955$ ,  $p=0.130$ ). The 95% CI for the leg difference at these visits was (-0.519 to 0.067).

5.3.2.4. STRATUM CORNEUM HYDRATION AT BASE OF LOWER LEGS.

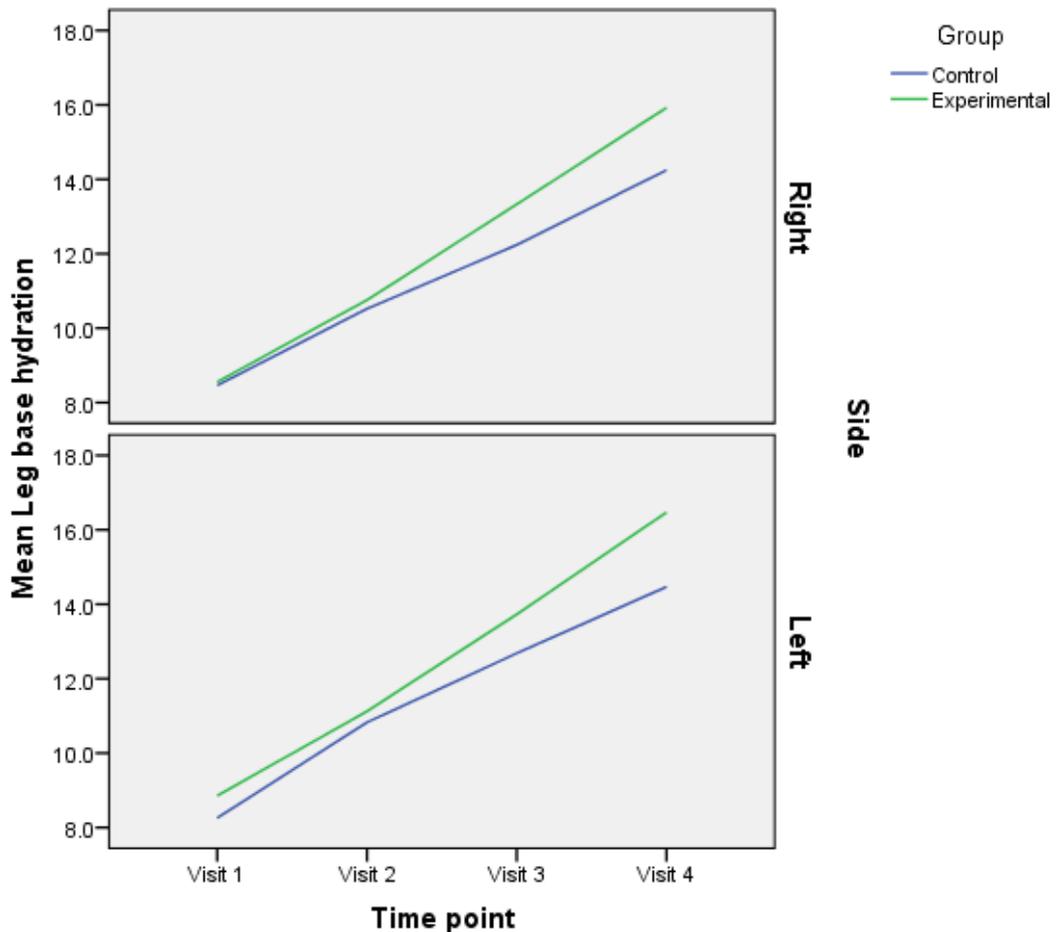
Table 5.10 presents the changes in SC hydration at the base of the lower legs from baseline by side and group.

**Table 5.10. Stratum corneum hydration at base of lower leg – changes over time by side and group.**

Leg base hydration	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit	Visit
1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
Mean	8.46	10.52	12.24	14.25	8.26	10.83	12.68	14.47	8.56	10.75	13.33	15.93	8.85	11.12	13.73	16.47
Median	7.55	10.60	12.25	14.40	7.10	9.10	12.30	14.25	7.30	10.20	13.00	15.90	8.20	10.60	13.50	16.00
Standard Deviation	3.95	4.37	4.52	3.84	4.01	4.85	4.74	4.41	4.66	4.35	3.99	3.80	4.36	4.34	4.09	3.40
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

Figure 5.11 illustrates the change in mean SC hydration at the base of the lower leg by side and group.

**Figure 5.11. Change from baseline in mean SC hydration at base of lower leg by group and side.**



At the base of the lower legs the mean SC hydration increased in both groups over the study period but the increase was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was -1.641 (SE=0.473); this difference was highly significant ( $t=-3.471$ ,  $df=186.308$ ,  $p=0.001$ ). The 95% CI for the group difference at this visit was (-2.574 to -0.708).

The estimated gender difference in SC hydration at the visits 2, 3 and 4 was -0.557 (SE=0.413); this difference was not significant ( $t=-1.349$ ,  $df=179.967$ ,  $p=0.179$ ). The 95% CI for the gender difference at these visits was (-1.373 to 0.258).

The estimated side difference in SC hydration at visits 2, 3 and 4 was -0.322 (SE=0.168); this difference was nearing significance ( $t=-1.916$ ,  $df=180.987$ ,

p=0.057). The 95% CI for the leg difference at these visits was (-0.654 to 0.010).

5.3.2.5. STRATUM CORNEUM HYDRATION ON THE TOP OF FEET.

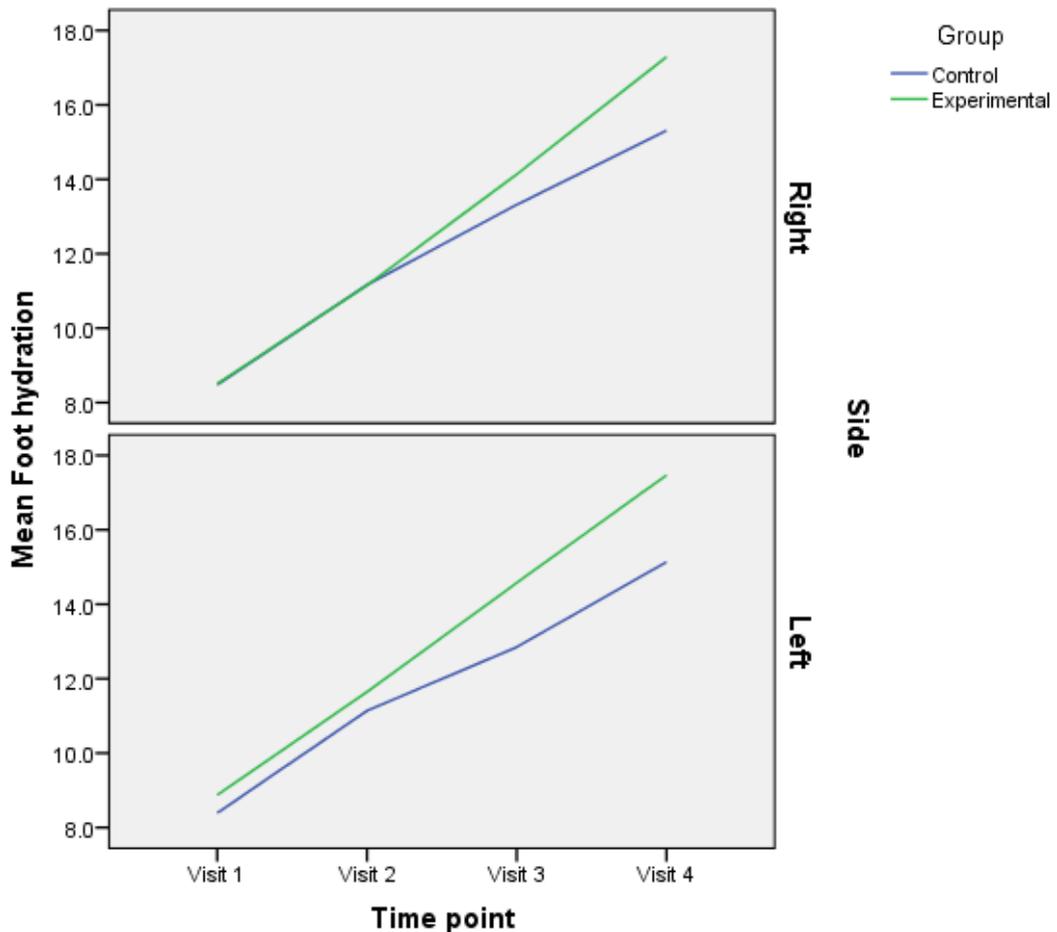
Table 5.11 presents the changes in SC hydration at the top of the feet from baseline by side and group.

**Table 5.11. Stratum corneum hydration on top of the feet - changes over time by side and group.**

Foot SC hydration	Group															
	Control								Experimental							
	Side				Side				Side				Side			
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	8.48	11.16	13.32	15.31	8.39	11.14	12.85	15.14	8.50	11.15	14.14	17.29	8.87	11.64	14.58	17.47
Median	6.45	9.00	13.45	14.60	5.80	8.50	13.00	15.10	5.70	9.30	13.90	16.70	6.30	9.90	13.50	16.60
Standard Deviation	5.52	6.15	5.38	4.54	5.97	6.38	5.66	4.92	6.30	5.90	5.17	4.59	6.72	6.43	5.70	4.90
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

The following Figure 5.12 indicates the change in the mean SC hydration on top of the feet from baseline by group and side.

**Figure 5.12. Change from baseline in mean SC hydration on top of the feet by group and side.**



At the top of the feet the mean SC hydration in both groups increased over the study period but the increase was greater in the experimental group. The estimated group difference from the mixed modelling was -2.041 (SE=0.572); this difference was highly significant ( $t=-3.565$ ,  $df=186.739$ ,  $p<0.001$ ). The 95% CI for the group difference at this visit was (-3.168 to -0.911).

The estimated gender difference in SC hydration at visits 2, 3 and 4 was -0.59 (SE=0.523); this difference was not significant ( $t=-0.876$ ,  $df=181.955$ ,  $p=0.382$ ). The 95% CI for the gender difference at these visits was (-1.492 to 0.574).

The estimated side difference in SC hydration at visits 2, 3 and 4 was -0.017 (SE=0.168); this difference was not significant ( $t=-0.101$ ,  $df=182.722$ ,

p=0.920). The 95% CI for the foot difference at these visits was 95% CI (-0.349 to 0.315).

The next section includes the results of the analysis of the clinical profile of legs/feet by group. Gender differences and differences between the right and left legs are presented where appropriate.

#### **5.4. GENERAL CLINICAL PROFILE OF LEGS/FEET.**

This section is organised as follows: stage of podoconiosis, mossy skin changes, presence of odour, number of wounds, leg and foot circumference, number of days work lost due to ADL, and correlation between the number of wounds and ADL.

##### **5.4.1. STAGE OF PODOCONIOSIS.**

Table 5.12 indicates the stages in each leg at baseline and fourth visit.

**Table 5.12. Stage of podoconiosis in each leg of all participants at baseline and 4<sup>th</sup> visit.**

Stage of podoconiosis	Right leg		Left leg	
	1 <sup>st</sup> visit	4 <sup>th</sup> visit	1 <sup>st</sup> visit	4 <sup>th</sup> visit
Nil	2	2	1	1
1	22	56	20	49
2	63	50	66	53
3	19	64	17	68
4	72	29	75	21
5	15	nil	14	nil
Missing	nil	1	nil	1
Total	193	193	193	193

At baseline 277 (54.4%) of all legs had stage 1, 2 or 3 (mild/moderate disease). This increased to 329 (89.35%) at the fourth visit. At baseline 29 legs (15.1%) had stage 5 disease at the fourth visit this reduced to nil. From the generalised estimating equation analysis there was no significant group difference in the odds of being in a more severe stage at the fourth visit (Log odds ratio=0.452 (SE=0.255), Wald chi square=3.138, df=1, p=0.076, 95% CI (-0.048 to 0.952).

There was no significant gender difference in the odds of being in a more severe stage of podoconiosis at visits after baseline (Log odds ratio= 0.027

(SE=0.233), Wald chi square=3.138, df=1, p=0.909, 95% CI (-0.048 to 0.483).

#### **5.4.2. MOSSY SKIN CHANGES.**

At baseline mossy skin changes were present in the right legs/feet in 153 (79.3%) participants and in the left legs/feet of 156 (80.8%). At the fourth visit mossy changes were present in 120 (62.5%) right legs/feet and 117 (60.9%) left legs/feet. Mossy changes reduced from baseline in both legs in both groups over the study period. From the generalized estimating equations there was no significant group difference in the odds of mossy changes being present on the legs/feet at the fourth visit (Log odds-ratio=0.224 (SE=0.354), Wald chi-square=0.401, df=1, p=0.527, 95% CI (-0.469 to 0.917).

There was a significant gender difference in the odds of mossy changes being present at visits after baseline. Males were significantly more likely to have mossy changes (Log odds-ratio=-1.29 (SE=0.446), Wald chi square=8.304, df=1, p=0.004, 95% CI (-2.161 to -0.411).

There was no significant side difference in the odds of mossy changes being present at visits after baseline (Log odds-ratio=-0.090 (SE=0.067), Wald chi square=1.800, df=1, p=0.180, 95% CI (0.221 to 0.41).

#### **5.4.3. LEG/FOOT ODOUR.**

Leg/foot odour reduced from baseline in both groups over the study period. At baseline odour was present in 114 (59.1%) of legs/feet. At the fourth visit odour was present in 2 (1%) of all right legs/feet and 1 (0.5%) of all left legs/feet. There was a significant group difference in the odds of leg/foot odour being present at visits 2, 3 and 4. The odds of leg/foot odour being present was significantly less in the experimental group (Log odds ratio=-0.866, (SE=0.401), Wald chi square=4.67, df=1, p=0.031, 95% CI (-1.652 to -0.080). The group difference was not clinically significant because the numbers in each group were so small.

There was no significant gender difference in the odds of having a reduction in leg/foot odour at visits after baseline (Log odds ratio=-0.164 (SE=0.408), Wald chi square=0.162, df=1, p=0.687, 95% CI (-0.964 to 0.635).

There was no significant side difference in the odds of a having a reduction of leg/foot odour at visits after baseline (Log odds ratio=0.001 (SE=0.068), Wald chi square=0.000, df=1, p=0.993, 95% CI (-0.135 to 0.133).

#### **5.4.4. NUMBER OF LEG/FOOT WOUNDS.**

At baseline 132 (68.4%) of participants had one or more wounds (skin breaches or areas of fungal infection) on the right lower leg/foot and 135 (69.9%) of participants had one or more wounds on the left lower leg/foot. The maximum number of wounds on both lower legs was eight. The majority of participants had 4 wounds, 55 (28.5%) of these were on the right leg/foot and 50 (25.9%) on the left leg/foot. Although wounds reduced in both groups over time there was still a significant group difference at the fourth visit from the generalised estimating equations. Those in the experimental group were expected to have fewer wounds (group ratio estimate =2.062 (SE=0.741), Wald chi-square=7.745, df=1, p=0.005, 95% CI (0.610 to 3.514). Most participants at the fourth visit had no wounds because of this the group difference was not clinically significant.

There was no significant gender difference in the odds of having fewer leg/foot wounds at visits after baseline (group ratio estimate = -0.262 (SE=0.387), Wald chi-square=0.458, df=1, p=0.499, 95% CI (-1.020 to 0.497).

There was no significant side difference in the odds of having fewer leg/foot wounds legs at visits after baseline (group ratio estimate = 0.021 (SE=0.049), Wald chi-square=0.181, df=1, p=0.670, 95% CI (- 0.075 to 0.117).

**5.4.5. LOWER LEG CIRCUMFERENCE.**

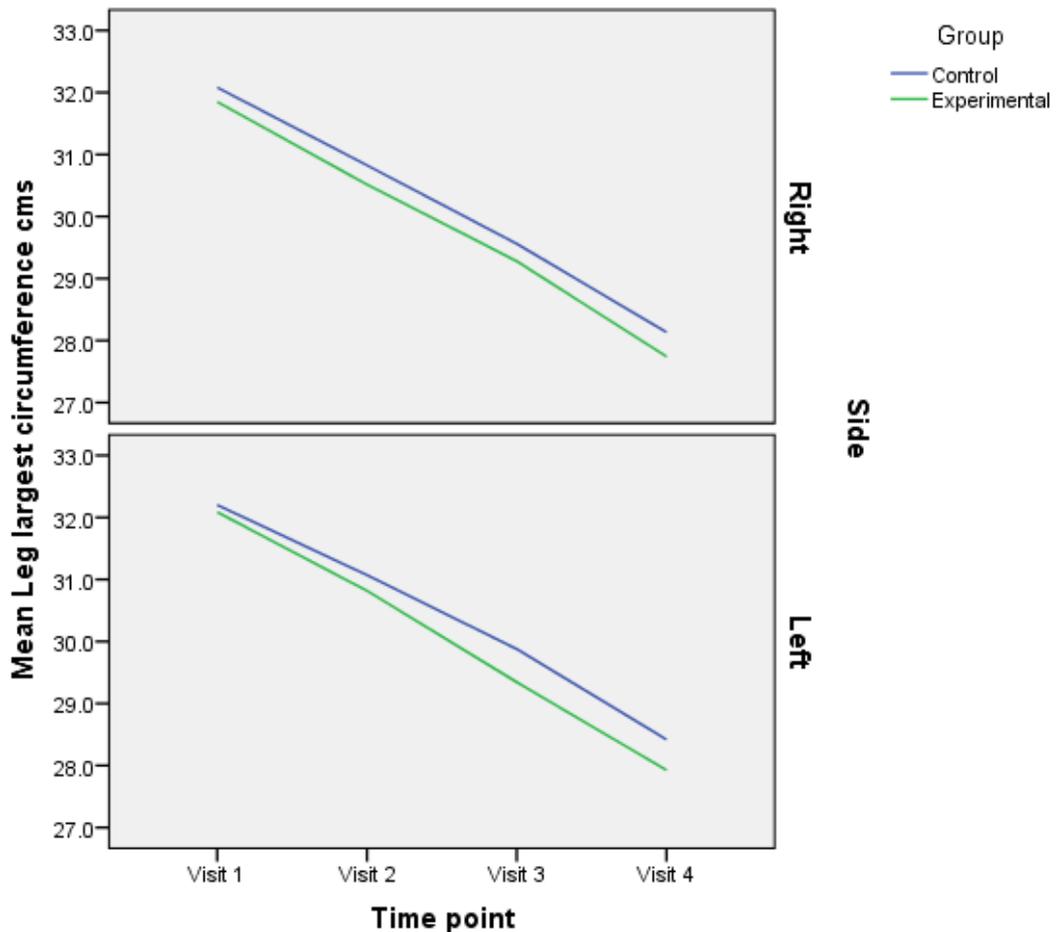
The following table 5.13 presents the changes in the lower leg circumference from baseline by group and leg.

**Table 5.13. Largest lower leg circumference in both legs by group and leg from baseline.**

Leg largest circumference cms	Group															
	Control								Experimental							
	Side				Side				Side				Side			
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	32.08	30.83	29.56	28.13	32.20	31.07	29.88	28.42	31.85	30.52	29.28	27.74	32.09	30.82	29.34	27.92
Median	32.00	30.00	29.00	28.00	32.00	31.00	30.00	28.00	32.00	30.00	29.00	28.00	32.00	30.00	29.00	28.00
Standard Deviation	3.22	2.93	2.80	2.77	3.22	2.94	3.17	2.87	2.95	2.23	2.16	1.65	3.02	2.51	2.10	1.83
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

The following Figure 5.13 represents the change in mean lower leg circumference between side and group.

**Figure 5.13. Change in mean lower leg circumference between side and group.**



In the control group, the mean largest lower right leg circumference reduced from baseline by 3.95cms and in left leg it reduced by 3.78 cms. In the experimental group the mean circumference in the right leg reduced by 4.11 cms and in the left leg it reduced by 4.17 cms. The mean lower leg circumference reduced in both groups over the study period but the reduction was greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was 0.288 (SE=0.204); however this difference was not significant ( $t=1.416$ ,  $df= 185.386$ ,  $p=0.158$ ). The 95% CI for the leg difference at this visit was (-0.113 to 0.690). The estimated gender difference at the fourth visit was 0.168 (SE=0.167); this difference was not significant ( $t=1.007$ ,  $df=161.922$ ,  $p=0.313$ ). The 95% CI for the gender difference at this visit was (-0.162 to 0.499). The estimated leg difference at the fourth visit was -0.129 (SE=0.65); this difference was not significant ( $t=-1.996$ ,  $df=164.060$ ,  $p=0.48$ ). The 95% CI for the leg difference at this visit was (-0.257 to -0.001).

#### 5.4.6. FOOT CIRCUMFERENCE.

Table 5.14 presents the changes in largest foot circumference from baseline by group.

**Table 5.14. Largest foot circumference - changes from baseline by side and group.**

Foot largest circumference cms	Group															
	Control								Experimental							
	Side								Side							
	Right				Left				Right				Left			
	Time point				Time point				Time point				Time point			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Mean	27.50	26.50	25.84	25.16	27.49	26.70	26.01	25.19	27.63	26.48	25.63	24.61	27.78	26.73	25.87	24.88
Median	27.00	26.00	25.00	25.00	27.00	26.00	25.00	25.00	27.00	26.00	25.00	24.00	27.00	26.00	25.00	24.00
Standard Deviation	2.94	2.75	2.46	2.20	2.94	2.70	2.63	2.26	3.00	2.61	2.29	1.85	3.10	2.74	2.50	2.02
Number of cases	98.00	98.00	98.00	97.00	99.00	99.00	99.00	98.00	3.00	93.00	93.00	93.00	93.00	93.00	93.00	93.00

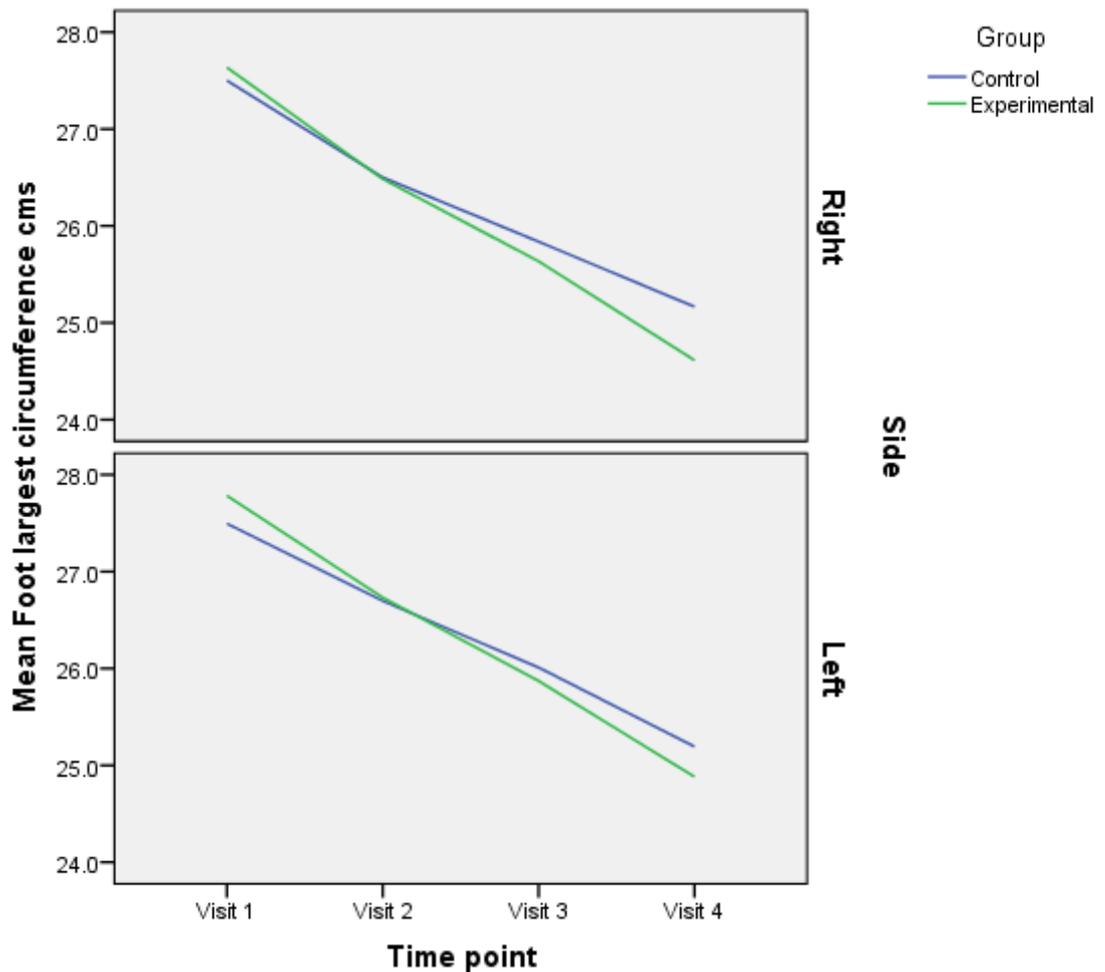
The mean foot circumference reduced over time in both feet in both groups. In the control group the mean right foot circumference reduced by 2.34cms and in the left foot by 2.34cms. In experimental group the mean right foot circumference reduced 3 cms and in the left foot by 2.90cms. The reduction was therefore greater in the experimental group. The estimated group difference from the mixed modelling at the fourth visit was 0.575 (SE=0.162); this difference was highly significant ( $t=3.550$ ,  $df=169.916$ ,  $p<0.001$ ). The 95% CI for the difference in foot circumference at this visit was (0.255 to 0.895).

The estimated gender difference at the fourth visit was 0.174 (SE=0.143); this difference was not significant ( $t=1.215$ ,  $df=154.628$ ,  $p=0.226$ ). The 95% CI for the difference in foot circumference at this visit was (-0.109 to 0.456). The estimated difference between right/left feet at the fourth visit was -0.149 (SE=0.046). The reduction in circumference was greater in the right foot; this difference was highly significant ( $t=-3.270$ ,  $df=152.994$ ,  $p=0.001$ ). The 95%

CI for the difference in circumference between feet at this visit was (-0.239 to -0.059).

The next Figure 5.14 indicates the change in mean foot circumference by side and group.

