DEFINING AND MANAGING ACUTE LYMPHANGIOADENITIS IN PODOCONIOSIS LYMPHOEDEMA IN NORTHERN ETHIOPIA

HENOK NEGUSSIE SEIFU

PhD 2017

DEFINING AND MANAGING ACUTE LYMPHANGIOADENITIS IN PODOCONIOSIS LYMPHOEDEMA IN NORTHERN ETHIOPIA

HENOK NEGUSSIE SEIFU

A thesis submitted in partial fulfillment of the requirements of the University of Brighton and the University of Sussex for a programme of study undertaken at Brighton and Sussex Medical School for the degree of Doctor of Philosophy

JULY, 2017

This thesis was supervised by

Prof Gail Davey,

Professor of Global Health Epidemiology, Brighton and Sussex Medical Scholl, UK

Prof. Melanie Newport,

Professor of Global Health and Infection, Brighton and Sussex Medical Scholl, UK

Prof Fikre Enquselassie,

Professor of Epidemiology and Biostatistics, College of Medicine and Health Sciences, Addis Ababa, University

Abstract

Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious disease arising in barefoot individuals in long-term contact with irritant red clay soil of volcanic origin. The condition is believed to be caused by the interplay between environmental factors and genetic susceptibility over a prolonged period of time. In the last decade significant progress had been made in research on podoconiosis. Acute dermatolymphangioadenitis (ADLA) is a common and disabling complication of podoconiosis lymphoedema and remain the most painful and distressing condition, with diverse health, social and economic ramifications, yet has been very little investigated to date. This PhD thesis is therefore, aimed at defining ADLA, validating this to measure the impact of ADLA, and to document the impact of a simple foot hygiene intervention on ADLA and quality of life among podoconiosis patients.

The study utilized several steps. A Rapid Ethical Assessment (REA) was conducted at the outset to understand how best to approach the community for consent and develop context-relevant information sheet and consent format. A case definition of ADLA was adapted from that used for Lymphatic Filariasis (LF) based on discussion with podoconiosis experts and trial methodologists. This was followed by developing and testing a simple, patient-held ADLA diary. Acceptability, feasibility and accuracy of completion were checked.

Subsequently, the incidence, duration and social impact of ADLA were measured. A total of 1339 patients were recruited, screened and mapped from 18 *kebeles* (smallest administrative unit) from Aneded *woreda* (district) in East Gojjam Zone, Amhara Regional State, from December 2014 to June 2015. Using randomized controlled design 321 and 329 patients were randomized to immediate and delayed treatment groups, respectively, were followed for a period of 12 months, from 2015-2016. Comparison of a simple foot hygiene intervention on ADLA and quality of life were made. Finally, a process assessment using qualitative techniques, Focus Group Discussions (FGDs) and In-depth Interviews (IDIs) were conducted to explore stakeholders' perceptions of the treatment and its key elements for feasibility and impact.

The REA guided the development of information sheet and consent forms. The diary was found to be acceptable and feasible to be completed by patients and was used in the main study. Almost all patients (immediate 341 (98%), delayed 341 (99%)) had ever experienced ADLA. The median (Inter quartile range) experiences of ADLA in the past 30 days at baseline were 2 (IQR 2-3) and 3 (IQR 2-3) with an average duration (in days) of 3 (IQR, 3-5) in the intervention and control groups, respectively.

No significant difference was found on the Incidence Rate Ratio (IRR) of number of ADLA in the past 30 days and sex (IRR=1.00, p=0.983, 95%CI=-0.90, 1.10), school attendance (IRR=0.96, p=0.53, 95%CI=-0.85, 1.08) at baseline. However, the number of ADLA episodes in the past 30 days were 13% higher among those aged 50 and over (IRR=-1.13, p=0.01, 95%CI=1.05, 1.25). Similarly, those with disease stage 3 and above had 39% and 37% higher rate of ADLA compared to those with stage 2 (p=0.02) and (p=0.03), for the left and right feet, respectively. Absence of inter-digital lesions was associated with significantly fewer episodes at baseline (p=0.04). Similarly, presence of wounds in both feet was associated with a higher rate of ADLA (p=0.001). Further, patients who washed their feet more than seven times per week had reduced number of episodes in the previous 30 days (p=0.002).

On the other hand, severity of the most recent episode, absence of swollen lymph nodes and wounds on the feet were associated with longer duration of symptoms of ADLA (p=0.001). Poisson regression of Dermatology Quality Life Index (DLQI) scores with feet washing practices and intensity of the most recent ADLA indicated that the more severely the most recent ADLA was rated by patients, the higher the DLQI scores were compared to than those reporting mild attacks (Log OR=0.13, p=0.001, 95% CI=0.05, 0.21). Those who washed more than once scored significantly lower compared to patients who washed their feet once per day (Logs OR=-0.25, SE=0.04, p=0.001, 95%CI=0.30, -0.20).

There were a total of 16,550 episodes of ADLA reported in the twelve months of observation, within 765.2 person years. The intervention group recorded 7,515 and delayed group 9,035 episodes within 387.1and 378.1 person years; incidence rates of 19.4 (95% CI 18.9, 19.9) and 23.9 (95% CI 23.4-24.4) episodes per person years respectively

(IRR) 0.81 (95% CI 0.69, 0.96, p<0.001). At 12 months follow up, patients who received the foot care and hygiene intervention had 1614 episodes and the delayed treatment group, 1935 episodes providing incidence rates of 18.5 (95% CI 17.6, 19.4) and 24.5 (95% CI 23.4, 25.6) for the two groups respectively (IRR= 0.76, 95% CI 0.62, 0.93) (p<0.001). Similarly, the total annual duration of symptoms of ADLA for the treatment group (95% CI) was 79 days (95% CI 78, 80), significantly lower than that of the control group at 107 days (95% CI 106, 108) (P<0.001).

At 12 months, there was a significant difference in percentages of presence of mossy lesions in both legs between the two groups in favour of the immediate treatment group (32%) and (42%) control group (p= 0.008). Similarly, at twelve months follow up, DLQI scores were 11 (5-16) and 14 (11-19) for the treatment and control groups, a decrease by 10 and 7 points, respectively (p<0.001).

Finally, the process assessment which explored patients' perceptions of the intervention and its components showed that the foot care and hygiene intervention was acceptable to patients their families and service providers, simple and easy to conduct at home and thought to bring about health, social and economic improvements in patients' lives.

The thesis had clarified the clinical expression of ADLA in podoconiosis lymphoedema as well as documented the incidence, duration and social impact of ADLA. Based on a practical approach to the preparation and conduct of a RCT, it has made a significant scientific and policy contribution to scale up treatment as a disease recognition and management tool in settings where both LF and podoconiosis lymphoedema exist.

The REA proved to be handy and practical in identifying approaches to communities with little experience in research such as in rural Gojjam in the context of preparing and launching a RCT among podoconiosis patients. The local term "m*ichader*" used to describe the symptoms of ADLA was understandable to patients in rural Gojjam. It would seem practical to be put to use in future intervention programs, for example, as a tool to monitor improvement in the incidence and duration of ADLA once treatment had been initiated.

The fact that absence of inter-digital lesions and wounds were associated with lower numbers of ADLA episodes in the past 30 days at baseline and that the foot care and hygiene intervention had significantly lowered the incidence and duration ADLA as well as DLQI scores compared to the controls ($p<0.001$), indicated the effectiveness of the hygiene intervention among podoconiosis patients. It also suggests the importance of educating patients in order to prevent, identify and promptly treat wounds and inter-digital lesions in the feet in order prevent recurrent episodes of ADLA. Accordingly, NGOs providing podoconiosis prevention and treatment services should be encouraged to adopt the treatment package as a safe, affordable and uniform package. However, from the process assessment it also appears that patients prefer treatment near where they live. Health Centres (HCs) seem to be far from remote villages and difficult to walk particularly for the elderly and visually impaired. On the other hand, consideration that the Health Extension Workers (HEWs) are already overburdened with many packages appears to make the Health Post (HP) as a less preferable option.

Thus, the full spectrum of the feasibility of these options *vis-à-vis* other formats of integration need to be assessed carefully for several reasons including compliance with treatment. Future treatment provision in other contexts should give due attention to availability of and unrestricted access to water, local availability and affordability of treatment products and the all too important gender differences in designing footwear as participants of the study indicated.

Table of Contents

List of Figures

List of Tables

List of Acronyms

AAU	Addis Ababa University
ADL	Acute adenolymphangitis
ADLA	Acute Dermatolymphangioadenitis
AE	Adverse Event
AFL	Acute Filarial Lymphangitis
ARS	Amhara Regional State
ASL	Above Sea Level
BSMS	Brighton and Sussex Medical School
CI	Confidence Interval
CIRS	Chancellor's International Research Scholarship
CIOMS	Council for International Organization of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
NCPHSBR	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
CPAs	Community Podoconiosis Assistants
CRF	Case Report Form
DCs	Data collectors
DF	Degree of Freedom
DS	Data Supervisor
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
EL	Endemic Lymphangitis
FGD	Focus Group Discussions

FMHACA	Food, Medicine and Health Care Administration and Control Authority
FMOH	Federal Ministry of Health
GHT	Global Health Trials
GoLBet	Gojjam Lymphoedema Best practice trial
GPELF	Global Program to Eliminate Lymphatic Filariasis
HC	Health Centre
HP	Health Post
HEW	Health Extension Worker
ICT	Immunochromatographic Card Test
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IDI	In-depth Interview
IOCC	International Orthodox Christian Charities
IPs	Intervention Products
IQR	Inter Quartile Range
IRR	Incidence Rate Ratio
KCTF	Kilifi Clinical Trials Facility
KWTRP	Kenya Medical Research Institute-Wellcome Trust Research Programme
LF	Lymphatic Filariasis
LMICs	Low and Middle Income Countries
LSM	Local Safety Monitor
MIV	Monthly Intervention Visit
MRC	Medical Research Council

NaPAN	National Podoconiosis Action Network
NCPHSBR	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
NTDs	Neglected Tropical Diseases
OR	Odds Ratio
pRCT	pragmatic Randomized Controlled Trial
RCT	Randomized Controlled Trial
REA	Rapid Ethical Assessment
RGEC	Research Governance and Ethics Committee
RHB	Regional Health Bureau
NRERC	National Research Ethics Review Committee
SAE	Serious Adverse Event
SD	Standard Deviation
SPH-AAU	School of Public Health, Addis Ababa University
SNNPRS	Southern Nations Nationalities and People's Regional State
SOP	Standard Operating Procedure
SUSAR	Suspected and Unsuspected Serious Adverse Reaction
US	University of Sussex
WHO	World Health Organization
WMA	World Medical Association
WoHO	*Woreda* Health Office

Acknowledgements

First and foremost, I would like to express my deepest gratitude to my supervisor Prof. Gail Davey who encouraged me to undertake my PhD studies and this line of scientific enquiry. As a mentor and supervisor, Prof. Davey patiently guided me through the endeavour, laying the very foundation of where I proudly stand today bringing my doctoral dissertation to fruition. The last three years, I had the privilege working with you were perhaps the most professionally satisfying and productive years in my professional career. You encouraged me to present papers locally and internationally. I won the Global Health Trials' 2014 international competition to celebrate International Clinical Trials Day and the photo board was presented at the Royal Society of Tropical Medicine and Hygiene Annual Meeting in Oxford, UK, in September 2014. Prof. Davey, you are a patient teacher, a compassionate critic and my role model for scientist. The same goes to Prof. Melanie Newport and Prof. Fikre Enquselassie who encouraged me all the way and for their insightful advice and suggestions about my studies.

I would like to extend my gratitude to the University of Sussex Chancellor's International Research Scholarship (CIRS, 2014-2017) and Brighton and Sussex Medical School for providing the opportunity to do my PhD studies.

I would like to thank the various ethics committees and regulatory authorities in the UK and Ethiopia for speeding up the approval process: The Research Governance and Ethics Committee, Brighton and Sussex Medical School; School of Medicine and Health Sciences, Addis Ababa, University; The Food Medicine and Health Care Administration and Control Authority; The National Research Ethics Review Committee, Ethiopian Ministry of Science and Technology; Ethics Committee of the Amhara Regional Health Bureau.

My gratitude also goes to members of my PhD panel: Dr. Sumita Verma, MBBS, MD, FRCP, Reader in Medicine and senior lecturer; Dr. Timothy Chevassut, MA, FRCP, FRCPath, PhD, Director of Academic training, Brighton and Sussex Medical School. Thank you for your encouragement and your invaluable comments and suggestions all the way through the PhD steps.

My deepest gratitude and appreciation goes to staff at Kilifi Clinical Trials Facility (KCTF) (KEMRI-Wellcome Trust), Kenya. Particularly, Esther Kivaya, a seasoned trial monitor, who showed me my ways in running clinical trials, and monitored the study. Prof Greg Fegan: for conducting the randomization; Prof Jay Berkley: for his guidance in the analysis. Moses Ngari (PhD student), for his support in all statistical aspects of the trial: randomization, analysis and monitoring the data base. The same goes to Dr. Meseret Molla who was the trial data manager and worked with data collection and entry teams as well as Kilifi staff.

My thanks also go to the Regional Health Bureau, Zonal Health Desk, and Aneded *Woreda* Health Office, East Gojjam zone, Amhara regional state. Experts at the Aneded WoHO provided continuous support from identifying study *kebeles* to support during field work. Health Extension Workers (HEWs) in the study *kebeles*, guided us to patients' houses during screening and enrollment, and deserve my gratitude. The WoHO also organized a successful results dissemination workshop.

I would like to thank the International Orthodox Christian Charities (IOCC-Ethiopia) country office for providing logistical support during the study: Dr Seifu Tirfie, Country Director, Hari Desta, Senior Programme Manager and Wolela Woldegebriel, Finance Manager. Although IOCC did not have experience in running a major clinical trial, they quickly understood the international requirements for ethics and quality and did a wonderful job in implementing the trial. The IOCC Debre Markos, field office was the coordinating site and the staff deserves my special thanks. First comes Abreham Tamiru (currently, PhD student, USA) for his assistance in improving our understanding of the study area, his contribution to the discussion of and selection of the study *woreda*, assisting in training of fieldworkers and his continued support in timely manufacture and supply of shoes for patients. Not different from his predecessor, Abebe Kelemework, (currently, coordinator of the Debre Markos project) continued supporting us.

Getnet Agidew (I admire him enviously) was instrumental in the validation study and the providing information about the study to patients. He is not only culturally competent but also has superior command of the subtle differences within the region. Getnet delivered the information to patients in such a way that was intelligible to communities with no

experience in research. It is no exaggeration to credit him to the level comprehension of information about the study we saw. Thank you, Getnet!

Tigist Getaneh deserves all my appreciation and gratitude. She assisted in training CPAs, and as internal monitor of the study, attended Monthly Intervention Visits regularly, including in the remotest of *kebeles*.

I would not leave Debre Markos Referral Hospital unmentioned. The support Tariku Beyene, then CEO, provided for the study was enormous, from providing refrigerated storage for Immunochromatographic test (ICT card), to field vehicles when we had technical problems with our own vehicles.

I would like to express my deepest gratitude to the Local Safety Monitors (LSMs) of the study. Dr. Worku Mekonnen, Surgeon, Debre Markos Referral Hospital, reviewed the Adverse Event (SAE) reports. He conducted nodulectomy procedures to patients who needed them; he did not mind travelling to remote *kebeles*, despite his tight schedules at the hospital. Dr. Biruk Lambisso, Orthopedic Surgeon, Black Lion Hospital, Associate Prof, Addis Ababa, University, reviewed the SAE reports for decision of causality.

Those brave young men and women who collected data and conducted delivery of the intervention deserve my special thanks and appreciation. They often travelled to remote *kebeles*, known for their very mountainous and unfriendly terrains. They stayed overnight in the field when necessary.

I would also like to thank all the drivers in the Addis Ababa and Debre Markos offices, for services back and forth between Addis Ababa and Debre Markos and dedication in negotiating unfamiliar terrains in the field.

I had a good time working with and am deeply grateful to Thomas Addissie (Social Anthropologist) and Ayenew Negesse (Public Health Nutritionist). I learned as lot from their immense qualitative research experiences while we did two very important aspects of this thesis, the Rapid Ethical Assessment and the trial's process evaluation studies, respectively.

Staffs at Wellcome Trust Brighton & Sussex Centre for Global Health Research deserve special thanks. Many, many thanks Debbie Miller and Steph Clark, for arranging administrative aspects of my PhD studies, and logistics for my travels abroad.

Thanks also go to officials of Debre Markos University for closely following the progress of the study. My special thanks, in no particular order, goes to, Girmaye Tsegaye (currently, PhD student, Australia), Moges Wubie, Genet Degu, Dube Jara, Nurilign Abebe, Desalegn Amare from the college of health sciences for arranging the three day Essential Clinical Research Skills training we conducted as a local capacity building initiative in collaboration with Global Health Trials (GHT) and the speakers, Dr. Demeke Wolie (PhD Developmental Psychology), Dr. Haimanot (PhD, Foreign Language and Literature), Getachew Hailu (MPH/Epidemiology and Biostatics), Dube Jara (MPH/Epidemiology and Biostatics)**.** The GHT funded the training and is duly acknowledged. Specifically, I thank Prof. Trudie Lang, (Professor of Global Health Research and Head of the Global Health Network University of Oxford, UK) and Tamzin Furtado (project manager, GHT, University of Oxford).

Last but my all means, not the least; I am deeply grateful to my family and friends for their patience and support on this PhD journey, I embarked on.

ABOVE ALL, I THANK GOD!

Author's Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to these or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed:  Date: July, 2017

Chapter 1: Introduction

1.1. Overview

Podoconiosis (endemic non-filarial elephantiasis) is a non-infectious disease arising in barefoot individuals in long-term contact with irritant red clay soil of volcanic origin[1] . The condition is believed to be caused by the interplay between environmental factors and genetic susceptibility over a prolonged period of time. In genetically susceptible individuals, small particles in red clay soil entering the lymphatic vessels of the lower limbs induce macrophage proliferation leading to fibrosis and obliteration of the lumen of the lymphatic vessels and the clinical consequence of progressive, bilateral swelling of the lower legs[1-3].

The pathogenesis of podoconiosis is not fully understood. However, small sized minerals in the macrophages of the lower limbs of people living barefooted in areas of irritant clay soils in Ethiopia have been described in early studies by Price and Henderson(1978)[4]. Recently, Molla *et al* (2014) described positive association between the amounts of smectite (P=0.007), mica and quartz (P=0.001) (crystalline silica) within the soil and podoconiosis prevalence[5]. In addition, genetic susceptibility was also suggested as a background to the role of soil minerals. The possibility of genetic involvement and that podoconiosis is a "geochemical disease" was first described in the 1970s and 80s by Price [6-7]. Subsequently, other studies described the occurrence of podoconiosis when genetically susceptible individuals are exposed to irritant red clay soils. Davey *et al* (2006) further described the heritability of podoconiosis as a "model for gene-environment interactions"[1] . A genetic study by Tekola *et al* (2012) identified the association of HLA class II types suggesting podoconiosis is a T-Cell mediated inflammatory disease[8]. Particles entering through the skin cause an inflammatory reaction and the release of chemicals and activation of the immune response. These mechanisms result in dilation of the primary lymphatic vessels, fibrosis and narrowing which eventually impedes lymph flow and results in gross lymphoedema[9].

Figure 1.1 A bare-footed farmer in northern Ethiopia (Photograph by Henok Negussie).

Acute Dermatolymphangioadenitis (ADLA) also known as an “acute attack” is a recurrent inflammatory swelling of lymphedematous legs. It is a common and disabling complication of podoconiosis lymphoedema. In Lymphatic Filariasis (LF), episodes of ADLA have been shown to accelerate damage to peripheral lymphatic vessels and to lead to fibrosis[10]. Recurrent episodes of ADLA remain the most painful and distressing condition in lymphoedema; accelerating damage to peripheral lymphatic vessels and leading to fibrosis and disease exacerbation as well as resulting in adverse social and economic consequences for patients suffering from filarial lymphoedema[11].

Accordingly, morbidity management and disability prevention, and treatment of acute disease remain priorities for the World Health Organization’s Global Program to Eliminate Lymphatic Filariasis (GPELF)[12]. To provide access to basic care for patients in endemic areas suffering from lymphoedema-related ADLA episodes and to prevent further disease progression, a well defined management tool is crucial. Currently, patients, communities and health care professionals are not well-versed with podoconiosis, its consequences and management [13-14]. In addition, although foot care has been recommended for prevention of acute ADLA episodes in LF, the treatment modalities are not well defined in podoconiosis[10]. One of the preliminary steps towards elimination and control of

podoconiosis is to define treatment strategies. This thesis, therefore, defines ADLA in podoconiosis, measures its incidence and duration, and measures the impact of a foot care and hygiene intervention on ADLA and quality of life among podoconiosis patients.

1.2. Disease burden/ Geographical distribution

The recognition of podoconiosis as distinct from filariasis was first made by Robles when he published his observations in Guatemalan highlands in 1938. Since then the geographical distribution of the disease reported from various locations in the world [15]. Podoconiosis exists in areas where the altitude is above 1000mm Above Sea Level (ASL) and annual rainfall of above 100mm. The disease has been reported in more than 20 countries where areas of high rainfall and high altitude: in Central America; Guatemala and Mexico; in South America; Brazil, Ecuador, Suriname and French Guiana, Honduras, El Salvador, Panama, Costa Rica, Columbia, Nicaragua, Venezuela; northwest India, Sri Lanka[9].

Figure 1.2 Distribution of podoconiosis (World Health Organization, website).

About 4 million people are said to be affected by the disease worldwide[16] and the disease is deemed a serious public health problem in at least 10 African countries, Central America and northern India [1]. In Africa, podoconiosis has been found in the Cameroon highlands[17], Rwanda, Burundi, Ethiopia, Sudan[2], Tanzania[18], Uganda[19], the islands of Bioko, Sao Tome & Principe[20], Equatorial Guinea and the Cape Verde islands. In Ethiopia, since the earlier market count by Oomen (1969)which counted 6770 cases per thousand [21] and subsequent studies which Price conducted in Ethiopia and other African countries[2], prevalence estimates have been made[22-28]. A recent nationwide mapping indicated the prevalence ranging from 0% to 54.6% with clusters of high prevalence (> 5%) exclusively found in Amhara, Oromia, and southern regional states representing most of the central highlands of Ethiopia where 34.9 million people inhabiting these endemic areas, and is widespread in other six regions (Amhara, Benishangul Gumuz, Oromia, SNNPR, Somali and Tigray) [29-30]. Deribe *et al* (2017) estimated the number of podoconiosis cases in Ethiopia using geostatistical methods. Accordingly, nationally 1,537,963 adults (95% confidence intervals, 290,923-4,577,031 adults) were living with podoconiosis nationally, in 2015. The three big regions (SNNP, Oromia and Amhara) accounting for 99% of the cases, with proportions of 39%, 32% and 29% of individuals with podoconiosis residing in these regions, respectively. While the contribution of Tigray and Benishangul Gumuz regions did not figure much to the reported number, podoconiosis is declared almost non-existent, elsewhere in the nation[31].

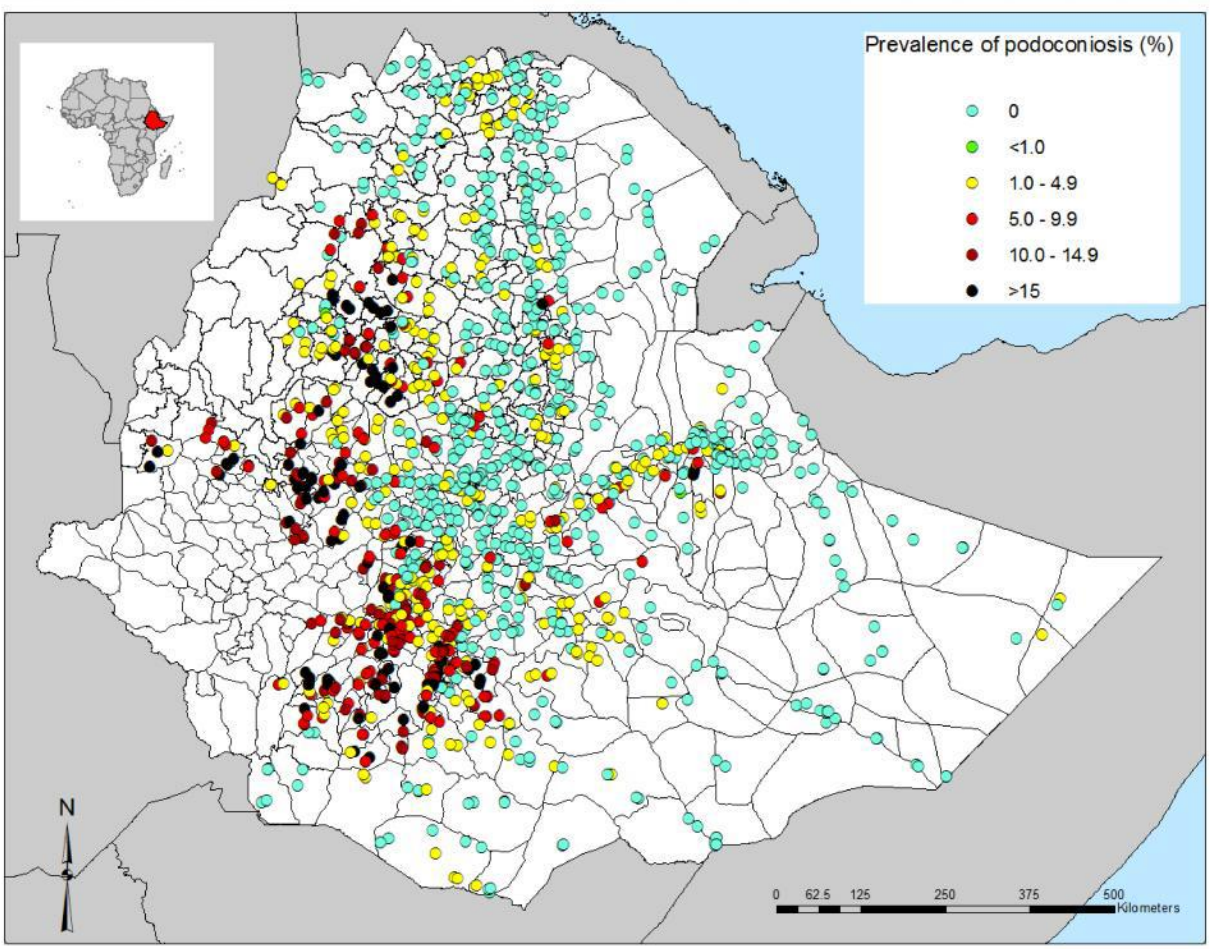


Figure 1.3 Distribution of podoconiosis in Ethiopia (Adapted from the nationwide mapping of podoconiosis in Ethiopia, 2013).

1.3. Economic consequences

Even though podoconiosis is rarely a direct cause of mortality, it has significant social and economic consequences. It causes disability resulting in substantial reduction in productive capacity and economic loss. A comparison of podoconiosis patients with their unaffected counterparts in southern Ethiopia indicated that patients lost equivalent to 45% of the total productive work-days and the condition cost US$16m and US$200m per annum to a zone with a population of 1.5 million and the nation, respectively[32]. Studies in Western and Southern Ethiopia found that 76-100% of podoconiosis patients were in the economically productive age groups of 15-64 years thus highlighting the urgent need for preventive action to mitigate the problem [33-34].

1.4. Social consequences

On the other hand, the disease leads to significant stigma. Studies have shown high levels of stigmatizing attitudes displayed by community members and health professionals themselves towards people with podoconiosis [17, 35-37]. Patients also report low quality of life[38]. Studies have indicated that the stigma associated with podoconiosis prevents patients from earning a living [34]. In addition, perceptions of the familial tendency of the disease make the stigma extend to family members and relatives [36, 39]. Studies in southern and northern Ethiopia indicated that podoconiosis-related stigma has an intense nature and is experienced by most patients. Manifestations range from unwillingness to marry affected patients or their relatives to shunning, exclusion from participating or differential treatment in social events like weddings and funerals, *iddir* and *Mahiber,* churches, denial of leadership roles in village or community affairs; not buying products from them in market places, avoiding physical contact; showing morally offensive acts such as pointing at them and pinching nose while walking past patients; unwillingness to share school desks to use of abusive terms[13, 37, 40-41]. People with podoconiosis exhibit more mental distress than their unaffected counterparts indicating a low quality of life and depression [42-43] which will apparently compel them to employ coping strategies. Active coping strategies described in a study in southern Ethiopia include wearing shoes on a regular basis, keeping feet clean, maintaining a neat appearance and dresses, seeking treatment and adhering to treatment regimens. On the other hand, more negative avoidant behaviors were avoiding participation in religious events, dropping out from school, funerals and weddings; not marrying non-affected community members, but instead using alternative actions like abduction; migrating to other places to live and using premarital sex as a leverage to ensure marriage, and divorce and in extreme cases, suicidal ideation[39] as well as avoidance of seeking treatment[41].

1.5. Clinical presentation and diagnosis

The clinical presentation of podoconiosis was first described by Ernest Price. Podoconiosis is a bilateral but asymmetric disease mainly affecting the lower legs. Burning sensations and itching in the feet are early symptoms. Although lymphoedema of other types can

exhibit similar symptoms, the lack of symmetry and scrotal involvement are indicative of podoconiosis. These early symptoms are followed by swelling of the feet and skin changes (mossy changes). Subsequently, as the lymphoedema sets in, patients exhibit different types of swelling from soft, water bag or hard, leathery elephantiasis and associated clinical features such as fibrous nodules (Figure 1.4).

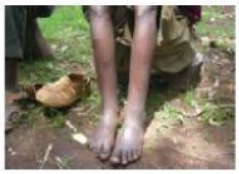
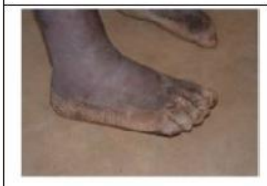
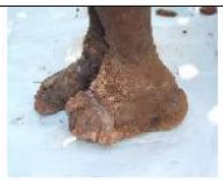
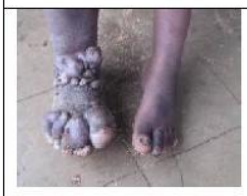
	Stage & Clinical signs		**Stage & Clinical signs**
	**Stage 1.** Swelling reversible overnight. The swelling is not present when the patient first gets up in the morning.		**Stage 4.** Above-knee swelling that is not completely reversible overnight; knobs / bumps present at any location.
	**Stage 2.** Below-knee swelling that is not completely reversible overnight; if present, knobs / bumps are below the ankle only.		**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.
	**Stage 3.** Below-knee swelling that is not completely reversible overnight; knobs / bumps present above the ankle.		

Figure 1.4 The five stages of podoconiosis (Adapted from clinical staging system for podoconiosis (endemic non-filarial elephantiasis) Tekola *et al*. (2008)[44].

As genetic susceptibility plays a role, any family history of similar condition will assist diagnosis. Studies have also shown that podoconiosis-affected patients report other members of their family and relatives as having the disease, although for reasons of avoiding social exclusion, the number of patients reporting other family members as affected may be an underestimate[23, 25, 45]. Understanding the clinical presentation will help health professionals at all levels to identify the disease early, prevent progression to

lymphoedema and introduce interventions in established lymphoedema cases and where the population is at risk [3, 46].

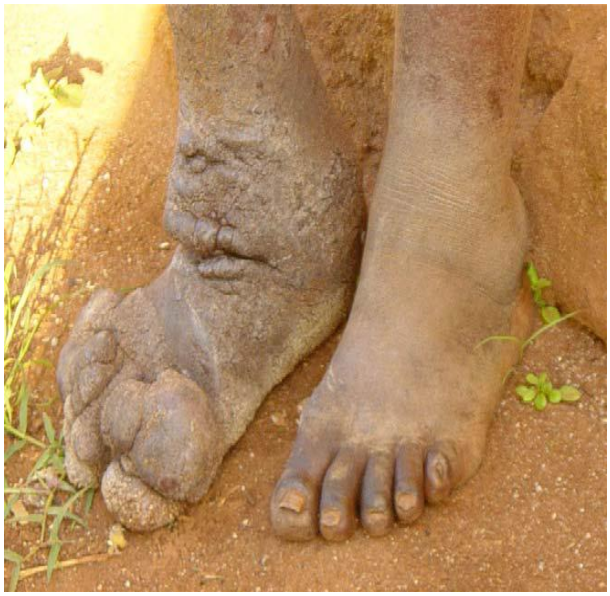


Figure 1.5 A patient with asymmetric nodular disease. Adapted from Davey *et al* (2006)[1].

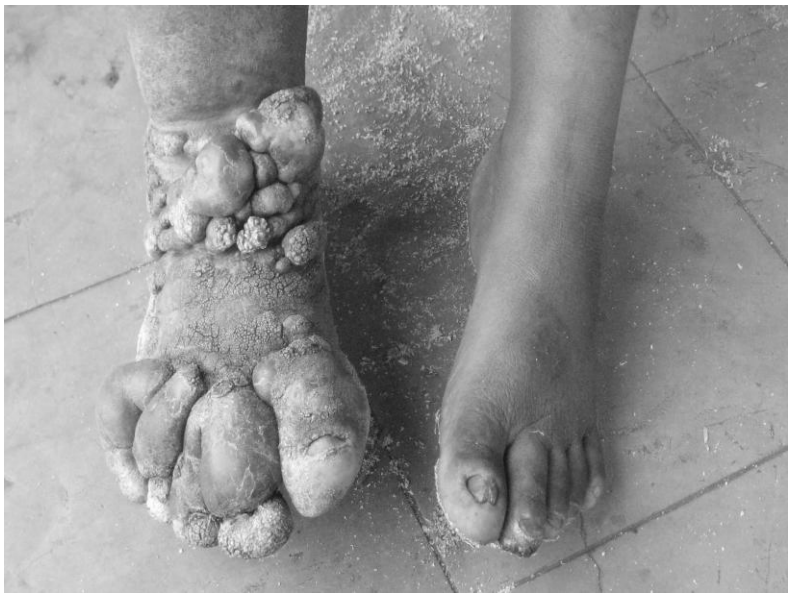


Figure1.6 Advanced, asymmetrical podoconiosis in a female patient from northern Ethiopia. Adapted from Davey G (2010)[9].

1.6. Incidence and duration of Acute Dermatolymphangioadenitis (ADLA)

The combination of symptoms used in definitions of an ADLA attack varies among studies in LF. In their study, Summa *et al* (2002) did not specify the symptoms used as a diagnosis of ADLA. In two studies, medical officers or physician asked and examined patients about occurrence of ADLA[47-48]. The term ADLA was first used by Olszewski (1996) and is clinically similar to cellulitis with symptoms constituting local pain and swelling as well as fever and chills[49]. Dreyer *et al* (1999) identified two clinical syndromes; acute filarial lymphangitis (AFL) caused by death of the adult worm, and ADLA considered to be secondary bacterial infection[50]. Accordingly, in their study in Guyana, McPherson *et al* (2005) defined ADLA as an episode of limb inflammation accompanied by systemic symptoms culturally understood as 'filarial flares'. In order to avoid confusion with local filarial lymphangitis caused by death of adult filaria, a description of ADLA was made to patients backed with pictures and a video[51]. In a "clinical description of filarial lymphoedema" McPherson *et al* (2006) used the same term 'filarial flares' backed with a question of history of red/swollen leg and associated symptoms[52]. A randomised controlled trial that compared the efficacy of three treatment regimens along with foot care management in morbidity management of filarial lymphoedema in Orissa, India, defined ADLA as pain, tenderness, local swelling and warmth in the groin or limb with associated constitutional symptoms such as fever, nausea and vomiting[11]. Addiss *et al* (2010) used a similar description; inflammatory episodes, characterized by intense pain, swelling, fever, and chills[53]. In another study in Burkina Faso, a leaflet describing signs of acute attack was given to each patient during training to identify episodes and taking patients' history. Additional dimensions to those signaling inflammatory episodes: peeling of the skin and painful inguinal lymph nodes and sometimes nausea and vomiting, were considered[54]. However, a more recent study on the impact of community-based lymphoedema management among patients with Lymphatic Filariasis in India considered ADLA as constituting a patient self-report of two or more of the following symptoms: redness, pain, or swelling of the leg or foot, with or without the presence of fever or chills[55]. A recent survey conducted in northern Ethiopia among podoconiosis patients who reported ADLA found that hot (49.8%) and tender (60.2%) swelling, and inguinal lymphadenopathy

(62.1%) were common[56]. Attacks are highly distinctive to patients, who in the study area, refer to these episodes in Amharic as *'michader'* -'the blight that casts you down causing you to spend the night where it hit you' [57].