**Figure 5.14. Change in mean foot circumference by side and group.**

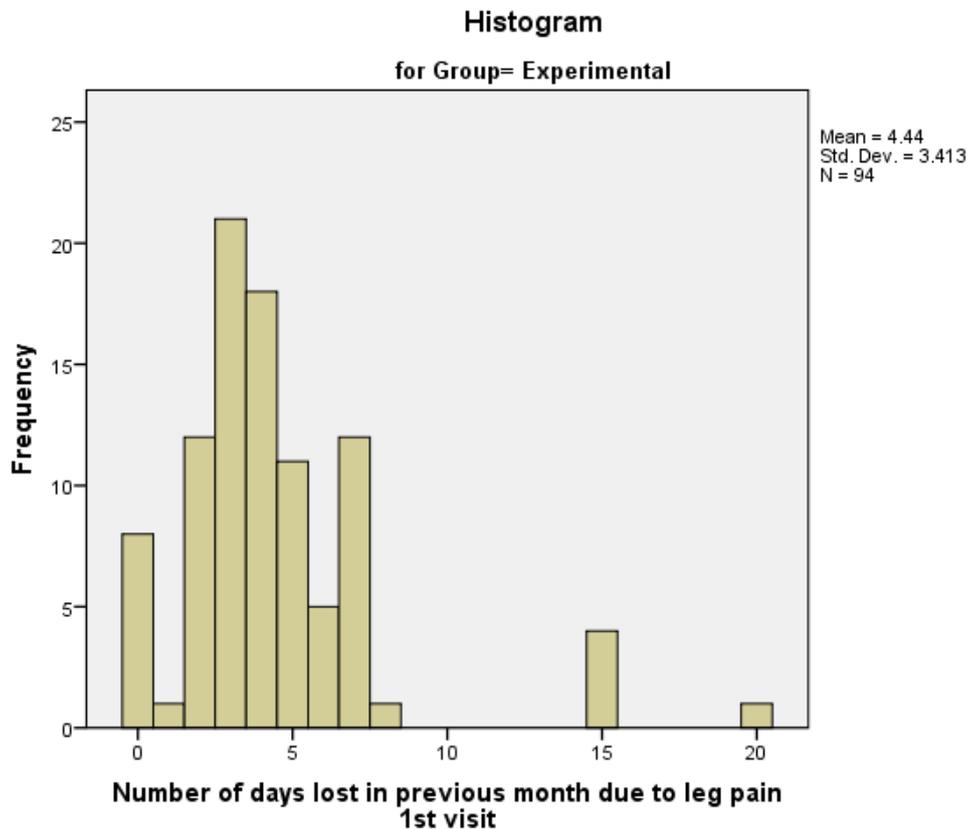
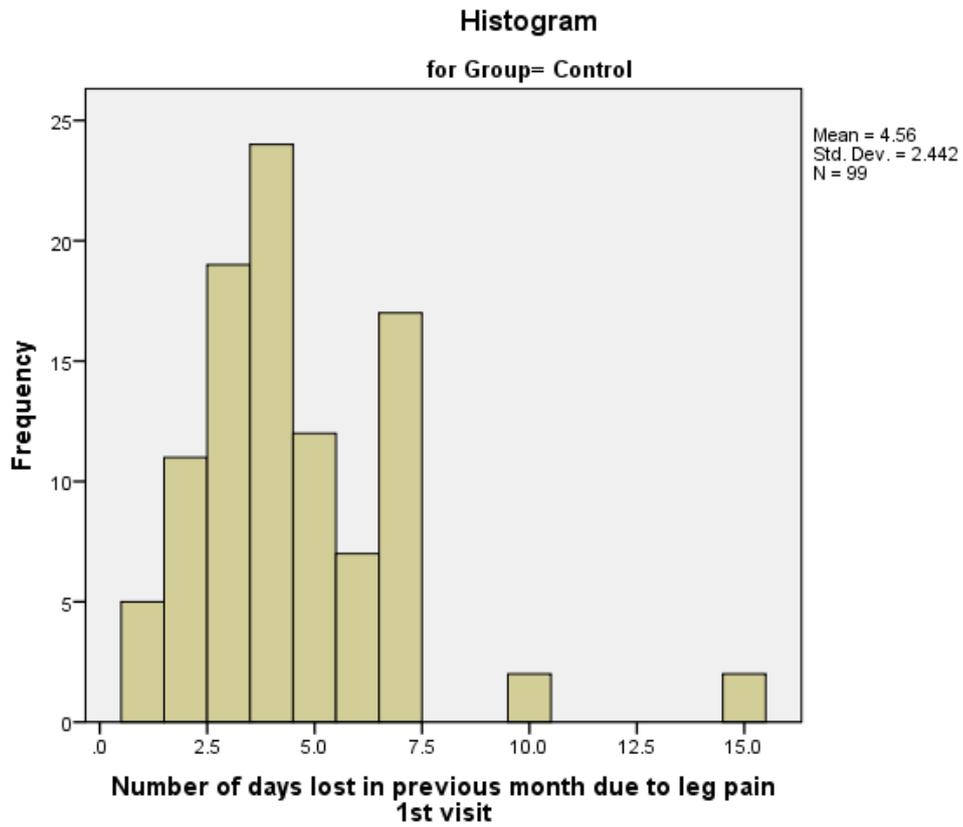


**5.4.7. NUMBER OF WORK DAYS LOST IN PREVIOUS MONTH DUE TO ADENOLYMPHANGITIS.**

At the first visit 185 (95.9%) of participants had lost work days in the previous month due to ADL. The majority (109, 56.4%) had lost 4 or more work days. Six participants (3.1%) had lost 1 day, 23 (11.9%) 2 days, 40 (20.7%) 3 days, 42 (21.8%) 4 days, 23 (12%) 5 days, 12 (6.2%) 6 days, 29 (15%) 7 days, 1 (0.5%) 8 days, 2 (1%) 10 days, 6 (15%) 15 days and 1

(0.5%) 20 days. The following Figures 5.15, 5.16 indicate the number of work days lost by each group at baseline.

**Figures 5.15 and Figure 5.16. Number of work days lost in previous month due to adenolymphangitis by each group at baseline.**



At baseline the mean number of days work lost in the previous month due to adenolymphangitis for the control group (n=99) was 4.6 (SD=2.422) and for the experimental group (n=94) 4.4 (SD=3.413). The mean number of work days lost due adenolymphangitis by group and side is indicated in Table 5.15.

**Table 5.15. Mean number of days work lost in previous month by group and side at each visit due to adenolymphangitis by group.**

		Group							
		Control				Experimental			
		Time point				Time point			
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 1	Visit 2	Visit 3	Visit 4
Number of days lost in previous month due to leg pain	Mean	4.56	1.20	.24	.08	4.44	1.45	.24	.01
	Median	4.00	1.00	.00	.00	4.00	1.00	.00	.00
	Standard Deviation	2.44	1.41	.61	.37	3.41	1.83	.56	.10
	Number of cases	99.00	99.00	99.00	98.00	94.00	94.00	94.00	94.00

There was a reduction from baseline in the mean number work days lost in the previous month due to ADL for all participants. The mean difference in the reduction in the numbers of work days lost due to ADL was 4.48 days for the control group and 4.43 days for the experimental group. Although both groups reduced over time, there was a difference which was approaching significance at the fourth visit. Those in the experimental group were expected to have fewer work days lost due to ADL (group ratio estimate = 2.090, (SE=1.102), df=1, p=0.058, 95% CI (-0.069 to 4.250). This difference may not be clinically important as in both groups the number of days lost reduced to almost zero.

There was no significant gender difference in the number of days lost in the previous month due to ADL at visits after baseline (group ratio estimate = -0.155 (SE=0.164), p=0.345, 95% CI (-0.477 to 0.167).

There was no significant difference between stages and number of work days lost in the previous month due to ADL at visits after baseline (group ratio estimate = 0.171 (SE=0.168), p=0.308, 95% CI (-0.158 to 0.501).

#### **5.4.8. CORRELATION BETWEEN DAYS LOST DUE TO ADENOLYMPHANGITIS AND NUMBER OF WOUNDS.**

Spearman's correlation indicated that there was a correlation between the number of lower leg/foot wounds totalled over both legs and the number of days participants were unable to work due to ADL. At all of the time points the correlation between the number of days work lost due to ADL and the number of wounds on the lower legs/feet was highly significant ( $p < 0.001$ ) but it was weak and therefore not clinically significant. The correlation at the first clinic visit was 0.252, at the second 0.306, at the third 0.291 and at the fourth 0.265.

The next section specifies the results of the analysis of the Quality of Life.

#### **5.5. QUALITY OF LIFE.**

There was a decrease in the mean DLQI in both groups from baseline. In the control group DLQI decreased by 17.49 and in the experimental group it decreased by 17.13. In the control group the mean DLQI reduced from 21.61 to 8.83 to 4.59 to 4.12 (SD 5.82, 4.88, 4.10, 4.29). In the experimental group the mean DLQI reduced from 21.07 to 7.97 to 4.06 to 3.94 (SD=7.49, 5.14, 3.82). The estimated group difference from the mixed modelling at the fourth visit was -0.063 (SE=0.540). This difference was not significant ( $t = -0.117$ ,  $df = 178.814$ ,  $p = 0.907$ ). The 95% CI for the group difference at this visit was (-1.129 to 1.002).

The estimated gender difference in DLQI at the fourth visit was 0.281 (SE=0.494). This difference was not significant ( $t = 0.501$ ,  $df = 188.025$ ,  $p = 0.571$ ). The 95% CI for the gender difference was (-0.695 to 1.2560).

The estimated difference between stages and DLQI at the fourth visit was -0.920 (SE=0.553). This difference was not significant ( $t = -1.664$ ,  $df = -1.664$ ,  $p = 0.098$ ). The 95% CI for the stage difference was (-2.011 to 0.171).

In summary the profile of participants in each group was similar. Compared to the control group those in the experimental group had greater reductions in TEWL and greater increases in SC hydration at all points on the leg/foot.

Those in the experimental group also had less wounds and less leg/foot odour. Some of the analysis indicated a difference in the results between legs and genders.

The following Chapter 5 discusses the study in more depth and the study results within context of the literature comparing the results with other previously published studies. The contribution of this research to the field is then presented. The chapter includes a section on the challenges of undertaking research in a resource-poor country.

## CHAPTER 6. DISCUSSION.

This chapter interprets and discusses the study results. Their relevance to the research question is then presented within the context of the existing literature. The research results are compared to previous studies and similarities and differences explored. This is followed by a discussion on the challenges of undertaking research in the rural environment of Ethiopia. The contribution of this research to the field is then presented.

### 6.1. OVERVIEW OF RESULTS.

The study indicated that those in the experimental group had a highly significant improvement in SBF compared to the control group. There were also some significant differences between the right and left legs/feet in some measurements. These differences are discussed further in section 6.2.3.6. Quality of life in both the control group and experimental groups improved. At the first visit podoconiosis had an extremely large detrimental effect on participant's quality of life which over the three months reduced to a moderate effect. There was no significant difference between groups in the change from baseline. This is discussed further in section 6.2.4.

The first objective of the study was to identify the current practice in podoconiosis clinics. This was accomplished and is presented in Table 2.6. To test the effects of the different interventions used in APCs to treat those with podoconiosis a pilot study was undertaken (Chapter 3). This was undertaken in the UK with ten older females with xerosis of the lower legs. The soap used had a pH10. The pilot study identified that the greatest mean increase in SC hydration level over the 5 days of intervention was for soap, 2% glycerine soak and *Vaseline*<sup>®</sup>. The greatest mean decrease in TEWL was also found for soap, 2% glycerine soak and *Vaseline*<sup>®</sup> although this was not significantly different to the changes seen for the other interventions used (Section 3.5). The application of soapy water increased TEWL more than any of the other interventions. The application of 2% glycerine and *Vaseline*<sup>®</sup> following the application of soapy water had a significantly positive effect on skin hydration compared to using soapy water alone or a water soak alone.

The second main objective was to evaluate the effectiveness of an evidence-based skin care intervention in terms of changes in skin barrier function in the affected area of those with podoconiosis and their disease related quality of life. The specific objectives were to investigate if after 3 months intervention those in the experimental group when compared to the control group had:-

1. less trans-epidermal loss at three specific points on the lower leg and on the top of the feet
2. increased stratum corneum hydration at three specific points on the lower leg and on the top of the feet
3. a reduced stage of the disease
4. less mossy changes
5. less leg/foot odour
6. fewer wounds on the lower leg/foot
7. reduced circumference on the lower leg and foot
8. less days of work lost due to ADL
9. an improved quality of life
10. if there was a correlation between the number of wounds and the days lost due to ADL.

All of these objectives were achieved.

The following section discusses the study results in detail within the context of published studies in the field.

## **6.2. STUDY RESULTS.**

This section divided into four main headings as follows: social and demographic profile of participants, skin barrier function, general clinical profile of legs/feet and quality of life.

## **6.2.1. SOCIAL AND DEMOGRAPHIC PROFILE OF PARTICIPANTS.**

### *6.2.1.1. AGE OF PARTICIPANTS.*

In this study as in other published studies the majority of those affected by podoconiosis were in the economically active age group of 16-65. The majority of participants (188, 97.1%) were aged 18-69 years. These percentages are similar to those in two other studies where 90.3% and more than 87% of patients were in the age range 15-64 years (Alemu, Tekola Ayele et al. 2011, Molla, Tomczyk et al. 2012a) (n=335 and n=1,704 respectively). The number of those over 50 years of age in this present study was 30.6%. Tora's study reported similar results with 45 (30%) over the age of 50 years (n=150) (Tora, Franklin et al. 2014). No mean age was calculated in this study because ages were recorded in bands of 10 years but these have been reported in other studies. In the Sikorski et al. (2010) study the mean age was 37.4 years. A slightly higher mean age of 44.3 years was recorded in Molla's study (Molla, Tomczyk et al. 2012a). The highest mean age of 50.3 years was recorded in the study by Campion (n=191) (Campion, Tamiru et al. 2015).

### *6.2.1.2. OCCUPATION AND GENDER OF PARTICIPANTS.*

The stratification that was used in the study ensured roughly equal proportions of males to females in both the control and intervention groups. Tekola recruited similar percentages of men and women in both the patient and control group (342, 48.7%, males v 360, 51.3% females). In their study 234 were patients and the remainder non-patients (n=702) (Tekola, Mariam et al. 2006). It reported lower percentages of those with podoconiosis as farmers (38.5% v 46.1%) and as housewives (31.2% v 42.5%). Compared with this current study many other studies have reported higher numbers of farmers and lower numbers of housewives (Alemu, Tekola Ayele et al. 2011, Molla, Tomczyk et al. 2012a, Molla, Le Blond et al. 2013, Mousley, Deribe et al. 2013). In a more recent quantitative structured questionnaire based study, none described themselves as a housewife (Campion, Tamiru et al. 2015). The difference between studies in the numbers describing themselves as farmers or housewives may be due to the difference in the

numbers of male and female participants. Some studies have reported more males affected by podoconiosis (Kloos, Bedri Kello et al. 1992, Destas, Ashine et al. 2003, Tora, Franklin et al. 2014), while others more females (Alemu, Tekola Ayele et al. 2011, Tekola Ayele, Alemu et al. 2013, Mousley, Deribe et al. 2013, Sikorski, Ashine et al. 2010). Furthermore while the greater proportion of farming may be carried out by men, women still contribute and may identify themselves as farmers as it may be seen as more prestigious. The age of the women and the number of young children they care for may also be a factor in whether or not they describe themselves as housewives. In this study there were no choices given of possible occupations. Participants were only asked 'What is your occupation? This may not have been the case in other studies which may have restricted the answers to a number of pre-selected choices thus limiting results.

#### *6.2.1.3. TIME FROM ONSET OF CLINICAL SIGNS OF PODOCONIOSIS TO CLINIC ATTENDANCE.*

In this study 143 participants (74.2%) had the disease for 1-6 years. Because the time from onset to the 1<sup>st</sup> clinic visit was recorded in time bands of 5 years it was not possible to calculate a mean time. A previous comparative cross sectional survey in the same region reported a mean time between the onset of leg swelling of one or both feet to time of first clinic visit of 9.13 years (SD 5.83) (n=234) (Tekola, Mariam et al. 2006). Molla reported an average of five years between the start of leg swelling and seeking treatment (Molla, Tomczyk et al. 2012a). Campion's Northern Ethiopian quantitative questionnaire based study noted that only 27.5% had the disease for 0-10 years before seeking treatment (n=191) (Campion, Tamiru et al. 2015). Few participants (n=7, 3.7%) in this study had the disease for over 10 years before attending a clinic and only three (1.6%) had the disease for over 12 years. Longer lengths of time have been recorded in other studies. An average time between onset and time of interview was recorded as 17 years in the Alemu cross sectional study, whereas in the Campion study 68.9% had the disease for over 11 years before seeking treatment ( Alemu et al. 2013,Campion, Tamiru et al. 2015). The shorter time between clinical signs and seeking treatment in this study compared with

others may be due to the time that the study clinics in the area had been operating. Both clinics used in this study opened in March 2012, almost two years before the study took place. During that time those with the disease may have been encouraged to seek help earlier after witnessing successful treatments by the clinic of others in their community. Other differences between studies in the time taken before seeking treatment may have been due to the distance and time taken to travel to clinics. Certainly distance was the main reason for discontinuing clinic visits in studies (Tora, Davey et al. 2012, Campion, Tamiru et al. 2015). It may therefore be the reason for those with the disease delaying clinic attendance until the disease was at a higher stage and causing very significant effects.

Public knowledge of the disease, knowledge of health care professionals, stigma and low formal education have also been identified as factors contributing to a delay in those with the disease seeking treatment. Public knowledge of podoconiosis prevention and treatment has previously been recorded as low. A Southern Ethiopian survey reported that only 41.4% knew that the condition was treatable (n=438) (Yakob, Deribe et al. 2008). A later survey in Northern Ethiopia revealed that fewer than 50% of patients said they either 'knew' or 'thought that' podoconiosis could be prevented (22.2% and 40.3%, respectively). Under 50% also 'knew' or 'thought that' it could be controlled (27.3% and 32.3%, respectively) (n=1319) (Molla, Tomczyk et al. 2012a, Molla, Tomczyk et al. 2012b). This lack of knowledge would mean that those with the disease would be unaware that the disease was treatable and would therefore not seek clinic treatment assuming one was available locally.

Knowledge of health care professionals concerning the disease may also have affected treatment seeking behaviour. Yakob reported that over half (53.9%) of health professionals in Southern Ethiopia incorrectly considered podoconiosis an infectious disease and were frightened of contracting the disease while providing care (n=275) (Yakob, Deribe et al. 2009). The knowledge of local HEWs regarding podoconiosis has also been recorded as low therefore patients visiting a HEW may not have received appropriate advice (Mengistu, Berhane et al. 2013). Stigma has been reported as the

reason patients did not identify themselves and/or discontinued clinic visits (Tora, Davey et al. 2012a, Tsegay, Wubie et al. 2014). With an increase in the number of treatment centres public/patient knowledge of the disease should improve and social stigma decrease. The numbers seeking treatment earlier should also rise as awareness of the causes of podoconiosis and its treatability spreads in the population. The level of patient education may also be a factor in delayed treatment. Several studies have reported lower literacy rates in those with podoconiosis. This is discussed later in section 6.2.6.1.

#### 6.2.1.4. TYPE OF SHOES WORN.

The decrease in those not wearing shoes shoe wearing over the study period from 18 (9.3%) to none is notable but there are no other studies for comparison. The numbers of those recorded as walking barefoot in the previous week at baseline is much lower than in other studies. Three studies in Northern Ethiopia noted that 23.6%, 70.8% and 30.9% respectively were barefoot at interview (Molla, Tomczyk et al. 2012a, Molla, Le Blond et al. 2013, Campion, Tamiru et al. 2015). A cross sectional study in Southern Ethiopia also reported higher numbers with 55.2% barefoot at interview (n=337) (Yakob, Deribe et al. 2008).

The differences between studies may have been due to different levels of income and shoe wearing customs. The reduction of those reporting walking barefoot to zero in this current study may have been due to the availability of the clinic, the effective teaching by clinic staff on the importance of shoe wearing and/or peer pressure from others in the clinic. Patients learning from each other is an important constituent of social learning theory (Bandura 1997, Bandura, Locke 2003). A survey also in Southern Ethiopia noted the presence of clinics in the area appeared to affect shoe wearing practices (Destas, Ashine et al. 2003). It reported that in four areas where there were podoconiosis treatment clinics the mean of those using shoes was 17.2% whereas in three areas without outreach clinic this was only 8.2% (n=33,678).

Shoe wearing *per se* does not necessarily indicate that they protect the feet to soil and trauma. While some shoes offer good protection most of those worn in the clinics offered very little. Hard plastic sandals were the most

common shoes worn in this present study. They are comparatively low cost and easily available in local markets but provide little protection and cause the feet to sweat. Because of this they may encourage fungal infections. Investigating this relationship was not however part of the present study. The numbers wearing plastic shoes remained similarly high between the 1<sup>st</sup> and 4<sup>th</sup> clinic visits (62.2% v 63.2%). This is much higher than in the Molla study which reported that only 18.3% of those with podoconiosis owned plastic sandals (n=460) (Molla, Le Blond et al. 2013). In the present study the number wearing canvas shoes nearly doubled during the study from 12.4% to 23.3%. Canvas shoes are more protective against soil and trauma than sandals. The increase in their use may again have been due to the education received by participants at the clinics and/or peer pressure from other clinic attendees previously mentioned. In the Molla study canvas shoes were owned by higher numbers (32.5%) (Molla, Le Blond et al. 2013). However their study was in Northern Ethiopia where shoe wearing practices and incomes may have been different. At the 4<sup>th</sup> visit three (1.6%) participants in the present study wore custom made leather shoes provided by APACs. These are provided to those with enlarged and perhaps deformed feet because locally available shoes would not fit correctly. Without this provision patients either go barefoot or wear ill-fitting shoes resulting in skin trauma. The present study only recorded the type of shoe worn in the previous week. It did not consider when, where or for how long they were worn. Other studies too may not have given a true overall picture of shoe wearing practises as shoe wearing was only recorded at the time of assessment (Alemu, Tekola Ayele et al. 2011, Yakob, Deribe et al. 2008).

The Molla study in Northern Ethiopia noted that wearing shoes had generally increased in the region in the last 30 years. The increase was before education on the treatment and prevention of podoconiosis was available in the area. Molla hypothesised that the rise in shoe wearing was due to an increase in adult literacy, improved health and generally higher incomes (n=460) (Molla, Le Blond et al. 2013). A more recent study reported that adults without podoconiosis viewed shoe wearing as a mark of 'dignity' and not wearing shoes as 'shameful' especially by younger people (Ayode,

McBride et al. 2013). This change in attitudes to shoe wearing particularly by the young will, no doubt increase shoe wearing in the future.

In this present study the type of shoes worn by males and females at baseline was similar. The greatest difference was in those wearing no shoes 5 (2.6%) males v 13 (6.7%) females. These results are different from those of other studies. Alemu, Tekola Ayele et al. (2011) reported that more males wore better quality shoes. In another study shoe wearing was reported to be less common in females with 23.6% barefoot at the time of interview of which 65% were female. They also reported that 7.3% (44) of males as not owning any shoes compared to 15.4% (87) of females (Molla, Tomczyk et al. 2012a).

Although shoe wearing may be increasing, routinely wearing shoes is still uncommon in parts of Ethiopia with cost cited most the most common obstacle. Yacob (2008) reported the cost of shoes as the reason why 69.3% were barefoot in a highly endemic area (n=337). In the study 96.4% of participants said they would wear shoes if they were provided. Barriers to shoe wearing were stated as: uncomfortable to walk and work in (64.8%), difficulty in finding the correct size (50%) and not having shoes (19.2%). Peer pressure was also given as the reason why 30.6% did not wear shoes (Yakob, Deribe et al. 2008). Barriers to shoe wearing reported also include the unsuitability of shoes for some activities, low perception of podoconiosis risk and fear of stigma related to custom made shoes supplied by NGOs (n=424) (Ayode, McBride et al. 2013).

Consistently wearing well-fitting protective shoes from an early age will help prevent the disease but sadly the cost of providing enclosed shoes is unaffordable to many families. Consequently unless the family's income increases financial support or free/low cost shoes may be required. Currently the charitable arm of an American shoe manufacturer provides shoes every six months to barefoot school children in some endemic areas of Ethiopia. Other NGOs provide custom made shoes to some of those who already have the disease and whose feet will not fit into locally available footwear.

Hopefully as young people begin to regard wearing shoes as a 'must have' as indicated by Ayode (2013) shoe wearing will become the norm.

The rise in education levels should also increase the frequency of foot washing (Molla, Le Blond et al. 2013). For those with podoconiosis a reduction in the swelling of their legs/feet, the number of wounds, leg odour, work days lost due to ADL and the consequential stigma may all help increase earnings. These improvements can all be achieved by consistently wearing protective footwear and a daily leg/foot hygiene regimen; this is discussed further in the following section.

### **6.2.2. SKIN BARRIER FUNCTION.**

No previous quantitative pre-post intervention studies of SBF in those with podoconiosis have been published to date. Yet improving SBF is a key component in the prevention and management of the disease. The treatment regime required to improve SBF is daily and lifelong taking approximately 45 minutes each day. It also requires extra water which may present a challenge and therefore a barrier to treatment although the lesser amount in the experimental group (1 litre v 6 litres) may aid adherence to the regimen. TEWL, the key determinant of SBF is discussed next.

#### **6.2.2.1. TRANS-EPIDERMAL WATER LOSS.**

TEWL increases in inflammatory skin diseases where SC is disrupted; therefore a reduction in TEWL indicates a positive effect on SBF. No previous studies have recorded TEWL in those with podoconiosis pre and post intervention. One earlier study compared TEWL in the leg and foot of those with podoconiosis (n=55) to a control group (n=20) (Ferguson, Yeshanehe et al. 2013). No difference was found but larger studies with similar numbers in each group may have indicated a difference.

From the results of the pilot study a mean difference in TEWL between groups of 1.05 gm<sup>2</sup>h was expected after three months treatment; the results were much greater than this. The decrease in the mean TEWL from baseline to the fourth visit became greater moving down to the foot. This increasing reduction may have been due to the initial mean levels being much lower

towards the feet reflecting a more compromised SBF and consequently giving greater scope for improvement.

In this present study there was a reduction in mean TEWL in both groups but the decrease was greater in the experimental group at all measurement points on the legs/feet; the differences were all highly significant. The results indicate the very positive effects on TEWL reduction of adding a small amount of glycerine (2%) to the leg/foot hygiene regimen currently used and taught in APA clinics. Previous studies have indicated statistically significant positive effects on TEWL of various concentrations of glycerine on those with healthy skin, older skin and with atopic dermatitis (Fluhr, Gloor et al. 1999, Gloor, Gehring 2001, Gloor, Gabard et al. 2001, Short, Chan et al. 2007, Breternitz, Kowatzki et al. 2008). All of the studies used higher concentrations of glycerine than in this study (5% - 85%) mostly as creams. None were on the skin of those with lymphoedema and trophic skin changes. No studies were found which used a 2% dilution of glycerine in water to increase TEWL, as in the study presented here. The lesser concentration of NaOCl (0.0045% less) in the water soak of the experimental group may have marginally reduced its pH and reduced its detrimental effect on TEWL; however pH 8 was detected via a litmus test in both the 0.0125% and 0.008% NaOCl concentrations.

In this study there was a difference between genders in the change in TEWL from baseline at most points on the leg/foot. Females had a greater increase in TEWL compared to males. The reason for the gender difference is unclear. It may be that females were more rigorous in following the treatment regime. In Ethiopia female legs are more visible to others because they wear skirts as opposed to the males whose legs are covered by trousers. This visibility may result in females being more eager to achieve more normal looking legs by more meticulously following the treatment regimen. No other studies on gender and TEWL in podoconiosis were found for comparison. Recent studies on healthy skin have reported conflicting results on the effect of gender on TEWL but none of these were on the skin of lower legs/feet or compared gender results pre/post intervention. In some studies TEWL was higher in males (Chilcott, Farrar 2000, Firooz, Sadr et al. 2012, Mizukoshi,

Akamatsu 2013a); however The International Guidelines on TEWL and gender state that there is no conclusive evidence of a gender difference (du Plessis, Stefaniak et al 2013).

In the study presented here there was difference in the change in TEWL from baseline between the right and left legs/feet; at all measurement points the reduction was greater in right legs/feet and was highly significant. The reason for these differences may have been the result of the anatomical differences in the blood flow and lymphatic drainage between the left and right legs or a preference for treating right legs as described in section 6.2.3.6. No other studies on the difference in TEWL between the right and left legs in those with podoconiosis were found for comparison. TEWL is closely related to SC hydration because unless TEWL is successfully treated it results in the cycle of dry skin which was presented in Figure 2.2. SC hydration is the subject of the next section.

#### *6.2.2.3. STRATUM CORNEUM HYDRATION.*

The SC only comprises 10% of the entire skin but contributes to over 80% of the SBF (Pouillot, Dayan et al. 2008). SC hydration is of major importance because it influences all the interrelated substances and activities within the SC (Rawlings, Harding 2004). To fulfil its functions the SC needs to contain at least 10% water (Warner, Lilly 1994).

Based on the pilot study for the two treatments a mean difference in SC hydration level between groups of 4.81 was expected after three months treatment; the results of the main study were less than this. The reason for the group difference in SC hydration being lower than expected and TEWL levels higher when both were based on the pilot results is unclear. It may be because the calculation of a group difference was based on the small numbers in the pilot study. It may also be due to a difference between the European older, female xerotic skin of those in the pilot study and the generally younger African skin of both genders in the research study.

In this present study there was an increase in mean SC hydration in both groups but the increase was greater in the experimental group at all

measurement points on the legs/feet; the differences were all highly significant. The results indicate the very positive effects on SC hydration of adding a small amount of glycerine (2%) to the leg/foot hygiene regimen currently used and taught in APA clinics. As with TEWL the lesser amount of NaOCl in the water soak of the experimental group may have marginally reduced its pH and although not detected via a litmus test reduced its detrimental effect on SC hydration when compared to the higher amount used in the control.

No previous studies were found which recorded SC hydration levels in those with podoconiosis pre and post intervention to allow comparison. In this current study at baseline and in both groups the mean SC hydration was lower at the base of the leg and top of the feet compared to points higher on the lower leg. The increase in SC hydration in both groups became greater moving down towards the foot. This may have been due to initial mean levels being lower towards the foot giving greater scope for improvement. A descriptive study comparing SC hydration in the legs/feet in those with podoconiosis with controls reported that those with podoconiosis had lower SC hydration with a significant group difference in the foot and shin (Ferguson, Yeshanehe et al 2012). Their study did not record SC hydration at the base or top of the lower leg.