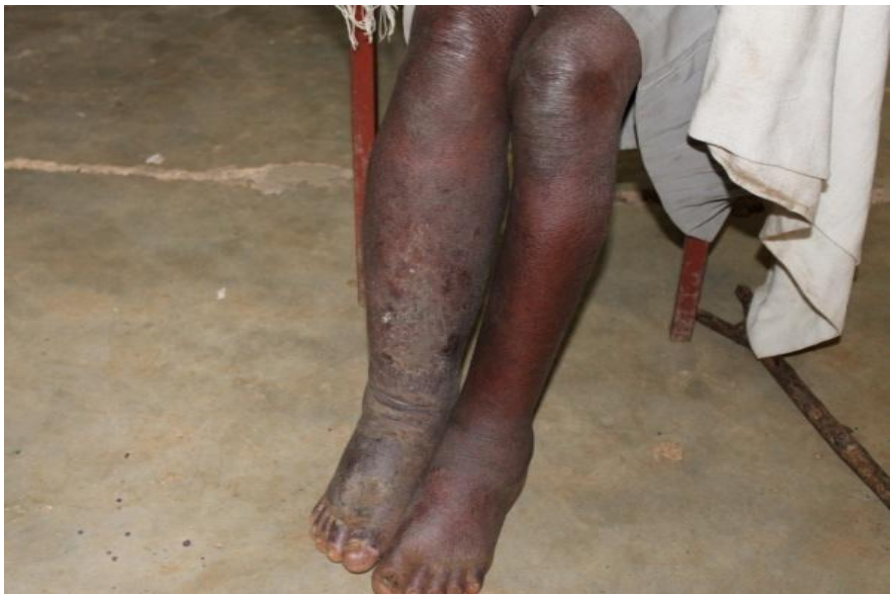


Figure 1.7 Female podoconiosis patient northern Ethiopia experiencing ADLA attack reporting redness, increased swelling and intense pain in the affected limb (Photograph by Henok Negussie).

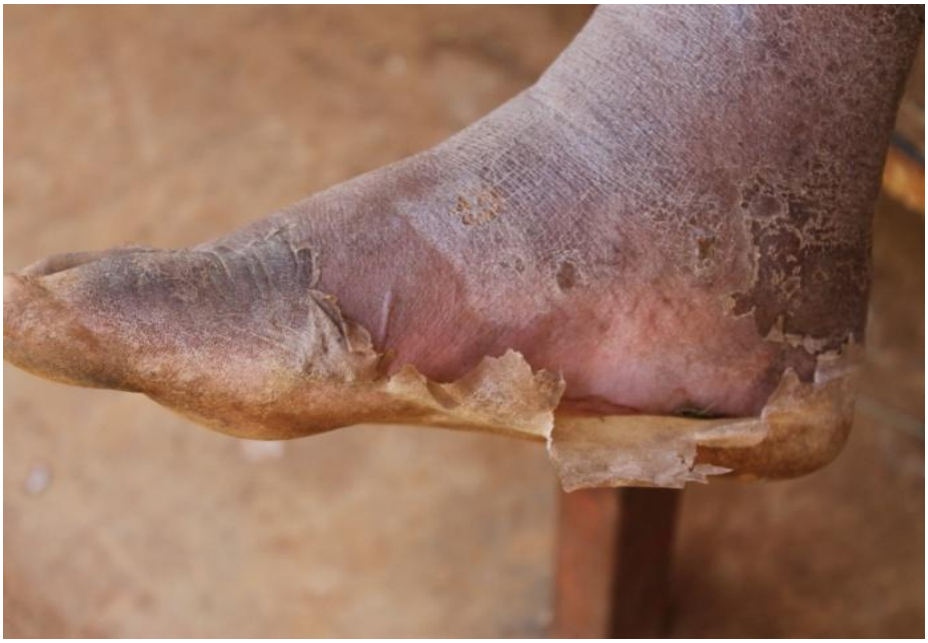


Figure 1.8 Peeling of the skin seen in podoconiosis patients after the ADLA had subsided (Photograph by Henok Negussie).

The incidence and duration of ADLA episodes determine the extent of health, social and economic losses patients have to endure. A number of studies have reported these measures. Among patients in LF-endemic areas, annual reported incidence of ADLA ranged from 1.5 to more than 7 episodes per patient with duration ranging from 1 to 16 days[10]. Similarly, according to studies conducted in northern and western Ethiopia, podoconiosis patients on average experienced five episodes of ADLA per year and up to 90 days per year incapacitated by ADLA[56]. However, some studies found the incidence of ADLA among podoconiosis patients in southern Ethiopia to be higher than that reported for filariasis in other countries [34, 58].

Observed differences in the incidence and duration of ADLA as well as the relationship between occurrence of ADLA and disease stage, quality of life and other social outcomes in LF appear to be due partly to the use of different case definitions, modes and measurement intervals and systems for staging lymphoedema. In this regard, some studies considered ADLA among lymphoedema patients with hydrocele, other researchers considered only cases with fever and some restricted focus to specific lymphoedema stages and patients who have had two or more ADLA episodes[48].

Some studies focused on occurrence, number, intensity and duration of ADLA attacks in the past year[48], while others elicited ADLA history every fortnight and calculated frequency for two time periods, a year prior to treatment and during the year of treatment[11]. A number of studies used frequency of episodes for the previous 12 months including episodes per year [51, 53, 59]. Recent studies considered ADLA in the month preceding interview for the study and during any point in the previous 30 days [54-55].

Similarly, the literature indicates variation in the recording of ADLA episodes used in different studies. Some used patient recall and medical officer examination[48, 54], another, patient recall and patient record[51] and others, patient recall alone [11, 53, 55]. Researchers identified that quarterly measurement showed an increased incidence of ADLA for the 3rd and 4th quarters of the study year, but no consistent seasonal pattern for

ADLA incidence was observed [53]. Investigators selected the end point based on previous indications of change observed in the 3 months after beginning the treatment. Those who selected a one month timeframe did this to minimize potential recall bias and the possibility that patients may not only have reported acute attacks from the preceding month but also earlier attacks [54]. Where ADLA was measured at baseline, 1, 2, 3, 6, 12, 18 and 24 months after enrollment in the program, a study reported maximal reduction in perceived disability between 2- 6months[55]. Others studies have reported similar time period as a maximum impact of management on ADLA[60]. However, investigators acknowledged that results based on patient recall of episodes in the past 30 days may be subject to recall bias[55].

Accordingly, methods of enquiry about occurrence of ADLA and measurement intervals have been the subject of methodological debate. For example, closely spaced follow up enquiries about occurrence of episodes may result in patients' responding positively to enquiries of attacks. Similarly, the accuracy of patient recall over a longer period is unknown, although some suggest the pain and suffering associated with ADLA make it an unforgettable event[53]. It is to be noted here that most studies relied on patient recall in calculating duration of ADLA episodes[10] and researchers identified the need to collect comparative prospective data on a control group[53].

In this regard, 'Health' diaries have been used to investigate health-related behaviors including medication adherence, the occurrence of specific health conditions such as cystic fibrosis, hormonal patterns, chronic mental health problems and pain-stress levels. Health diaries have also been used in Low and Middle Income Countries (LMICs) to record episodes of colds, coughs, diarrhoea and fever in children, the volume and composition of breast milk transferred from mothers to their infants and the health effects of air pollution. Thus, it appears feasible to use diaries in LMICs characterized by low-literacy communities to collect data on a range of health questions if clear instructions and images as well as information on when and how to complete diaries are provided to participants[61].

1.7. Managing Acute lymphangioadenitis

The importance of identification and measurement, prevention and prompt treatment of ADLA in lymphoedema morbidity management is paramount. The basic principle behind the WHO-recommended lymphoedema morbidity management measures is that it is very easy and affordable. Basic self-care includes frequent washing with soap and water, limb elevation while sleeping, a range of motion exercises, and application of topical creams or ointments to decrease the incidence of ADLA which in turn will slow progression of lymphoedema and reduce loss of productivity associated with ADLA. Thus, reducing the frequency and severity of ADLA remains the most important objective of morbidity management in resource-poor settings[62].

The effectiveness of foot care and hygiene management in reducing the frequency of ADLA and improving other social and economic aspects of LF patients has been reported in different contexts. In this regard, a study by Suma *et al* (2002) retrospectively evaluated the efficacy and sustainability of a foot care program in preventing ADLA in Brugian Filariasis. Out of the 127 patients who were enrolled in a previous trial that evaluated the role of penicillin, diethylcarbamazine (DEC) and foot care in the prevention of ADLA attacks (recalled and examined), 95.3% stated that they either had no ADLA attacks at all or had less severe episodes which reduced the period of time they were unable to work. In addition, during the one year unsupervised period, the frequency of ADLA was reduced by 72.5%, providing evidence to the program's efficacy and sustainability [48].

Similarly, a study in Leogane, Haiti (an area endemic for Bancroftiian Filariasis) examined the effectiveness of basic lymphoedema management. In the initial phase, while emphasis was on compression bandaging, ADLA incidence was 1.56 episodes per person-year. Later, the program focus shifted towards use of basic hygiene and skin care, and ADLA incidence dramatically dropped to 0.48 episodes per person-year. However, due to ethical concerns of withholding treatment, researchers were unable to collect comparative data on an untreated control group[62]. Another study by Jullien *et al* (2011), in Burkina Faso which aimed to evaluate the efficacy of home-based lymphoedema management embedded in the national health system and implemented nationally, indicated that out of 1089 patients and

monitored for 4.5 months, 78.1% (95%CI: 75.5-80.5) had acute attacks of adenolymphangitis and cellulitis in the month preceding consultation. After four and half months of lymphoedema management this was reduced by half, to 39.1% (95%CI: 36.2-42.1)[54]. A comparative study conducted in north eastern Nigeria, on the clinical effectiveness, acceptability and cost of three strategies: Community Care (CC), Patient Care (PC) and Health Care (HC) on lymphoedema management among persons with lymphoedema and adenolymphangitis, frequency of ADLA declined from 94% to 6.5%, most noticeably in the Community-Care arm, with a reduction from 43.1% to 4.4% at 12months of treatment among patients who had two ADLA episodes per month [63].

Although foot care has been recommended for prevention of acute ADLA episodes and it has been shown to lead to significant improvements in clinical and social outcomes such as quality of life among LF patients, there are no clear treatment modalities for either lymphoedema or acute episodes in LF[10]. In addition to improvements in ADLA incidence and frequency, other aspects of LF lymphoedema also were reported to have improved. The Haiti study, found that out of 175 patients, 137 (78.3%) exhibited reduction in 66.4% of lymphedematous legs after 12 months of treatment. The mean decrease varied among disease stages with decrease of 59mL (stage 2, $p<0.01$), 93mL (stage 3) and 571mL (stage 4) among patients with disease stage 0-4 significantly among those disease stages two (4%) and three (17.1%)[53].

On the other hand, studies in LF also reported improvements in Quality of Life (QOL). Studies using the Dermatology Life Quality Index (DLQI) reported significant improvement in all stages after 12 months of treatment [64]. Similarly, using the World Health Organization Disability Assessment Schedule (WHO DAS II) a decrease in composite disability scores from an average of 66.2 at baseline to 60.4was reported at 24 months ($P<0.0001$)[55].

Although, a number of studies in LF endemic areas reported similar findings regarding the effectiveness of lymphoedema management in improving the various aspects of patients' lives, research on the effectiveness of management of podoconiosis lymphoedema is scarce. In this regard a one year non-controlled follow up study among podoconiosis patients in

southern Ethiopia conducted by Sikorski *et al,* (2010). The study reported improvements in clinical and social outcomes after 12 months. Clinical stage decreases in 51% of patients and increased in none (mean decrease, 0.67, p<0.001, 95%CI 0.38-0.96). In addition, the mean reduction in leg circumference was observed to be 2cm (p<0.001, 95%CI 1.26-2.74). Only 22.2% still had mossy changes, while leg circumference had decreased ranging from 19.0–31.0 cm (mean 24.22 cm, median 24.00 cm). Similarly, a reduction in DLQI score was observed in every patient, with a 10 point or more change observed in 96.3%. The study also identified the importance of qualitative exploration of patients' perceptions of the treatment and its key elements to assess its feasibility and impact before scaling up the program to other areas in Ethiopia as well as internationally. To this effect, the need for a better designed study including a control group was apparent[65]. Another recent RCT by Brooks *et al* (2017), evaluated a new skin regimen among podoconiosis patients in southern Ethiopia (n=193). Although the study reported after three months of follow up a reduction in the mean scores on DLQI the difference between the experimental and control groups was not significant (p=0.907)[66].

In sum, studies in different LF endemic countries, spanning more than a decade indicate the effectiveness of lymphoedema management in improving health, social and economic aspects of patients' lives, and these works are considered to be transferable to podoconiosis. Nevertheless, podoconiosis has its own disease course. For example, in view of the differences in disease progression and pathogenesis between LF and podoconiosis beyond the earliest stages, it quickly became apparent that the Dreyer staging system needs to be adapted to podoconiosis. As a result of the pioneering work by Tekola *et al* (2008) which developed and tested a *de novo* clinical staging system (with only five stages) for podoconiosis[44], a range of Non-Governmental Organisations (NGOs) implementing the foot care and hygiene intervention in Ethiopia used the staging system to measure improvements. However, regarding the components of the foot care and hygiene intervention, there are similarities as well as differences between the various groups. For example, organizations may use toilet, laundry or herbal soaps. Some use Vaseline, others use Whitfield's ointment and still others use neem oil (an extract of neem tree), due to unavailability of other forms of ointments. The ethical and scientific issues surrounding the

use of diluted bleach as an anti bacterial in the foot hygiene practice also remain controversial. Practice over use of bandages, antibiotics and surgery also vary (NaPAN workshop of NGOs working on Podoconiosis prevention and treatment, 2013).

1.8. Rationale of the thesis

From the foregoing discussion it is apparent that developing a standardized definition and valid measures for ADLA among podoconiosis patients remains crucial for improved knowledge about morbidity management. Clarifying the clinical expression of ADLA in podoconiosis lymphoedema and assessing and documenting the incidence, duration and social impact of ADLA are also important. Comparing the impact of a simple foot care and hygiene intervention on ADLA incidence and duration using a randomized controlled design will be a significant scientific contribution. The need to standardize the treatment procedure in a way that is simple, affordable and easy to implement is of paramount importance and highly will undoubtedly inform the recent master plan to control Neglected Tropical Diseases (NTDs) in which podoconiosis is identified and as one of the eight targeted NTDs for control[67].

1.9. Thesis objectives

1.9.1. General objective

The overall aim of the thesis is to develop a standard case definition for ADLA, to validate this, to measure the impact of ADLA, and to document the impact of a simple foot hygiene implementation for ADLA management.

1.9.2. Specific objectives

1. To develop and validate a standard case definition of ADLA;
2. To estimate the incidence, duration and social impact of ADLA among podoconiosis patients;
3. To measure the impact of a foot hygiene intervention on ADLA and quality of life among podoconiosis patients;
4. To assess patients' and providers' perceptions of the foot care and hygiene intervention in ADLA management (process assessment).

1.10. Thesis outline

The thesis is structured into eight chapters beginning with a general introduction and overview (chapter 1) and a methods and methodologies (chapter 2). Rapid Ethical Assessment (Chapter 3) was conducted based on the importance of identifying effective means of approaching individuals and for the study. Chapter 4 deals with the validation of a patient-completed ADLA diary. The essence of designing and putting to use a diary was based on the fact that, assessment of methodologies previous studies to gather and record ADLA events varied and the need to minimise recall bias[54, 68] and sets the stage for Chapters 5 and 6, to measure the incidence, duration and social impact of ADLA at baseline and the effect of foot hygiene intervention on ADLA, respectively . Chapter 7, provides further evidence supporting the previous two chapters thereby helping interpret the quantitative results as well as further understanding and evidence of acceptability of the intervention in the management of ADLA, to patients, treatment service providers and policy makers on contextual aspects that may need to be considered should the intervention be implemented on a larger scale[69]. Finally, Chapter 8 synthesizes the studies into meaningful cohesion in light of the ADLA recognition and management in wider context.

Table 1.1 Outline of the thesis.

Chapter 1. Introduction and overview
Chapter 2. Methods and methodologies
Chapter 3. Rapid Ethical Assessment
Chapter 4. Developing & validating a case definition of ADLA
Chapter 5. Incidence, duration and social impact of ADLA at baseline and 12 months of intervention
Chapter 6. Process assessment of RCT
Chapter 7. Discussion and conclusion

Chapter: 2 Overall Methods

2.1. Overall methodology

In this section study designs, data collection methods and tools employed in the various stages of the project are discussed in some detail. Qualitative studies were conducted to gain an in-depth understanding through discussions and interviews. While quantitative approaches were used to compare the outcome of interest. Randomised controlled trials (RCTs) are the most rigorous way to evaluate the health and social impacts of the foot care and hygiene interventions in reducing ADLA. Chapters 3 & 7 used a qualitative approach while chapter 4 combined both qualitative and quantitative techniques. Chapters 5 & 6 used quantitative techniques.