Several other studies have reported that glycerine hydrates skin, reducing dryness and increasing plasticity (Fluhr, Gloor et al. 1999, Lodén, Wessman 2001, Chrit, Bastien et al. 2006, Breternitz, Kowatzki et al. 2008, Atrux-Tallau, Romagny et al. 2010). Fluhr stated that a combination of 85% glycerine and occlusion had the most statistically significant hydrating effect compared to glycerine alone (Fluhr, Gloor et al. 1999). A later study reported prolonged water retention when *Vaseline*<sup>®</sup> was applied at a thickness of 0.2-0.5mm following the application of 20% glycerine twice in 30 minutes (Alekseev, Szabo et al. 2008). In this present study significant effects on SC hydration were produced using a lesser dilution of a 2% glycerine soak for approximately 30 minutes followed by lesser amount of *Vaseline*<sup>®</sup>.

The use of *Vaseline*<sup>®</sup> to provide occlusion on skin where infection may be present has the potential to exacerbate the infection; however the amount of *Vaseline*<sup>®</sup> used in the present study was < 0.66 mg/cm<sup>2</sup>. This is considerably less than the 3 mg/cm<sup>2</sup> that would be required to provide 100% occlusion (Teichmann, Jacobi et al. 2006). The number of wounds in the lower legs/feet decreased in both groups to almost zero so the application of this lower amount of *Vaseline*<sup>®</sup> does not appear to have had any adverse effect.

Most previous published studies on the effect of glycerine on SC hydration have been on glycerine at concentrations of 5% - 85% (Appendix 3) not that of the dilution applied in this study. Only two small published studies were found which measured the effect of lesser concentrations. The first used a dilution of 2% dilution of glycerine which restored SC hydration to base values following the application of an irritant (n=4) (Atrux-Tallau, Romagny et al. 2010). The second study compared daily bathing for 2-3 minutes in warm water over six months with and without the addition of 0.02% glycerine. SC hydration levels improved significantly in the glycerine group at the forearm and forehead but although hydration levels were higher in other skin areas they were without significance (n=78) (Iiyama, Kawahira 2008).

In this current study no difference was found in the change from baseline in SC hydration between genders or between the right and left legs. No other studies on SC hydration by gender in the legs of those with podoconiosis were found for comparison. Recent studies on gender differences and SC hydration in healthy skin report conflicting results. None of the studies were on the skin of the lower legs/feet and none compared gender results pre/post intervention. Firooz et al (2012) found no significant gender difference in SC hydration in those with healthy skin (n=50). Higher SC hydration levels in males have been reported in some studies (Mizukoshi, Akamatsu 2013, Luebbarding, Krueger et al. 2013b). One study noted that SC hydration was only higher in males compared to females in those aged 13-35 years (Man, Xin et al. 2009). This current study provides new information to the field on SC hydration in those with compromised SBF due to an inflammatory response with consequential lymphoedema.

The following section provides the general profile and discussion on the various aspects of the legs/feet that were recorded. It includes; stage of podoconiosis, mossy skin changes, number of wounds on the lower legs/feet and odour, work days lost due to ADL, correlation between work days lost due to ADL and leg and foot circumference.

### **6.2.3. GENERAL CLINICAL PROFILE OF LEGS/FEET.**

#### *6.2.3.1. STAGE OF PODOCONIOSIS.*

In this study the treatment used in both groups successfully reduced the stage of disease reflecting an improvement in disease severity; however the group difference in stage after three months intervention was not significant. The only other pre-post intervention study using the same staging tool developed by Tekola, Ayele et al. 2008 reported that 80% of patients had stage 2 or above at baseline with a mean stage of 2.07. After 12 months treatment the clinical stage decreased in more than half the patients with a mean decrease in stage of 0.67 (Sikorski, Ashine et al. 2010). In this present study the mean decrease in stage for all legs in both groups after only 3 months treatment was greater at 0.88. The stratification used in this study ensured equal numbers of those with mild/moderate disease (stages 1/2/3) and those with severe disease (stages 4/5) therefore comparisons with other studies are difficult. There was a significant difference in stage between legs at the fourth visit ( $p=0.033$ ). This again may have been due to anatomical difference between the right and left legs or a preference to focus on treating the right leg stated in section 6.2.3.6. In this study only three participants had only one leg with clinical signs of podoconiosis and 25 participants had different stages in each leg (stage 1/2/3 as opposed to stage 4/5). In the Molla study which used the same staging tool, legs that were at different stages on the same participant were all at stages 1-3. None had less severe disease in one leg and severe in the other (Molla, Tomczyk et al. 2012a).

#### *6.2.3.2. MOSSY CHANGES.*

At baseline mossy changes were observed to be present in the right legs/feet in 153 (79.3%) participants and in the left legs/feet of 156 (80.8%) participants. After the interventions they were seen to be present in 120

(62.5%) right legs/feet and 117 (60.9%) left legs/feet. These numbers are higher than reported in the Alemu, Tekola Ayele et al. (2011) study where mossy changes were stated to be present in 175 (53%) of patients. Molla et al. (2012a) noted an even higher percentage with 97.9% of those with podoconiosis having mossy changes. In the Sikorski study numbers were lower with only 33% having mossy changes at baseline and with no significant change after one year's intervention (Sikorski, Ashine et al. 2010). In their study clinical stage at baseline was lower ranging from 1-3. Mossy changes are less likely at stage 1 of the disease (Tekola, Ayele et al. 2008). In this current study the reduction in mossy changes post intervention was significantly less in males. No other studies were identified for comparison. The lower number of females with mossy changes after 3 months may again have been due to their more rigorous and conscientious intervention procedure. It would seem that a high percentage of those with podoconiosis have mossy changes to their legs/feet. Significantly reducing these trophic changes over a three or even a 12 month treatment period seems to be a difficult clinical challenge.

#### *6.2.3.3. THE NUMBER OF WOUNDS AND ODOUR ON THE LOWER LEGS/FEET.*

There was a reduction in wounds in both groups over the intervention period although those in the experimental group had fewer wounds than the control group. The group difference at the fourth visit was significant but as most participants had no wounds this was not clinically significant. No other studies recorded pre and post intervention data for these measures. The number of wounds at baseline was much higher than those reported in another study where 24.7% patients had 'open wounds'. However the definition of an 'open wound' was not given (Alemu, Tekola Ayele et al. 2011). Again no definition was given in the Molla et al. (2012a) study where open wounds were recorded as present on 53% of legs (n=1319). In this study the numbers were perhaps higher because the definition of a wound included areas where skin surfaces were compromised by fungal infections. The effect of soap in removing pathogens and soil, the antibacterial and virucidal effects of NaOCl added to the soaking water and the use of *Whitfield's ointment* in those with fungal infections would all have contributed

to fewer wounds. Those in the experimental group had fewer wounds despite using a lesser amount of NaOCl.

Normalization of SBF and improvement of skin hydration are essential for the process of wound healing (Fluhr, Darlenski et al. 2008). The positive changes from baseline in both SC hydration and TEWL were significantly greater in the experimental group. These differences would have boosted the wound healing process by normalizing the skin. The difference in the intervention between groups was that 2% glycerine and the lesser amount of NaOCl (0.0045% less) was added to the soak of those in the experimental group. The antibacterial and virucidal effects of glycerine which promoted faster wound healing noted by Fluhr, Cavallotti et al. (2008) may have had a small effect although the concentrations used in this study were much less than the 85% dilution reported as being effective (Saegeman, De Vos et al. 2007, Saegeman, Ectors et al. 2008).

Odour is caused by pathogens, exudate and necrotic tissue in wounds. It would therefore be expected that as the number of wounds reduced there would be a consequential decrease in odour. After three months intervention the change in the reduction in leg odour between groups was significant. The experimental group had significantly less odour (0% v 1.5%). The numbers in each group were so low that this was probably not clinically significant. No other studies were found which recorded odour pre-post intervention. In the developed world odour is stated by patients as the most distressing of all wound related symptoms, contributing to social isolation, depression and feelings of guilt and revulsion (Chase, Whittemore et al. 2000, Grocott 2007, Probst, Arber et al. 2009). In Ethiopia it is also cited to have negative psycho-social effects. In one study stigmatising behaviours reported by patients included others pinching their noses as they walked by (Tekola, Bull et al. 2009). Reducing odour would therefore contribute to reducing the social stigma of the disease and its impact of quality of life. It should also help reduce the higher mental distress noted in those with podoconiosis (Mousley, Deribe et al. 2013).

#### *6.2.3.4. DAYS OF WORK LOST DUE TO ADENOLYMPHANGITIS.*

In this study the number of days participants were unable to work due to ADL in both groups reduced over the intervention period. This reduction was greater in the experimental group. In the control group the mean number of days of work lost due to ADL fell to 0.08 and in the experimental group to 0.01, even with the possible reduced disinfection of the lesser amount of NaOCl; however the group difference was not significant. The difference between groups was possibly not clinically important because the number of work days lost in both groups reduced to nearly zero. No other studies recorded pre and post intervention data for these measures. The average number of work days lost per month at baseline in this study is similar to the study in Western Ethiopia where patients experienced ADL an average of 5.5 times annually with each episode averaging 4.4 days (Alemu, Tekola Ayele et al. 2011). Molla, Tomczyk et al. (2012a) also noted similar data with a reported average of 5 days in bed during every episode of ADL, 49% of participants having an attack during the previous year with the average of five attacks per year (n=1299). In another study the number of participants who stated they had ADL attacks weekly was 26 (13.6%), 33 (17.3%) every two weeks and 68 (35.6%) every month. Only 35 (18.3%) said they had never had ADL attacks (Campion, Tamiru et al. 2015).

Reducing the days lost due to ADL is important not only because of pain and suffering it causes but because any loss of income to those who are already poor may have greater consequences than for those more affluent. The economic effects on individuals, their family and the wider community were discussed in section 2.3.9.

#### *6.2.3.5. CORRELATION BETWEEN WORK DAYS LOST DUE TO ADENOLYMPHANGITIS, NUMBER OF WOUNDS AND STAGE OF PODOCONIOSIS.*

In this study by the fourth visit the number of days work lost due to ADL had reduced in both groups to a mean of 0.08 for the control group and 0.01 for the experimental group; the group difference was not significant. At every time point there was a statistically highly significant yet weak correlation between the number of lower leg/foot wounds and the number of days

participants were unable to work due to ADL. The only other published study found reported a highly significant relationship between presence of an open wound and ADL in those with podoconiosis ( $p=0.009$ ) ( $n=460$ ) (Molla, Le Blond et al. 2013). The higher numbers on their study may have been the reason for this difference.

In this current study no significant difference was found in the relationship between the number work days lost due to ADL and stage of podoconiosis. Molla, Le Blond et al. (2013) also found no statistically significant association between frequency of ADL and stage of disease. Alemu, Tekola Ayele et al. (2011) found the frequency and duration of ADL to be significantly higher in those with larger lower leg circumference; this may have been due those with larger legs/feet having more skin folds and fungal infections.

The antibiotic and virucidal properties of glycerine may help to accelerate wound healing although these properties have only been reported with dilutions of 85% (van Baare, Buitenwerf et al.1994, Saegeman, De Vos et al. 2007, Saegeman, Ectors et al. 2008). Reducing the number of leg/foot wounds would reduce odour and episodes of ADL consequentially increasing the number of days worked.

#### *6.2.3.6. LEG/FOOT CIRCUMFERENCE.*

An increase in the circumference of the leg/foot is a manifestation of disease progression and a reduction an indicator of effective treatment. The skin management regime of daily washing with soap, drying and application of *Vaseline*<sup>®</sup> helped to normalize the skin and its functions. This reduced inflammation and lymphoedema and consequently leg/foot circumference in both groups. In the experimental group the addition of 2% glycerine together with the lesser amount of NaOCl to the soaking water enhanced these effects resulting in a greater reduction in circumference but the group difference was not statistically significant.

In the only other pre/post intervention study recorded a much lower mean leg circumference at baseline of 26.22cm (range 20-33). No foot circumference was recorded. The mean reduction in leg circumference after 12 months

intervention was 2 cm (Sikorski, Ashine et al. 2010). In this study after 3 months intervention the mean reduction was greater than this at 3.4cm for the control group and 4.5cms for the experimental group.

In this study there was a highly significant difference in the reduction in circumference in right feet compared with left feet. The reason for the difference is unclear. It may be a result of the right leg being used more than the left leg when walking in those who have a right side preference. Exercise contracts the muscles of the lower legs propelling lower-extremity circulation upwards thus reducing venous congestion. Exercise including walking is known to improve circulation and reduce oedema (Lymphoedema Framework 2006). It may also have been due to anatomical and physiological differences between the left and right legs. The left iliac vein is longer than the right iliac vein and enters the right cardinal vein at a right angle which impairs venous drainage in the left leg and may result in leg oedema (Schrale, Ryan 2011).

The greater difference in the reduction of foot circumference between groups compared to the other points on the leg may be the result of the immersion of the feet in the 2% glycerine soaking water compared to splashing it on rest of the limb. The greater decrease in SC hydration and higher increases in TEWL in the foot compared to the rest of the leg could account for the comparatively greater decrease in foot circumference. This is because a lower TEWL and higher SC hydration would have resulted in less inflammation and therefore less swelling. The scope for an increase in TEWL and SC hydration on the top of the feet was also greater as baseline levels of SC hydration were lower and TEWL higher than on other points on the legs.

#### **6.2.4. QUALITY OF LIFE.**

In the present study the mean Amharic DLQI in both groups reduced from an extremely large effect on participants lives to a mild effect but without a significant group difference. The interpretation of the DLQI score is in Appendix 24B. The control group reduction was from 21.61 to 4.12, and the

experimental reduction was 21.07 to 4.12. In another study with equal numbers of new patients and those with podoconiosis treated for a minimum of 3 months the median Amharic DLQI 3 for the treated patients and 13 for the new patients (n=100) (Henok, Davey 2008). Amharic DLQI also reduced the only other pre/post treatment study on podoconiosis in which the mean Amharic DLQI reduced 15.04 from 21.11 to 6.07 over the longer time period of 12 months but with a much smaller number of participants (n=27) (Sikorski, Ashine et al. 2010). In this study DLQI reduced very substantially between the first and second visit. In the control this was from 21.61 (extremely large effect) to 8.83 (moderate effect) in the experimental group from 21.07 (extremely large effect) to 7.97 (moderate effect). The reduction in the impact of the disease on quality of life following the first visit was before any significant positive changes in the leg/foot would have been visible. The reason for this rapid improvement may have been due to the care and support given by the staff at the clinic and/or by other patients. The knowledge that they were not the only ones to have the disease and that effective treatment was available may also have contributed. The knowledge that it was not infectious and liable to infect others may also have been a factor. After the second visit DLQI continued to reduce but much more slowly. It would seem that the quality of life increases when daily hygiene treatment regimens are followed. This may be due to a visibly more normal looking leg with fewer wounds and less odour. It may also have been due to the support and encouragement given by the clinic staff and other podoconiosis patients raising awareness of an effective treatment and increasing self-esteem.

Other issues regarding the study challenges including the probes used to measure TEWL and SC hydration, cost of glycerine, clinic context and study challenges, clinic attendance, issues of literacy and the validity, reliability and limitations of the study are now discussed.

#### **6.2.5. STUDY CHALLENGES AND CHALLENGES OF ENSURING TREATMENT FIDELITY.**

Because the study was undertaken in rural Ethiopia it presented many challenges in terms of equipment, cost of interventions, distance, clinic

attendance, illiteracy, language issues and high ambient temperatures. These are discussed next.

#### *6.2.5.1. USE OF THE PROBES IN ETHIOPIA TO MEASURE TRANS-EPIDERMAL WATER LOSS AND SC HYDRATION.*

This study supports the Ferguson study (2013) in the successful use of the *VapoMeter*<sup>®</sup> and *MoistureMeterSC*<sup>®</sup> in the demanding environmental conditions found in Ethiopia. Using the probes required minimal staff training and staff quickly became very proficient. The probes were found to be light, easy to use, to clean and store. There was a potential issue of the reliability of the probes. This is discussed in Section 6.3.

#### *6.2.5.2. COST OF GLYCERINE.*

The addition of 2% glycerine increased the cost of treatment for the experimental group. The cost of 3 months treatment of each participant in the control group was £1.95 for those in the experimental group it was £5.10. The cost of a jug (39p) was included for both groups but is a one off cost as is the 2p cost of a syringe for those in the experimental group. This would result in an on-going monthly cost for each participant of either £1.56 or £4.71. To reduce the cost the bulk purchase of glycerine could be explored.

#### *6.2.5.3. DISTANCE AND LANGUAGE*

The distance and travel time between the PIs base in the UK and the outreach clinics in Ethiopia was a challenge. The PI's Ethiopian base was 5 hours south of the international airport at Addis Ababa. The two podoconiosis clinics in which the research was conducted were a further 2<sup>1/2</sup> - 3 hours' drive away in the highlands of the south west. This resulted in a daily round trip to visit clinics of 5-6 hours on mainly dirt roads which were often in poor repair. A 4 wheeled drive vehicle with an experienced driver was essential. An early start was necessary to avoid travelling after 7pm when it was dark and the journey became more hazardous.

Participants were required to visit the clinics monthly to enable monitoring of their condition, data collection and for them to collect their supplies. The vast majority walked to the clinics which for some took several hours. Those who

lived at greater distances would sleep in the clinic grounds that night and return to their village the following day. This resulted in them leaving their family and losing work time. The terrain they travelled was difficult with few made-up roads and often rivers without bridges which needed to be crossed. This was made more difficult during the study period due to the short rainy season in March and another longer one in late June to late August. In these periods the rivers flooded and tracks became extremely muddy making walking difficult and rivers impassable. A few patients hired motor bikes to travel to clinics but these were beyond the finances of the majority. The challenges of clinic attendance are discussed in more detail in Section 6.2.5.4.

There are many local languages in Ethiopia so verbal communication was challenging. Fortunately the nurse and social worker in both clinics spoke a little English as well as the national language of Amharic and the local language, due to the language issue and in order to monitor the quality of the teaching and data collection a supervisor was appointed (Table 4.6). He was an Ethiopian with a master's degree in public health who spoke Amharic and good English. He had an interest in podoconiosis having recently completed his master's degree on health extension worker's knowledge of podoconiosis. He travelled with the PI to all clinic visits. As power supplies, internet and phone connections were all intermittent the supervisor visited the clinics regularly to support staff and ensure accurate data collection. Initially this was weekly but then gradually reduced. He kept the PI regularly informed by E mail of any issues and progress. The PI travelled to Ethiopia four times during the seven month data collection period. Each time to each clinic was visited daily for a week to oversee the teaching, recording of data and progress of data collection. Issues of participant's clinic attendance and literacy are discussed in the next section.

#### *6.2.5.4. CLINIC ATTENDANCE AND LITERACY OF PARTICIPANTS.*

Ensuring the participants regular monthly clinic attendance was a challenge. Eighteen participants (9.32%) did not return to clinic in a timely manner following their first visit. This was defined as more than one week after the expected day of return. Sixteen of these were from Clinic B an area with

more difficult terrain than Clinic A. To encourage their return the SWs contacted the Health Extension Workers (HEWs) working in their village. HEWs have mobile phones supplied by the government. HEWs then contacted participants to encourage their return. They had still not returned after several weeks. SWs later identified the reasons for non-return as: the distance they had to walk to the clinic, the time taken by clinic appointments, leg pain (ADL), work commitments, fear of rape on the journey to/from clinic, the weather and the difficult terrain. To overcome these issues the nurses took supplies and equipment to participant's homes on hired motor bikes with drivers. Hiring motor bikes is expensive because they are imported and a heavy import duty levied. The nearest fuel supply was approximately 3 hours away from the clinics. Due to these issues research costs increased. Where possible, in order to reduce time and cost several participants were treated on the same day in each village or kebele. Visits were made early in the day to ensure that the skin probes were not affected by the midday heat. All 18 participants were restarted on the study and data recorded as a first visit.

Time spent travelling to/from a clinic plus the time at the clinic was given as one of the reasons for non-attendance. The time taken was not calculated in this study but in another study it amounted to an average of four lost work days per patient over a three month period (Tekola, Mariam et al. 2006). It has been identified as the reason for non-return to other podoconiosis clinics. In the Campion study 85.6% of participants lived in rural areas. The reported travelling time to the clinic was up to six hours with a mean of 1.95 hours. The most common reason reported for stopping attending the clinic was distance. This was significantly related to living greater distances from the treatment site (Campion, Tamiru et al. 2015). Tsegay reported remoteness of clinic site, financial considerations, expectations of 'special support', worries about increasing stigma, misconceptions about treatment and illness including ADL as reasons for non-attendance at clinics (n=53) (Tsegay, Wubie et al. 2014). Campion also cited ADL attacks as the reason why some patients did not attend clinic (Campion, Tamiru et al. 2015). These attacks have been related to long walks (Molla, Tomczyk et al. 2012a). Yet long walks are often required in order to attend a treatment centre.

Although data on literacy was not specifically collected the majority of the participants on the study were illiterate. Due to this inability to read or write careful verbal explanation of the research was necessary. Most signed with a thumb print or a cross to confirm their informed consent. A greater time was required to explain and demonstrate the podoconiosis prevention and treatment regimens. All study participants received the same basic information on the causes, prevention and treatment of podoconiosis. They were all taught verbally and by demonstration the daily leg/foot hygiene treatment required and encouraged to ask questions. Demonstrations and explanations of the whole procedure were repeated at each clinic visit to ensure understanding.

Ethiopian literacy rates in 2004 for those over 15 years of age was 22.8% females and for 40.5% for males (UNESCO 2013). In 2008-2012 the total adult literacy was estimated at 39% (UNICEF 2012). Tekola's study in the Wolaita zone, Southern Ethiopia which was conducted in the same zone as this present study noted higher illiteracy rates of 74.4% (mean age 37.93 years) in those with podoconiosis compared to 62.4% for those without (mean age 37.4 years) (Tekola, Mariam et al. 2006). A study of those over 15 years of age with podoconiosis in Northern Ethiopia recorded illiteracy levels of 76.6% (mean age 44.3 years) (n=1319) (Molla, Tomczyk et al. 2012a). Lower numbers of those with podoconiosis had 'ever gone to school' 128 (27.9%) compared to 281 (40%) of controls. Of the cases 10 (18.6%) had primary school level education versus 53 (19%) of controls, 5 (3.9%) had secondary school education versus 21 (7.5%) of in controls and none had higher education compared to 2 (0.7%) of controls. Only 15% of cases had received podoconiosis treatment. Another study of those with podoconiosis in which the majority were over 35 years of age reported illiteracy rates of 65.5% (n=150) (Tora, Franklin et al. 2014). In a recent study 65.4% (mean age 50.3 years) said they had never attended school (n=191) (Campion, Tamiru et al. 2015). This lack of education may be related to the hereditary nature of the disease. Older members of the family with the disease would be unable to work during episodes ADL. This may result in their children working to ensure an income instead of attending

school. Education would seem to be crucial in both preventing and treating those with podoconiosis. Molla's study after adjusting for gender and disease status reported that the level of education was significantly associated with frequency of foot washing ( $p=0.008$ ) ( $n=460$  cases, 707 controls) (Molla, Le Blond et al. 2013).

UNESCO estimated that adult literacy rates would increase in 2015 to 40.5% for females and 56.9% for males an average of 48.7% (UNESCO 2013). It would seem that literacy rates in those with podoconiosis who are generally in the working age group of 16 to 65 years are well below this expected level. It will clearly take time before the Ethiopian Government's focus on raising literacy levels in the population is reflected in those with podoconiosis.

### **6.3. VALIDITY AND RELIABILITY OF THE STUDY.**

The CONSORT Statement on trial reporting (2010) was followed as a guide to ensure the validity and reliability of the research and aid clarity to reporting the study (Appendix 16). Horner's 2012 recommendations for ensuring treatment validity were also followed. These included ensuring the intervention was the same for all participants in each group (intervention fidelity), standardized training and monitoring and evaluation of participants understanding of the information provided. The methods used in this study for ensuring these issues were followed are provided in Chapter 4. In this study the temperature in the clinics often reached over 30<sup>0</sup>C around midday. The clinic rooms were small with corrugated metal roofs which reflected the heat. This was problematic as skin probes do not work correctly above 30<sup>0</sup>C (Appendix 2). To avoid this problem, participants were encouraged to attend clinics early in the day. Patients were also treated outside the clinics under trees where it was cooler and late arrivals had their measurements taken later in the day. The further clinical use of the probes in resource-poor countries could possibly be constrained by their high cost and the need to regularly calibrate the *VapoMeter*<sup>®</sup> in a factory setting. In this study factory calibration had already been undertaken on the *VapoMeters*<sup>®</sup> and further calibration was not required in the time period. The

*MoistureMeters*<sup>®</sup> were calibrated by the PI with the manufacturer's calibration device prior to their use. Visually ensuring all participants used the daily regime taught in the clinics exactly as instructed in their homes was not practical. It was discussed previously in this chapter. The accuracy of measurements, data recording and participant's adherence to the treatment regimen are discussed in the next section.

### **6.3.1. ACCURACY OF DATA RECORDING.**

At the beginning of the study the PI provided a teaching programme which included how to use the measuring instruments and accurately record data. The PI was present at each clinic all day for five consecutive days teaching these skills to staff and the supervisor and supervising their practise. The teaching programme of staff and participants was discussed in Chapter 4. The PI then visited each clinic during the data collection period a further 3 times for a week each time to check the precision of measurement and data collection. Data forms were also checked randomly to ensure the precision and completeness of the data. The treatment regime was repeated and demonstrated by clinic staff to participants at each clinic visit to re-inforce learning. The supervisor visited with the PI. He also visited the clinics separately every few weeks to observe the staff teaching and demonstrating the treatment to participants. Their data collection and accuracy of the completed forms was also checked.

### **6.3.2. ADHERENCE OF PARTICIPANTS TO TREATMENT REGIME.**

Treatment fidelity is an essential element in study design and implementation as it supports the reliability of research findings (Horner 2012). Adherence of participants to the treatment regime was an essential component of treatment fidelity.

To ensure this as far as practically possible all participants were given a measuring jug at the first visit. At each clinic visit were given a month's supply of soap, bleach (NaOCl), *Vaseline*<sup>®</sup> and if required *Whitfield's ointment*. Those in the experimental group were also given a month's supply of glycerine and at the first visit a syringe for measuring the NaOCl. The

syringe was marked with tape to indicate the amount required. Those in the control were taught to measure the NaOCl with the bleach bottle top which has a capacity of 10mls. Measuring ½ cap for the extra 5 mls required may not have been as accurate as participant's perceptions of ½ a cap may have differed. All participants were taught how to undertake the appropriate intervention and measurement of liquids both verbally and by demonstration depending on their group. Questions regarding the treatment regime were encouraged. The teaching was repeated at each clinic visit. Syringes were replaced if lost. It was difficult to be precise about the amount of *Vaseline*<sup>®</sup> required for each individual lower leg due to the variation in each participant's lower leg/foot skin surface. The amount given to participants each month was 100 grams. This provided a daily amount 3.3 grams for both legs/feet or approximately 1.7 grams per leg/foot daily. It was estimated that in females with normal sized lower legs/feet 5 grams (1 teaspoon) would be required on each leg/foot to give a coverage of 2mg/cm<sup>2</sup> which provides some occlusion (Marques, Basso et al. 2007, Patzelt, Lademann et al. 2012). Only *Vaseline*<sup>®</sup> applied at a rate of 3mg/cm<sup>2</sup> *Vaseline*<sup>®</sup> has been demonstrated to provide 100% occlusion (Teichmann, Jacobi et al. 2006). The amount given to participants provided approximately 1/3 of this amount (0.66 mg/cm<sup>2</sup>) although their legs/feet were often very much larger.

It was not possible to observe each participant daily to ensure they accurately followed instructions as taught and demonstrated. The time taken to wash the feet /legs in soapy water and the soaking time may have varied but it was assumed that participants followed the instructions given to some degree because as discussed in section 2.4.4 dry skin does not improve without therapeutic intervention it only deteriorates. At the monthly clinic visit the condition of participant's skin was seen to slowly improve. This improvement was confirmed by measurements.

### **6.3.3. AMBIENT TEMPERATURE AND HUMIDITY.**

The probes used to measure TEWL automatically record ambient temperature and relative humidity each time they are used. During the data collection the mean ambient temperature varied from 26.22<sup>0</sup>C to 27.44<sup>0</sup>C

(SD 1.957-2.4999). The mean relative humidity varied from 28.2%-53.2% (SD 9.630-11.703). Only one other study was found which measured TEWL and SC hydration in those with podoconiosis in Northern Ethiopia used the same type of probes as in this study (Ferguson, Yeshanehe et al. 2013). The mean temperature in their study was lower at 23.3<sup>0</sup>C compared to 26.22<sup>0</sup>C-27.44<sup>0</sup>C in this study. The mean relative humidity was 40.46% compared to 28.2%-53.2% in this present study.

The following Chapter 7 presents the key conclusions of the research and of the pilot study. The study limitations, its significance and contribution to the field and how the research findings will be disseminated are also discussed.

# ***CHAPTER 7. CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS.***

This chapter provides a summary of the thesis drawing on the study results, conclusions, key limitation significance and contribution to the field, implications for practice, research and education and the dissemination of the research findings.

## ***7.1. KEY CONCLUSIONS.***

This study provides new evidence on the skin treatment currently used to treat those with podoconiosis in Ethiopia. It is the first RCT on the disease comparing pre and post intervention effects of the current treatment and a new evidence based treatment. It is the first research to use 2% glycerine (v/v) in the treatment of podoconiosis, incorporating this dilution into 1 litre of soaking water (1/6 less than currently used) and 0.008% (0.0045%) less NaOCl. Both the control and the experimental interventions resulted in improvements in TEWL and SC hydration, stage of podoconiosis, mossy changes, number of wounds, days of work lost due to ADL, leg and foot circumference and DLQI. Compared to the control group those in the experimental group had a significantly greater reduction in TEWL at all points on the lower leg/foot, a significantly greater increase SC hydration at all points on the lower leg/foot and a significantly greater reduction in foot circumference. All those providing treatment for individuals with podoconiosis should consider adding a 2% dilution of glycerine into their current skin regimen, reducing the dilution of NaOCl to 0.008% and using less soaking water.

### ***7.1.1. HYPOTHESIS TESTING.***

The null hypothesis was that -

*Exposure of those in Ethiopia living with podoconiosis to an evidence-based skin care intervention to promote skin barrier function does not improve skin*

*barrier function in the affected area and/or their disease related quality of life when compared to the control group using the existing skin care intervention.*

The research indicated that after 3 months intervention those in the experimental group had highly significant improvements to SBF compared with the control group. This improvement was indicated by the greater increase in SC hydration at all points on the lower leg ( $p=0.001$ ), lower TEWL at all points on the lower leg ( $p<0.001$ ), lower TEWL at the top of the foot ( $p=0.002$ ) and decreased foot circumference ( $p<0.001$ ). It indicates the highly beneficial effects on SBF of the addition of 2% glycerine (v/v) to the soaking water. The number of wounds and leg/foot odour decreased more in the experimental group but without clinical significance because the numbers in each group at the fourth visit were both almost nil. The number of days lost due to ADL was less in the experimental group but with minimal significance as again the numbers in both groups reduced to almost zero. The correlation between days lost due to adenolymphangitis and number of wounds was highly significant ( $p<0.001$ ) although weak so was not clinically significant. In both groups the mean DLQI decreased over the 3 months initially having an extremely large effect on the participant's quality of life but rapidly reducing after the first month of treatment and then more gradually to a final moderate effect.

No previous RCTs were found which compared different skin hygiene and moisturising regimens in those with podoconiosis to allow comparisons. No published research was found employing a dilution of 2% glycerine to increase SC hydration and decrease TEWL so again comparisons were not possible.

#### **7.1.2. PILOT STUDY.**

The pilot study although small, indicated that the soapy water compared to the other interventions had the greatest detrimental effect on TEWL. The combination of soapy water, 2% dilution of glycerine for 30 minutes and the application of a thin layer of *Vaseline*<sup>®</sup> indicated both the greatest mean increase in SC hydration and the greatest mean decrease in TEWL when applied to the skin for 30 minutes a day over five days. These changes were

statistically significant difference for skin hydration levels but not for TEWL ( $p=0.002$  and  $0.185$  respectively).

## **7.2. KEY LIMITATIONS OF STUDY.**

The study was not a blinded RCT which would have strengthened credibility by minimizing bias; but providing the control group with bottles of water labelled as glycerine instead of glycerine which has an entirely different consistency would not have been feasible and the differences between the real and counterfeit glycerine quickly exposed by the clinic staff and study participants. Stratification ensured there were similar numbers of participants from each clinic and that in each clinic there were similar numbers with less severe v severe disease and comparable numbers of males and females in each disease category. Although the groups were matched as far as possible there may have been other factors which were not identified such as dietary factors or co-morbidities particularly related to blood flow in the feet/legs. Of the differences recorded in the study there were slightly fewer participants in the experimental group aged 18-29, 50-59, 60-69 years and slightly more aged 40-49 years and 70 years plus compared to the control. The mean time since clinical onset of the disease was different being slightly higher in the experimental group (3.94 years v 3.39 years). The diagnosis of podoconiosis was made by the clinic nurse based on the high altitude, the volcanic soil and the high rainfall in the area in conjunction with the clinical manifestations of the disease in the lower leg/foot. No differential diagnosis was made to exclude those with swelling of the lower leg due to other diseases such as lymphatic filariasis, liver or heart failure onchocerciasis or leprosy; however due to the high altitude, the high prevalence of the disease in the area and the fact that the swelling in podoconiosis starts in the foot the diagnosis of podoconiosis is highly likely to be correct.

The study relied on staff in the clinics to collect accurate data. Although staff were taught how to collect and record the data and this was closely monitored by a supervisor and the PI who visited the clinics on a regular basis they were not monitored all of the time. The study also relied on participants accurately answering questions such as the type of shoes they

wore in the previous week. Some of the answers given by participants may have been influenced by 'social desirability' which is a tendency to answer in a manner which makes the respondent look good rather than being accurate or truthful (Holtgraves 2004).

Clinic staff were initially taught and then practised using the tape measures and probes to collect the quantitative data and record it on the forms. They were then observed over several consecutive days and their data collection and recording checked. These observations and checks reduced as they became proficient. In the experimental group glycerine was measured using the bleach bottle top, the water with a measuring jug and the NaOCl with a 2 ml syringe. Measuring the amount of *Vaseline*<sup>®</sup> applied was not so precise. It was not measured quantitatively but a thin occlusive layer was applied. The amount was subjective and may have varied.

It was not possible to monitor the participants' treatment regimens on a daily basis in their homes to ensure treatment fidelity however demonstrations of treatments were given at each clinic visit and any questions answered by staff. Research in adherence to dermatology regimens is mainly confined to the developing countries. A review of 20 years of adherence to dermatology therapies 1985-2005 which resulted in 17 articles fulfilling the criteria noted that adherence to topical therapies was difficult to measure (Hodari, Nanton et al. 2006). Cost, interference with life style, lack of transportation, poor understanding of the chronic nature of the disease, poor baseline quality of life assessments were all cited in the review as common reasons for poor adherence. Strategies to improve adherence included frequent follow up, ensure patients understanding of the purpose and outcome of the treatment, provide clear instructions and demonstrations and emphasise the importance of adherence. The clinic staff included these strategies at the monthly attendance so that optimum adherence could be achieved. It was presumed that participants followed the skin hygiene and moisturizing regime that was taught, to an extent as pododermatitis has not been known to improve without a daily skin care regimen.

### **7.3. SIGNIFICANCE OF FINDINGS AND CONTRIBUTION TO THE FIELD.**

The study was the first randomised control trial on skin treatments for those with podoconiosis. The daily skin care regime over 3 months which included a 2% dilution of glycerine in the reduced amount of soaking water and a lesser amount of NaOCl (0.0080% v 0.0125%) indicated a highly significant positive effect on the SBF of those with podoconiosis compared to the control. No adverse skin reactions on the legs/feet were noted on any participants in the experimental where glycerine was added to the intervention. The study provides significant new information to the field of skin treatment for those with podoconiosis. The treatment may prove effective in other skin diseases where there is an impaired SBF such as psoriasis and eczema and in other lymphoedematous skin diseases.

The *VapoMeter*<sup>®</sup> and *MoistureMeterSC*<sup>®</sup> used in the study were easy to use, clean and store. Previous studies have noted their reliability and ease of use. They required minimal staff training and proved suitable for use where temperatures did not exceed 30<sup>0</sup>C. Their high cost may make them beyond the financial cost of some research studies. Long term use in resource-poor countries may also prove difficult as they require batteries which in rural Africa may be difficult to source. The *VapoMeter*<sup>®</sup> also requires calibration in a factory setting on an annual basis where they are in regular use. This again may prove difficult to arrange in resource-poor countries.

In rural areas of Ethiopia water has to be carried to houses from a source which is heavy time consuming work. In the experimental group the amount of soaking water was reduced by 1/6<sup>th</sup>. This reduction of 5 litres per daily treatment was a very significant saving and may encourage regime adherence. If adopted this change may make the treatment regime easier to follow and thus improve patient adherence.

#### **7.3.1. PRACTICE, RESEARCH AND EDUCATIONAL IMPLICATIONS.**

The addition of a dilution of 2% glycerine is simple yet effective therapy for improving the SBF of those with podoconiosis. It is low cost and could be incorporated into the treatment of all those with podoconiosis. Combined

with wearing shoes it could also help prevent the disease. This is because dust and dirt has even been found in those wearing enclosed shoes. Importantly the number of heel cracks and foot trauma have been found not to be related to type of shoe worn (n=168) (Watanabe, McBride et al. 2014). Further studies are required to validate this study. Lesser concentrations of glycerine could also be trialled in order to reduce costs. It may be possible to soak a gauze bandage in a 2% dilution of glycerine thereby using smaller quantities of both water and glycerine. The cost of the bandage which would probably need to be renewed daily versus the reduced cost of the glycerine would have to be calculated to assess any cost implications. Patient acceptability would also need evaluating.

Further work is required educating those without the disease to wash their feet daily, apply moisturizers, wear enclosed shoes and seek treatment at the first signs of podoconiosis. From the research it seems that treatment nearer to patient's homes is required. Currently in Ethiopia only NGOs provide specialist clinics for those with podoconiosis awhile some also provide home visits. Extending the number of clinics or staff travelling to individual villages and homes is not a viable long term solution because of the high financial cost. Training long term patients to undertake teaching to others in their own localities as in Mossy Foot may be a way forward for other NGOs. Another solution would be to fully incorporate podoconiosis services into the government health services. In order to achieve this education of health care staff would be required as studies have indicated that their knowledge of podoconiosis is currently low (Yakob, Deribe et al. 2009, Mengistu, Berhane et al. 2013). Local health extension workers (HEWs), who have received specific training on podoconiosis, could have a particularly central role in identifying those with the disease, providing teaching on the causes and prevention of the disease and information on the treatment in local areas. The Ethiopian Government has already identified podoconiosis as one of its eight priority neglected tropical diseases and included the disease in the 2013–2015 integrated master plan for disease control (Addis Ababa Ministry of Health. 2013).

## **7.4. DISSEMINATING THE RESEARCH FINDINGS INTO CLINICAL**

### **PRACTICE.**

The research was presented at the 23<sup>rd</sup> World Congress of Dermatology in Vancouver in 2015, a poster of the research was also selected a 'featured poster'. In October 2015 the PI presented the research at Sodo University, Ethiopia which had given ethical permission for the study. Members of the University particularly those in undertaking public health degrees, APA staff and other interested parties attended. An abstract and a poster presentation have been accepted by the International Conference of Skin Biophysics and Imaging to be held in Lisbon in June 2016. Papers on the pilot study and the research are being prepared for publication in peer reviewed high impact internationally recognised dermatology journals.

In 2010 the Ethiopian Health Ministry agreed to prioritize podoconiosis control and mapping of the disease was commenced in 2013. The rationale for this was to help target government resources and encourage investment in the prevention, control and elimination of the disease (Ministry of Health, Federal Democratic Republic of Ethiopia. 2013). It is envisaged that eventually the care of those with the disease will be incorporated into the Ethiopian Health Care system. Until then NGO's provide the vast majority of public education and treatment of podoconiosis. Because of this the study results need to be disseminated among all NGOs involved in podoconiosis. All the NGOs should consider the addition of a 2% dilution of glycerine in a lesser amount of soaking water which contains 0.008% NaOCl into their current skin management regimen.

Participants dropping out of treatment was an issue in this study but was resolved with home visits. Drop out from clinics is an issue which has been highlighted in other studies often due to the distance of the clinic from their homes (Tora, Davey et al. 2012, Tsegay, Wubie et al. 2014, Campion, Tamiru et al. 2015). ADL has also been linked by patients to walking long distances (Molla, Tomczyk et al. 2012a). To ensure that those requiring treatment clinics are accessible they should be sited within a reasonable

distance of those with the disease. NGOs need to work closely together ensure that this is achieved. Interventions should continue to be provided at no-cost or low-cost to ensure they are accessible to the majority of those with the disease. In order to drive forward podoconiosis control, awareness of the disease needs to be raised not only among existing doctors, nurses, midwives but among teachers, social workers and those in local government particularly in endemic areas. HEWS, because they work at village level should be given a particularly important role in this work, educating the public about podoconiosis prevention and treatment and identifying those with the disease. Consideration should be given to providing information on podoconiosis prevention and treatment in the core training of all health care professionals. Early treatment would prevent disease progression, reduce stigma and decrease the number of work days lost through ADL. These measures could have a significant effect on improving the lives of individuals and their families and also have a positive impact on the nation's health and economy.

### ***7.5. SUMMARY OF MAIN POINTS.***

Compared to the current skin care regimen used in Action on Podoconiosis Clinics in Ethiopia the addition of 2% dilution of glycerine together with the reduction in the amount of NaOCl to 0.008% and reduction in the amount of soaking water to 1 litre significantly improved SBF in terms of TEWL and SC hydration at all points on the leg and foot over a three month period compared to the current treatment. The improvement in SBF can be measured with non-invasive probes via the quantitative measures of a decrease in TEWL and an increase in SC hydration. The probes are suitable for use in Ethiopia. Adding glycerine to the treatment of those in the experimental group was not problematic. The glycerine was easy to use, low cost and readily available in Ethiopia. No adverse effects related to its use were noted.

At all points on the lower leg TEWL decreased significantly more in the right leg more than in the left over the same period. The circumference of the right foot also decreased significantly more than in the left. This supports the

differences in venous return between legs caused by the anatomical differences previously reported. This study presents new knowledge to the field of skin care regimens where the skin disease is caused by inflammatory reactions resulting in lymphoedema and more especially to the field of podoconiosis.

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## APPENDICES

### 1. LITERATURE SEARCH.

The data bases CINAHL, MEDLINE, Academic Search Premier, PsycLIT, PsycINFO PsycARTICLES and Pubmed were searched literature was searched from 1990 to 2015. The time limit focussed on the most recent studies. Other articles cited in papers already accessed were also obtained if relevant. The terms used in the literature search were single or in combination. They were:

skin, dermatol\*, function, stratum corneum, SC, barrier, disease, xerosis, psychol\*, dry, environment, hydrat\*, water, purification, drinking, quality, sodium hypochlorite, wound\*, pathogens, virus\*, bacteria, ethnic\*, race, Black, Asian, Caucasian, cutaneous, trans-epidermal, water, loss, TEWL, stigma, podoconiosis, mossy foot, teach\*, lymphatic filariasis, elephantiasis, Africa, Ethiopia, resource-poor, developing, third, world, prevalence, quality of life, QoL, research, randomise, control trial, blind\*, review\*, Consort Statement, self-reports, social, desirability.

The WHO, UNICEF, APA, Mossy Foot, lymphatic filariasis, lymphoedema web sites and the Podoconiosis Drop Box (a drop box for all of those interested in podoconiosis research and regularly updated) were also searched. The Cochrane data base was also searched.

The grey literature bases were searched but no PhD research thesis was found using the terms: non filarial filariasis, mossy foot or podoconiosis.

## 2. PROBES USED TO MEASURE SKIN HYDRATION AND TRANS-EPIDERMAL WATER LOSS.

The instruments used were Delfin instruments (Delfin Technologies Ltd, Kuipio, Finland). These were used in previous study of skin barrier function in podoconiosis in Ethiopia (Ferguson, Yeshanehe et al. 2013). Some of the following information was gained from their web site [www.delfintech.com](http://www.delfintech.com):

The *MoistureMeterSC*<sup>®</sup> was developed and validated as a portable handheld wireless device specifically for fieldwork. It measures changes in SC capacitance equivalent to changes in dielectric constant due to hydration, and expresses results as rescaled interval units (due to the complexity of expressing capacitance). It includes a pressure sensor to reduce inter-measurement variability. It was placed on the skin for 4 seconds, after which the numerical hydration value was shown on the LED display. Three measurements were taken close together on each site and the mean value recorded.

TEWL was determined using a handheld *VapoMeter*<sup>®</sup> (an instrumental measure of water flux through the SC). For fieldwork, the *VapoMeter*<sup>®</sup> has the advantage of being a closed-chamber device, reducing to a minimum any variability due to environmental factors such as air movement. It was placed on the skin surface for approximately 10 seconds, with the exact time varying slightly from site to site, dependent on measurement stability determined by the instrument. Single measures of TEWL were recorded on each site as grams of water vapour flux per square meter per hour ( $\text{gm}^2 \text{ h}$ ).

### 3. STUDIES OF THE EFFECTS OF GLYCEROL (GLYCERINE) ON HUMAN SKIN A SUMMARY OF EXPERIMENTAL DATA AND CLINICAL TRIALS FROM 1998 (adapted from Fluhr et al. (2008 (2)) and updated).

Type of study	Numbers	Amount of glycerine	Glycerol effect	Type of glycerol effect	Reference
<b>Skin barrier function</b>					
No information found	No information found	20%, 40%	Dry skin on legs - dose dependant effect (20%, 40%).	No information found	(Bissett, McBride 1984)
No information found	No information found	10% , 20%	Oil in water emulsion	More efficient as vehicle than water in oil (dose dependant effect (10%, 20%).	(Fluhr, Vrzak et al. 1998)
Comparative. Skin treated 3 times a day for 3 days	27 test subjects (12male, 15 female)	10% glycerine oil in water emulsion	Compared to oil in water emulsion alone or with 10%, urea or with 10% propylene glycol.	Significant effect of glycerine in quantitative tests	(Bettinger, Gloor et al. 1999)
Comparative	12 healthy females	99.8%	Test site: previously tape stripped skin on volar forearm. Sites treated for 3 days with 0.1ml of glycerol	Skin hydration measured higher (significant effect) independent of mode of application (open or occluded for 24 hours).	(Fluhr, Gloor et al. 1999 (a))
Comparative	19 healthy volunteers (7 male and 12 female )	25%, 50% glycerol dilutions of 85% glycerol in water	Repeated open washing with 2% SLS on volar forearm for 3x a day for 4 days. Then treated with different ointments 3 x day for 3 days and 1 week later.	Significant effect of 25% and 50% glycerol compared with vehicle. Differences statistically significant 7 days after completion of the treatment.	(Fluhr, Gloor et al. 1999)
Double blind randomized study on volar forearms	20 healthy volunteers	5%	Post treatment of test site with acetone and SLS over 14 days.	Significant hydrating effect of glycerol compared with vehicle.	(Gloor, Gabard et al. 2001)
Comparative test on volar forearms	13 healthy volunteers.	15% emulsion of water in oil	Standardized washing SLS model: long term use (6 weeks) effect.	The glycerol emulsion had a significant hydrating effect compared to 2 other emollients and no treatment. This was maintained over the 6 weeks.	(Gloor, Gehring 2001)
Bilateral double blind study over 10 days	17 healthy patients	20% glycerine cream	Compared with placebo after repeated applications.	Increased hydration, no change in TEWL.	(Lodén, Wessman 2001)
Randomised double blind study. Assessment by patient and dermatologist	197 patients with atopic dermatitis	20% glycerine cream	Compared to 4% urea/4% saline cream and to cream only. Treated daily for 30 days.	No difference in reported/observed in dryness. Less smarting with glycerine cream.	(Lodén, Andersson et al. 2002)
Double blind occlusive test. Measurements daily for 4 days.	64 healthy volunteers in 2 groups of 32.	5%, 10% 20%	After acute irritation with SLS and NON.	Applications twice a day for 6 days. Significant effect compared to canola oil, nifedipine and (-) alpha-bisadol; dose dependent effect (5%, 10%, and 20%).	(Andersen, Hedegaard et al. 2006 (1))
Randomised study	26 female volunteers aged 24-59 years with	3% glycerine cream	Increased hydration in entire thickness of SC 1 hour after	Highly significant increased hydration of SC	(Chrit, Bastien et al. 2006)

	dry skin. 3 test sites on each volar forearm		application using Raman micro-spectroscopy.	(p=0.004) but not statistically significant compared to vehicle (p=0.14).	
Randomised double blind study	24 patients	20%	Patients with atopic dermatitis treated twice daily for 2 weeks.	Increased hydration in the wash out period (2 weeks after the end of application) compared with glycerol free placebo.	(Breternitz, Kowatzki et al. 2008)
<b>Skin barrier repair</b>					
Comparative	12 healthy females	85% occluded and open.	2 sites each forearm treated for 3 days.	Reduction of TEWL values of open and occluded areas.	(Fluhr, Gloor et al. 1999 (a))
Comparative test on volar forearms	13 healthy volunteers.	15%	Standardized washing model long term use (6 weeks) product containing 15% of glycerol at 85% dilution.	Reduction in TEWL.	(Gloor, Gehring 2001)
Double blind randomized study	20 healthy volunteers	5% cream	Cream containing 5% glycerol and 5% aluminium chlorohydrate compared with glycerol 5%, 5% aluminium chlorohydrate, a standard positive control cream, vehicle alone and control.	60 minutes after application significant reduction in TEWL. Further significant decrease in TEWL when combined with aluminium chlorohydrate which is present in anti-perspirants.	(Gloor, Gabard et al. 2001)
Double blind trial over 30 days	109 patients	20% glycerine cream.	Patients with atopic dermatitis.	Compared to placebo and cream with 4% urea. No difference in TEWL between glycerine and placebo. TEWL lower in urea than glycerine.	(Loden, Andersson et al. 2001)
Double blind randomized study over 28 days	15 females	10% glycerine in moisturizer.	Patients with moderately photo-aged forearms treated twice daily.	Epidermal thickness increased (p=0.005) and barrier function increased (TEWL decreased by 13%).	(Short, Chan et al. 2007)
Controlled, double blind, randomised prospective study over 4 weeks	24 patients	20% glycerol cream	Patients with atopic dermatitis	Those treated with glycerol cream showed significant decrease in TEWL. SC hydration significantly improved and epidermal barrier was restored compared to placebo.	(Breternitz, Kowatzki et al. 2008)
<b>Anti-irritant effect</b>					
Comparative controlled	9 volunteers. Following tape stripping or irritation via application of dimethyl sulfoxide (DMSO), SLS and sodium hydroxide.	3 mls glycerine solution (70%) applied under occlusion. Control - water under occlusion.	Acute irritation model	After 5 hours significant improvement in SBF following SLS and DMSO.	(Bettinger, Gloor et al. 1998)
Double blind study,	17 healthy patients	20%	Challenge of skin	No difference	(Lodén,

bilateral		glycerol cream	with SLS between glycerol containing cream and its vehicle		Wessman 2001)
Double blind	64 healthy volunteers in 2 groups of 32. Measurements taken daily over 4 days. Occlusive test	5%,10%, 20%	Cumulative irritation model	Glycerine effect dose dependant Best effect when compared to canola oil, nifedipine and (-) alpha-bisadol and vehicle	(Andersen, Hedegaard et al. 2006 (1))
Double blind randomized study	32 healthy volunteers. 4 sites and 4 treatments. 3 daily arm washes for 7 days with 10% SLS on one arm and 30% NON on the other. Then twice daily washes with the same irritants for further 12 days	20% glycerol in ointment	Cumulative irritation model	Glycerol effective against SLS and NON induced irritation in contrast with triamcinolone acetonide which was only effective against NON	(Andersen, Hedegaard et al. 2007)
Comparative	4 healthy volunteers 24-28 years old	1-10%	10% SLS applied as irritant on volar forearms under occlusion in an area 2x2cms for 3 hours. Then aqueous solution of glycerine 1-10% under occlusion applied for 3 hours. Air dried for 15 to 30 minutes.	TEWL and capacitance measured. Skin hydration restored to base values with 2% glycerol concentration. Plateau effect above 5%	(Atrux-Tallau, Romagny et al. 2010)
<b>Penetration enhancing</b>					
Controlled comparative	17 volunteers	3 mls glycerine solution (70%) applied under occlusion. Control = water under occlusion.	Hexyl nicotinate 10 mmol/L applied followed by the glycerine solution	After 5 hours penetration of hexyl nicotinate improved	(Bettinger, Gloor et al. 1998)
<b>Skin mechanical properties</b>					
In vivo	14 volunteers one leg treated other was the control	10% in water applied twice daily for 3 weeks		Significant long term effect on extensibility -1 week after stopping treatment.	(Aubert, Anthoine et al. 1985)
Comparative in vivo	16 healthy volunteers mean age 34 years. Volar forearms.	Glycerine dilution not stated	Compared to tap water, paraffin oil, and ethanol. More supple skin after 10 minutes application of all products except ethanol.	Improvement in skin hysteresis, dispensability. Glycerine had more prolonged effect than water or paraffin oil	(Overgaard Olsen, Jemec 1993)
Comparative on volar forearms	23 healthy volunteers.	Glycerine dilution not stated	Hysteresis (extensibility of skin resulting from repeated stretches).  Distensibility (elevation of skin in response to the force applied it reflects the stiffness / resistance of the skin when stretched).	More rapid increase with glycerine after 3 minutes (p=0.005) compared to water (12-15 minutes). Transient increase.	(Pedersen, Jemec 1999)
Comparative.	27 test subjects (12male ,15 female)	10%	Skin on forearm treated 3 times a day for 3 days for 3	Significant effect	(Bettinger, Gloor et al. 1999)

			hours in 5 cm areas with 10 % glycerol, 10% urea or 10% propylene glycol Improvement in skin deformability and epidermal plasticity.		
<b>Quality of life</b>					
Prospective, randomized double blind study. Intra-individual for 7 days followed by use of product on all xerotic areas for 49 days and measurement at day 56.	Legs of 99 patients with uremic xerosis. 74% had pruritus.	15% glycerol in oil in water emulsion.	Improvement in QOL which was significantly compromised at baseline. Twice daily application of 10% paraffin and 15% glycerol in an oil and water emulsion to one leg, emulsion alone to the other applied twice daily.	Highly effective treatment response in 73% patients. 44% responded to comparator (p= 0.0001 inter-group analysis). Difference between baseline cores and day 56 scores was statistically significant for all quality of life scores used (p<0.0001).	(Balaskas, Szepietowski et al. 2011)
SLS = sodium lauryl sulphate, NON = non anoic acid , DSMO = dimethyl sulphoxide					

#### 4. PODOCONIOSIS STAGING SHEET (Podoconiosis-Endemic Areas) (Tekola, Ayele et al. 2008).

##### **Staging for Field Workers Instructions**

The field worker is expected to look at and examine the right and left leg of each patient in turn and give a score to each leg separately.

- ‘Swelling’ here means a general increase in size of part of the foot or leg.
- ‘Reversible swelling’ here means a swelling that is not present when the patient first gets up in the morning and becomes more marked as the day advances.
- ‘Persistent swelling’ here means a swelling that is present all the time.
- ‘Knob or bump’ here means a discrete, hard lump that can be seen or felt to protrude from the rest of the foot or leg.
- ‘Ankle’ here means the level of the two ankle bones when the patient is standing.
- ‘Knee’ here means the level of the top of the knee cap when the patient is standing.

In addition to the numerical stage, the field worker should measure the greatest below-knee circumference and record the presence (M+) or absence (M) of mossy changes. For example, if a patient’s right leg has irreversible below-knee swelling, nodules below the ankle, mossy changes around the heel and a circumference of 48 cm, the staging should be recorded as Stage 2, M+, 48.

**Stage 1.** Swelling reversible overnight.

The swelling is not present when the patient first gets up in the morning.