2.2. Rapid Ethical Assessment

Prior to initiation of the trial, Rapid Ethical Assessment (REA) was conducted to assist development of the Information Sheet and consent process.

2.2.1. Study setting

The study was carried out in Amber *woreda* (district), part of East Gojjam Zone in Amhara regional state located 280 km North West of Addis Ababa and 20 km south east of the zonal capital, Debre Markos. There are 19 *kebeles* (smallest administrative unit) with a total population of 91,224, with 89,446 living in rural *kebeles* [70]. According to the Ethiopian Demographic & Health Survey 2011, 62% of women and 37% of men in Amhara Region cannot read at all[71]. There are 4 Health Centres (HCs) and 20 Health Post (HPs) in the *woreda*. The HPs are the lowest level in the health care system to implement the health extension package at *kebele* level and are staffed with two trained, female Health Extension Workers (HEWs), supervised by Health Centers (HCs) and the *Woreda* Health Office (WoHO) [72]. The main ethnic group is, Amhara, using the language Amharic. Although communities in the region share cultural beliefs and practices, marriage, funeral, religious and social ceremonies, there's a slight variation even between East and West Gojjam zones and among *kebeles* in the study *woreda*. There are two distinct sects of the Orthodox Christian religion: *Tewahido* and *Kibat*. (Describe both briefly). Based on this, religious days

observed vary slightly in the *kebeles* selected for the study. Subsistence farming is the main means of income with *Teff* being the major product for consumption as well as food.

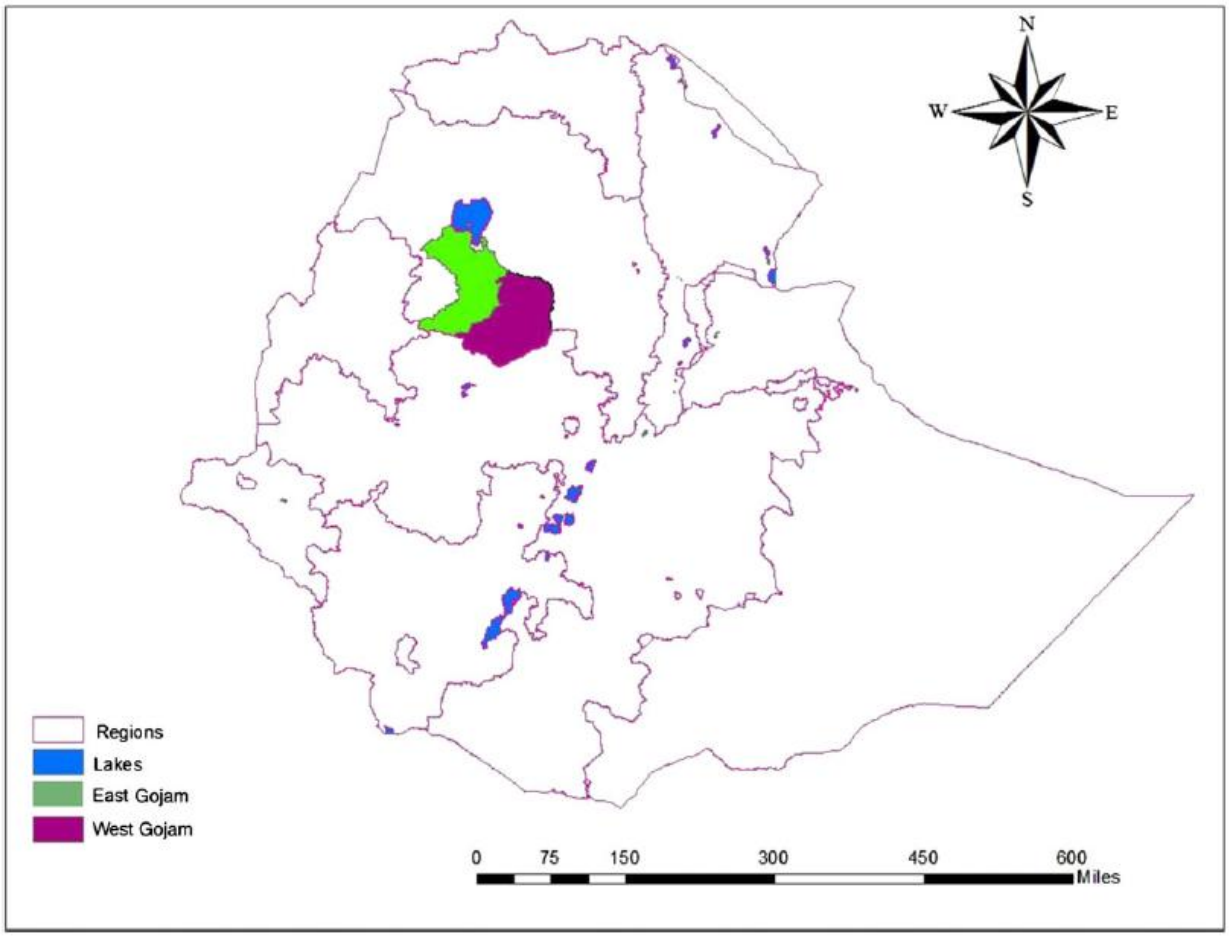


Figure 2.1 Map of Ethiopia showing position of East and West Gojjam zones.

2.2.2. Study design

Qualitative In-Depth Interviews (IDIs) and Focus Group Discussions (FGDs) were used in the REA. Semi-structured interview guides were used with items from instruments previously used REA in Ethiopia and the Gambia [73-74]. The discussion schedules varied slightly for each category of respondents. However, discussion items were structured in such a way they followed procedures anticipated in the main study. The first question related to assessing the knowledge and experiences of communities in the area about

research and consent processes. This was followed by identifying effective ways of approaching patients for participation and providing information about the study to prospective participants, including what information prospective participants wish to know about the research. Subsequent questions were designed to assess decision making traditions in communities, what constraints there're that hinder participation and identifying effective way to explain concepts of randomisation and delayed treatment. For researchers and podoconiosis experts, additional items were included to provide understanding about how understanding of information provided about the study could be provided and assess their perceptions regarding applicability of international ethical guidelines to the local context and how these can be aligned with local culture and values. Core questions for IDIs and FGDs are given (Appendix I).

2.2.3. Sampling and participants

A purposive sampling technique was used to identify potential interviewees and discussants. Experts and researchers were selected from podoconiosis prevention and treatment service providers from International Orthodox Christian Charities (IOCC), Debre Markos University. At *woreda* level, experts from the various offices health and agricultural experts, development agents were included. Finally, at *kebele* level, community, *iddir* (a form of social insurance group) and religious leaders and community members, identified through Health Extension Workers (HEWs) from three *kebeles: Wonga Nifasam, Yewobi* and *Mislawash kebeles* were selected based on their distances from Amber town, the *woreda* capital. Each FGD consisted of ten participants from three *kebeles*: remote and less remote. Accordingly, a total of 14 IDIs and 8 FGDs were conducted. The FGDs were separate for both sexes and for people with podoconiosis and non-affected community members.

2.2.4. Data collection

Initially, the objectives of the study was explained to individual participants and oral consent obtained. All discussions were digitally recorded. The interviews were conducted in offices and community; *kebele* compounds, HCs and HPs. In order to themes that emerged and modify items where necessary, data collection was stopped to analyze the first few interviews. Amharic, the local language was used in all IDIs and FGDs and each

lasted on average one to one-and-a-half hours, respectively. Data were collected by a public health expert (HN) and a social anthropologist (TA). The REA was conducted from July to August 2013.

2.2.5. Data analysis

We started data analysis alongside data collection to allow modification as well as identifying subsequent data collection activities and participants. Discussions and interviews records were all transcribed verbatim and translated into English. Coding of translated material was conducted by a team of two with the investigator leading the team debriefing meetings analysis. Constant comparison of coding was conducted and differences resolved as they arose.

2.2.6. Ethical consideration

The study was approved by the Research Governance and Ethics Committee of Brighton & Sussex Medical School and the Institutional Review Board of the College of Health Sciences, Addis Ababa University. Introductory letters were presented to regional, zonal and *woreda* level health authorities.

2.3. Developing and validating a case definition of Acute Dermatolymphangioadenitis (ADLA)

This phase of the study was intended to develop a valid definition of ADLA in order to measure the incidence and duration ADLA. To this effect, a case definition of ADLA used by different researchers was considered was adapted from that used in LF studies (Table 2.1). Feasibility, reliability and validity of the definition as used by patients and health professionals were measured. Initially, discussion with podoconiosis experts and trial methodologists was done followed by developing and testing a patient-completed, diary in which ADLA episodes were to be recorded every day. Patients and health professionals were trained on diary completion. In the following pages the process followed are described in detail.

2.3.1. Defining ADLA

The various definitions and measurement intervals used by different research in different countries in their LF studies was presented for discussion with research supervisors, experts, trial methodologists and trial monitors early in 2013. After considering definitions used by studies in LF (Table 2.1) and symptoms identified through physical examination as common features of ADLA among podoconiosis patients in a survey conducted in the area by Molla *et al* (2011); hot (49.8%) and tender (60.2%) swelling, and inguinal lymphadenopathy (62.1%), ADLA was defined for this study as "an episode of ADLA was defined as pain, redness, increased swelling of the foot/leg and swelling of the inguinal lymph nodes with or without constitutional symptoms (e.g. chills)". In addition, based on discussions on the *pros* and *cons* measurement strategies and intervals on accuracy of information by patient recall and adherence to completion a daily measurement and recording by patients using a simple diary was decided.

Table 2.1 Definitions and measurements used for acute dermatolymphangioadenitis (ADLA) in studies among patients in Lymphatic Filariasis.

Study	ADLA definition	Recording	
Suma *et al* 2002	Medical officer asked patients about occurrence of ADLA in the past year	Patient recall and medical officer examination ADL	For the year before the interview (Pre treatment, treatment and observation years)
McPherson *et al* 2005	An episode of limb inflammation accompanied by systemic symptoms. 'Filarial flares' and pictures/ video of a patient with ADLA.	Patient recall and patient-recorded estimate	Number of attacks in the past year and estimation of acute attack frequency over the past few years.
Kerketta *et al* 2005	Pain, tenderness, local swelling and warmth in the groin or limb with associated constitutional symptoms such as fever, nausea and vomiting (WHO 1992)	Patient recall of episode	Every fortnight. Frequency for year prior to treatment and during the year of treatment

McPherson *et al* 2006	A history of a red/swollen leg and associated symptoms	Patient reported frequency of ADLA	During past year
Dreyer *et al* 2006	ADLA	Patient recall (interview)	ADLA episodes during previous 12 months
Addiss *et al* 2010	Inflammatory episodes, characterized by intense pain, swelling, fever, and chills	Patient recall of episodes during a routine 4-6 weeks follow-up, additional information on ADLA since last visit not observed by staff	During the previous 12 months (frequency during the year before study
Jullien *et al* 2011	Painful, warm, red and swollen skin, peeling of the skin, painful lymph node in the inguinal area, fever, headaches, chills and sometimes nausea and vomiting†	In the month preceding consultation	Patient recall of ADLA and cellulitis or observed by the care-giver
Budge *et al* 2013	Two or more of the following symptoms: redness, pain, or swelling of the leg or foot, with or without the presence of fever or chills	Patient recall/ self-report	During any point in the previous 30 days

† A leaflet describing signs of acute attacks that had been given to each patient during their training was used to identify acute attacks

2.3.2. Diary design

In consultation with a local artist, a picture diary was designed and further discussed with advisors and podoconiosis experts working locally in study area and finalized for testing in the field. The diary depicts two people on a separate page: well people working in the farm with the description "I'm not experiencing michader-ADLA" under it and parallel to this a person sick person in bed with a description "I'm experiencing *michader*-ADLA" under it, on each page of the diary. Each page contains seven boxes (spaces with dates) under each image representing days of the week to be completed every day for a month. In addition, a

description of how the diary should be completed was given in the first pages. A sample diary is given in (Appendix 9). The validation of ADLA diaries involved three phases.

2.3.3. Comprehension/acceptability study

The first phase sought to investigate whether patients are able to understand the diary without training; acceptability and clarity of the images and date indicators used in the diary as well as convenience of the size and to confirm acceptability of the pictures drawn by local artist are easily recognizable by individual patients of different sexes and age groups.

2.3.3.1. Study site

A series of Focus Group Discussions (FGDs) were conducted with male and female patients currently receiving treatment in three IOCC clinics (Amanuel, Debre Elias, Dembecha) and non-affected community members, selected purposively to provide the most productive sample. A total of 6 FGDs (3 with each group, separate for male and female) were carried out. Participants were informed about the nature of the study and oral consent was obtained for participation and recording the discussions.

The following topics were covered in the discussions. Whether it is acceptable to use a diary to describe experiences of m*ichader* among podoconiosis affected patients; whether texts in the instruction to complete the diary and texts under the images and date indicators are readable, understandable. Then participants were asked what they understood the images as representing? Are the images clear/ visible? Whether the images could be seen embarrassing/offensive to patients; whether the size is convenient and easily kept at home without being damaged for a month and what could be done to minimise accidental damage. This was followed by discussion of patients' capacities to complete the diary on daily basis; anticipated difficulties hindering daily completion and suggestions to remind daily completion and suggestions to improve the diary. All tape recorded discussions were listened to and transcribed in Amharic.

2.3.4. Feasibility study

The aim was to see whether patients can be trained to understand the diary, estimate the length of time required for training and whether patients and can fill in the diaries on their own. To this effect, an IOCC Health Education expert was trained on the diaries to explain to patients. The use of a local expert was to be able to con vey the diary using local analogies understandable to patients. The diaries were then given to fifty-two patients attending current IOCC clinics to complete for a period of 30 days. The completed diaries were collected on the following monthly clinic visit and a short exit interview administered to qualitatively assess experiences in filling the diaries. The clinic sites for this phase were different from those where the acceptability aspect of the pilot study took place. Item in the exit interview included a three-point scale responses to questions on difficulties to complete the diary on daily basis, degree of bother associated with completion, general appearance of the diary and recommendation to be used with patients.

2.3.5. Accuracy of completion (reliability) study

The final phase was to compare patients' reports of ADLA episodes with that of health worker diagnoses. Three Health Extension Workers (HEWs)[1] and their immediate supervisor were trained on identifying acute attack episodes and provided with a clinical assessment form to be completed for all patients reporting episodes. Forty-four patients (20 females and 24 males) from two adjacent villages were trained on how to complete the diary. The procedure followed was patients mark on their diaries and report to HEWs whenever they experience acute attacks and report to HPs for verification by the HEWs. The training of Health Extension Workers from the two *kebeles* included the following: what podoconiosis is, about the trial, ADLA; diagnosis; signs and symptoms, treatment, research (validation study), clinical disease staging; completion of the clinical assessment form and data quality. The following equipments were provided: staging equipment (L-shaped IOCC type measuring board); clinical staging manual; Mid Upper Circumference (MUAC) tapes; pen (black) and clinical assessment forms. This was followed by patient

[1] Female salaried health workers located in each *Kebele*. Two HEWs are located in each Kebele.

recruitment. HEWs identified patients and appointed them for clinic days and screened in the presence of research team and investigator (HN). This was followed by training on diary completion, reporting of ADLA attacks promptly to HPs. Completed dairies were collected monthly. Whenever HEWs are in the communities for delivery of other health related home-visits, they checked the status of diary entries, made corrections using religious days as necessary and encouraged daily completion as much as possible. Data collection took place from May-July, 2014. At the end of the study patients were given intervention supplies: soaps, Whitfield's ointment, socks and shoes.

2.3.5.1. Clinical assessment form/questionnaire

Whenever patients came to the HP, HEWs completed a detailed clinical assessment form adopted from McPherson *et al*, 2006[52]. Items in the format included lymphoedema stage, lower leg and foot circumference and specific symptoms reported by patients and observed the HEWs: presence of wounds enlarged inguinal lymph nodes, tenderness, warmth and redness in the feet and peeling of the skin. The reported symptoms included increased swelling of the feet, pain, redness, and enlarged, painful inguinal symphonies, fever and chills. Finally, HEWs assessment of whether patients were currently suffering from ADLA was recorded.

2.4. Measuring the Incidence and duration of ADLA

2.4.1. Study design

The study was a pragmatic Randomised Controlled Trial (RCT) with two arms comparing podoconiosis lymphoedema management in the community with delayed treatment (as the control).

2.4.2. Sample size

Sample size calculation was based on a mean (SD) baseline incidence of ADLA of 5.6 (4.9) episodes/year reported in a survey conducted in this population[75], and assuming a reduction in ADLA frequency of 28 % (from 5.6 to 4.0 episodes per year). Based on a sample size calculation for comparison of two means, a power of 90 %, an α- level of 0.05, and a 40 % increase to enable adjustment for four confounders, and 15 % drop-out

rate[76], that is, adjusting the sample size per group (206 × 1.4/0.85), we would need a total 680 patients: 340 patients in each arm.

2.4.3. Preparatory phase

2.4.3.1. Sensitisation workshop

Based on suggestions from participants of the REA (chapter 3), a sensitization workshop was held at *woreda* level to disseminate information about the study before the initiation of screening and enrolment. A total of 46 participants attended: held at *woreda* level. Health Extension Workers, heads of health centres, *kebele* leaders from the selected nine study *kebeles*, officers from the *Woreda* Health Office, representatives of government communication, education, agriculture, administration offices. Presentations were made on what podoconiosis is and its impact, the difference between treatment services and research, the objectives and relevance of the proposed trial, and the need for support and collaboration from all sector offices for the successful completion of the study. In addition, procedures for identification of study *woreda*, *kebeles*, and prospective participants, concepts such as randomisation and delayed treatment were explained using agricultural analogies[77]. Finally, expected benefits of the results of the study to individual participants in the *woreda* as well as patients in other places were discussed.