**Stage 2.** Below-knee swelling that is not completely reversible overnight; if present, knobs/bumps are below the ankle ONLY.

Persistent swelling that does not reach above the knee. If knobs or bumps are seen or felt, they are only present below the ankle, NOT above the ankle.

**Stage 3.** Below-knee swelling that is not completely reversible overnight; knobs/bumps present above the ankle. Persistent swelling that does not reach above the knee. Knobs or bumps can be seen or felt above the ankle as well as below.

**Stage 4.** Above-knee swelling that is not completely reversible overnight; knobs/bumps present at any location. Persistent swelling that is present above the knee. Knobs or bumps can be seen or felt at any place on the foot or leg.

**Stage 5.** Joint fixation; swelling at any place in the foot or leg. The ankle or toe joints become fixed and difficult to flex or dorsiflex. This may be accompanied by apparent shortening of the toes.

##### **Description for Health Professionals**

A more detailed and technical description of the changes that may be present at each stage is given, although the definitions for each stage remain the same. The stages represent severity of disease, and do not necessarily represent the disease process: it is possible, for example, for an individual to have Stage 5 disease but never to have had above-knee swelling. The following terms are used in the descriptions:

- Dermal nodules: elevated, non-translucent lesions >0.5 cm diameter, with width approximately equal to length.
- Dermal ridges: elevated lesions >0.5 cm width, with length greater than width
- Dermal bands: palpable, but non-elevated ridges
- Mossy changes: round or fusiform, either fluid-filled (and hence translucent) lesions, or papillomatous hyperkeratotic horny lesions giving the skin surface a rough velvet-like appearance.

**Stage 1.** Swelling reversible overnight. The swelling is not present when the patient first gets up in the morning. Changes such as hyperpigmentation and nail dystrophy are unusual, but may be seen. The swelling is usually confined beneath the ankle.

**Stage 2.** Below-knee swelling that is not completely reversible overnight; if present, knobs/bumps are below the ankle ONLY. Persistent swelling that does not reach above the knee. If present, knobs or bumps do not extend beyond the ankle. The 'knobs or bumps' may take the form of dermal nodules, ridges or bands. Tourniquet-like effects may be observed at this stage or any subsequent stage, depending on the position of dermal ridges and nodules in relation to joints. Mossy changes may be apparent, but their presence depends on a range of factors including the use of plastic footwear. Interdigital maceration and hyperpigmentation are often present at this stage, and nail dystrophy almost always present.

**Stage 3.** Below-knee swelling that is not completely reversible overnight; knobs/bumps present above the ankle. Persistent swelling that does not reach above the knee. Dermal nodules, ridges or bands are seen or felt above the ankle. Tourniquet-like effects are frequently observed at this stage. Any of the other changes mentioned in Stage 2 may also be present.

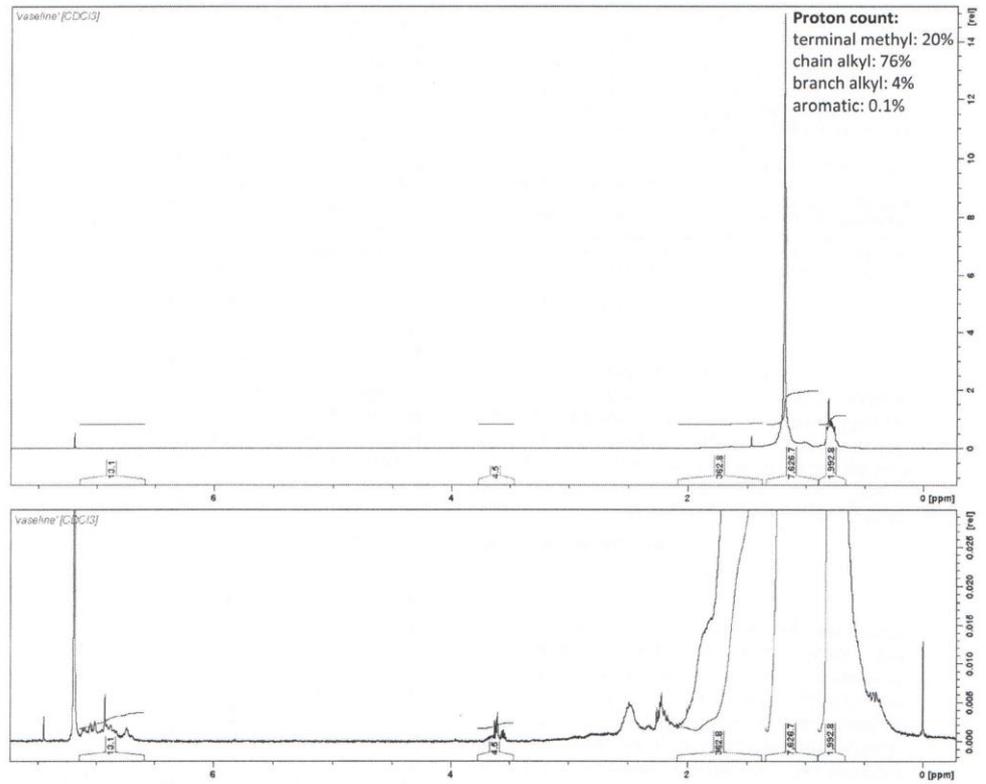
**Stage 4.** Above-knee swelling that is not completely reversible overnight; knobs/bumps present at any location.

Persistent swelling that is present above the knee. Any of the other changes mentioned in Stage 2 may also be present. In addition, signs of lymphectasia (distension of lymph gland) may be apparent, particularly on the thigh.

**Stage 5.** Joint fixation; swelling at any place in the foot or leg. The ankle or interphalangeal joints becomes fixed and difficult to flex or dorsiflex. This may be accompanied by adhesion and fusion of the toe web spaces, making the toes appear short or indistinct. Sensation is preserved. X-rays show tuft resorption and loss of bone density.

## 5. ANALYSIS OF SOAP AND VASELINE®.

'Vaseline' (Ethiopia/ Zenith G Esher Ltd.)



LIT2357/26

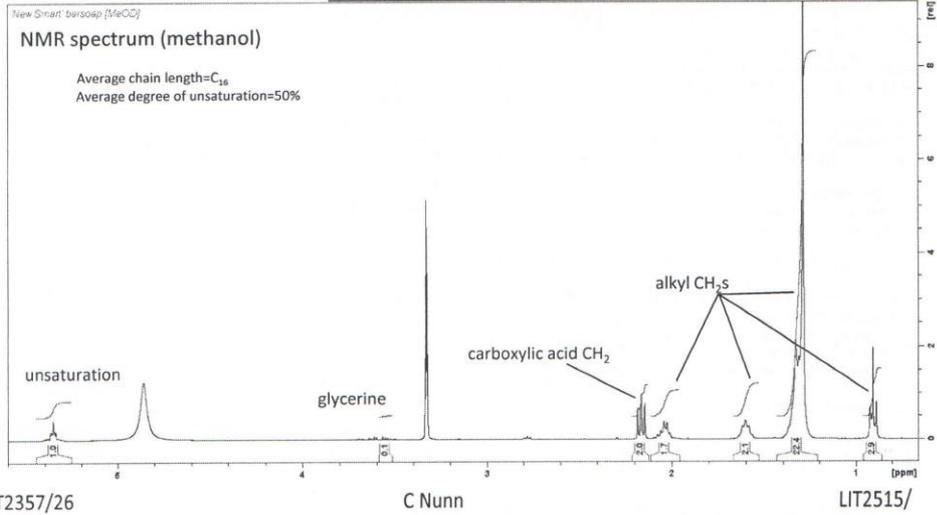
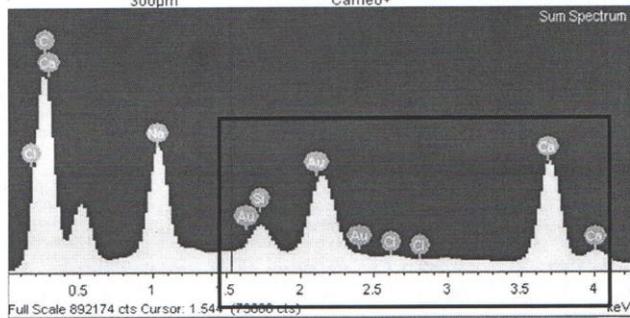
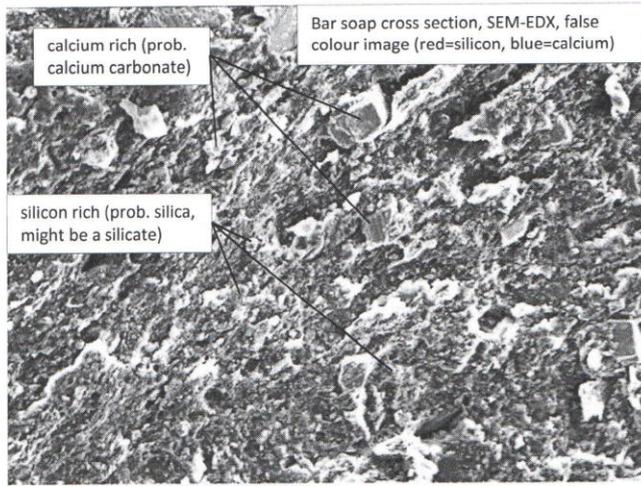
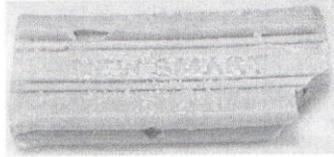
C Nunn

LIT2515/

'New Smart' bar soap

High levels of calcium (carbonate?) and silicon (silica?) rich particles.

- ~1% glycerine
- ~50% fatty acid (as C16 acid)
- Dark particles also observed (iron rich).



## 6. PODOCONIOSIS STIGMA SCORE (Franklin, Tora et al. 2013).

Patients answered – ‘yes’, ‘possibly’, ‘uncertain’ or ‘no’ to each question. A score of 3 was given for a ‘yes’ response to an item on the scale, 2 for ‘possibly’, 1 for ‘uncertain’ and 0 for ‘no’

### **Patients felt stigma Scale**

#### **Interpersonal interactions**

1. Have you avoided taking part in labour or other activities which require group involvement with unaffected people?
2. Have you tried to use household utensils separately from other family members?
3. Have you felt your family are proud of you?
4. Have you continued seeing and spending time with your (unaffected) friends?
5. Have you avoided asking neighbours for help, or to borrow items because of your condition?
6. Have you tried to kill yourself because of the demeaning treatment you receive as a result of your condition?
7. Have you tried to change your place of residence because of the way you are treated as a result of your condition?

#### **Major life areas**

1. Have you avoided any invitation to be employed for wage labour/job fearing stigma in the work place?
2. Have you feared unaffected individuals may feel uncomfortable working with you because of your condition?
3. Have you avoided marriage to an unaffected person fearing mistreatment after marriage?
4. Have you feared that marriage with an unaffected person may end in divorce?
5. Do you feel your condition has affected your other family member’s chances of marrying?

#### **Community, social and civic life**

1. Do you think that your condition deprives you from playing a leadership role in the community?
2. Have you avoided visiting public places like church, school or market?
3. Have you felt able to move around the community freely (without being stared at, pointed at or people noticing you?)

### **Patients enacted stigma scale**

#### **Interpersonal interactions**

1. Has anyone in your neighbourhood deterred you from taking part in group activities?
2. Have your family members avoided sharing household utensils with you?
3. Have friends been visiting you less or spending less time with you because of your condition?
4. Have you received insults from others regarding your foot?

#### **Major life areas**

1. Is there an example where you or another person you know has been denied a job opportunity because of the condition?
2. Have you or another person you know been forced to leave a job because of the condition?
3. Have you or another person you know been mistreated at your work place due to the condition?

4. Have you or another person you know been forced to dissolve marriage plans because of the condition?
5. Have you or another person you know experienced divorce because of the condition?
6. Has your condition made it difficult for an unaffected member of your family to marry?

#### **Community, social and civic life**

1. Is there an example where you or another person you know has been denied the chance of a leadership role due to the condition?
2. Is there an example where you or another person you know have been denied the chance to make decisions in community matters?
3. Have people ignored you, talked over you or told you to be quiet because of your condition?
4. Have you or another person you know been welcomed (by unaffected people) while attending church, school or other community meeting places?
5. Is there an example where you or another person you know have been treated in isolation at a social event?
6. Is there an example where you or another person you know have not been invited to appear at public places?
7. Is there an example where you or another person you know has been stared or pointed at when attending a social event?

#### **Unaffected community felt stigma scale**

##### **Interpersonal interactions**

1. Have you seen or heard of someone with this condition who fears bringing items to the market thinking they may not be sold?
2. Have you seen or heard of someone with this condition hesitating to visit a health centre fearing that health professionals may pity them?
3. Have you seen or heard about the children of someone with this condition dropping out school?
4. Have you seen or heard of someone with this condition avoiding taking part in group activities such as labour with unaffected people?
5. Have you seen or heard of someone with this condition trying to use household utensils separately from other family members?
6. Have you seen or heard of someone with this condition avoiding preparing food for other family members?
7. Does someone with this condition feel their family is proud of them?
8. Do you think someone with this condition is happy seeing or spending time with unaffected friends?
9. Do you think someone with this condition feels comfortable asking neighbours for help, or to borrow items?
10. Have you seen or heard of someone with this condition who has committed or tried to commit suicide?
11. Have you seen or heard of someone with this condition who has changed or tried to change the place where they live?

##### **Major life areas**

1. Have you seen or heard of someone with this condition who feels uncomfortable working with unaffected individuals?
2. Do you think someone with this condition feels they are as capable or productive as others?
3. Have you seen or heard of someone with this condition who has avoided marrying an unaffected person fearing mistreatment after marriage?

4. Does someone with this condition feel confident asking an unaffected person for marriage?
5. Do you think someone with this condition fears that marriage to an unaffected person might end in divorce?
6. Do you think someone with this condition feels their condition has affected other family member's chances of marrying?

#### **Community, social and civic life**

1. Do you think someone with this condition feels comfortable participating in community affairs?
2. Is someone with this condition afraid to accept a leadership offer or play a leadership role in the community?
3. Do you think someone with this condition is afraid to take part in decision making fearing their ideas might be discredited?
4. Does someone with this condition feel confident appearing at public places?
5. Have you seen or heard about someone with this condition who has avoided visiting public places like church, school or market?
6. Do you think that unaffected people and people with this condition should be served separately in public places?
7. Do you think someone with this condition fears others will stare or point at them in public places?

#### **Unaffected community enacted stigma scale**

##### **Interpersonal interactions**

1. Has someone with this condition selling items at market been avoided?
2. Have you seen or heard of anyone with this condition being pitied by a health professional?
3. Have you seen or heard of any children of someone with this condition being mistreated by friends or teachers at school?
4. Has someone with this condition been stopped from taking part in group activities in your neighbourhood?
5. Have people avoided sharing or borrowing household utensils with someone with this condition?
6. Have people avoided sitting near or sharing a seat with someone with this condition?
7. Have you seen or heard about anyone with this condition being mistreated by their family compared to unaffected members?
8. Have you seen or heard about someone with this condition being isolated by their friends, family members or neighbours?
9. Have you seen or heard insults being called out to someone with this condition?

##### **Major life areas**

1. Do you know of anyone who has not been offered a job because of this condition?
2. Have you seen or heard of anyone who was forced to leave their job because of this condition?
3. Have you seen or heard of anyone who has been mistreated in the work place because of this condition?
4. Have you seen or heard of anyone who has avoided marriage with someone because they had this condition?
5. Have you seen or heard of anyone who has been divorced because of this condition?
6. Have you seen or heard of anyone who has been mistreated by their by spouse due to this condition?

7. Have you seen or heard of someone where their condition made it difficult for their unaffected family members to marry?

**Community, social and civic life**

1. Has there been an example where someone has been denied the chance of a leadership role because of this condition?

2. Has there been an example where someone with this condition has been denied the chance to make decisions in community matters?

3. Has there been an example where someone with this condition has not been listened too or ignored when talking?

4. Has there been an example where someone with this condition has not been invited to appear at public places?

5. Has someone with this condition been isolated at a social event you have attended?

6. Has someone with this condition been stared or pointed at while attending a social event?

7. Have you experienced someone with this condition being excluded from using public facilities, such as public transport?

## 7. Pilot Ethics Application.



### FACULTY OF HEALTH AND SOCIAL CARE RESEARCH ETHICS COMMITTEE PROPOSAL FORM

#### (FORM A)

REF NO.....DATE OF MEETING.....  
(Office use only)

#### 1. SUBJECT INVOLVEMENT

Does the research involve ANY patients in a NHS or Social Services environment (clinical or non-clinical)? Please highlight the answer that applies	
<p style="text-align: center;"><b>Yes</b></p> <p>If Yes, <b>STOP HERE.</b></p> <p><b>A.</b> If it concerns <b>NHS patients, YOU MUST</b> apply for permission and approval for your research via the Integrated Research Application System (IRAS), which can be accessed at: <a href="https://www.myresearchproject.org.uk/">https://www.myresearchproject.org.uk/</a> and complete <b>FORM B.</b> The IRAS will require you to apply for approval via a NHS Research Ethics Committee (REC). <b>THERE IS NO NEED TO COMPLETE FORM A</b></p> <p><b>B.</b> If it concerns: ‘<b>Adult social care research study proposals, intergenerational studies involving adults and children or families, use of social care databases and some proposals for social science studies</b>’; then apply via the Social Care Research Ethics Committee (REC) which can be accessed from <b>the Social Care Institute for Excellence</b> website at <a href="http://www.screc.org.uk/index.asp">http://www.screc.org.uk/index.asp</a> <b>THERE IS NO NEED TO COMPLETE FORM A</b></p> <p><b>Students please contact your research supervisor in the first instance BEFORE completing Form A as to which is the appropriate research ethics committee for you to submit your proposal.</b></p>	<p style="text-align: center;"><b>No but Ethical Approval from NHS Ethics Committee via IRAS will still be sought. This has been discussed at length with NHS REC and Dr. Fiona Cowdell (supervisor). It has been agreed that this will be the process. It will go for Proportional Review.</b></p> <p style="text-align: center;">(If <b>No</b>, then please go to <b>question 2</b>)</p>

#### 2. FULL TITLE OF THE RESEARCH

Pilot study to investigate the quantitative effect of soapy water, tap water, Vaseline<sup>®</sup> and glycerine used singly and in combination on the hydration and water

loss on the skin of the outer lower legs of those with dry skin.

### 3. LAY SUMMARY OF THE RESEARCH

Pilot study to measure the effect of different substances on skin dryness and skin water loss.

### 4. INTRODUCTION (BACKGROUND AND LITERATURE REVIEW)

Skin provides a barrier which protects the body against physical agents and prevents the loss of body fluid. It prevents desiccation and death in a terrestrial environment (Feingold *et al.*2007). To enable this barrier to function the skin needs to be adequately moisturised and hydrated.

Dry skin (xerosis) on the legs affects 75% of those over 75 years of age in the developed world (Barco and Gimenez-Arnau (2008). The disease is caused by a breakdown in skin barrier function. This is much the same cause as a skin disease in Ethiopia called podoconiosis. This affects over 1 million people (Davey *et al.* 2007). Current treatment of podoconiosis in Ethiopia consists of washing the legs in soapy water, soaking in water with sodium hypochlorite added (making it equivalent to UK tap water) and the application of Vaseline®. The treatment is based on custom and practice.

Because both diseases have the same cause the pilot study will be undertaken in the UK on those with xerosis.

The pilot study will quantitatively measure the effect on the moisture content and the water loss from the skin of soapy water, UK tap water, 2% glycerine and Vaseline®. It will measure the effect of these used substances alone and in combination on the surface of dry skin of older people. Glycerine has been added to the study as it is known to hydrate the skin (Overgaard 1993. Pederson and Jemec 1999 and Orth and Appa 2000).

There are currently few studies on the effects of these products on dry skin when used singly and none when used in combination. The results of this pilot will inform a larger study which will be based in Ethiopia which aims at improving the management of podoconiosis.

Please provide a rationale, justification, and underlying principle for the research with supporting literature (maximum 300 words).

### 5. AIM(S) OF THE RESEARCH

This aim of the pilot study is to provide evidence on the quantitative effect of soapy water, tap water, glycerine 2% and Vaseline® on the hydration and the water loss of xerotic skin.

### 6. RESEARCH OBJECTIVES

To inform the experimental arm of a larger study on those with podoconiosis.

### 7. DURATION OF STUDY 6 days

7.1	What is the anticipated start date of the research? Mid/late April 2013
7.2	What is your expected completion date? Late April /early May 2013

## 8. DESIGN OF THE RESEARCH

1.1	Please state what research method you intend to use and justify why. Quantitative measures of skin moisturization and skin water loss using non-invasive probes which are placed on the surface of the skin.
1.2	What is the sample (description and size)? Please give rationale also where possible. 10 older people in a private care home. This is the number used in similar published studies and agreed with Dr Eric Gardiner, statistician, University of Hull.
1.3	How are the subjects going to be recruited and by whom? Identified initially by staff and owners of care home. At least 4 days before the start of the research potential participants will be given an information sheet which will be discussed with them by the principal researcher. They will be encouraged to ask questions. If they agree they will then sign the consent form
1.4	How are you proposing to analyse and interpret data? SPSS ANOVA
1.5	Please list the principle inclusion criteria (the most important first). Adults, Dry skin on legs (assessed on appearance and feel). Able to give informed consent. No dementia diagnosis. No leg ulcers or other skin disease on lower legs.
1.6	Please list the principle exclusion criteria (the most important) and explain why they have been excluded. Participants without dry skin on legs as this is a study of those with compromised skin. Unable to give informed consent or with a diagnosis of dementia as this would be unethical. With existing leg ulcers as this would make undertaking the study very difficult due to dressings on lower legs.
1.7	If applicable, what arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (e.g. translation, use of interpreters) For those with sight problems the study would be verbally explained if necessary. The participant information sheet and consent forms are in large font. There is currently no one in the home whose first language is not English. If participants were unable to understand and give informed consent they would not be part of the study.

9. **RESEARCH PROCEDURES (these include seeking consent, interviews, questionnaires that will be received by the research participants).** All participants will be given an introductory letter, information sheet and consent form. GPs will be informed if this is the participants wish. They will all have the research verbally explained and be encouraged to ask questions.

9.1 If applicable, please give details of all <b>CLINICAL INTERVENTION(S) and PROCEDURES(S)</b> that will be received by the research participants and complete the columns for each. If not applicable, circle N/A			
<b>How many interventions in total - 5 and a control site</b>			
Specify each intervention/procedure  All sites on lower leg on areas 5cm x 5 cm	How long will each take to complete? (i.e. hours)	Who will conduct the intervention/procedure All will be undertaken by principal researcher	Where will the intervention/procedure take place (i.e. location)  In a private care home who have given written consent for the study to

<p>Site 1. Control</p> <p>Site 2. Gauze wetted with 1½ mls soapy water applied and covered with cling film for <b>10 minutes</b></p> <p>Site 3. Tap water on gauze covered with cling film for <b>30 minutes</b></p> <p>Site 4. A thin film <i>Vaseline</i><sup>®</sup> (petroleum jelly) applied to the area at a rate of 2mg/cm<sup>2</sup>.</p> <p>Site 5. Gauze wetted with 1½ mls soapy water applied and covered with cling film for 10 minutes followed by 1½mls tap water on gauze covered with cling film for 30 followed by a thin film of <i>Vaseline</i><sup>®</sup> at a rate of 2mg/cm<sup>2</sup>. <b>Total 45 minutes</b></p> <p>Site 6. Gauze wetted with 1½ mls soapy water applied and covered with cling film for 10 minutes followed by 1½ mls tap water on gauze with 2 % glycerine added covered with cling film for 30 minutes, followed by a thin film of <i>Vaseline</i><sup>®</sup> (at a rate of 2mg/cm<sup>2</sup>). <b>Total 45 minutes.</b></p> <p>Measurements of the skin's water loss on each site on day 1 (before interventions) and day 6 (the day after completion of interventions). A total of 24 minutes for each participant for all measurements.</p>			take place on their premises
<p><b>9.2</b> Please give details of all <b>NON-CLINICAL INTERVENTION(S) and PROCEDURES(S)</b> that will be received by the research participants and complete the columns for each. If not applicable, circle N/A</p>			
<p><b>How many interventions in total</b></p>			
Specify each intervention/procedure	How long will each take to complete? (i.e. hours)	Who will conduct the intervention/procedure	Where will the intervention/procedure take place (i.e. location)
Explanation and discussion with each participant and answering questions	15 minutes on average	Principal investigator	Private Care home

**10. RISKS AND ETHICAL CONSIDERATIONS**

<p><b>10.1</b> Risk Limitations-Describe potential risks and hazard to research participants. Possible dry skin on intervention areas on lower leg</p>
<p><b>10.2</b> Specify precautions to avoid or limit these risks. Care staff will be advised to note any dry skin on legs after the study and treat with emollients</p>
<p><b>10.3</b> How long do you expect each research participants/patients/public/user/carer to be involved in the research in total? Max 6 hours</p>
<p><b>10.4</b> Describe any inconveniences to study participants, including limitations or restrictions to normal lifestyle. Participants to be available for 45 minutes daily for 5 days and for a maximum of 10 minutes on day 6 . Patient will be unable to take</p>

	an immersion bath for 5 days. As most residents in the home have a weekly bath this bath will be arranged before and after the study.
<b>10.5</b>	Describe any potential benefits of participation in research study subjects. Benefits are limited but may include extra attention during trial and possible change by home in skin care practices.
<b>10.6</b>	Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing, or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study? No <i>If Yes, please give details of procedures in place to deal with these issues:</i>
<b>10.7</b>	What are the potential risks for the researchers themselves? <i>(if any) None</i>

## 11. RECRUITMENT AND INFORMED CONSENT

<b>11.1</b>	How will potential participants, records, or samples be identified? Who will carry this out and what resources will be used? Potential participants will be identified by the home owners and care staff in the care home.
<b>11.2</b>	Will the identification of potential participants involve reviewing or screening personal information of patients, service users or any other person? No
<b>11.3</b>	How will potential participants be recruited, who will be approached and how much time will they be given to consider participation? Principal researcher will approach all potential participants who will have been identified by home owners and care staff. They will be given at least 4 days to consider their participation in the study.
<b>11.4</b>	What arrangements will you make for any unforeseen circumstance and what plans will you make to ensure participants receive any information that may become available during the course of the research that could be relevant to their continued participation? Nil envisaged but if any participant wishes to or is required to withdrawn for any reason during the study they will be able to without giving a reason and their normal care will not suffer in any way.

## 12. CONFIDENTIALITY AND DATA PROTECTION. Storage and use of personal data during the study

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

<b>12.1</b>	Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)? (Please highlight all that apply). <b>If any apply so as not breach confidentiality and to ensure that consent has been obtained, YOU MUST answer sections 12. 4 and 12.5.</b>
	Electronic transfer by magnetic or optical media, email or computer networks. <b>YES</b> but participants will be allocated a unique code number only known to the principal investigator so no participant could be identified.
	Sharing of personal data with other organisations <b>No</b>
	Export of personal data outside the EEC <b>No</b>
	Use of personal addresses, postcodes, faxes, emails or telephone numbers <b>No</b>
	Publication of direct quotations from respondents <b>No</b>

<p>Publication of data that might allow identification of individuals <b>No</b></p> <p>Use of audio/visual recording devices <b>No</b></p> <p>Any other method <b>No</b></p>
<p><b>12.2 How do you intend to store personal data? (please be specific)</b> On the principal investigators password protected home desk top which has anti-virus software which is only used by her.</p>
<p><b>12.3 Please describe the physical security arrangements for storage of personal data during the study including long-term arrangements for storage of research data after the study has ended and who will have control of and act as the custodian for the data generated by the study? (To ensure anonymity place state 'principal investigator' or another person assisting in the study).</b> Only the principal investigator will store coded non identifiable anonymised information. She is a registered nurse and bound by codes of confidentiality at all times.</p>
<p><b>12.4 How will you ensure the confidentiality of personal data?</b> <i>Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.</i> All participants will be given a unique code number only known to the principal researcher. All information stored will be anonymised.</p>
<p><b>12.5 How will you obtain consent from the participants?</b> Participants will be asked to sign the consent form 4 days after being given the Introductory Letter, the Information Form and after discussion of the study and the answering of any questions by the principal investigator.</p>
<p><b>12.5 Who will have access to participants' personal data during the study?</b> <i>Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.</i> Only the principal investigator</p>
<p><b>12.6 Where will the data generated by the research study be analysed and by whom?</b> By the principal investigator on SPSS on her desk top computer</p>
<p><b>12.7 Who will have control of and act as the custodian for the data generated by the study? (To ensure anonymity place state 'principal investigator' or another person assisting in the study).</b> Principal investigator only. A data management plan will be developed.</p>
<p><b>12.8 List the people and organisations with access to data.</b> Jill Brooks Principal Investigator, Anonymised data only would be accessible to Dr. Fiona Cowdell University of Hull, Prof Steven Ersser University of Hull, Prof Paul Matts, Procter and Gamble and Visiting Professor London University</p>
<p><b>12.9 How long will personal data be stored or accessed after the study has ended?</b> Only data containing participants code number will be stored for less than 3 months</p>
<p><b>12.10 For how long will you store raw research data?</b> Five years</p>
<p><b>12.11 Are all individuals/organisations with access to these data registered</b></p>

and compliant with the Data Protection Act 1998? YES

**13. HOST INSTITUTION e.g. who has indemnity for the study?**

Please indicate which institution(s) are to act as host for your study  
University of Hull

**14. STUDY SITE**

If applicable, please specify all NHS/University/other departments and services (e.g. service specialities, pharmacy, outpatients, intensive care) involved in any way with the procedures or subjects in the study. State whether formal permission has been granted from the head of each department/service.

None

Department/Organisation:

Sotwell Hill House Care Home

Permission granted : Yes

**15. Please list all appendices submitted with the proposal. Prior to submission, please ensure that all appendices are anonymous, i.e. consent forms, questionnaires, information sheets etc.**

Introduction letter, Information sheet, Consent form

**16. Please give your peer reviewer the checklist for reviewers form to complete, and provide a copy of their response with this proposal submission**

Name of Reviewer  
Fiona Cowdell

Position  
Senior Research Fellow FHSC

**Please submit this form electronically to Jeanette Gilchrist at [J.L.Gilchrist@hull.ac.uk](mailto:J.L.Gilchrist@hull.ac.uk)**

Thank you

## 8. PILOT CHECKLIST FOR REVIEWERS.



### FACULTY OF HEALTH AND SOCIAL CARE

#### (Checklist for Reviewers)

Name of Reviewer: Fiona Cowdell	
Position of Reviewer: Senior Research Fellow	
Contact Details of Reviewers: ext 3362 or email <a href="mailto:f.cowdell@hull.ac.uk">f.cowdell@hull.ac.uk</a>	
Title of study: Pilot study to investigate the quantitative effect of soapy water, tap water, Vaseline® and glycerine used singly and in combination on the hydration and water loss on the skin of the outer lower legs of those with dry skin.	
Date: 19 <sup>th</sup> March 2013	
Signature: Fiona Cowdell	
	Yes/No/Comments
1) Does the proposal clearly describe what the researcher intends to do.	Yes, this is a pilot study investigating the impact of cleansing and moisturising products in various combinations on hydration and water loss of skin.
2) Are methodology and methods used appropriate for addressing the research objective(s)/ question(s).	Yes, a sound quantitative approach has been devised and agreed with supervisors and statistician.
3) Is the sampling or selection of participants clearly described?	Yes, participants will be approached by home staff and then seen by researcher if they wish to take part.  Need to add something about how dry skin will be assessed for inclusion.
4) Is the proposed study feasible and can it be achieved within the timescale given by the researcher	Yes and the study will provide valuable information for the larger future RCT.
5) Does the participant Information provide enough information to allow participants to decide whether or not they wish to take part?	Letter to participants contains the essential information but would benefit from a neater layout.  PIS needs to add sections at beginning introducing research and advising of complaints procedure
6) If a participant information is used, does it address the following: a) The purpose of the study? (The background and aims of the study should be given here).	Need to add some of the information from the letter to PIS

<p>b) Explain, why they have been chosen? <i>(The researcher should explain how the participants were chosen and approximately how many other participants will be involved).</i></p> <p>c) Do I have to take part? <i>(It should be clear that taking part in the research is voluntary).</i></p> <p>d) What will happen if I take part? <i>(A clear explanation of what taking part in the proposed study will involve for the participant(s)).</i></p> <p>e) What is the intervention that is being tested? <i>(The participant(s) should be given an explanation of what question/ procedure/ intervention is being investigated).</i></p> <p>f) What are the possible disadvantages and risks of taking part? What are the possible benefits of taking part?</p> <p>g) Will my taking part in this study be kept confidential? <i>(Issues of confidentiality, anonymity, and privacy (including data protection) should be addressed).</i></p> <p>h) What will happen to the results of the research study? <i>(Participants should be clear about how the findings may be used; for example, for an educational award, publication, and/ or conference presentation).</i></p> <p>i) Are contact details for further information included?</p>	<p>As above</p> <p>Need to make this clearer</p> <p>Very clear explanation given</p> <p>Combination of products explained well, need to remove reference to swimming pool water</p> <p>Needs to be added</p> <p>No personal data will be collected; participants will be allocated a study number.</p> <p>Need to add more information</p> <p>Need to be added</p>
<p>7) If the researcher is carrying out the project at her/ his own place of work, has sufficient consideration been given to dual roles, for example service provider and researcher?</p>	<p>NA</p>

8) Does the researcher's proposal demonstrate that he/she has examined the ethical implication of the proposed study?	Yes
9) Does this proposal require NHS Research Ethics Committee review?	Yes, but it needs faculty REC approval before the PVC agrees university sign sponsorship which is required prior to NHS approval
10) Will the study involve accessing vulnerable groups? <i>(if yes; an enhanced CRB check is required for the researcher(s)).</i>	All participants will be competent, self-funding older people who are able to make informed decisions about participation. Jill is an experienced community nurse who regularly works with older people

## 9. APPROVAL FOR PILOT STUDY.



Ms Jill Brooks  
Faculty of Health & Social Care  
University of Hull

**FACULTY OF HEALTH  
AND SOCIAL CARE**  
T: 01482 464524  
E: [j.kelly@hull.ac.uk](mailto:j.kelly@hull.ac.uk)

**OUR REF 097**  
26 March 2013

Dear Jill

**Re: Pilot study to measure the effect of different substances on skin dryness**

Thank you for your swift and comprehensive responses regarding the above. Following these responses, I am delighted to be able give Chair's approval for the study.

May I wish you every success with your study.

Yours sincerely

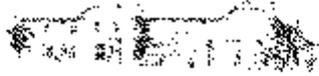
A handwritten signature in black ink that reads "Jc Kelly". The signature is written in a cursive style with a long horizontal stroke at the end.

Janet Kelly  
Chair, FHSC Research Ethics Committee

cc: file

10. CARE HOME OWNER CONSENT.

# Sotwell Hill House



Sotwell Hill House • Sotwell Hill • Sotwell • Wellingford • Oxon • OX10 3PS  
Tel - 01491 836 885 • Fax - 01491 839 385  
Website - [www.sotwellhillhouse.co.uk](http://www.sotwellhillhouse.co.uk)  
Email - [sotwellhillhouse@btinternet.com](mailto:sotwellhillhouse@btinternet.com)

18<sup>th</sup> January 2013

To whom it may concern

I give my consent for Jill Brooks from Hull University to undertake research for dry skin on the lower legs of our residents at Sotwell Hill House. The details of the research have been explained to me.

Yours sincerely

JOSEPHINE BUTTERFIELD  
Manager

Dear .....

Pilot study to measure the effect of different substances on skin dryness.

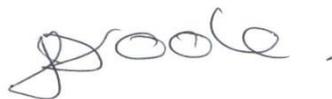
I am a student undertaking PhD level research at the University of Hull on the most effective treatment for dry skin which is a particular problem for older people.

You have been asked to take part in the study because you have this problem. Several others from your care home will also be asked to take part. Before you decide I would like you to understand what the study involves for you, why it is being done and what it would involve for you. I will go through the Patient Information Sheet with you and answer any questions you may have and explain anything that is unclear. You may talk to others about the study if you wish.

Please take time to decide whether or not you wish to take part.

It is up to you to decide if you wish to take part in the study. If you agree you will be asked to sign a consent form. You are free to withdraw from the study at any time without giving a reason. This will not affect the care you receive. Your care home has given permission for the trial to take place on their premises and if you wish your GP will be informed.

Yours sincerely

A handwritten signature in blue ink, appearing to read 'j brooks', enclosed within a thin blue rectangular border.

Jill Brooks. M.Phil., BA (Hons), RGN, DN, Dip Trop Nurs.,  
PhD student, University of Hull

### **Pilot study to measure the effect of different substances on skin dryness**

The purpose of the research is to find out the effect of soapy water, tap water, *Vaseline*<sup>®</sup>, and glycerine used alone and in combination on dry skin. Dry skin especially of the legs is a particular problem for older people. It often causes flaking and itching. The results of this study may be of benefit to you and others who have this and similar conditions. It will be used for the study of a skin condition affecting people in Ethiopia.

Ethical approval for the study has been obtained from the Ethics Committee of the University of Hull. This is a group of independent people who review research to protect the dignity, rights, safety and well-being of participants and researchers

If you decide to take part in the research I will visit you every day for 6 consecutive days. During this time you will not be able to get your legs wet.

For five mornings/afternoons I will apply different things to 5 small (2inch x 2 inch) areas of your lower legs. These will be:

1. Soapy water on a small piece of gauze covered with a dressing for 10 minutes.
2. Tap water on gauze covered with cling film for 30 minutes.
3. A thin layer of *Vaseline*<sup>®</sup>.
4. Soapy water for 10 minutes then tap water for 30 minutes and then a layer of *Vaseline*<sup>®</sup>.
5. Soapy water applied on gauze and covered with cling film for 10 minutes followed by 1½ mls tap water with added 2% glycerine on gauze covered with cling film

for 30 minutes, followed by a thin film of *Vaseline*<sup>®</sup>. Glycerine is naturally found in skin and has no side effects.

The areas will be marked by a dot in each corner with a water-proof marker. There will be a 6<sup>th</sup> area that will not be treated. It will be used as a comparison. The study will take about 45- 50 minutes a day.

The dryness of the skin on your legs will be measured before anything is applied to your legs and the day after the trial on day 6. The measurements will be taken with special meters which will be gently placed on the surface of your skin for a few minutes. It will not hurt or harm you. It will indicate the effects of the different substances on the dryness of your skin.

Your name and personal details will not be collected. The information collected by me will be kept on a computer and stored securely.

The anonymised results will be analysed and may be used in future studies or published.

If the skin in the areas is dry following the trial you may treat it with skin moisturizers. If you have any concerns during the study or require further information please contact me.

I will visit you after the trial to inform you of the results.

Yours sincerely

A handwritten signature in blue ink, appearing to read "jbrooks", enclosed in a light blue rectangular box.

Jill Brooks, M. Phil., BA (Hons), RGN, DN, Dip Trop Nurs.,  
PhD student, University of Hull

13. PILOT CONSENT FORM.

**CONSENT FORM**

3.4.13

Patient identification no \_\_\_\_\_

**Consent Form**

**Pilot study to measure the effect of different substances on skin dryness**

Thank you for considering taking part in this research study. If you have any questions please ask me before you decide if you wish to take part. You will be given a copy of this consent form to keep and refer to at any time.

*Please initial in box if you agree*

I confirm that I have read and understood the information sheet dated 3.4.13 version P1V1 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my care or legal rights being affected.

I understand that the anonymised data collected during the study may be looked at by individuals from the research team and may be published. I give permission for this to occur.

I understand that if I withdraw from the study the data collected up to that point may be destroyed if I wish.

I wish my GP to be informed of my participation in this study

I agree to take part in the above study.

Name of Participant (please print)

\_\_\_\_\_ Signed \_\_\_\_\_ Date \_\_\_\_\_

Name of Researcher \_\_\_\_\_ Signed \_\_\_\_\_ Date \_\_\_\_\_

Cc Participant, researcher and medical notes

14. PILOT GP LETTER.

Marlow House  
Brightwell cum Sotwell  
OX100RJ  
jb284@btinternet.com  
2.5.13

Dear Dr.....

This is to inform you that your patient .....who is a resident in Sotwell Hill House has agreed to take part in a research trial. She has asked me to inform you of this.

The research is a pilot and will investigate the effects of various substances on the dry skin on the lower legs. The substances are:

Glycerine 2%  
Soapy water  
Tap water  
*Vaseline*<sup>®</sup>

These will be applied singly and in combination to 5 areas each 5cm x 5cm on the lower outer leg. Quantitative measurements will be taken before and after their application with a corneometer and evaporimeter. These are probes which are placed on the skin and are non- invasive. The evaporimeter measures the skin's water loss and the corneometer the skin's moisture content.

The research will commence on 13.5.13 and will last 6 days. Participants will be informed of the outcome of the study. The results will inform a larger research study to commence later in the year in Ethiopia.

The University of Hull Ethics Committee has approved this research.

If you have any questions on this research do not hesitate to contact me

Yours Sincerely



Jill Brooks M.Phil, BA (Hons), RGN, Dip Trop. Nurs., PhD Student University of Hull

15. PILOT STUDY DATA COLLECTION FORMS.

**Participant number 1. Pre intervention (date) .....**

**Age..... Gender M/F.....**

**Interventions**

**Right lower leg sites.**

1. Upper- nil,
2. Mid - soapy water 10mins,
3. Lower - tap water 30 mins,

**Left lower leg sites.**

4. Upper - Vaseline®
5. Mid - soapy water 10mins, tap water 30 mins then Vaseline®
6. Lower - Soapy water 10 mins, tap water with 2% glycerine 30 mins then Vaseline®

Site - lower leg	1 right upper - nil	2 right mid	3 right lower	4 left upper	5 left mid	6 left lower
Skin moisture level						
	Mean=	Mean=	Mean=	Mean=	Mean=	Mean =
Skin water loss (grams of water per metre squared per hour g/m <sup>2</sup> /h)						

# PILOT STUDY

**Participant number 1 Post intervention (day 6).**

Date.....

**Age.....Gender M/F.....**

Site- lower leg	1 right upper	2 right mid	3 right lower	4 left upper	5 left mid	6 left lower
Skin moisture level						
	Mean=	Mean=	Mean=	Mean=	Mean=	Mean=
Skin water loss (grams of water per metre squared per hour g/m <sup>2</sup> /h)						

## 16. CONSORT (2010) CHECKLIST OF INFORMATION TO INCLUDE WHEN REPORTING A RANDOMISED TRIAL (Moher et al. 2010).

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract	1a	Identification as a randomised trial in the title	12
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts 45 65)	
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	18-89
	2b	Specific objectives or hypotheses	101, 115-116
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	116
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	118
	4b	Settings and locations where the data were collected	118
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	119-121
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	126-128
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	122-123
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
<b>Randomisation</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	122
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	122
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	124
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	124-125
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	121
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	133-137
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
<b>Results</b>			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	137
	13b	For each group, losses and exclusions after randomisation, together with reasons	137
Recruitment	14a	Dates defining the periods of recruitment and follow-up	137, 125-128
	14b	Why the trial ended or was stopped	125

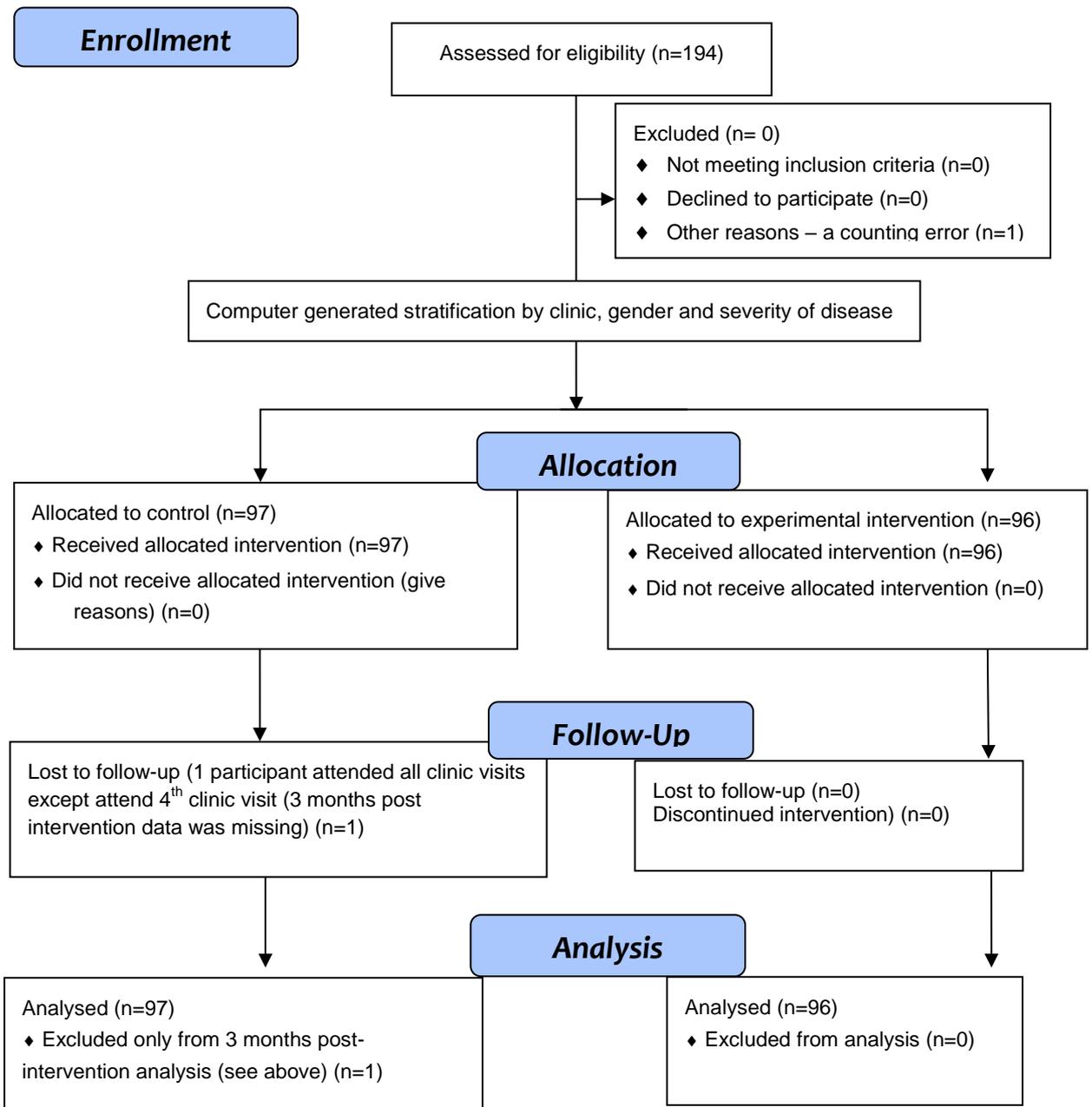
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	137-142
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	137
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	142-171
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	142-171
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms <sup>42</sup> )	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	196-198,202-203
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	204-205
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence. Other information	200
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	University of Hull
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11,15

We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials,<sup>40</sup> non-inferiority and equivalence trials,<sup>39</sup> non-pharmacological treatments,<sup>43</sup> herbal interventions,<sup>44</sup> and pragmatic trials.<sup>41</sup> Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).

16B. CONSORT FLOW DIAGRAM.



**CONSORT 2010 Flow Diagram**



## 17. E MAIL FROM DELFIN INSTRUMENTS.

7.8.13.

Dear Jill

Many thanks for your inquiry regarding Delfin's *MoistureMeterSC*<sup>®</sup> and *VapoMeter*<sup>®</sup>. If you're working on lymphoedema and TEWL, these instruments are ideal – and also the *MoistureMeterSC*<sup>®</sup> Compact which uses similar technology to the MMD but measures at a single 2mm depth below the surface.

A few comments on their use in hot climates.

In principle both *VapoMeter*<sup>®</sup> and *MoistureMeterSC*<sup>®</sup> Compact can also be used in hot environments (although they are originally intended to be used in a laboratory environment). However, we know that they have both been successfully used in field conditions. The basic rule is not to leave these instruments anywhere that's not good for your mobile phone. For example, on the dashboard of a car under direct sunlight. Also do not store the device where it may be exposed to moisture or excessive dust. We recommend charging the battery of *MoistureMeterSC*<sup>®</sup> Compact indoors and if possible in temperatures between 10 C and 30 C.

Some comment to measurement in these kinds of field conditions:

The *MoistureMeterSC*<sup>®</sup> Compact is a very good instrument for detecting skin disease induced local lymphedema and these measurements should not be affected so much by the hot climate and its effect on human physiology. However, still it might be wise to standardize measurements so that each measurement site is wiped off with a soft tissue paper to reduce a potential effect of residual sweat. Instead when measuring TEWL in hot environment, one should take into account the effect of physiological sweating since the *VapoMeter*<sup>®</sup> (as with all evaporation meters) measures both skin barrier related TEWL and sweat gland activity induced sweating.

Kind regards

Chris

Chris Budleigh, Director  
Delfin Technologies UK Limited  
2 Boxhill Station House  
Westhumble Street  
Dorking  
Surrey  
RH5 6BT  
Tel: 07801 520059

[chris.budleigh@delfintech.com](mailto:chris.budleigh@delfintech.com)

[www.delfintech.com](http://www.delfintech.com)

18. RESEARCH ETHICS APPLICATION.



FACULTY OF HEALTH AND SOCIAL CARE  
RESEARCH ETHICS COMMITTEE PROPOSAL FORM  
(FORM A)

REF NO.....DATE OF MEETING.....

(Office use only)

<b>1) SUBJECT INVOLVEMENT (see guidance notes)</b> Does the research involve ANY patients in a NHS or Social Services environment (clinical or non-clinical)?	
No involvement of NHS as research is in Ethiopia	<b>NO</b>  a) If <b>No</b> , then once FHSC Research Ethics Committee have provided you with written confirmation that ethical approval has been granted, you are able to proceed with your research study. b) Please go to <b>question 2.</b>
<b>2) TITLE OF STUDY</b> <u>An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.</u>	

<b>3) INVESTIGATOR(S)</b>  Name: Jill Brooks  Email address: jb284@btinternet.com  Contact telephone number: 01491 839044 Mob – 07917 682005
-------------------------------------------------------------------------------------------------------------------------------------------------------------------

#### 4) STUDENT INVESTIGATOR (IF APPLICABLE)

Name:

Email address:

Contact telephone number:

#### 5) NAME OF PEER REVIEWER (N.B If a student, this MUST be a different person from your supervisor(s)) **A completed Peer Review form MUST be submitted with all applications**

Name: Tim Alexander

Position: Research Tutor, University of Hull

Email address: [t.alexander@hull.ac.uk](mailto:t.alexander@hull.ac.uk)

Contact telephone number: 01482 464030

#### 6) LAY SUMMARY OF THE RESEARCH

Please provide a brief summary of the research (maximum 200 words) using language that can easily understood by a lay reviewer. If necessary, please provide a glossary of terms.

A randomized control trial to measure the effects of a skin care intervention on skin health and the disease related quality of life of those in Ethiopia with podoconiosis. Podoconiosis is a skin disease which causes severe swelling of the legs.

#### 7) INTRODUCTION (BACKGROUND AND LITERATURE REVIEW)

Please provide a rationale, justification, and underlying principle for the research with supporting literature (maximum 300 words).

Podoconiosis is an incurable but treatable skin disease occurring in those walking barefoot on volcanic soil. It occurs in ten countries including Ethiopia where 1 million have the disease and 18% of the population are at risk (Davey *et al.* 2007). Soil silica (like small shards of glass) and pathogens enter cracks in the foot due to dry skin and trauma causing an inflammatory reaction. This leads to lymphoedema with gross swelling of the feet and legs. Patients are stigmatized and unable to marry. Podoconiosis does not improve without intervention (Sikorski 2010, Rawlings and Matts 2004). The two NGOs working with podoconiosis patients in Ethiopia are the Action on Podoconiosis Association (APA) and Mossy Foot. Their current treatment is based on custom and practice consisting of washing the feet/legs daily with soap, soaking the legs in non-drinkable water with added weak bleach and applying *Vaseline*<sup>®</sup>. In one study (n= 27) this has been shown to reduce inflammation and swelling over one year (Sikorski 2010) although anecdotal evidence suggests this may be quicker. Legs/feet may return to normal size. My UK pilot study used this regime minus the bleach (UK tap water already contains bleach) over 5 days on those with another inflammatory skin

disease. This regime was compared to the same regime with 2% glycerine added. Previous studies have shown that glycerine hydrates skin, improves skin barrier function, improves skin mechanical properties, and has antimicrobial properties and no detrimental effects (Appa and Orth 1997 and Fluhr *et al.* 2008).

In my pilot study the glycerine regime had clinically significant positive effects on skin condition. Skin water loss reduced ( $p=0.071$ ) and skin moisture increased ( $p=0.006$ ), thus improving skin barrier function.

Disease related quality of life (DLQI) will be measured with the dermatology life quality index. The Amharic version (national Ethiopian language) is available and was used in a study at podoconiosis outreach clinics (Henok and Davey 2008).

This study will compare the effects on skin of the current treatment compared with the glycerine treatment over 3-6 months. The Amharic DLQI will be used to measure changes over time.

## 8) AIM(S) OF THE RESEARCH

To assess the impact of an evidence-based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.

## 9) RESEARCH OBJECTIVES

1. To review the current skin care intervention used on the feet and legs of those with podoconiosis in Ethiopia (as a baseline for resource-poor a pragmatic intervention).
2. To evaluate the effectiveness of an evidence-based skin care intervention in terms of changes in skin barrier function in the affected area and disease related quality of life.

## 10) DURATION OF STUDY

a) What is the anticipated start date of the research? **Late January/early Feb 2014**

b) What is your expected completion date? **Late July/August 2014**

## 11) DESIGN OF THE RESEARCH

- a) Please state what research method you intend to use and justify why. A randomised control trial (RCT) will be used. Participants will be randomly assigned to the control or experimental arm of the study. An RCT is considered to be the gold standard of a clinical trial. It will test the efficacy of the glycerine 2% regime against the current regime. Measures of skin barrier function over time have never been previously undertaken in those with podoconiosis. Only one study has been undertaken on changes in leg circumference. This was over 12 months

(Sikorski, Ashine et al. 2010). No other pre and post studies were found. No pre and post measures such as changes in leg and foot circumference, the stage of podoconiosis, changes in DLQI have been undertaken over 3-6 months.

**b)** What is the sample (description and size)? Please give rationale also where possible.

Adult patients with podoconiosis attending APA outreach clinics.

Based on the results of the pilot study for moisture level for the two treatments soapy wash +water soak +*Vaseline*<sup>®</sup> and soapy wash + 2% glycerine soak +*Vaseline* a mean difference in moisture level of 4.81 is expected after three months of treatment. The within-group standard deviation is expected to be around 3.93, leading to an expected effect size of around 1.23. To detect this effect size with 80% using a two-sided t-test with a 5% significance level, 24 participants are required, divided equally between the two treatment groups. It is expected that increased power will be achieved by using the baseline moisture levels as a covariate in an analysis of covariance.

Based on the results of the pilot study for TEWL for the two treatments soapy wash +water soak +*Vaseline*<sup>®</sup> and the soapy wash + 2% glycerine soak +*Vaseline*<sup>®</sup> a mean difference in TEWL of 1.05 grams squared per hour is expected after three months of treatment. The within-group standard deviation is expected to be around 1.47, leading to an expected effect size of around 0.72. To detect this effect size with 80% using a two-sided t-test with a 5% significance level, 64 participants are required, divided equally between the two treatment groups. It is expected that increased power will be achieved by using the baseline moisture levels as a covariate in an analysis of covariance.

**c)** How are the subjects going to be recruited and by whom?

Subjects will be recruited from two of the Action on Podoconiosis (APA) outreach clinics. The board of APA and the nurses and social workers (SW) in these clinics are aware of the research. It has been discussed with them by the principal investigator. Before the study the social worker in each clinic will visit remote villages, schools and village elders in the surrounding areas to inform them about the clinic to increase numbers attending for the first time. New patients coming to each clinic will be screened by the nurse/SW to ensure they fulfil the inclusion and exclusion criteria Over the past year 413 new patients have attended one of the clinics and 396 the other (approx. 30 a month). The nurse/SW will read the study information sheet to possible participants in their local language. They will be encouraged to ask questions. The consent form will then be read out to the possible participants in their local language by the nurse/SW.