2.4.3.2. Developing Standard Operating Procedures (SOPs)

A two-weeks training was provided to the PI on practical aspects of running a clinical trial at Kilifi Clinical Trials Facility (KCTF) in Kenya. These included the development of Standard Operating Procedures (SOPs), study logs, Intervention Product (IP) management, handling office files, Adverse Event (SAE) monitoring and reporting. Accordingly, 14 SOPs and 11 study logs were specifically developed for the study and translated to Amharic. In addition, all fieldworkers and the PI took Good Clinical Practice (ICH-GCP) certification from www.globalhealthtrials.org. A sample certificate for fieldworkers is in (Appendix 9).

Table2.2 Standard Operating Procedures (SOPs) and logs used in the study.

Study Standard Operating Procedures (SOPs)	Study Logs
• Screening and Enrolment • Clinical Staging • Immunochromatographic Test (ICT) • Informed Consent ion • Intervention procedures • ADLA diary completion • Safety Reporting • Handling IPs • Communications • Local Safety Monitor • Randomization • Data Management • Data entry • Data archiving	• Screening and enrolment • ICF • CRF completion • Protocol deviation • Fieldworkers' duty delegation • Home description form • Home follow up form • IP stock inventory • IP dispensing and accountability • Monitoring • SAE reporting

2.4.3.3. Recruitment and training of fieldworkers

Community Podoconiosis Assistants (CPAs) and Data Collectors (DCs) were recruited from each study *kebele*. This was to minimise difficulties in communication and access to *kebeles* and villages that would be created had fieldworkers were recruited from other areas. High school completion was a criterion for both CPAs and DCs. Females and over 18 was requirement for CPAs.

A five-days training was provided on the following areas: research, ICH-GCP, responsibilities, investigator responsibilities, data quality, background to the study, study procedures; screening and enrolment, informed consent, essential documents, monthly intervention visits, Adverse events,; definition, documenting and reporting, communication within teams and responsibilities.

Table 2.3 Training of Community Podoconiosis Assistants (CPAs) and Data Collectors (DCs).

Screening and enrolment
Clinical/disease staging
Immunochromatographic Test (ICT)
Informed Consent SOP
Intervention procedures
Handling of intervention products
ADLA diaries
Safety reporting,
Communications
Randomisation, data entry

2.4.3.3.1. Immunochromatographic Test (ICT)

A Binax-Filariasis rapid antigen test (Immunochromatographic Test (ICT) was used to rule out lymphatic filariasis. The test was conducted by an experienced laboratory technology expert working at IOCC Debre Markos field office. An SOP describing working instructions on conducting the ICT test and procedure for discussing test results with patients and disposal of ICT card test items. None of the participants tested positive during enrolment.

2.4.3.3.2. Podoconiosis staging

Cognizant of the fact that podoconiosis progression at later stages is quite different from that of LF, Tekola *et al* (2008) developed and tested a five scale clinical staging for podoconiosis. Accordingly, the first stage has swelling limited to below the ankle and reversible overnight. This swelling is not reversible overnight; it would be classified as the second stage. The third stage is swelling above the ankle, which could be nodular or soft (water bag). Above the knee swelling and joint fixation represent, the fourth and fifth stages, respectively. The system was unambiguous with a high inter-observer agreement

between health professional as well as health professionals and CPAs (0.71 and 0.64, respectively) [44]. The system was used by several studies which sought comparison. A prevalence study in East and West Gojjam[56], a study in southern Ethiopia which assessed the effectiveness of a similar intervention[76], a recent nationwide mapping of podoconiosis in Ethiopia [29] and a randomised controlled trial to determine effectiveness of a skin care intervention to improve skin barrier function in southern Ethiopia[66]. Community Podoconiosis Assistants (CPAs) were trained on the theoretical as well practical aspects of disease staging and measuring foot and leg circumference.

2.4.3.3.4. Procurement of supplies and intervention products

Supplies and consumables required for the trial were procured from markets within the country. Toilet soaps (GIV international white) were obtained from Addis Ababa, while Whitfield's ointments were procured from Addis Pharmaceutical PLC in Ethiopia. Immunochromatographic card tests (ICT) were procured obtained from EPHI, a study of mapping LF and Podoconiosis [29].and then transported to the field following the appropriate cold chain procedures using cold boxes.

2.4.3.3.5. Obtaining ethical approvals

Ethical approvals were obtained from the five institutions. The Research Governance and Ethics Committee of the University of Sussex (RGEC) in the UK and College of Health Sciences, Addis Ababa University (AAU), Food, Medicine and Health Care Administration and Control Authority (FHMACA), National Research Ethics Review Committee of the Ministries of Health and Science and Technology in Ethiopia (NRERC) and Ethics Committee of the Regional Health Bureau, Amhara Regional State, in Ethiopia (Table 2.4).

Table 2.4 Institutions from where ethical approvals for the study were obtained.

Institution	Approval number	Approval date
Research Governance and Ethics Committee of the University of Sussex (RGEC)	13/107/DAV	12/08/2014
College of Health Sciences, Addis Ababa University (AAU)	056/2014; protocol number 071/13/SPH	12/01/2014
Food, Medicine and Health Care Administration and Control Authority (FHMACA)	02/6-1/05/39	09/04/2014
National Research Ethics Review Committee of the Ministries of Health and Science and Technology in Ethiopia (NRERC)	3-1/794/06	02/06/2014
Ethics Committee of the Health Bureau, Amhara Regional State, Ethiopia		02/12/2015

2.4.3. Study setting

The study was conducted in Amhara Regional State, East Gojjam Zone, Aneded *woreda* and based at the International Orthodox Christian Charities (IOCC), Debre Markos Podoconiosis Project[75]. The *woreda*, has an estimated total population of 89,446[70], and made up of 19 *kebeles* (smallest administrative sub-unit) each with an average population of approximately 5,000 people and 4 Health Centres. Eighteen *kebeles* were included in the study.

Selection of w*oredas* for the study considered existence of podoconiosis prevention and treatment services. From *woredas* in East Gojjam zone, Aneded was selected for the reason that there was no government or Non-Government Organisations providing the service in 2013. Once the *woreda* was selected, discussion was held with *woreda* Health Office exerts to identify *kebeles* in which highest number of cases are located and list the nearest to the

woreda capital Amber. Nine *kebeles* were selected. Table 2.5 lists study *kebeles* and number of participants.

Table 2.5 Number of participants included from each *kebele* selected for the study.

Kebele	№ of patients (%)
Yewobi	26 (3.7)
Wonga Nifasam	54 (7.7)
Jama	104 (14.9)
Addisge	63 (9.0)
Amber Zuria	63 (9.0)
Gudalema	54 (7.7)
Yewish	41 (5.9)
Shimbrima	19 (2.7)
Talak Amba	52 (7.5)
Enaskay	29 (4.2)
Gentua	18 (2.6)
Zinkir	20 (2.9)
Chendefo	23 (3.3)
Daget	18 (2.6)
Mislawash	24 (3.4)
Sendeba	27 (3.9)
Tikur Adber	27 (3.9)
Zengoba	36 (5.2)
Total	698 (100.0)

The largest number of participants was recruited from big *kebeles* where podoconiosis prevalence was reported to be higher. Discussion with *Woreda* Health Office (WoHO) experts revealed that larger numbers of patients were observed in: Jama 104 (14.9) followed by Addisge, Amber Zuria, Wonga Nifasam and Talak Amba. However, since the required number of patients for the study was not met in these *kebeles*, in the next phase of recruitment, *kebeles* in which smaller numbers of patients were observed were considered. Accordingly, Enaskay, Genetua, Chendefo, Daget, Mislawash. Sendeba, Tikur Adber and Zengoba had smaller percentage of patients (Table 2.5).

2.4.4. Participant recruitment

The prevalence of podoconiosis in northern Ethiopia is estimated to be 3.4%[78]. Participants were drawn from adults aged 18 years and older podoconiosis affected patients in Aneded *woreda*. There was no government or private treatment for podoconiosis anywhere in the region. In 2010, a podoconiosis project was established by IOCC and began treatment of 200 patients. Initially, podoconiosis patients from nine *kebeles* of Aneded *woreda* were invited to participate. The recruitment procedure followed was that first, community sensitisation through *woreda* and *kebele*-level officials was conducted. Then, Health Extension Workers in *kebeles* selected for the study were asked to list patients in their respective *kebeles*. All patients identified by Health Extension Workers (HEWs) were then visited at home by data collectors who during the visit requested consent for preliminary evaluation against eligibility criteria (table 2.6). Once agreement is obtained, data collectors mapped these patients by recording Geographic Information System (GIS) coordinates of their houses This generated a target list of approximately 850 potential participants. Patients who agreed to participate were then given appointment dates for enrollment. If more than one eligible patient is found in one household, one will be randomly selected using a lottery method.

2.4.5. Eligibility criteria

Table2.6 Inclusion, exclusion and withdrawal criteria used for the study.

Criteria		
Inclusion	**Exclusion**	**Withdrawal**
Be at least 18 years old	Already undertaking self-treatment comparable to the intervention	Wishes to withdraw consent to participate in trial
Have provided informed consent	Nodular disease preventing use of shoes (will be referred for nodulectomy)	Move outside study w*oreda*
Have a diagnosis of at least Stage 2 podoconiosis (i.e. podoconiosis lymphoedema) confirmed by the trial team	Complex wounds (will be referred for specialist care in Debre Markos Hospital)	Experiences of SAEs considered by trial coordinator to compromise ability to participate
Have a negative ICT card test	Patient has a history of allergic reaction to treatment materials	Experiences of SUSAR
Intends to remain within the area during the study period	Mental health or learning disorder affecting ability to adhere with treatment	
	Physical disability beyond podoconiosis precluding attendance at group sessions	
	Disease considered by the Trial Co-ordinator to affect	

ability to self-treat.

2.4.6. Enrolment and consent procedures

Based on information from the REA, eligible participants were appointed to health facilities (HPs and HPs). On arrival, a trained Health Educator conversant in the local dialect provided group information about the trial. This was followed by individual consent being requested. Where a participant/s was unable to read and write, an impartial witness signed the consent form after asking the individual participants if they had clearly understood what participation entailed. Those who responded "YES", were asked to describe in their own words main aspects of participation: study procedure, risk/benefits, privacy, voluntary participation, and understanding of how to get further information. A copy of the signed consent form and information sheet was then provided to each potential participant to take home to for later reading. Once consent is obtained, patients undertook the Immunochromatographic test (Binax-Filariasis rapid antigen test) and those with negative results were then subjected to the baseline questionnaire and informed to wait for information on their group allocation. Finally, a passport size picture of each participant was taken and a study identification card provided.

2.4.7. Randomisation and blinding

The thesis was a pragmatic individually randomised RCT with two arms. Using a sample frame of households within *kebeles*, and enrolment list generated patients were randomised on a 1:1 ratio to the two study groups: "immediate" and "delayed" treatment by statisticians at Kenya Medical Research Institute-Wellcome Trust Research Programme (KWTRP). Patients were randomised in excess of the required sample size to allow for those who decline the invitation to participate or who are later found not to fulfill the inclusion criteria. The trial could not be blinded for two reasons. First, although a separate team was allocated for delivering the intervention and data collection, data collectors mat deduce the trail status of their patients when they see supplies being given to some and not others. Similarly, statisticians couldn't be blinded. Instead, in order to minimise bias during analysis *a prioi* analysis plan was developed and adhered to. Randomization took place in

two phases. The first wave enrolled 401 participants from 9 *kebeles.* Since the required sample size was not met other *kebeles* were considered. The second cycle of randomization included 295 patients. The second randomisation included remote and inaccessible *kebeles*. Study team had to travel up to six hours to reach some of the remotest *kebeles* with ragged unfamiliar terrain.

2.4.9. Data collection instruments and follow up visits

The study follow up visits were quarterly from baseline at 3, 6, 9 and 12 months. The baseline questionnaire (Appendix 12) consisted of enrollment and eligibility check for confirmation. Both at baseline and 12 months, socio-demographic information, shoe wearing and foot washing experiences, history of ADLA attacks in the past 30 days, clinical assessment form: disease stage, presence of wounds, mossy and inter-digital lesions, swollen lymph nodes (both sides), and signs of ADLA, the Amharic version of Dermatology Quality Life Index (DLQI)[38]. Experiences of Adverse Vents (SAEs) were actively followed at each Monthly Intervention Visits (MIVs) in the immediate treatment group and through enquiries in the delayed treatment group (Table2.7).

Table 2.7 Data collected at baseline and at 12 month follow up.

Data collected	**Baseline**	**12 Month**
Socio-demographic	✓	✓
ADLA	✓	✓
SAEs	✓	✓
DLQI	✓	✓
Foot & leg circumference	✓	✓
Clinical stage	✓	✓
Mossy lesions	✓	✓
Inter-digital lesions	✓	✓

2.4.10. Endpoints

Primary endpoint: incidence of ADLA (total number of incident episodes at baseline and 12 months follow-up).

Secondary endpoints: clinical stage of disease (Using a scale specifically developed for use in podoconiosis patients), foot and leg circumference (Measured in centimeters at mid-calf and mid-foot) presence of mossy changes, wounds and inter-digital lesions; duration of ADLA days and Quality of life (Using validated Amharic translation of Dermatology Life Quality Index.

2.4.11. Study monitoring

The study was monitored by staff from Kilifi Clinical Trials Facility (KEMRI-Wellcome Trust). There were a total of four monitoring visits: site initiation, first and second routine monitoring visits and closing out visit (Table 2.8). In addition, data base was monitored by statisticians remotely. Any discrepancies and queries were flagged and instantly check and remedied.

Table 2.8 Study monitoring and activities conducted during each visit.

Visits	**Dates**	**Agenda/activities**
Site initiation	8-12 Dec, 2014	Assess participating health facilities/clinics, overall study population and screening data, assess coordinating site, study supplies availability and storage, field staff availability, and training, Review site files, regulatory approvals
First routine monitoring	27 Mar-1 Apr, 2015	Review CRFs, enrollment logs, attend first Monthly Intervention in two *kebeles*, review ICFs, monitor site files, study supplies management
Second routine monitoring	7-14 Nov, 2015	Check ICFs, enrollment logs, completed diaries, site files, study supplies management

Close out monitoring	24-26 May, 2017	Check all documents are available and approve for archiving

2.4.12. Adverse event monitoring

Patients randomised to the immediate treatment group were asked the following question: "Have you felt different in any way since the last time we met here while using Whitfield's ointment?" on each MIV. Similarly, any deaths, or SAEs were being recorded in Adverse Event Form and reported to the Trial Co-ordinator on the same day (maximum 12 hours). The coordinator will then notify the Local Safety Monitor (LSM) at Debre Markos Referral Hospital (DMRH) who'll in turn consult with an Addis Ababa-based LSM and decide whether the event was related to the intervention or not. Table x describes SAEs, diagnosis or cause of death and attribution to the intervention.

2.4.13. Data quality control and field supervision

Diary and adherence data were collected by CPAs while data on follow up visits were collected by data collectors. Accordingly, both data collection activities were supervised in the field by CPA and DC supervisors as well as senior research team members: investigator and trial data manager. Before each regular follow up visit, refresher trainings were provided on data quality and ensure consistency. In the actual field supervisions, emphasis was given to adherence to the protocol as well as standard operating procedures. Data were checked for completeness and accuracy at field level and immediately at office. In the field, CPAs and supervisors checked and verified the occurrence of ADLA events by recall using religious holidays as reminders for patients. Once the data arrived in the office, the ADLA diaries and adherence formats were checked and signed by supervisors and countersigned by senior team member (HN) and stored for transport to the main data entry site along with the quarterly data.

2.4.14. Data entry

Data from the field was checked once again at the study site office. All diaries collected were matched with corresponding questionnaires completed for each patient and bound before being transported to Addis Ababa, IOCC country office. The data transfer log were completed and signed by CPA and DC supervisors and countersigned by the trial coordinator. Data entry was done by two independent data entry clerks supervised by a data manager. Data was entered into OpenClininca software. Data entry was also monitored remotely by statisticians and trial monitors from KEMRI in Kenya, checked at regular monitoring visits and queries resolved regularly and before analysis.

2.4.15. Data analysis

The analysis was conducted based on Intention-to-Treat (ITT), i.e. by including all participants enrolled. The sum of ADLA episodes recorded in diaries was used to estimate ADLA incidence and duration. However, where diary data were missing, with the patients still in the study, missing data were estimated by patient recall of number of episodes over the past 30 days and multiplying that figure by three to provide a one year estimate.

Baseline characteristics of participants in both groups are presented using descriptive statistics; percentages for categorical data and median (IQR) for continuous and no comparisons or statistical tests performed. Statistical analysis of differences at baseline was believed to be unnecessary[79]. Instead, the factors associated with the number of ADLA in the past 30 days, duration of ADLA symptoms and scores on Dermatology Life Quality Index (DLQI)[38] at baseline characteristics were tested using Poisson regression. Subsequently, a comparison was made between the immediate treatment and control groups in the number of ADLA episodes in the past 30 days, duration of ADLA symptoms and changes in DLQI scores at 12 months and any relevant differences discussed in chapter 5. Using date of enrolment as starting point and study conclusion through voluntary withdrawal, loss to follow-up, death, or trial completion as the last observation for end of participation, the number of days in between was used as the duration of observation for each participant in each group. Accordingly, for participants who were lost to follow up or didn't complete the study, ADLA data recorded up to the last day were calculated. To this

effect, the total person-years of observation, the total number of new episodes of ADLA reported, the incidence ADLA (95% CI) by dividing new reports of ADLA by the total observation time (per person-year), the incidence rate ratio (95% CI) were calculated for individuals in each arm. The total duration of ADLA episodes and symptoms (in days) calculated on the basis of days of observation were calculated and compared among individuals in each group using rank sum test.

2.4.16. Quality of Life

Scores on DLQI were used to compare from baseline to 12 month follow up. Poisson regression models at baseline were used to determine factors associated with DLQI scores. At 12 months follow up median scores for the two groups were compared using rank-sum (Mann-Whitney) test.