**d)** How are you proposing to analyse and interpret data?

SPSS v 20 will be used. ANOVA, analysis of covariance, box plots, and T tests will be used to analyse data as advised by Eric Gardiner, Faculty Statistician.

**e)** Please list the principle inclusion criteria (the most important first).

1. Patients in Ethiopia with a diagnosis of podoconiosis. The definition of this

is: - those living over 1000 feet above sea level with above 1,000mm rain annually, with foot or leg oedema, with sensation in their feet and no hand involvement (Price and Bailey 1984, Davey 2007). A lack of sensation in the feet and/or hands would be an indication of leprosy. The diagnosis will be determined by the nurses and social workers at the outreach clinics.  
 2. Patients who are able to understand instructions and give informed consent. This will be determined by the nurses and social workers at the outreach clinics.

**f)** Please list the principle exclusion criteria (the most important) and explain why they have been excluded.

1. Patients not diagnosed with podoconiosis as determined by nurses /social workers at the outreach clinics. This is because the skin and quality of life of those with podoconiosis is the focus of the research.
2. Patients who are unable to understand instructions or give informed consent as determined by nurses at the outreach clinics. This is because it would be unethical to include in the study those unable to understand instruction or give consent.

**g)** If applicable, what arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs? (*e.g. translation, use of interpreters*) As the majority of potential participants are illiterate the nurse and the social worker based at each clinic speak the local language (and English) and will read out to possible participants the information sheet and consent information.

**12) RESEARCH PROCEDURES** (these include seeking consent, interviews, questionnaires that will be received by the research participants).

If applicable, please give details of all **CLINICAL INTERVENTION(S)** and **PROCEDURES(S)** that will be received by the research participants and complete the columns for each. If not applicable, write N/A

**How many interventions in total – 3 new interventions**

Specify each intervention/procedure	How long will each take to complete? i.e. hours)	Who will conduct the intervention/procedure?	Who will conduct the intervention/procedure?
<b>Measure skin moisture levels and skin water loss with a <i>MoistureMeterSC</i><sup>®</sup> and a <i>VapoMeter</i><sup>®</sup>. These are non-invasive probes which are placed on the surface of the skin for 4 – 10 seconds. They have been commonly used</b>	<b>15 minutes at each monthly clinic</b>	<b>Nurse /social worker following instruction and observation from principal investigator</b>	

<p>by dermatologists and skin researchers for many years. They and do not require calibration and have been tested in the Ethiopian climate.</p> <p>Normal practice will continue but in the experimental group 2% glycerine will be added to the foot/leg water soak.</p>	<p>2 extra minutes daily</p>	<p>The nurse/social worker will demonstrate to participants at monthly clinic visits how to measure the glycerine. Then patients will be encouraged to do this daily at home.</p>	
<p>Please give details of all <b>NON-CLINICAL INTERVENTION(S)</b> and <b>PROCEDURES(S)</b> that will be received by the research participants and complete the columns for each. If not applicable, write N/A</p>			
<p style="text-align: center;"><b>How many interventions in total</b></p>			
<p>Specify each intervention/procedure</p>	<p>How long will each take to complete? i.e. hours)</p>	<p>Who will conduct the intervention/procedure</p>	<p>Who will conduct the intervention/procedure</p>
<p><b>Collection of data at monthly clinic visits. Most of the data is already collected by the clinics. The extra data will be:-</b></p> <ol style="list-style-type: none"> <li><b>1. Foot circumference</b></li> <li><b>2. Number of wounds on leg/foot</b></li> <li><b>3. Numbers of days lost in previous month due to leg pain</b></li> <li><b>4. Type of shoes worn in last week.</b></li> <li><b>5. Amharic</b></li> </ol>	<p><b>10 minutes</b></p>	<p><b>Nurse/social worker</b></p>	

Dermatology of Life Quality Index			
<b>13) RISKS AND ETHICAL CONSIDERATIONS</b>			
<p>a) Risk Limitations - Describe potential risks and hazard to research participants.  <b>None</b>  <b>The nurse /SW will ensure that all participants understand the study and consent to taking part.</b></p>			
<p>b) Specify precautions to avoid or limit these risks</p>			
<p>c) How long do you expect each research participants/patients/public/user/carer to be involved in the research in total? <b>3 months (baseline visit and 3 consecutive clinic visits).</b></p>			
<p>d) Describe any inconveniences to study participants, including limitations or restrictions to normal lifestyle.  <b>Patients attending the clinics already spend time daily washing and soaking their legs and applying Vaseline®, They visit clinics monthly to obtain supplies of bleach (sodium hypochlorite), soap, Whitfield's ointment and Vaseline®. This is the only method currently of improving their disease. The time spent on these activities would be the same for patients in both arms of the study since only glycerine is added to the soaking water of those in the experimental group.</b></p>			
<p>e) Describe any potential benefits of participation in research study subjects  <b>Normal looking skin on legs. Normal size legs/feet. Improved quality of life. Less leg/foot infections. Less time in bed not working as a result of infections and pain in legs. From the pilot it is expected that improvements will be greater and quicker in the experimental group compared to the control group.</b>  <b>If the study shows a significant positive effect this treatment will be provided for all patients post trial.</b></p>			
<p>f) Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing, or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?  <b>NO</b>  <i>If Yes, please give details of procedures in place to deal with these issues:</i></p>			
<p>g) What are the potential risks for the researchers themselves? <b>None. The principal investigator will be at the clinics in Ethiopia for 2 weeks at the beginning of the study observing practice, ensuring that new procedures are properly followed and data is collected correctly. PI will visit after 4/6 weeks of starting data collection to ensure correct practice and form completion.</b></p>			
<b>14) RECRUITMENT AND INFORMED CONSENT</b>			

a) How will potential participants, records, or samples be identified? Who will carry this out and what resources will be used?  
**Participants will be recruited by the social worker and nurse at the two clinics from new patients attending. The nurse and social worker at each clinic speak English and the local language.**

b) Will the identification of potential participants involve reviewing or screening personal information of patients, service users or any other person? **Clinic staff will identify patients; the research team will not have access to personal data.**

c) How will potential participants be recruited, who will be approached and how much time will they be given to consider participation?  
**They will be recruited from new patients attending the outreach clinics by the social worker and nurse at the clinic. The participant information sheet will be read to them in their local language and they will be encouraged to ask questions. They will be given 1 hour to consider their involvement with the study and sign the consent form. A random number list will be generated and sealed envelopes produced which will be opened once the patient is entered into the trial.**

Patients walk over rough ground barefoot with their enlarged feet and legs for many kilometres (up to 70) to attend clinics. The clinics are in very remote areas. They come to the clinics for education on podoconiosis, treatment and to collect the supplies which enable them to undertake daily treatment at home.

If they were asked to consider being part of the research for longer than this it would make their day with a long journey to and from the clinic even longer. So they would not enter the research.

If they were asked to consider and return to clinic another day they very probably would not enter the research or never return.

d) What arrangements will you make for any unforeseen circumstance and what plans will you make to ensure participants receive any information that may become available during the course of the research that could be relevant to their continued participation?

**Any new information will be considered and if any of it is deemed detrimental to the participants the whole study would be reconsidered.**

**There will be back-up probes for measuring skin condition in the event of the devices proving faulty. The probes have already been tested in Ethiopia.**

**15)CONFIDENTIALITY AND DATA PROTECTION.** Storage and use of personal data during the study **MUST** be the **Data Protection Act 1998**. In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

a) How do you intend to store personal data? (please be specific)  
**A master list of names and ID numbers will be held locally. The research team will not record any personal data. Participants will each be given a unique code number by clinic staff that will hold a master list which will be kept in a locked cupboard in a locked**

<b>building with a security guard on site 24 hours a day.</b>	
<p>b) Describe the physical security arrangements for the storage of personal data during the study including long-term arrangements for storage of research data after the study has ended.  <b>No personal data will be recorded on data collection forms as each participant will be assigned a unique participation code. The master list linking participant names to participation code will be stored as in 15 a).</b></p>	
<p>c) How will you ensure the confidentiality of personal data? <i>Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data</i>  <b>As above</b></p>	
<p>d) How will you obtain consent form the participants?  <b>The large majority of the participants will be illiterate so the nurse/social worker will read the information sheets to them and answer any questions. Participants will be asked to sign with signature, a mark or cross on the consent form if they are willing to partake in the study.</b></p>	
<p>e) Who will have access to participants' personal data during the study?  <i>Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.</i> <b>None recorded on the data collection form. Only the nurse and SW at the clinics will be aware of participant's name.</b></p>	
<p>f) Where will the data generated by the research study be analysed and by whom? <b>In the UK by the principal researcher stored on SPSS on a personal desk top computer which has antivirus software and is password protected.</b></p>	
<p>g) Who will have control of and act as the custodian for the data generated by the study?  <b>The principal researcher. A data management plan has been completed.</b></p>	
<p>h) List the people and organisations with access to data  <b>Nurse and social worker at the APA clinics in Ethiopia</b></p> <p><b>Those below will have access only to anonymised data:-</b></p> <p><b>Jill Brooks, Principal researcher</b>  <b>Prof Steve Errser, University of Hull; Dr Fiona Cowdell, University of Hull and Dr Paul Matts, Research fellow, Procter and Gamble, Visiting Professor London University</b>  <b>Eric Gardiner, Faculty Statistician, University of Hull</b></p>	
<p>i) How long will personal data be stored or accessed after the study has ended? <b>No personal data stored but anonymised data stored for 5 years</b></p>	
<b>16)STUDY SITE</b>	
If applicable, please specify all NHS/University/other departments and services (e.g. service	

specialities, pharmacy, outpatients, intensive care) involved in any way with the procedures or subjects in the study. State whether formal permission has been granted from the head of each department/service.

<b>Department/Organisation:</b>	<b>Permission granted and costs agreed by:</b>
<b>Action on Podoconiosis Association, Ethiopia.</b>	<b>Permission granted for the study at their outreach clinics. No extra costs</b>

**17) Appendices** i.e. consent forms, questionnaires, information sheets etc.  
**Please list all appendices submitted with the proposal**

- Participant information sheet**
- Data collection form**
- Consent form**
- Data management form**
- Peer review form**

**Please submit this form as ONE file** i.e. attach consent forms, questionnaires, information sheets, peer review form, Data Management Form and send to:

[fhsc-ethicssubmissions@hull.ac.uk](mailto:fhsc-ethicssubmissions@hull.ac.uk)

**Thank you**

19. REVIEWER CHECKLIST FOR RESEARCH ETHICS APPLICATION.



**FACULTY OF HEALTH AND SOCIAL CARE (Checklist for Reviewers)**

<p>Name of Reviewer: Dr Tim Alexander</p> <p>Position of Reviewer: Research co-ordinator</p> <p>Contact Details of Reviewers: t.alexander@hull.ac.uk</p> <p>Title of study <b>An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.</b></p> <p>Date: 11/11/2013</p> <p>Signature:</p>	
	Yes/No/Comments
11) Does the proposal clearly describe what the researcher intends to do.	Yes
12) Are methodology and methods used appropriate for addressing the research objective(s)/ question(s)?	Yes
13) Is the sampling or selection of participants clearly described?	Yes
14) Is the proposed study feasible and can it be achieved within the timescale given by the researcher?	Yes
15) Does the participant Information provide enough information to allow participants to decide whether or not they wish to take part?	Yes
16) If a participant information	Yes to all

is used, does it address the following:

- a) The purpose of the study?  
*(The background and aims of the study should be given here).*
  
- j) Explain, why they have been chosen?  
*(The researcher should explain how the participants were chosen and approximately how many other participants will be involved).*
  
- k) Do I have to take part?  
*(It should be clear that taking part in the research is voluntary).*
  
- l) What will happen if I take part?  
*(A clear explanation of what taking part in the proposed study will involve for the participant(s)).*
  
- m) What is the intervention that is being tested?  
*(The participant(s) should be given an explanation of what question/ procedure/ intervention is being investigated).*
  
- n) What are the possible disadvantages and risks of taking part? What are the possible benefits of taking part?
  
- o) Will my taking part in this study be kept confidential?  
*(Issues of confidentiality, anonymity, and privacy (including data protection) should be addressed).*
  
- p) What will happen to the results of the research study?  
*(Participants should be clear about how the findings may be used; for example, for an educational award, publication, and/ or conference presentation).*
  
- q) Are contact details for further information included?

17) If the researcher is carrying out the project at her/ his own place of work, has sufficient consideration been given to dual roles, for example service provider and researcher?	<b>N/A</b>		
18) Does the researcher's proposal demonstrate that he/she has examined the ethical implication of the proposed study?	<b>Yes</b>		
19) Does this proposal require NHS Research Ethics Committee review?	<b>No although any approval required from the clinic in Ethiopia should be checked</b>		
20) Will the study involve accessing vulnerable groups? <i>(If yes; an enhanced CRB check is required for the researcher(s)).</i>	<b>No</b>		

## 20. RESEARCH ETHICS APPROVAL.



Ms Jill Brooks  
Faculty of Health and Social Care  
University of Hull

**FACULTY OF HEALTH AND  
SOCIAL CARE**  
T: 01482 464680  
E: [j.dyson@hull.ac.uk](mailto:j.dyson@hull.ac.uk)

**OUR REF: 125**  
29 November 2013

Dear Jill

**Re: An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with Podoconiosis**

Thank you for your detailed responses to the Faculty Ethics Committee letter dated 28 November 2013.

Given the information you have provided, I am able to give Chair's approval for your study as per the Committee's Terms of Reference.

I wish you every success with your research.

Yours sincerely

Dr Judith Dyson  
Chair, Research Ethics Committee

cc: file/supervisors



## Faculty of Health & Social Care

# Data Management Plan

(NB: This form should be completed at the start of all projects where data are not being stored in alternative sources, eg Clinical Trial Data held in the NHS). **Shaded areas are considered essential.**

<b>Date</b>	<b>9/11/13</b>
<b>Researcher(s)</b>	<b>Jill Brooks</b>
<b>Project title</b>	<b>An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.</b>
<b>Brief description</b>	<b>An evaluation of the effect on skin barrier function and quality of life of a research based skin management regime on those with podoconiosis living in Ethiopia. The study will be a randomized control trial comparing current practice with the experimental intervention.</b>

For detailed, updated explanations of the various parts of the document that require completion, please refer to the accompanying Appendices.

## Contents

Section 1: Project Information.....	3
Section 2: Data, Materials, Resource Collection Information .....	4
Section 3: Ethics, Intellectual Property, Citation.....	5
Section 4: Access and Use of Information .....	6
Section 5: Storage and Backup of Data.....	7
Section 6: Archiving and Future Proofing of Information .....	8
Section 7: Resourcing of Data Management .....	9
Section 8: Review of Data Management process .....	10
Section 9: Statements and Personnel Details .....	11
9.1 Statement of Agreement .....	11
9.2 Expertise of Researchers *** .....	13
Section 10: Appendices .....	15
10.1 Specific Help with completing the Plan .....	15
10.2 Notes.....	16
10.3 Relevant Contacts.....	22

## Section 1: Project Information

<p><b>1.1. An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.</b></p> <p>1.1</p>
<p>1.2 Project duration: from late January/February 2014 to late July/ August 2014 depending on numbers recruited</p>
<p>Partners (if applicable)</p> <p>This is part of a PhD study which involves working with 3 supervisors Prof. S Ersser, Dr. Fiona Cowdell, Dr. Paul Matts</p> <p>1.3</p>
<p>Brief description</p> <p>An evaluation of the effect on skin barrier function and quality of life of a skin management regime on those with podoconiosis living in Ethiopia. The control group will continue with their current practice and the experimental group will be subject to an evidence based skin care intervention.</p>
<p>1.4 Faculty or University requirements for data management none</p>
<p>1.6 Funding body(ies)</p> <p>PhD funding by Procter and Gamble</p>
<p>1.7 Budget (estimate if necessary)</p> <p>It is customary in Ethiopia to pay those who collect data. In this instance the nurse/ social worker in each clinic will be paid £40 when they have recruited a total of 100 participants to each arm of the study. Total £160. A local student at Sodo University who is currently undertaking a Master's in Public Health and known to the principal investigator and the Podoconiosis Association who run the clinics will be paid £100 for checking the data collection and recruitment onto the study at each clinic. Total £100</p> <p>The grand total £260 will be paid from the principal investigators PhD expenses.</p>

No funding is required for data storage.

1.8 Funding body requirements for data management

Funding body agreed with this DMP

## Section 2: Data, Materials, Resource Collection Information

2.1 Brief description of data sources

Paper data collection forms completed by nurse/ social worker from patients attending two outreach clinics in Ethiopia.

2.2 Data collection process

Data collected on the data collection forms by the nurse /social worker at clinics

2.3 Will data be available in electronic format (if so then state format(s))?

Data will be collected manually by the PI and be entered onto SPSS v20 on her computer at home in the UK

2.4 Will the data be available in hard copy (if so then state format(s))?

Data collection forms will be in paper copy

2.5 Will the data stand alone and be comprehensible to a third party or be accompanied by explanatory documentation?

Yes it will stand alone and be comprehensible to a 3<sup>rd</sup> party

2.6 Describe quality assurance process for data management

Data collected monthly from participants at 2 out-reach clinics by either the nurse or social worker. The principal investigator will teach them how to complete data forms and observe collection for 1 week in each clinic. The PI will manually collect the forms on visits to Ethiopia and bring them back to the UK for entry on her computer at home.

A local university public health master's student will observe data collection and ensure forms are completed adequately. PI will visit after 4/6 weeks of starting data collection to ensure correct completion.

Completed data collection forms will be kept locked in a cupboard in APA premises which are locked. There is a security guard on the premises 24 hours a day.

Data may continue to be collected after 3 months dependent on recruitment numbers



### **Section 3: Ethics, Intellectual Property**

3.1 How have the ethical aspects of data storage and subsequent access been addressed?
All patients will have a unique code number. All data collected will be anonymised.  Only the PI will enter the data onto SPSS
3.2 Will the data comply with relevant legislation such as Data Protection Act, Copyright and Intellectual Property?
Yes
3.3 If several partners are involved how will compliance with 3.2 are assured?
This is a PhD study so PI together with supervisors will ensure compliance.

### **Section 4: Access and Use of Information**

4.1 Are you required, and with whom, to share the data subsequent to completion of the project?
Supervisors: Prof. Steve Ersser, Dr. Fiona Cowdell, University of Hull and Dr Paul Matts, Research Fellow, Procter and Gamble, UK.  Dr. Eric Gardiner, University of Hull statistician
4.2 If 'yes' to 4.1, in what format will data be shared?
Anonymised
4.3 Will the data have to be stored for a specific period (if so, how long)?
As required by the University of Hull for 5 years post study.
4.4 Who may need to have access to the data?
PI, statistician, supervisors
4.5 How do you anticipate the data being used subsequent to the project?
It will be analysed to inform the research project and this analysis will be used in subsequent publications.

## Section 5: Storage and Backup of Data

5.1 Where and how will the data be stored <u>during the lifespan of the project?</u>
On a home computer which has antivirus software and is pass word protected. This is because the PI is based in the south of the UK at a distance from the University of Hull.
5.2 Where and how will the data be stored <u>on completion of the project?</u>
As above
5.3 What provision is being made for backup of the data?
Back up computer systems are in situ
5.4 Will different version of the data be stored?
no

## Section 6: Archiving and Future Proofing of Information

6.1 What is the long-term strategy for storage and availability of the data?
Kept on PI's home computer for time period required by University of Hull i.e. 5 years after submission of PHD
6.2 Will the information be kept after the life of the project, for how long and in what format?
Kept on home computer for time period required by University of Hull 5 years after submission of PHD.
6.3 If the data include confidential or sensitive information, how will these data be managed?
No confidential or sensitive information will be recorded
6.4 If meta data or explanatory information is to be stored, how will this be linked to the data?
NA
6.5 How will the data be cited?

NA

## Section 7: Resourcing of Data Management

7.1 List the specific staff that will have access to the data and denote who will have the responsibility for data management.

Jill Brooks, Principal Investigator - responsible

7.2 How will data management be funded?

As part of PhD funding

7.3 How will data storage be funded?

As part of PhD funding

## Section 8: Review of Data Management process

8.1 How will the data management plan be adhered to?

Assessment of progress by PhD supervisors

8.2 Who will review the data management plan?

PhD supervisors

## Section 9: Statements and Personnel Details

### 9.1 Statement of agreement

I/we agree to the specific elements of the plan as outlined:

#### Principal investigator

Title	Mrs
Designation	PhD Student, University of Hull, Faculty of Health and Social Care
Name	

	Jill Brooks
Date	9.11.13
Signature	Jill Brooks

### **Researcher**

Title	
Designation	
Name	
Date	
Signature	

### **9.2 Expertise of Researchers**

Title	
Name	
Contact Details	
Expertise	

## **Section 10: Appendices**

### **10.1 Specific Help with completing the Plan**

In certain instances, specific guidance may be required in order to complete this Data Management Plan. Assistance should be sought by following the flow chart below:

Escalate the process by requesting assistance from the Departmental Head of Research. Typically this will entail contacting the Data Manager, IT Services and/or Library Services. Specific assistance may be available through the Research Office as well.

## **10.2 Notes**

These notes refer to the specified sections and subsections in this document. Any areas not addressed may be referred to the project lead, supervisor, or the Head of Research. Technical issues may be addressed to the HDMP development team in the first instance.

### **Front Cover**

Details are required to ensure the correct future referencing, storage and archiving of the Data Management Plan. There will be strict adherence to applicable law, including the Data Protection Act; this information will not be made available outside of the specific remit of the Faculty of Health and Social Care of the University of Hull.

### **Section 1: Project Information**

- 1.1 No specific guidance available
- 1.2 No specific guidance available
- 1.3 Required for funded projects – this refers to organisations other than the University of Hull
- 1.4 If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text.
- 1.5 State what local requirements are in place – details from Head of Research
- 1.6 Details may be requested from the project Supervisor, or the Head of Research.
- 1.7 Applies specifically to funded projects. If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text.
- 1.8 Applies specifically to funded projects. If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text. Details may be requested from the project Supervisor, or the Head of Research.

## Section 2: Data, Materials, Resource Collection Information

- 1.1 If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text. NOTE: details may change as the project evolves; provide a best estimate.
- 2.2 If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text.
- 2.3 It is vital that there is a clear understanding of exactly which data types are being discussed in order to plan for future storage, accessibility and integrity. Example data types and formats are available at <http://en.wikipedia.org/wiki/Listoffileformats>.
- 2.4 A great deal of non-digital data may need to be stored securely and/or archived. Various examples of this type of data are:
  - Documents: Printed digital, Original artefact, , etc.
  - Images: Photographs (size, print type, age), posters, etc.
  - Artefacts: Physical model (scale/non-scale, size, availability), archaeological, etc.
  - Film: 8/16/32mm, Video, microfilm, negative, etc.
  - Other: Live performance, logical model, etc.
- 2.5 “Standalone” implies a provided information resource that requires no further explanation and may be used “as is” without additional resource. Accompanied implies information that is informed by accompanying documentation or resource(s) which help to understand the resource. For example, a database may need to be accompanied by a “metadata” informative document which explains the purpose, use of specific fields, and instructions for utilisation. Details may be requested from the project Supervisor, or the Head of Research.
- 2.6 Quality Assurance/Management in this context refers to the concise provision of a breakdown of what will be done to ensure that the project’s progress will be monitored for accuracy, quality of work or research, and timely delivery at regular intervals. Typically, this would be the remit of the Research Supervisor, the Project Lead, or the Head of Department. Details may be requested from the project Supervisor, or the Head of Research.

## Section 3: Ethics, Intellectual Property, Citation

- 3.1 If your research has an impact on the welfare, confidentiality or economic status of any individual or corporate group, this should be clearly stated. If necessary, further information may be provided on an attached, clearly labelled **typed** or **printed** sheet. For online forms, the space will automatically be increased to accommodate extra text. **NOTE:** details may change as the project evolves; provide a best estimate.
- 3.2 It is vital to comply with applicable law. Provide a brief outline of how relevant legislation and regulations will be complied with where appropriate. Where there is any doubt, the first line of contact is the project Supervisor, or the Head of Research.
- 3.3 See note 3.2 above. Partners in the project must be held to the same legal and regulatory standards. Partners are also protected by applicable law and may avail themselves of the prospect of legal recourse in the event of any perceived illegality or infringement by any party. This applies to all participants effecting or affected by the research project. Where there is any doubt, the first line of contact is the project Supervisor, or the Head of Research.

#### **Section 4: Access and Use of Information**

- 4.1 Sharing data, i.e. making it publically available, may be a requirement of a funding bid, or of a University research project (e.g. Doctoral thesis or research project). Details may be requested from the project Supervisor, or the Head of Research.
- 4.2 Provide details of how you intend to share your data (if relevant). This may include several options, such as an online accessible dataset or database, or online images. It could also be in the form of a paper based document or set of documents. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 4.3 If your data are sensitive (e.g. not suitable for general access until you have completed, or contains personal data or information) you may need to keep the data secure until you are ready to publish – if at all. Similarly, if the project funder requires “mile-stone” releases, this should be indicated. If in doubt, check this with the project Supervisor, or the Head of Research.
- 4.4 It is vital that you have a clear perspective of who the outcome of your research is intended to reach. Funding bodies may stipulate specific outcomes – e.g. public access, etc.
- 4.5 Funding bodies will typically require an explanation of the usefulness of your research once completed, and you should be able to provide a clear idea of

what will be done with your data once published or released. Certain obvious options should not be overlooked, such as: paper presented at conference for history community, or book chapter published for community and public research/interest, etc.

## **Section 5: Storage and Backup of Data**

- 5.1 It is vital that the research materials and data are kept *safely at every stage* of the research process lifespan. There may be help available from IT Services, the Library or the Department. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 5.2 As for 5.1 above, it is vital that you have a clear understanding of how, where and when the research materials and data will be maintained after research process lifespan. This is particularly true where funding bodies have specific outcome criteria (e.g. making a public website available, etc.). There may be help available from IT Services, the Library or the Department. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 5.3 Similarly to 5.1 and 5.2 above, it is vital that you have a clear understanding of how, where and when the research materials and data will be backed up and kept safely, both during and after the after the research process lifespan. This is particularly true where funding bodies have specific outcome criteria (e.g. ensuring that online datasets are maintained for a specific period after the end of a project, etc.). There may be help available from IT Services, the Library or the Department. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 5.4 Very often work is added to, revised or altered and older versions are either overwritten, left as they were, or deleted. It may be wise to maintain a clearly labelled and stored set of older versions of current work in order to backtrack if necessary. It is imperative that a logical and sequenced filing system is used. On computer systems this may be attained by uniquely numbering each version. A useful means of achieving this is by using the current date and time as the unique numbering reference – e.g. “yyyymmdd FHSC Data Management Plan”.

## **Section 6: Archiving and Future Proofing of Information**

- 6.1 Provide information about how you intend for the project outcome(s) or deliverable(s) to be maintained after the end of the project. For example, a dataset may be perpetually maintained by the University’s online provision. However, this

will need to be confirmed. There may be help available from IT Services, the Library or the Department. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.

- 6.2 Any information that is kept after the lifespan of a project will still need to be stored safely, maintained and be provided in a useable format. If specific file formats are used, they may become unusable after a few years as new software replaces the old. Also, media such as DVDs, CDs and diskettes may become unusable after a while. There may be help available from IT Services, the Library or the Department. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 6.3 It is vital that any confidential data (e.g. personal information about any individual who is protected under the terms of the Data Protection Act, or information that may infringe copyright if released, etc.) must be kept and maintained in a secure environment. All reasonable steps should be taken to ensure the safety of such information. This applies to any information that is kept after the lifespan of a project as well. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 6.4 Datasets, databases, standalone documents, and even artefacts may prove useless without explanatory notes (metadata) accompanying them. These materials need to be clearly linked to the materials so that they can adequately inform any future user about the material. For example, a published dataset will typically be accompanied by a metadata document that explains the various fields, their usefulness and summarises the purpose of the dataset in general. These documents will be stored along with the dataset and are accessible in the same manner as the dataset (e.g. online, or download). Examples of such accompanying documentation are available for download. If you wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 6.5 Typically, any stored data, materials, artefacts, etc. will need to be cited when accessed and referenced by other researchers. It is useful to provide clear and concise citation information for researchers to access. This can be done via the accompanying documentation (metadata) indicated in 6.4 above. If you wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.