2.5. Process assessment of the study

The study was conducted to evaluate the acceptability, feasibility of the intervention and impacts (health, social and economic) from the perspectives of participants and deliverers.

2.5.1. Study context

The study was conducted as part of a randomised controlled trial of podoconiosis treatment in northern Ethiopia (GoLBet). The trial was conducted in Aneded *woreda*, East Gojjam Zone, Amhara Regional State where prevalence of podoconiosis is 3.4% in the adult population[78]. The *woreda* is located 280 km North West of Addis Ababa and 20 km south east of Debre Markos, the zonal capital. According to the 2007 Census, Aneded w*oreda* is made up of 19 *kebeles* (smallest administrative unit) and has a total population of 91,224, with 89,446 living in rural *kebeles* [70]. It has 4 Health Centres (HCs). During selection of participants for the trial, patients already undertaking self-treatment comparable to the intervention were excluded [57] . Focus Group Discussions and In-depth Interviews were conducted at Health Posts (HPs) and Health Centers where the trial intervention was delivered.

2.5.2. Study design

A qualitative study using was carried out from February to June 2016. Employing qualitative techniques to elicit data for the study enabled researchers to explore and describe perceptions about the intervention procedures. In-Depth Interviews (IDIs) and Focus Group Discussions (FGDs) were conducted among patients and their families, Community Podoconiosis Assistants (CPAs) and their supervisors as well as Health Extension Workers in selected study *kebeles*. Differing semi-structured interview guides were developed to address the research questions and translated to Amharic (the local language). Focus groups with trial participants were designed to explore: acceptability and feasibility of the intervention; adherence to and unanticipated consequences of the intervention; perceived impacts of the intervention (health, economic and social); satisfaction with the way intervention was delivered; barriers to implementing the intervention at home and improvements required for future treatment and sustainability. Interviews with CPAs explored: training and understanding of research; adherence with the intervention; barriers to practicing the intervention and likely implications for translation into routine policy and practice. In addition, on-site visits and direct observations of Monthly Intervention Visits (MIVs) were made, and one Key Informant Interview was conducted with a *woreda* health office expert. Focus groups were conducted with male and female patients in selected *kebeles* on the days of MIVs. Further, at each MIV, patients were requested to invite a family member (person closely following or assisting patient in the day-to-day treatment at home) to the Health Post (HP) on the next day (or the same afternoon, if villages were close by) to participate in the interviews.

2.5.3. Participants

The trial participants included 680 patients from 18 *kebeles* in the *woreda*. From those randomised to the 'immediate treatment' arm (340) of the trial, a purposive sampling strategy was employed to select individual participants to achieve maximum variation with respect to location (*kebele*) and gender and select the most productive sample to answer the research question. Intervention sites, Health Posts and Health Centers were selected to represent the range of settings in the trial, so that both urban and rural sites were included.

Since randomisation for the trial was carried out in two phases, selection captured views of participants in both phases. However, the selection of participants for FGDs and IDIs was an iterative process. Once the preliminary interviews had been reviewed and analyzed, further data collection was arranged and new participants identified. Accordingly, 10 FGDs were conducted with patient and CPAs, and 18 IDIs were conducted with family members, HEWs, CPA supervisors, a *Woreda* Health Office expert, patients who had completed treatment and patients who had voluntarily left the study. The number of participants in each FGD ranged from 7-10.

2.5.4. Data collection tool

Items in the discussion guides were developed based on framework recommended by the Medical Research Council (MRC) [80-81].

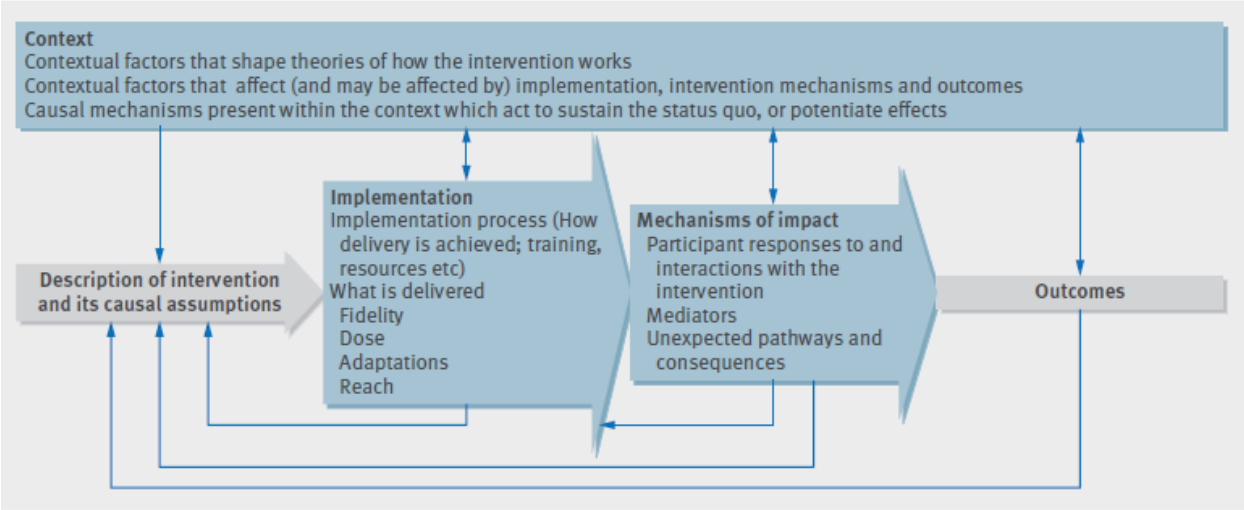


Figure 2.2 Key functions of process evaluation and relations among them (blue boxes are the key components of a process evaluation. Investigation of these components is shaped by a clear intervention description and informs interpretation of outcomes), adapted from Moore *et al* (2015)[80].

Accordingly, the following areas were explored: acceptability and feasibility; adherence to and unanticipated consequences of; perceived impacts (health, economic and social); satisfaction with delivery; barriers to implementation; sustainability and suggestions for improvements in the future.

2.5.5. Data collection

A previous non-controlled, follow-up study among podoconiosis patients in *Wolaita* indicated differences in periods of observed improvement in health and social related outcomes. For example, very rapid improvements were detected in quality of life measures (within the first 3 months), but slower clinical changes, with statistically significant changes being after 6-9 months of follow-up[65]. Accordingly, in order to capture an accurate assessment of perceptions and expectations about the intervention, data collection was carried out between 6-9 and 3-6 months of intervention. Interviews were carried out in Amharic (the local language). Participants' permission was obtained to record all discussion. In addition, notes were taken during discussions. Interviews and FGDs were led by a public health expert from Debre Markos University. The expert had considerable experience in qualitative research as well as the culture of the study area and the region but was independent of the trial. The study coordinator led the development of interview schedules and clarified issues that arose in the field. Debriefing sessions were held after each field activity. Data collection continued to the point of saturation.

2.5.6. Data analysis

Data analysis was initiated alongside data collection. *Information about data collection activities were recorded in a log sheet. All data collected including interview tapes, transcribed and translated material, and field notes were constantly checked, indexed and systematically categorized.* First, all interviews and FGDs were transcribed and translated into English and checked for consistency. This was followed by close reading of the transcripts and coding. Final data analysis was performed using a thematic approach based on themes identified *a priori* and others that emerged during the analysis. Data were organized using NVivo 11 Pro for Windows[82].

2.5.7. Ethical considerations

The Ethics Review Committee of the Amhara Regional Health Bureau approved the study. Participants were informed about the objectives and the voluntary nature of the qualitative study at the outset, and oral consent to participate was requested from those interested.

Participants were also informed that any information they provided would be kept confidentially and that the final report would not include personally-identifiable information. Interview tapes will be destroyed after five years of completion of the study (as per University of Sussex policies). The trial is registered with International Standard Randomised Controlled Trial, Registration number: ISRCTN67805210. Date of registration: 24 January 2013[57].

Chapter: 3 Rapid Ethical Assessment

3.1. Overview: The Roots of research ethics

Violation of human participant rights in the past begins with the troubling legacy of the Tuskegee Syphilis study, in 1932[83], the Nazi war crimes (1941-1945), and the 1966 Thalidomide scandal in Europe[84]. During World War II, prisoners were coerced into "Medical Experiments" and tortured to death in the name of science and without their consent to such experiment. These atrocities demanded an urgent response which led to the development of subsequent legislation. The 1947 Nuremberg trials confronted the difficult question of medical experimentation on human beings and outlined ethical and moral principles governing clinical experiments, known as the "Nuremberg Code". This first international code of research ethics served as the model for many professional and governmental codes. The ten principles included: consent given voluntarily, participants anticipating scientific benefits, benefit must outweigh risk, animal experiments should be conducted first, avoidance of human suffering, avoiding intentional death or suffering of participants, protection from harm, subjects' freedom to withdraw, the requirement for qualified investigators and that investigators to stop treatment immediately if harm occurs[85].

In 1964, in what was determined to be the first move towards developing guidelines to regulate research undertakings, the statement of ethical principles was issued by World Medical Association (WMA). This became known as the "Declaration of Helsinki" to provide guidance to physicians and other participants in medical research involving human subjects. Requirements such as rigorous scientific standards, qualification of investigators, a research protocol and written informed consent for participation were set. Subsequently, the Council for International Organization of Medical Sciences (CIOMS) and the World Health Organization (WHO),developed guidelines [86]. In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report; ethical principles and guidelines for the protection of human research subjects. Respect for autonomy, beneficence and justice were the basic ethical principles outlined[87]. Further, the need for harmonization of technical requirements for

registration of pharmaceutical products for human use was considered an urgent requirement by representatives of regulatory agencies and industry in Europe, Japan and the USA including other stakeholders such as the WHO, Canada and some Nordic countries. The 1996 meeting, based on the Declaration of Helsinki, gave birth to the Good Clinical Practice (GCP) guideline which sets informed consent as one of its main tenets[88].

3.2. Informed consent requirements

The Informed Consent (IC) process, as specified in international, legal and ethical guidelines such as the Nuremberg Code[85], The Declaration of Helsinki[89], The Belmont Report[87] and The Council for International Organizations of Medical Sciences (CIOMS)[86], became a mandatory requirement in clinical research. IC is a process where an individual voluntarily agrees to participate in research after explanation of the purpose, risks and alternatives of the study. The ethical principle of "Respect for Persons" identifies the consent process as containing three key elements: the provision of study-related information, comprehension of information provided, and voluntary decision to participate[87]. First and foremost, the consent process means respecting autonomy and decision-making capacity of potential participants of a study. Secondly, through provision of information about potential risks of participation, it serves as a mechanism for protecting participants by enabling them to make informed choices about participation or declining to partake in studies[90].

More specifically, establishing genuinely informed consent requires the following conditions. The concept of voluntariness as declared in many documents is a decision made by participants to take part in a study without any coercion, undue influence or harassment. Secondly, capacity relates to an individual's ability to decide based on ability to understand the information provided. Disclosure involves provision of all relevant information about the research to participants, including its nature, purpose, risks and potential benefits as well as the alternatives available[91]. Understanding implies that research participants are able to comprehend the information provided and appreciate its relevance to their personal situations. Decision is the final conclusion that is made to

participate, or not. Potential participants must be allowed adequate time to make a voluntary and informed decision about participation [86, 88, 92-93].

Nevertheless, a spectrum of factors affects decision making to participate in a study. Among others, comprehension of information provided about the research influences the decision to participate in a scientific investigation. Studies have shown that information provided in information sheets and informed consent documents may be completely alien to potential participants. Studies in other contexts have indicated that participants found the "Experimental nature of study", "Potential risks or discomforts", "Benefit to self", and "Compensation" difficult to understand [94-97]. In developing countries, limited access to health care, low literacy levels, lack of experience of participating in clinical research, decision-making and consent procedures, may all affect understanding [98-99].

Although some have suggested that understanding of information increases with level of education, studies in some SSA countries do not support this. A study in the Gambia found no significant association between understanding and level of education among respondents [100]. This stresses the fact that illiterate participants are generally able to comprehend information, but indicates that information provision should take a different approach[101]. In the context of the developing world, international guidelines such as the Nuffield Council on Bioethics[102], CIOMS[86], the European Union guideline on clinical trials and the National Bioethics Advisory Committee recommend strategies for researchers to develop culturally appropriate approaches of obtaining informed consent in ways that observe and respect communities and individuals that participate in clinical research[101].

Thus, researchers are required to provide potential participants with sufficient information about a trial. This should include the study objectives, design and procedures to be followed, identification of procedures which are experimental, risks and benefits of participation, expected duration of the study, their rights as participants, a disclosure of alternative courses of treatment, extent of confidentiality of records, and an explanation of whom to contact with questions about the research and research subjects' rights. Potential participants must be allowed adequate time to make a voluntary and informed decision

about participation. Developing strategies to provide information in a language prospective participants are capable of understanding, and assessing understanding, are critical in obtaining genuine consent before trial enrollment[86, 88, 103].

Among the many factors that shape approaches to implementing informed consent is the nature and cultural context of the study[98]. Unlike developed countries, where informed consent procedures are highly structured and regulated, consideration of inherent socio-cultural and educational differences warrant examining informed consent in developing countries. Krogstag *et al* (2010) consider several differences between developed and developing countries. For example, decision making to provide informed consent in developed countries directly involves participants, unless otherwise minors are involved. On the contrary however, communal decision-making is prevalent in rural areas of sub-Saharan Africa [103]. Family members, neighbours and community leaders may influence decisions and voluntariness. In some cultures commonly accepted gender roles expressed through responsibilities and representations influence decision-making. That is, male heads of family may have the final say when it comes to matters affecting the family [104-106]. A study on the impact of gender on the decision to participate in a clinical trial in Brazil indicated the increased likelihood of females' decisions to be influenced by their families, than their male counterparts[107]. A genetic study conducted in southern Ethiopia showed the tradition of decision-making involves consultative approval of participation where families need to be given sufficient information before individual participants are approached[108].

On the other hand, in developing countries where the majority of the communities are not literate and are research-naïve, understanding of the differences between research and routine health care services may be lacking. This blending by research subjects of research and medical care (referred to as the "therapeutic misconception") has serious implications on informed consent as well as trust with researchers. The therapeutic misconception was first described by Applebaum *et al* (1982). It refers to the belief that research has direct health benefit as an outcome to participation instead of the possibility of potential benefits to others in the future as a result of the knowledge gained through the research[109]. A recent study prior to a genetic study among podoconiosis patients in north-western

Cameroon found that participants were able to paint a picture of the differences. However, participants thought research was a diagnostic procedure. Only a small number of participants thought of research as having immediate therapeutic benefit [110]. Similarly, REA in southern and northern Ethiopia indicated the existence of the 'therapeutic misconception', including the understanding of health research as a form of laboratory investigation prior to treatment [73, 111]. Thus, mixing the concepts of research and health care is common and researchers must endeavor to clarify the differences in an attempt to encourage participation, retention and protection of participants' rights as well as for continued involvement of the community in similar future research[73, 112-114]. On the other hand, incorrect attribution of therapeutic aspects of trial procedures leads patients to underestimate risks and /or overestimate benefits[115].

Other concepts in research such as the right to refusal and randomisation[116] are also difficult to explain in communities with low literacy[93].The probability of participants from developing countries understanding the concepts of voluntary participation and freedom to withdraw at any time was lower than others. Reasons that refusal and withdrawal are uncommon include fear of disapproval from researchers[117]. Misunderstanding of inclusion and exclusion criteria may also produce adverse consequences. Participants included in the study may consider their inclusion as an indication for having the disease or condition being studied. On the other hand, excluded community members may be plagued by the thought of being deprived of benefits of participation. In poor communities, this could be benefits such as safety net programs[111]. Thus, approaching study participants through people trusted by the community and conducting community sensitisation before commencing recruitment remain crucial [73, 104, 118].

Research participants in rural areas may prefer not to know details about research procedures and tend to provide consent immediately based on the perceived social standing of researchers and the belief that all health personnel work only to improve their health. However, in settings, particularly, those with little or no previous exposure to research[118], this implies the importance for researchers to discuss the study with potential participants and ensure they know they can refuse to take part without

jeopardizing their right to regular medical care[116]. Nijhawan, *et al* (2013) described challenges that face informed consent as language barriers, religious influence, false expectations, patient perceptions, children, vulnerable people and groups[119].

Similarly, cultural differences in rural areas in developing countries pose different issues for researchers. Among others, the taking of blood, traditional beliefs of causes of diseases and culturally acceptable approaches for participation in research are important socio-cultural realities that need consideration in rural areas. In some areas, people may associate the drawing of blood only with HIV testing. Secondly, providing blood samples may also create apprehension, based on thoughts that it might end up with revealing unanticipated results such as cancer, without the possibility of getting treatment for those conditions[111]. Researchers in developing countries are also faced with difficulties in effectively informing participants about the purpose, method, risks and benefits of the research. Cultural taboos in communities in some African countries prevent use of some Western terms locally. In Western Nigeria, words such as "sexual intercourse" among unmarried persons is not permitted and that traditionally "sleeping together" is used instead, which doesn't necessarily mean sexual intercourse[120]. Similarly, in northern Ethiopia "vaginal discharge" was found to be difficult to explain, as it was confused with "menstrual discharge" and "secretions produced during sexual intercourse". Further, some terms may not have local equivalents and may be difficult to explain. The acronym "HPV" had no local equivalent in Tigray and was confused with "HIV" [111].

Furthermore, obtaining signed and dated consent forms, written documentation of informed consent for studies can be particularly problematic in certain cultures[73]. Individual participants and communities may be reluctant to put their signatures or thumbprints on a document because of previous experiences of having signed "legal" forms that resulted in political, economic and social victimization including loss of property and sanctions against them [121]. In northern Ethiopia, signing a document was associated with legal responsibilities and accountability such as obligation to participate in environmental protection campaigns such as reforestation and soil conservation. Assumptions are made that participation in research is an obligation and requesting signature is an indication of that obligation and could be used later to penalize

nonconformists and prevent withdrawals. Participants may not trust investigators' assurances of confidentiality, and so be less likely to raise discussion questions freely, with instead a tendency to focus on positive aspects without expression of true feelings. Accordingly, oral presentation of study information may be preferred[111].

Nguyen Thanh Tam *et al* (2015) conducted a systematic review and meta-analysis of participants' understanding of informed consent in clinical trials over the past three decades. One hundred three studies evaluating 135 cohorts of participants were included. The pooled proportion of participants who understood components of IC varied from 52.1% to 75.8%. Seventy-five percent understood freedom to withdraw at any time, 74.7% the nature of study, 74.7% the voluntary nature of participation, 74.0% potential benefits, 69.6% the study's purpose, 67.0% potential risks and side-effects, 66.2% confidentiality, 64.1% the availability of alternative treatment if withdrawn, 62.9% knowing that treatments were being compared, 53.3% placebo, and 52.1% randomization. Most participants, 62.4%, had no therapeutic misconceptions and 54.9% could name at least one risk. Age, educational level, critical illness, the study phase and location, significantly affected understanding and indicated that the proportion of participants who understood informed consent had not increased over 30 years and that investigators could do more to help participants achieve a complete understanding[93].

These issues demonstrate the need to orient requirements specified in international guidelines to the local context in which a study is to be conducted. Thus, when clinical trials are to be conducted in low-income countries, especially in communities with little or no previous experience of participating in research, providing information that is both comprehensive and comprehensible may be very challenging. Relevant training for fieldworkers, discussion with stakeholders, communicating with participants at different stages and providing incentives are important for successful recruitment and retention of subjects in clinical trials[122]. Information should be communicated to individual participants beginning from recruitment and screening to study conclusion [119]. In addition, for researchers with little or no understanding of the study area, the role of local guides, local investigators, and socio-anthropologists is critical[101].

3.3. Rapid Ethical Assessment

There is increasing recognition that not all Western ethics principles translate directly to developing countries, and that they may require careful modification to fit local sociocultural values [90, 120, 123]. Rapid Ethical Assessment (REA) began with the understanding that there was no previous empirical research designed to guide information provision and the consent process[123]. Accordingly, the informed-consent process cannot simply be transferred from developed to developing countries without considering the cultural, socioeconomic, and educational factors that influence international research[103]. Since provision of information and understanding of information by potential participants is an integral part of a truly informed consent, Western ethical principles need to be adapted to the local context in developing countries.

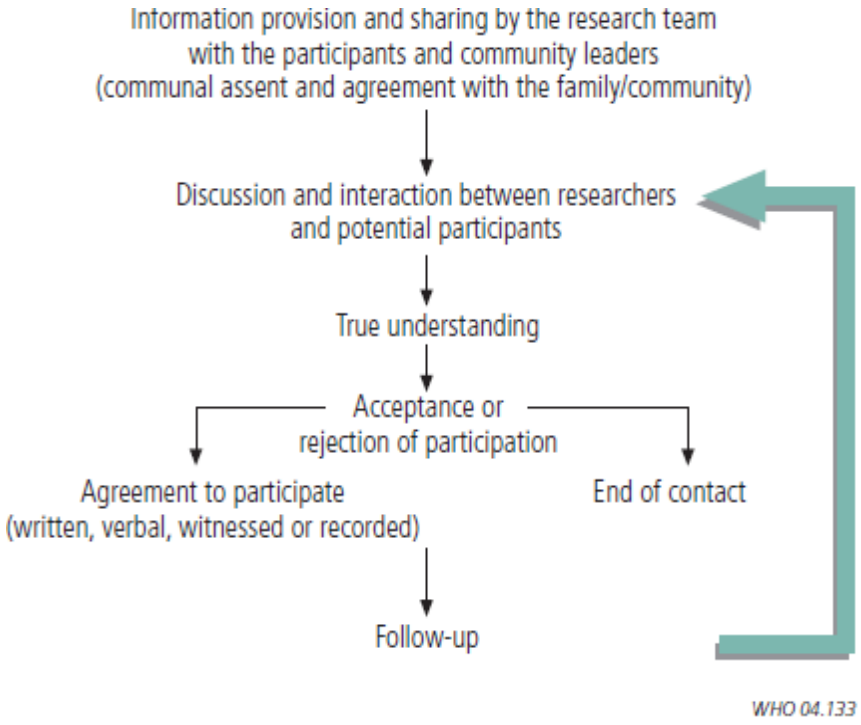


Figure 3.1 Conceptual framework for obtaining informed consent (Adopted from Z.A Bhutta, 2004)[124].

Rapid Ethical Assessment (REA) is a brief qualitative intervention designed to map the ethical terrain of a research setting prior to recruitment of participants and has been

proposed as one means of improving the consent process in research-naïve settings [74, 125]. It uses rapid ethnographic techniques to better understand the ethical issues that are relevant to a specific piece of research in a given study setting and conducted before participants are recruited into a research project guide the consent process. The approach has been used prior to research projects in Ethiopia, Cameroon and The Gambia, and its potential role in improving the consent process in Ethiopian context has been shown [73, 90, 123, 126-128].

3.4. Results

There is an increasing understanding that Rapid Ethical Assessment is an ideal tool to understand the research context especially in research-naïve settings and before implementing complex studies. The methods utilized to conduct the REA in the study setting are described in chapter 2. This chapter presents the findings of the study in some detail.

A total of 94 participants (42 females and 52 males) took part in 14 in-depth interviews and 8 Focus Group Discussions (FGDs - 10 participants each). The age of participants ranged between 19 and 80 years. The majority, 79, were married, while 5 were not married and 10 were widowed. The qualifications of the health professionals and experts ranged from diploma to Master's degree level. Almost all community participants had little or no formal education (Table 2). In the following paragraphs, study findings are organized under the following thematic areas: approaching patients, provision and comprehension of information, decision making, constraints to participation and explaining randomisation and delayed intervention.

Table 3.1 Characteristics of the study participants of the REA.

Characteristics		Number
Sex	Male	52
	Female	42
Average age (in years)		38.5
Marital Status	Married	79
	Single	5
	Widowed	10
Educational Status	Can read and write	10
	Cannot read and write	70
	Elementary and High School	5
	Higher education	9
Podoconiosis status	Affected	40
	Non-affected	54

3.4.1. Knowledge about research

Most participants agreed communities in the study area have limited knowledge about research. The reasons for this could be lack of previous exposure to studies and approaches previously used by other researchers. This is related to lack of previous experience in participating in research, views communities have about research by mixing it with treatment or aid package, and associating it with immediate personal gains in the form of financial incentives training or health education. In relation this, in addition to exposure, some institutions appear to have approached communities as an aid program, but conducted studies which led to the mixing of the two concepts. The following excerpts explain the participants' thoughts…

> "Compared to others, this area is where not many studies have been conducted. Communities near universities have seen lots of research and may not cooperate to

participate in a research. But, as the university was recently established, only about five years ago, not many studies have been conducted in communities". On the other hand, some organizations approach communities as an aid program, but conduct studies and communities which have been approached in this manner previous, may develop and attach the concept of aid to research" (Podo expert).

"To begin with, in our country, if I am not mistaken, most people know about is vaccination, people don't even know about treatment let alone research… people can't differentiate vaccination they took from medicine they took for other reasons…most don't know... for example, if you ask a woman if she was ever given something with a needle she will say yes…when you ask 'when'?... she will tell you some time ago people gave vaccines to a lot of the people… you can't know whether that was for research or a vaccine in childhood, so anything with a needle may be associated with treatment…even teachers around here don't know about it" (Researcher).

"There are immediate benefits expectations people bring along…it could be financial, treatment wise or to provide training and counseling…communities' understanding about research is low" (Podo expert).

"In previous studies conducted not only among podoconiosis patients but also in the general population, when researchers come from other places/ Addis Ababa, it is believed they came either to provide training or treatment and so on" (Podo expert).

"It's the same...people get treatment after examination, so they're one and the same" (P3, non patient, male).

"It is the same, there's no difference…you examine and then you treat…you'll see what kind of illness he has and then you treat him" (P6, non patient, male).

"It's about the place we live, our neighbors…to study and examine them, about me and about the people who live with me…the community what they're, how they live" (P7, non patient, female).

> "Research means, first taking sick people to where they can get treated…second, if there're people in the family who have a health problem, we advice those with the problem how to take care of their health and protect themselves" (P6, non patient, female).

> "Research, is to identify the sick from the healthy people and study where they live" (Non patient, female).

In the FGD with female patients, since the participants all responded they had not heard about research, the question about the difference between research and treatment was not asked. However, male patients' thought of research as a form of diagnosis before treatment is provided -

> "What I understand is, research is knowing what the disease is and getting treatment for it….after the research we know what the sickness is and then we get treated…so I think it's the same" (P1, patient, male).

> "Research means knowing what the disease is and looking for its treatment…it's the same" (P3, patient, male).

Understanding depends on the level of information provided about the trial. However, a health professional thought that people might consider the study to be a treatment program since they did not know the difference between the two concepts -

> "Although understanding will depend on the kind of information we give them…but I think people will see it as a treatment, because they don't know the difference between the two" (Health Professional, male).

On the other hand, this confusion might influence participation in the study. For example, perceptions of the study as free treatment or aid may lead to increased willingness to participate. Therefore the difference between research and free treatment needs to be clearly explained to everyone before enrolment.

> "It may influence participation. If it is perceived as aid and/or free treatment everyone will fight to be enrolled and that'll be harmful for the study…those who are not enrolled will discourage others from participating" (Podo expert, male).

Accordingly, explanation about the differences between research and treatment should be given priority by comparing research with podoconiosis prevention and treatment services such as those delivered by the International Orthodox Christian Charities programme -

> "It requires you to go in research as the main purpose and clearly explain the difference between aid and research using simple language that they can understand… it should be clearly explained that materials provided to participants are only part of the study and that it has been approved…it needs to be stressed to local administrative bodies as well as the community that based on the findings of the study, government and other nongovernmental organizations will develop/ plan interventions for treatment of those patients who did not participate in the study as well as those in other places in the future" (Podo expert 3, male).

> "The difference between the services IOCC provides and the study should be clearly explained…they can agree to participation mixing treatment versus research. Therefore, they should be made to understand the differences between the two" (Podo expert 4, male).

3.4.2. Approaching patients

Strategies to approach communities and individual participants and provide study related information are pivotal in obtaining truly informed consent. Participants suggested approaching communities before approaching individuals. *Kebele* leaders and local law enforcement were suggested routes -

> "The *kebele* leader will guide you…he knows all the patients. The local police department know where all the patients live, and the two can work together…they'll call patients to a meeting and everyone will attend, since they respect and obey the orders of the *kebele* leader" (P5, Non-patient, Male).

> "Without the *kebele's* assistance, it will be like walking in darkness…you can't go without the *kebele* helping you!" (P6, Non-patient, Male).

Accordingly, the order of approach community members suggested was that *kebele* officials be approached first. They then could arrange meetings with the community either in a *kebele* compound or in a church on a specific religious day, at which point information about the study could be provided to the community in general.

> "For example, you can use St. Michael's day when everyone will be attending the Church (P7, Patient, male).

Once the community is informed about the intended study, researchers can proceed to approach individual patients for consent. Participants indicated that individuals should be approached for consent at their homes in one of two ways. The first would be to identify and train locally known individuals and send them to patients' houses. Secondly, researchers could go to patients' houses accompanied by a local guide.

> "We take them (people coming from other places) to peoples' houses in the community, greet them and explain the purpose of our visit, they'll listen and give their responses, we then continue to next household" (P7, Non-patient, Female).

A range of views was expressed on researchers going house-to-house unaccompanied. Focus group participants explained that patients would not refuse to meet anyone offering help to treat their illness:

> "It is for their own benefit, so they don't need a lot of explanation, they'll accept an invitation to participate" (P3, Non-patient, Female).

However, most preferred the assistance of the Health Extension Workers (HEWs) in reaching individual patients.

> "The responsibility should only be given to HEWs, as they go house-to-house to deliver the various health service packages. Thus, Health Extension Workers know where there're pregnant women, which children were absent from school and houses where podoconiosis patients live" (Podoconiosis expert 1).

3.4.3. Provision and comprehension of information

It is to be noted here that the responses included in this section are mainly those of researchers and podoconiosis experts because focus group participants rarely discussed the kind of information that should be provided.

International ethical guidelines require that information about potential risks, inconvenience or restrictions should be balanced against any possible benefits. It is very interesting and rather worrying to note, however, that the expert participants in this REA repeatedly suggested de-emphasizing information on risks or possible negative consequences that participation in the study may have on individuals.

> "We stress the purpose of the study and its importance in improving patients' conditions...patients should not feel too much about risks" (Podoconiosis expert 1).

> "When informed about risks, although some may rarely occur, people focus more on risks instead of the benefits...your study has minimal risks associated with participation, except maybe the discomfort of being identified as a podo patient" (Podoconiosis expert 3).

This invited a follow up question about applicability of other aspects of international ethical guidelines locally. Participants believed one size would not fit all and that international guidelines needed to be contextualized.

> "The main problem is adopting guidelines prepared by western standards if we provide levels of information suitable for literate people to those who're illiterate; it will become boring and unclear for most community members" (Podoconiosis expert 3).

Similarly, although international ethical guidelines require provision of relevant information such as contact details of researchers and their institutional affiliation, to assist participants with information needs and to answer queries, reflecting on previous experience, a researcher said:

> "I don't think the majority in our community will phone requesting additional information…we have never given contact information to individual participants (laughing)…that information exists only on paper (study document/proposal)...if and when they ask, mostly we show them the introductory letter from the *woreda*" (Researcher 2).

Different views were offered regarding whether information should be provided in groups or individually -

> "It is preferable to provide information as a group, for example, for people gathered in a *kebele* compound...once information about the study is presented, inviting a discussion will help to get people's opinions. The majority is illiterate so using flyers would be difficult" (Expert 1).

> "We approached individuals on a house-to-house visit…explained the purpose of the study, asked willingness to take part, and where agreed, asked for signature, as indication of agreement. Then Health Extension Workers collected the data" (Researcher 1).

When it comes to who should provide information, some thought that anyone could provide information, while others thought the person providing information should thoroughly understand the cultural milieu of the area -

> "Someone who is from that community understands the culture and is trusted by the people" (Researcher 2).

In relation to checking comprehension of information, the simplest way would be asking potential participants to recount the most important aspects of information provided -

> "To check the extent of understanding, ask a few questions focusing on important elements of the study, repeating questions if necessary" (Researcher 1).

A few FGD participants maintained there was no need for information, and that requesting willingness to participate suffices, because in the end it is for their own benefit:

"First of all no one will refuse to participate, since they're all ill" (P3, Patient, Female).

"We all want to be healthy and thus no one will refuse" (P4, Patient, Female).

Finally, when it comes to signing the written consent form, participants stressed the importance of understanding the study. Experts who had experience conducting research in the area said:

"I've seen people agreeing orally, but refusing to sign the consent form. This is because they fear the purpose is to confiscate their lands...you've to clearly explain the purpose and meaning of signing the form…if they trust you, they'll sign" (Podoconiosis expert 1).

"People in our communities are very fearful of signing anything. If asked to sign something, they always think it is linked with some form of legal issues, something that will later result in a legal obligation and responsibility. But, can be achieved through discussion, especially if community leaders are involved in discussions and made to understand the purpose clearly" (Podoconiosis expert 2).

3.4.4. Decision Making

Participants suggested that consent to participate depends on the type of research. For example, for short projects and those involving interviews and surveys, obtaining consent may not be that difficult. However, for long term studies such as the trial in question, which demand considerable investment of time from participants, the decision may require permission of other family members, especially if the potential participant happens to be the family breadwinner. Others thought there was no general formula for reaching decisions -

"It varies according to the situation...parents decide on behalf of children. Heads of households both men and women, decide for themselves" (Podoconiosis expert 3).

Several others said that the decision to participate rested with individual patients:

"It is the patient who makes that decision". (Community leader)

"They shoulder the disease burden and its social consequences…patients decide for themselves" (Researcher 2).

Others thought that the authority to make a decision differed for men and women. Men could decide for themselves while women needed to consult and get their spouse's approval before consenting

"What we commonly see is, women don't decide without first consulting with and obtaining their husband's permission" (Podoconiosis expert 2).

However, female participants asserted that both men and women decide after discussing with family members. Where women are household heads, (through divorce or widowhood), they decide without consulting others -

"We decide after discussing with family members and considering their advice…but sometimes we can decide ourselves". (P2, Non-patient, Female)

"Since we ask men for advice, they do the same before they decide". (P6, Non-patient, Female).

"I discuss with my neighbours, I don't decide alone". (P3, Patient, Female)

"I decide on my own, I don't have anyone to discuss with" (P5, Patient, Female).

Some suggested that in the context of rural Ethiopia, any important decision had to involve significant other people; family members, relatives, neighbours, community elders and religious leaders -

"It is hard to get consent without any influence from others…in this area (Amhara region); community leaders have a big influence" (Podoconiosis expert 3).

"In rural areas, individuals don't live distinct from others…individuals' decisions will be affected by others and vice versa. Therefore, for long term studies, it's appropriate to obtain the family's permission too" (Researcher 1).

3.4.5. Constraints to Participation

Although focus group participants all agreed there were no clear reasons hindering patients from participating in the trial, in-depth interviewees argued reasons that might deter individuals and explained ways to deal with them -

> "I think people will be willing to participate, but my concern is our community has expectations, such as monetary rewards and sometimes for time they spent, when asked, especially by people from other areas to participate in some activity" (Health Professional).

Participants also said false rumors about the study's purpose may create misconceptions which will impact on decisions to participate. Fertile ground for rumors may be created by botched community sensitisation, and misleading information reaching communities before the study team had a chance to discuss directly with individuals. In order to prevent misconceptions, garnering the support of community, religious and political leaders, ensuring clear understanding of the nature of the study at all levels and proceeding to enter the community in as short a time interval as possible after district level sensitisation are all important -

> "Rural communities are small, close-knit villages, and word about any outside visitors will spread very quickly...personal beliefs such as 'visitors are talking to people with swollen legs and their families, it looks like they're going to give them aid' will start to fly around" (Podoconiosis expert 1).