## **Section 7: Resourcing of Data Management**

- 7.1 In the event that this is an individual project or piece of research, your own name

should be listed. Include any other staff or assistants are to be involved in the project as well. It may be necessary to include staff from other departments of the University. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.

- 7.2 Funding strategies are often outlined by funders and will include a data management aspect. The costs of any materials, equipment and specialist knowledge will need to be factored to arrive at a reasonable estimate. Include any materials or equipment that will be funded by the University and/or you. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 7.3 As in 7.2 above, funding strategies are often outlined by funders and will include a data management aspect. Typically the University will support on-going research projects, and assist in facilitating post project maintenance and/or presence of outputs. However, this needs to be confirmed to ensure that the service will be available in the form that is required. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.

## **Section 8: Review of Data Management process**

- 8.1 Funders will need to be informed about how the data management process will be implemented. Provide specific information about how you intend to follow through with the commitments and processes that have been discussed in the rest of this document. Typically, regular reviews, reports and assessments of progress will suffice, but some funders may require specific means of identifying adherence to the plan. If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.
- 8.2 Based on 8.1 above, list those who will be carrying out the reviews and subsequent reports or processes necessary to ensure the successful implementation and completion of the data management plan. Typically, in the event of smaller research projects or individual research, the project Supervisor will fill this role. In the event of PhD research, this role will be carried out by the PhD Supervisor(s). If you are uncertain, or wish to explore this avenue further, the first line of contact is the project Supervisor, or the Head of Research.

## **Section 9: Statements and Personnel Details**

- 9.1 The Statement of Agreement is necessary to clarify the areas of responsibility and work that will be carried out by the various researchers engaged in the project. This information is vital for funding bodies that will require these details.

- 9.2 As in 9.1 above, the Expertise of Researchers is necessary to clarify the areas of responsibility and work that will be carried out by the various researchers engaged in the project. This information is vital for funding bodies that will require these details in the form of a brief résumé for each researcher.

## **Section 10: Appendices**

10.1 Assistance with completing the Plan; follow the instructions to obtain help specific to each section.

10.2 Follow the guidance for each specific section as necessary.

10.3 This list of Relevant Contacts will be reviewed and altered regularly.

### **10.3            *Relevant Contacts***

The following list of contacts will be regularly revised as appropriate:

FHSC Head of Research	Julie Jomeen Associate Dean (Research) Phone: +44(0)1482 464618 Email: <a href="mailto:j.jomeen@hull.ac.uk">j.jomeen@hull.ac.uk</a>
Library Services	Chris Awre Head of Information Management Phone: +44 (0) 1482 465441 Email: <a href="mailto:c.awre@hull.ac.uk">c.awre@hull.ac.uk</a>
IT Services	IT Helpdesk Phone: +44 (0)1482 462010 E-mail: <a href="mailto:help@hull.ac.uk">help@hull.ac.uk</a>
Dean of Faculty	Steven Ersser Dean Phone: +44 (0)1482 304582 Email: <a href="mailto:s.e.ersser@hull.ac.uk">s.e.ersser@hull.ac.uk</a>
Document Author	Roger Watson Professor of Nursing Phone: +44 (0)1482 464525 Email: <a href="mailto:r.watson@hull.ac.uk">r.watson@hull.ac.uk</a>

22. ETHICAL APPROVAL SODO UNIVERSITY, ETHIOPIA.

በ.አ.ፌ.ዲ.ሪ. ትምህርት ሚኒስቴር  
የወላይታ ሶዶ ዩኒቨርሲቲ  
ጤና ሳይንስና ህክምና ኮሌጅ  
ወላይታ ሶዶ



F.D.R.E. Ministry Education  
Wolaita Sodo University  
College of Health Sciences and medicine  
Wolaita Sodo

ቁጥር/Ref.No.APD 24/214/2013

ቀን/Date 27 December 2013

TO WHOM IT MAY CONCERN

Principal Investigator: Jill Brooks

Supervisors: Prof. Steve Ersser, Dr. Fiona Cowdell, University of Hull and Dr Paul Matts, Research Fellow, Proctor and Gamble, UK. Dr. Eric Gardiner, University of Hull statistician

Project title: An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podoconiosis.

This is to verify that the above research project is ethically cleared (approved) with recommendation by the Institutional Ethics Review Committee of College of Health Sciences and Medicine, Wolaita Sodo University, Ethiopia. The approval is valid as of December 27, 2013.

With Regards



አስክድር ወልታ ወተቻ  
Eskinder Wolka Woticha (MPH)  
የኮሌጁ ስነ-ምግባር  
Academic Process  
Directorate Director

☒ Box.138 ☎ Tel. ☎ 251-46-5511370

መልስን ሲጻፉን የእኛን ቁጥር ይጥቀሱ

E-mail: Wsuniv@ethionet.et Fax 251-46-5515113 In replying. Please quote our ref. number

## 23. PROTOCOL FOR USING PROBES.

### Protocol for staff using the *MoistureMeterSC*<sup>®</sup> and *VapoMeter*<sup>®</sup>

**THESE PROBES ARE EXPENSIVE. PLEASE ENSURE THEY ARE KEPT IN A SAFE PLACE AND TREATED CAREFULLY. HANDLE THEM GENTLY. DO NOT GET WATER ON THEM AND DO NOT LEAVE THEM IN SUNLIGHT**

1. Measurements should be undertaken in the morning or late afternoon **not** in the hottest part of the day. Participants should sit still in the shade for 20 minutes before the tests with their shoes and socks off.
2. Patients should avoid touching or crossing the legs as this might affect the measurement sites.
3. Avoid hot drinks for 30 minutes before the test.
4. Hair on measuring sites should be carefully removed with scissors.
5. All measures should be taken on the outer lower leg as follows:
  - 8cm below the head of the fibula
  - 8cm above external malleolus
  - Midway between these two points
  - Middle of the top of foot

#### *MoistureMeterSC*<sup>®</sup>



- Switch the device on, and when the 'ready' message displayed place the probe head on a dry smooth skin surface. Avoid wounds or areas of hair. If necessary the hair may be carefully removed using scissors. Avoid excess pressure; use just enough pressure to maintain the green status bar (indicating optimum probe–skin contact).
- After 5 seconds the stratum corneum (outer layer of skin) moisture status is shown in units on the LED display.
- Take **three** measurements in a tight triangle pattern on the measurement site. Clean the end of the probe between each use on a tissue.
- To calculate the skin moisture level **add the three** readings and **divide by three** to give the mean value. This is the measurement to be recorded.  
For example if the 3 measurements were 20, 18.5, 17 = 55.5 divided by 3 = 18.5. Then 18.5 is the number to be recorded.

## VapoMeter®



- Turn on the device and ensure that the 'normal' operating mode is selected.
- The device calibrates before counting down for 3 seconds, after which the operator placed the probe onto the skin surface (only moderate pressure is needed to achieve an efficient seal with the skin surface). A long bleep will be heard.
- The device will count up to 10 seconds while water loss is measured and calculated. The measurement is shown on the LED display in grams of water per meter squared per hour.
- Measure once per site. Record this.
- Wave probe between using on each site to clear chamber
- Press the device button again to display ambient temperature and relative humidity before powering down. Record this.

## 24. DERMATOLOGY LIFE QUALITY INDEX (DLQI).

Hospital No:

Date:

Name:

Score:

Address:

Diagnosis:

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick  one box for each question.**

- |     |                                                                                                                                                     |                                              |                                                                                                              |                                                                                                              |                                       |
|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|---------------------------------------|
| 1.  | Over the last week, how <b>itchy, sore, painful</b> or <b>stinging</b> has your skin been?                                                          |                                              | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | <input type="checkbox"/>              |
| 2.  | Over the last week, how <b>embarrassed</b> or <b>self conscious</b> have you been because of your skin?                                             | A lot                                        | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | <input type="checkbox"/>              |
| 3.  | Over the last week, how much has your skin interfered with you going <b>shopping</b> or looking after your <b>home</b> or <b>garden</b> ?           | relevant <input type="checkbox"/>            | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 4.  | Over the last week, how much has your skin influenced the <b>clothes</b> you wear?                                                                  | relevant <input type="checkbox"/>            | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 5.  | Over the last week, how much has your skin affected any <b>social</b> or <b>leisure</b> activities?                                                 | relevant <input type="checkbox"/>            | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 6.  | Over the last week, how much has your skin made it difficult for you to do any <b>sport</b> ?                                                       | relevant <input type="checkbox"/>            | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 7.  | Over the last week, has your skin prevented you from <b>working</b> or <b>studying</b> ?                                                            | Yes                                          | No                                                                                                           | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
|     | If "No", over the last week how much has your skin been a problem at <b>work</b> or <b>studying</b> ?                                               |                                              | A lot<br>A little<br>Not at all                                                                              | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/>                             |                                       |
| 8.  | Over the last week, how much has your skin created problems with your <b>partner</b> or any of your <b>close friends</b> or <b>relatives</b> ?      | A little                                     | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 9.  | Over the last week, how much has your skin caused any <b>sexual difficulties</b> ?                                                                  | relevant <input type="checkbox"/>            | Very much<br>A lot<br>A little<br>Not at all                                                                 | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not                                   |
| 10. | Over the last week, how much of a problem has the <b>treatment</b> for your skin been, for example by making your home messy, or by taking up time? | Very much<br>A lot<br>A little<br>Not at all | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | Not relevant <input type="checkbox"/> |

**Please check you have answered EVERY question. Thank you.**

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## 24B. DLQI INSTRUCTIONS FOR USE.

### **Dermatology Life Quality Index (DLQI)**

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self-explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes.

### **Scoring**

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

**\*\*Please Note:** That the scores associated with the different answers should not be printed on the DLQI itself, as this might cause bias\*\*

### **Meaning of DLQI Scores**

- 0-1 = no effect at all on patient's life
- 2-5 = small effect on patient's life
- 6-10 = moderate effect on patient's life
- 11-20 = very large effect on patient's life
- 21-30 = extremely large effect on patient's life

### **Detailed analysis of the DLQI**

The DLQI can be analysed under six headings as follows:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3

Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

### **Interpretation of incorrectly completed questionnaires**

There is a very high success rate of accurate completion of the DLQI. However, sometimes subjects do make mistakes.

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered 'yes' this is scored 3. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
4. If two or more response options are ticked, the response option with the highest score should be recorded.
5. If there is a response between two tick boxes, the lower of the two score options should be recorded.
6. The DLQI can be analysed by calculating the score for each of its six sub-scales (see above). When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored.

### **Minimal Clinically Important Difference of the DLQI**

In order to help the clinical interpretation of the DLQI scores a banding system (consisting of 5 bands) has been validated. According to this system, a DLQI score 0-1 = no effect at all on patient's life, DLQI score of 2-5 = small effect on patient's life, DLQI score of 6-10 = moderate effect on patient's life, DLQI score of 11-20 = very large effect on patient's life, DLQI score of 21-30 = extremely large effect on patient's life.

The Minimal Clinically Important Difference (MCID) of the DLQI in inflammatory skin diseases (range=2.2-6.9) has been estimated in 5 studies. For details please refer to the following article:

*Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008; 159:997-1035.*

For general inflammatory skin conditions a change in DLQI score of at least 4 points is considered clinically important (based on our latest published data). This means that a patient's DLQI score has to either increase or decrease by at least 4 points in order to suggest that there has actually been a meaningful change in that patient's quality of life since the previous measurement of his/her DLQI scores.

## 25. E MAILS REQUESTING AND APPROVING USE OF DLQI.

To: "dermqol@cf.ac.uk" <dermqol@cf.ac.uk>  
From: Jill Brooks <jb284@btinternet.com>  
Date: 10/22/2013 05:04PM  
Subject: DLQI

Hello,

I am a PhD student at the University of Hull. My supervisors are Dr. Fiona Cowdell and Prof. Steve Ersser. I am studying podoconiosis a skin disease which is prevalent in Ethiopia.

As part of this study I would like to use the Amharic version of the DLQI. I believe I require your permission for this. I hope to start the research in January 2014.

Thanking you in anticipation of your help.

Jill  
Jill Brooks

Dear Jill

I am writing this email on behalf of Professor Finlay. Thank you for your interest in the DLQI. We are happy to give you formal permission to use the DLQI in the Podoconiosis Study as you have described. There will be no charge. It is a requirement that the copyright statement must always be reproduced at the end of every copy of the DLQI. You can find the validated Amharic translation of the DLQI, as well as further information, at [www.dermatology.org.uk](http://www.dermatology.org.uk) (click on Quality of Life).

Please do not hesitate to contact me should you require any further clarification or help.

Best Wishes,  
Faraz

**Dr Faraz Mahmood Ali MBBCh MRCP**  
*Clinical Research Fellow in Dermatology*

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e: [alifm@cf.ac.uk](mailto:alifm@cf.ac.uk)

t: +44 (0)29 2074 5874      +44 (0)29 2074 5874

## 26. PARTICIPANT INFORMATION SHEET.

### **A study to measure the effect of different skin treatments on the legs and feet of those in Ethiopia with podoconiosis and the effect of this on their quality of life.**

#### **Invitation to take part**

You are being invited to take part in a study that will compare the usual treatment of the skin of the legs and feet in the Action on Podoconiosis Clinics with a different evidence-based skin treatment. If you decide to take part you will be randomly chosen to have either the usual treatment or the new treatment.

The usual treatment involves washing, soaking, drying and applying Vaseline. The new treatment includes adding glycerine to the soaking water. Glycerine is naturally found in your skin. It improves the skin condition. It has no known harmful effects.

#### **Why have I been invited to take part?**

You have been invited because you have a diagnosis of podoconiosis.

#### **Who has reviewed this study?**

Ethical approval for the study has been obtained from the Faculty of Health and Social Care Ethics Committee of the University of Hull, UK and from Sodo University, Ethiopia. This is a group of independent people who review research to protect the dignity, rights, safety and well-being of participants and researchers.

#### **Do I have to take part?**

It is up to you to decide; participation is voluntary. We will describe the study and go through this information sheet with you. We will then ask you to sign a consent form to show that you have agreed to take part. You will be given a copy of the signed consent form. You are free to withdraw at any time without giving a reason. The treatment and standard of care you receive from the clinic will not be affected if you decide not to take part or to withdraw.

#### **What are the benefits of taking part?**

Whichever group you are assigned to your condition should slowly start to improve although this cannot be guaranteed. The purpose of the study is to find out which treatment works best. By taking part you will be helping us to understand which treatment might best help other people who have podoconiosis.

#### **What are the risks of taking part?**

There are no known risks of harm from either treatment and the only cost to you is the time it takes to complete the treatment every evening which is around one hour and the time taken to attend the clinic each month.

#### **What will happen if I decide to take part?**

You will be randomly assigned to the usual treatment or the new treatment group. You will not be able to choose which group you are assigned to. The nurse and social worker at the clinics will take some details about you. They will

measure the condition of your skin with probes which they will place on the surface of your skin on your legs and feet for a few moments. The probes will not hurt or harm you. You will be taught how to care for the skin on your legs and feet and you will be given supplies to take home. At home your skin should be treated every evening as the nurse/social worker has shown you. If you do this daily your legs and feet should slowly improve. The study will last for 4 months.

### **Every day**

1. Wash your legs and feet in soapy water for 10 minutes.
2. Using fresh water add the bleach. The nurse or social worker will show you how to measure the water and the bleach which cleans the water. Soak your feet legs for 30 minutes (the same as the time to make and coffee).
3. If you are given glycerine add this to the water too. The nurse or social worker will show you how to measure this.
4. Air dry your legs as you have been shown by the nurse or social worker.
5. If you have a wound the nurse social worker will have given you some *Whitfield ointment* in a tube. Apply this to the wound as you have been shown.
6. Apply the *Vaseline*<sup>®</sup> in a thin layer to the lower leg and foot as you have been shown.

The treatment will take nearly an hour a day.

Each month when you come to the clinic you will be given fresh supplies. Measurements will be taken of the size of your legs and feet. Measurements of the condition of your skin will also be taken with probes which will be placed on your skin and you will be asked how podocloniosis is affecting your life.

### **Will my taking part in this study be kept confidential?**

All of the information that is collected by the nurse or social worker will be stored safely at the clinic. No information with your name on will be available to the research team. All information will be confidential and you will not be identified in any subsequent reports or publications. It will then be given to me and kept on a computer in the UK and stored securely.

The anonymised results will be analysed and may be used in future studies or published.

I will visit the clinic after the trial to inform you of the results. The nurse or social worker will let you know when this will be.

Thank you for taking time to go through this information sheet. If you have any questions please ask.

Jill Brooks, M. Phil., BA (Hons), RGN, DN, Dip Trop Nurs., PhD student,  
University of Hull.

27. CONSENT FORM.

Patient identification no .....

**Consent Form**

**An evaluation of the effectiveness of an evidence based skin care intervention to improve skin barrier function in the affected area and enhance the disease related quality of life of Ethiopian people with podocniosis.**

Thank you for considering taking part in this research study. If you have any questions please ask me before you decide if you wish to take part. You will be given a copy of this consent form to keep and refer to at any time.

*Please initial in box if you agree*

The study has been explained to me. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my care being affected.

I understand that the anonymised data collected during the study may be looked at by individuals from the research team and may be published. I give permission for this to occur.

I understand that if I withdraw from the study the data collected up to that point may be destroyed if I wish.

I agree to take part in the above study.

Name of participant (please print)

\_\_\_\_\_ Signed \_\_\_\_\_ Date \_\_\_\_\_

Name of person taking consent \_\_\_\_\_ Signed \_\_\_\_\_  
Date \_\_\_\_\_

Cc Participant, researcher.

## 28. CODING FOR MAIN STUDY.

Variable	Level of Measurement	SPSS variable name	Coding Instructions
Clinic	Nominal	Clinic	1=A 2=B
Group	Nominal	Group	1=Control 2=Experimental
Age	Interval	Age in years	1=18-29 2=30-39 3=40-49 4=50-59 5=60-69 6=over 70
Gender	Nominal	Gender	1=Male 2= Female
Occupation	Nominal	Occupation	1=Farmer 2=Housewife 3=Student 4=Other
Time since onset of podoconiosis in years	Interval	Duration	1=less than 1 year 2=1-4 years 3=5-9 years 4=10-14 years 5=15-19 years 6=20-24 years 7=25-29 years 8=over 30 years
Type of shoes worn in last week	Nominal	Shoes	1=None 2=Hard plastic sandals 3=Open sandals made with tyres 4=Other sandals 5=Canvas shoes 6= APA shoes 7=Other enclosed shoes
Number of days of work lost in previous month due to leg pain	Interval	workdayslostmthpain	Number
Right leg stage podoconiosis	Ordinal	Rtlegstage	1=Stage 1 2=Stage 2 3=Stage 3 4=Stage 4 5=Stage 5
Left leg stage of podoconiosis	Ordinal	Ltleg stage	1=Stage 1 2=Stage 2 3=Stage 3 4=Stage 4 5=Stage 5
Mossy changes right lower leg	Nominal	Rtlegmossychanges	1=No 2=Yes
Mossy changes left lower leg	Nominal	Ltlegmossychanges	1=No 2=Yes
Odour present right lower leg/foot	Nominal	Rtlegodour	1=No 2=Yes
Odour present left lower leg/foot	Nominal	Ltlegodour	1=No 2=Yes
Number of wounds right lower leg/foot	Interval/Ratio	Wounds leg R	Number
Number of wounds left lower leg/foot	Interval/Ratio	Wounds leg L	Number

Largest lower leg circumference right leg	Interval/Ratio	Rtlegetc	Number
Largest lower leg circumference left leg	Interval/Ratio	Ltlegetc	Number
Largest foot circumference right	Interval/Ratio	Rtfoot circ	Number
Largest foot circumference left	Interval/Ratio	Ltfootcirc	Number
Rt leg TEWL 8cm below head of the fibula	Interval/Ratio	RtfootTEWL	Number
Rt TEWL midway	Interval/Ratio	RtfootTEWL	Number
Rt TEWL 8cm above external malleolus	Interval/Ratio	RtfootTEWL	Number
Rt foot TEWL mid top	Interval/Ratio	RtfootTEWL	Number
Left leg TEWL 8cm below head of the fibula	Interval/Ratio	LtfootTEWL	Number
Left leg TEWL midway	Interval/Ratio	LtfootTEWL	Number
Left leg TEWL 8cm above external malleolus	Interval/Ratio	LtfootTEWL	Number
Left foot TEWL mid top	Interval/Ratio	LtfootTEWL	Number
Rt leg mean skin hydration 8cm below head of the fibula	Interval/Ratio	Rtfootskinhydrat	Number
Rt leg mean skin hydration midway	Interval/Ratio	Rtfootskinhydrat	Number
Rt leg mean skin hydration 8cm above external malleolus	Interval/Ratio	Rtfootskinhydrat	Number
Rt foot mean skin hydration mid top	Interval/Ratio	Rtfootskinhydrat	Number
Lt leg mean skin hydration 8cm below the head of the fibula	Interval/Ratio	Ltfootskinhydrat	Number
Lt leg mean skin hydration midway	Interval/Ratio	Ltfootskinhydrat	Number
Lt leg mean skin hydration 8cm above external malleolus	Interval/Ratio	Ltfootskinhydrat	Number
Lt foot mean skin hydration mid top	Interval/Ratio	Ltfootskinhydrat	Number
Amharic Dermatology Quality of Life (DLQI) score	Ordinal	DLQI	Number
Ambient temperature	Interval/Ratio	Temp	Number
Ambient humidity	Interval/Ratio	Humidity	Number

**Please follow these instructions very carefully.**

1. Wash legs and feet in soapy water for 10 minutes every evening. Throw away the soapy water.
2. Measure 1 litre of water with a 1 litre jug. Place in bowl and add 1.6 mls bleach measured with a syringe and 20 mls glycerine (2 bleach bottle caps full).
3. Soak the feet and legs in this for 30 minutes (the time it takes to make coffee) frequently splashing the soaking water onto the whole of the feet and the legs below the knee.
4. Air-dry the feet and legs on a clean surface
5. Apply *Vaseline*<sup>®</sup> in a thin layer to the whole of the leg and foot in downwards movements.
6. Apply *Whitfield's ointment* to any areas with a fungal infection.

**It is very important that you come to the clinic every month so that the nurse can take measurements of your legs and feet and ensure the treatment is working. She will also give you 1 months' supply of glycerine, soap, *Vaseline*<sup>®</sup> and *Whitfield's ointment* if you need it. Every 6 months you will be given a bottle of bleach.**

**Jill Brooks, Principal Investigator.**

30. DATA COLLECTION FORMS.

**FORM 1. Baseline Data at first visit**

Participant research number.....Date.....

<b>Age of patient</b>								
<b>Gender (please circle)</b>	Male/ female							
<b>Occupation</b>								
<b>Time since onset of podoconiosis (years and months)</b>								
<b>Type of shoes worn in last week (please circle)</b>	1. none 2. hard plastic sandals 3. open sandals made from tyres 4. other sandals 5. canvas shoes 6. APA shoes 7. other enclosed shoes							
<b>Number of days of work lost in previous month due to leg pain (adeno-lymphangitis)</b>								
	<b>Right Leg</b>				<b>Left Leg</b>			
<b>Stage of podoconiosis</b>								
<b>Mossy changes lower leg/foot. Yes or No</b>								
<b>Odour present lower leg/foot. Yes or No</b>								
<b>Number of wounds lower leg/foot</b>								
<b>Largest lower leg circumference (cms)</b>								
<b>Largest foot circumference (cms)</b>								
	8cms below head of fibula		midway between		8cms above malleolus		middle of top of foot	
	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>
<b>Trans-epidermal water loss (water lost from skin). Measured with VapoMeter.</b>								
<b>Ambient temperature and humidity</b>								
<b>Skin hydration (moisture in skin). Measured with MoistureMeter. Mean of 3 measurements</b>								
<b>Amharic Dermatology Life Quality Index (DLQI) score</b>								

**Form 2.**

**Data after 1 month's treatment**

Participant research number.....Date.....

<b>Type of shoes worn in last week (please circle)</b>	1. none 2. hard plastic sandals 3. open sandals made from tyres 4. other sandals 5. canvas shoes 6. APA shoes 7. other enclosed shoes							
<b>Number of days of work lost in previous month due to leg pain (adeno-lymphangitis)</b>								
	<b>Right Leg</b>				<b>Left Leg</b>			
<b>Stage of podoconiosis</b>								
<b>Mossy changes lower leg/foot. Yes or No</b>								
<b>Odour present lower leg/foot. Yes or No</b>								
<b>Number of wounds lower leg/foot</b>								
<b>Largest lower leg circumference (cms)</b>								
<b>Largest foot circumference (cms)</b>								
	8cms below head of fibula		midway between		8cms above malleolus		middle of top of foot	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
<b>Trans-epidermal water loss (water lost from skin). Measured with VapoMeter.</b>								
<b>Ambient temperature and humidity</b>								
<b>Skin hydration (moisture in skin). Measured with MoistureMeter. Mean of 3 measurements</b>								
<b>Amharic Dermatology Life Quality Index (DLQI) score</b>								

**Form 3.**

**Data after 2 month's treatment**

Participant research number.....Date.....

<b>Type of shoes worn in last week (please circle)</b>	<ol style="list-style-type: none"> <li>1. none</li> <li>2. hard plastic sandals</li> <li>3. open sandals made from tyres</li> <li>4. other sandals</li> <li>5. canvas shoes</li> <li>6. APA shoes</li> <li>7. other enclosed shoes</li> </ol>							
<b>Number of days of work lost in previous month due to leg pain (adeno-lymphangitis)</b>								
	<b>Right Leg</b>				<b>Left Leg</b>			
<b>Stage of podoconiosis</b>								
<b>Mossy changes lower leg/foot. Yes or No</b>								
<b>Odour present lower leg/foot. Yes or No</b>								
<b>Number of wounds lower leg/foot</b>								
<b>Largest lower leg circumference (cms)</b>								
<b>Largest foot circumference (cms)</b>								
	8cms below head of fibula		midway between		8cms above malleolus		middle of top of foot	
	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>
<b>Trans-epidermal water loss (water lost from skin). Measured with VapoMeter.</b>								
<b>Ambient temperature and humidity</b>								
<b>Skin hydration (moisture in skin). Measured with MoistureMeter. Mean of 3 measurements</b>								
<b>Amharic Dermatology Life Quality Index (DLQI) score</b>								

**Form 4.**

**Data after 3 month's treatment**

Participant research number.....Date.....

<b>Type of shoes worn in last week (please circle)</b>	1. none 2. hard plastic sandals 3. open sandals made from tyres 4. other sandals 5. canvas shoes 6. APA shoes 7. other enclosed shoes							
<b>Number of days of work lost in previous month due to leg pain (adeno-lymphangitis)</b>								
	<b>Right Leg</b>				<b>Left Leg</b>			
<b>Stage of podoconiosis</b>								
<b>Mossy changes lower leg/foot. Yes or No</b>								
<b>Odour present lower leg/foot. Yes or No</b>								
<b>Number of wounds lower leg/foot</b>								
<b>Largest lower leg circumference (cms)</b>								
<b>Largest foot circumference (cms)</b>								
	8cms below head of fibula		midway between		8cms above malleolus		middle of top of foot	
	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>	<b>Rt</b>	<b>Lt</b>
<b>Trans-epidermal water loss (water lost from skin). Measured with VapoMeter.</b>								
<b>Ambient temperature and humidity</b>								
<b>Skin hydration (moisture in skin). Measured with MoistureMeter. Mean of 3 measurements</b>								
<b>Amharic Dermatology Life Quality Index (DLQI) score</b>								

## 32. ABBREVIATIONS.

ADL – adenolymphangitis

APA - Action on Podoconiosis

APACs - Action on Podoconiosis clinics

C - centigrade

cm - centimetres

DLQI - Dermatology Life Quality Index

Gms - grams

HEW - health extension worker

mins - minutes

mls - millilitres

NGO - non-government organisation

NMF - natural moisturizing factor

pH - measure of the acidity or alkalinity of an aqueous solution. A pH < 7 is acidic and a pH > 7 is alkaline.

RCT - randomised control trial

SBF - skin barrier function

SC - stratum corneum

SW - social worker

TEWL - trans-epidermal water loss

T-gase – transglutaminase

gm<sup>2</sup>h - grams of water loss per meter squared per hour

## 32. GLOSSARY.

*Kebele* – smallest administrative district in Ethiopia

*Woreda* – a district consisting of a number of kebele