> "First, authorities at different levels need to clearly understand the purpose of the study, risks and benefits followed immediately by entry into the community to break any rumors that may arise in the intervening period" (Podoconiosis Expert 3).

> "People with no connection with the study may be the ones that start false information…if non-affected people know the purpose of the study; they can stop rumors when they arise (*Woreda* Health Office expert).

3.4.6. Explaining Randomisation and Delayed Intervention

The main object of this REA was to furnish information on how best to design the consent process for a randomised controlled trial of podoconiosis treatment, so conveying the concept of randomisation was expected to be very important. In the following paragraphs, understanding of randomisation and local analogies used to help explain randomisation is presented. This is followed by suggestions on how to keep participants in the delayed treatment group motivated to continue participating in the trial even when not receiving treatment.

Several local analogies exist that could be used to explain randomisation. The following social organisations were mentioned -

> "Everything from '*Iqqub'*, '*Mahiber*' and '*Senbete*' work based on the concept of chance…it is important to show people that everyone has been registered before the lottery is drawn; simply tell people, we'll draw similar to *iqqub* and those who win will be treated immediately and the rest will wait for a year…they'll understand" (Podoconiosis expert 1, and Health Professional).

('*Iqqub'* is an Amharic term used to describe a traditional saving system where people form groups and pay an agreed amount of money at an agreed interval into a common pool. Each member of the group, selected randomly, will receive one large sum of money, and this continues until everyone has received the sum they've contributed in the end. '*Mahiber*' and '*Senbete*' are terms referring to a voluntary and mutual religious gathering of a group of people in a church or at home to celebrate a common religious (saint's) holiday while feeding the poor, on a rotational basis).

A health professional with considerable experience working in the *woreda* provided two examples of explaining randomisation through agricultural analogies used previously by agricultural experts assessing poultry farming and the use of modern fertilizers in the community:

> "Most people were suspicious of modern fertilizers, but after a comparison of the use of compost with modern fertilizer was made, farmers witnessed the difference

> in the year's crop both yielded and began to use modern fertilizers. A similar example could be the chicken farms…there was a problem of which breed to use; foreign or hybrid chickens, then experts demonstrated the difference in the number of eggs laid and convinced farmers" (*Woreda* Health Office expert 1).

Several other analogies for randomisation were given in patient and non-patient focus groups. "*Kircha"* is an Amharic term to describe the traditional system for sharing the meat of slaughtered animals (usually a cow or an ox) and "*Worefa*" a description of waiting in line or of a waiting list:

> "Yes, we know and use lottery method for '*kircha'*...but, we haven't seen this in meetings" (P All, Non-patient, Female).
>
> "Lottery is lottery and '*worefa*' is '*worefa*', they'll understand it (P1, Non-patient, male).
>
> "Most of the things we do, we do them by '*worefa*' even we wait in line to be blessed by the priest's cross…even you put firewood one after the other, not all at once (P4, Non-patient, Male).
>
> "When we take out the herd for grazing, we cast lots to decide who will tend to the cattle first, second and so on" (P6, Non-patient, Male).

Participants suggested several ways to explain delayed treatment

> "Explain you are testing the effectiveness of the treatment, if after 12 months' of observation the treatment needs modification, we will modify it and the delayed group will get the improved treatment...they will understand, most have lived with the disease for a long time so waiting for another year will not be intolerable" (*Woreda* Health Office expert 2).
>
> "Assure them that they will get treated in a year and that probably they will get a better, improved treatment, next year" (Researcher).

> "These people have lived with podoconiosis for long and do not mind waiting for another year. It is also important to inform them that although this is a small scale intervention, the findings will be expanded to a large number of patients in other parts of the country" (Podoconiosis expert 2).

> "You should have coffee ceremonies with patients to discuss and inform them the number of patients assigned in this group who are also waiting. Also explain that the result will be of benefit not only for them, but for a lot of other patients in other places" (*Woreda* Health Office expert 1).

Participants in the FGDs said:

> "My sister is a podoconiosis patient and this is how I'll explain it to her...it's based on chance, if her chance allows, she'll get treated now otherwise she'll wait for some time and get treated" (P6, Non-patient, Male).

> "Everyone will participate and no one will feel unhappy to wait…it's like walking on a narrow road where people travel in a row; one in front and another following, in the end both will reach their destinations…the second group will get treated later and won't mind waiting"(P6, Non- patient, Male).

> "Yes, we'll wait, it is based on chance and lottery is not biased, does not favour anyone" (P2, Patient, Female).

> "Tell them in a way everyone can understand...for example, when the government builds roads, they can't build all the roads at the same time, it takes time…similarly, in this research, those who get the chance will get treated first and others have to wait" (P3, Patient, Male).

Several views were put forward regarding encouraging continued participation of the delayed treatment group. These ranged from explaining the waiting list scenario at the IOCC treatment and prevention project, mentioning the average waiting time, to regular meetings with the control group, to discussing over coffee to explain the wider benefits. Several respondents felt it was important to guarantee treatment for the control group

after a year. However, others seemed to suggest since all are ill and desperate, none would complain, or drop out.

> "You need to be able to provide an incentive for the group that has to wait for a year. I don't think they will wait for a year without getting treated" (Researcher 1).
> "More focus should be given to those in the delayed treatment group, as they may be expected to complain. First, explain that a year is a short period to wait; some have waited for 7 to 10 years to get treatment. Then explain that random selection will be used to assign people into one of the groups, they'll understand and be contented no one was favoured". (Podoconiosis expert 1)

In sum, although there seemed to be a range of approaches, most participants appeared confident that participants would stay in the study given these explanations.

3.5. Discussion

This Rapid Ethical Assessment (REA) provided useful insights into many aspects of preparing for and conducting a trial of foot care and hygiene intervention on podoconiosis treatment in northern Ethiopia. The 6 weeks' fieldwork activities for this REA cost around 31, 000 ETB (US $1,550). A recent assessment on feasibility of REA in three community based studies in Ethiopia estimated an average of 42,815.5 ETB (US $2,140) and duration 4-6 weeks to conduct an REA[129].

It helped the research team to adopt specific strategies. The importance of holding sensitisation meetings called by local leaders; asking Health Extension Workers to accompany the research team to patients' houses; employing a local health education expert to provide information about the study; ways of explaining randomisation using local analogies from agriculture and social organisations; giving the opportunity for prospective participants to discuss their participation in the study with their families before committing to themselves; offering incentives in the form of small packets of coffee to participants in the 'delayed' intervention arm encourage continued participation; and employing key figures in the community to rectify rumors that may arise as the study progresses. Thus, the approach followed in main study was first holding sensitisation

workshop by including representatives from the various *woreda* level offices, *kebele* chairs, community and religious leaders, who went to cascaded down the information further. This was followed by briefing the Health Extension Workers and asking them to list patients they thought have podoconiosis in their respective *kebeles* and lead study team members to their houses. A similar approach was used in southern Ethiopia, where sensitisation meetings preceded introductions to specific patients, although in that context, members of the local Patient Association accompanied the research team to patients' homes rather than Health Extension Workers [74]. Although the police were mentioned as useful for approaching communities for sensitisation about the study, approach which has not been reported in other contexts. However, this approach was not employed, given that it's potential for undue influence and the impact it might have on the voluntariness of the informed consent process was unclear. Whether these roles might be extended to community sensitisation would be an interesting focus for future research.

The REA had some very practical utilities. We provided information to patients as a group where participants were encouraged to ask questions. Finally, their understanding was verified when consent to participate was requested individually after decisions were reached after consultation with family members, neighbours and friends[73]. In addition, variation in dialect within Gojjam itself necessitated that information be best conveyed by a health educator from East Gojjam zone itself. Experts in this REA suggested de-emphasizing the risks associated with participation, justifying their decision on the assumption that complete disclosure 'boring' or incomprehensible. A similar study in southern Ethiopia reported that the information participants most wanted to hear was the expected benefit of the research[73] . However, first underestimation of the potential risks attached to research, particularly in the context of a clinical trial, would weaken the informed consent process [87, 89, 102, 130]. Secondly, the mainstay of IC is the presupposition that subjects understand the potential risks and benefits of their participation, and that it is research, not therapy, in which they will participate [131]. Moreover, misconstrued study risks have critical ethical consequences such as violation of specifications in The Declaration of Helsinki that adequate communication of study risks is imperative for ethical conduct of a research[89]. In other words, without fully understanding risks participating in the study

involves, it'd be difficult for participants to make a truly informed decision as to the level of risks they are willing to accept by participating.

Accordingly, the information sheet used to orient potential participants included details about the: objectives of the study, study procedures, risks and benefits of participation, participants' rights to refusal and withdrawal, how information was to be stored, confidentiality of personal records and who will have access, whom to contact for further queries, ethical approvals obtained, funding sources and who the investigators were. In order to reduce the effect of the 'therapeutic misconception' in the actual trial, the difference between research and treatment was clearly explained in the information sheet (Appendix 11). In addition, following international guidelines that require all study staff including investigators and fieldworkers were required be adequately trained on the principles of International Conference on Harmonization, Good Clinical Practice (ICH-GCP), online course (Globalhealthtrials.org) were attended and certificates obtained.

There were conflicting views regarding decision-making power; men, women or consultative and where women were heads of households through divorce or widowhood. The decision was in the context of northern Ethiopia, women can be approached for and provide consent in consultation with their families or by themselves. REA conducted in Cameroon advocated male responsibility for giving consent[104]. On the other hand, in line with National and international guidelines for ethical conduct in research recognize that some standards, such as that requiring individual informed consent be given voluntarily by competent participants, must be met whatever the cultural context within which research is conducted [87, 102, 130, 132], in communities in rural Gojjam, the permission of local traditional authorities and community leaders was not required before individual consent to participate in a study was given. The role suggested here for local community and religious leaders, was to facilitate entry into the community and rectify false information about the study when it arises. This is suggestion is unlike the findings of REA in Cameroon[104], but in line with the one in southern Ethiopia[73]. The role of community and religious leaders were one of facilitating entry into community and rectifying false information about the study when it arises. Respondents in other REA advocated proxy decision-making, for example in north-west Cameroon (21).

The gap between *woreda/kebele* level sensitisation and approaching individual patients was one of the factors identified for misleading information reaching the communities. In order to prevent misconceptions, the support of community, religious and political leaders to quell rumors was found very helpful. For example, this was used during enrolment to counter misconceptions being spread by individuals who were opposed to the trial. Based on based on information from a fellow patient (who refused participation) claiming health professional advice that this is an incurable disease and that the only treatment to improve the condition is surgical removal of the affected leg, participants questioned whether the treatment works at all. Subjects also speculated that the true intent of the trial, as rumour had it, was religious conversion.

Agricultural analogies were thought to be useful ways of explaining the two intervention groups, randomisation and delayed treatment. The concept of the lottery method ('*Ita'* in the Amharic language) is well known in these communities and is used in social, financial and religious activities and these analogies were all used at times in explaining the trial to potential participants. In addition, to encourage continued participation of the control group, the IOCC waiting list scenario and waiting time was explained in the information sheet. In addition, regular follow-up study visits were used to inform participants in the delayed treatment group the time remaining before they received treatment and provide small packets of coffee as an incentive. During these sessions, explanation were made about how their participation would help provide evidence on the effectiveness of the treatment for policy formulation at national and international levels, and thus benefit a large number of people with podoconiosis in other places.

This study therefore, further highlighted the utility of REA prior to clinical trials involving complex procedures and concepts and provided practical information on the approach for and conducting a randomised controlled trial to estimate the incidence, duration and social impact of ADLA and measure the impact foot care and hygiene intervention on ALDA.

Chapter 4 Developing & validating a case definition of ADLA

4.1. Overview

Diaries have been used to collect patient-related outcomes in a range of fields of research[133]. They have been used to investigate health and health-related behaviors including medication adherence[134], hormonal patterns[135], chronic mental health problems and pain-stress levels. In low and middle income countries (LMICs), diaries were used to record episodes of colds, coughs, diarrhoea and fever in children, the volume and content of breast milk transferred from mothers to infants and the health effects of air pollution. According to Wiseman *et al* (2005) it is feasible to use diaries in LMICs characterized by low-literacy communities to collect data on a range of relevant health related questions. However, for this to be realized, clear instructions, images and information on when and how to complete diaries must be provided to participants[133]. Establishing the validity of research diaries can be difficult and the volume of data reported is important[136-137]. It may be demanding in terms of literacy skills and motivation to continue participation because of difficulties associated with diary completion and data quality[138]. Before launching any quantitative study, the measuring process needs to be evaluated using feasibility and reliability studies on a sample reflecting the characteristics of the population to be used for the study. Feasibility is a critical characteristic of a patient-reported measure not previously used in a specific population. Thus, feasibility and acceptability, compliance and technicalities of measurement are very important in terms of quality and meaningful interpretation of data collected, especially in clinical trials[139].

Prompts encourage regular and accurate completion of diaries. One way of ensuring these is regular interviews and checking for missed and incorrect entries. Further, it is important to identify the level of support and supervision that may be required to ensure data quality. In addition, the frequency of completion, collection from participants and storage of diaries at home, the amount of time needed to complete the diaries should also be carefully planned and assessed [133, 139].

While interviews conducted by fieldworkers have the advantage of reliability and accuracy of data as well as higher response rates, they may be costly in terms resources, particularly

the time required to travel to households in communities[140]. In addition, the approach is not suitable for daily measurements over long periods of follow up. Therefore, we used diaries to measure incidence and duration of episodes of acute attacks using a standard definition. As described in chapter 2, first the definition of ADLA was adapted from studies in LF. This was followed by development and testing of the acceptability, feasibility and reliability of the diary [57].

4.2. Results

4.2.1. Comprehension/acceptability study

This phase sought to investigate whether patients understood the diary without training; the size and clarity of the images and date indicators used in the diary, and the acceptability and recognizability of the pictures drawn by a local artist.

Participants were asked "what do you understand from the drawings in the diary" which most described accurately-

> *"The first person is saying I'm not experiencing michader and working in the field…the next drawing shows the person is sick and in bed* (P4, patient, male).

In addition, patients will not have difficulty marking the diary according to their *michader* status.

> *"No I don't think it'll be difficult to understand…it says "I'm experiencing michader" and "I'm not experiencing michader"…it can't be easier"* (P3, Male non-affected).

Another patient confirmed his understanding -

> *"When I'm healthy and working I mark under the person working and when ill, I mark under the person in bed (P5, patient, male)".*
>
> *"Just show patients what kind of mark they need to make, then it'll be easy for them…show them where they have to mark, with examples" (P5, patient, male).*

Regarding acceptability of drawings depicting podoconiosis patients, participants unanimously endorsed the drawings as acceptable and not in any way offensive. However, non-affected community members held slightly different views -

> *"When we see a sick person, we sympathize…there're also others who think a patient brought the disease upon himself and make jokes about it….so it really depends on our nature". (P1, non-affected, male)*

Regarding date indicators used in the diary, participants were asked a series of dates such as "is St. Rafael's day on the 13th? What about 16? Which was confirmed all participants-

> *"The dates used are applicable to most rural Gojjam kebeles" (all participants)*.

The next question asked was 'do you think patients can mark this on their own without assistance?' Participants indicated that as long as they did not need to write details and the mark was simple, patients could complete by themselves

> *"What mark should we place? I say this because there're people who can't read and write, so you should specify…if it's a simple mark chiret (a scratch), then it's easy "(P6, patient, male).*

A natural extension to the above question was 'what about the elderly and visually impaired?' Similarly, participants stressed the importance of training and assistance from family members, school children and neighbours-

> *"It won't be difficult…it's just to show them how to complete…"train them and they can mark" (P3, patient, female).*

Regarding size of the diary (700X12cms) in a booklet format, participants viewed it as convenient to keep at home and bring to MIVs every month, if patients can cover it with protective material to keep it dry and undamaged.

> *"To prevent dirt and water it should have a strong cover" (P6, patient, male). "It should be covered with plastic" (P4, patient, male)*.

"This is sufficient…exercise book size is very good to keep…but should be covered"(P2 non-affected, male).

4.2.2. Feasibility study

Figure 4.1 Training patients on completion of ADLA diary at an IOCC treatment clinic in East Gojjam (Photograph by Henok Negussie).

4.2.3. Exit interview

Fifty-two diaries were given out. The returned diaries were low 16/52. The majority of the interviewees found remembering to complete the diary easy (9, 60%), and not bothersome in relation to activities of daily life (6, 40%). Similarly, 14 (93%) said that overall the diary was suitable to handle and keep for a month and recommended it to be used with podoconiosis patients in the planned trial.

4.2.4. Difficulties experienced

Nine diaries were completed accurately, four were partially filled and two were not marked at all. Two patients completed the diary themselves while 13 were completed by a family member, a spouse or a child. The most frequently mentioned difficulty expressed during the exit interviews was inability to complete every day. The reasons given were - forgetfulness, inability to read and write, and feeling tired after a full day's farm work. In addition, experiencing ADLA made it difficult to mark diaries.

"My main problem was forgetting to complete every day" (P9).

"Since we'll be very tired after working in the field all day, it was difficult to remember to complete it every day" (P14).

"I am unable to read and write as well as have poor eyesight and forget to mark every day" (P, 12).

"When I went home, I told my children how it's completed, the way you showed us and then since we become very sick and get struck down, when michader starts, looking at my condition, my children completed the form" (P5).

"It's difficult to complete it when we're experiencing the attack, since it strikes us down completely and we can only ask for water, but we can complete it, once we're better" (P7).

4.2.5. Suggestions for improvement

Suggestions to overcome the difficulties encountered related to provision of adequate training, the importance of religious days as reminders and the need to seek the involvement of family members to act as scribes-

"It's very good but, patients should be properly trained on how to complete it" (P10, male).

"I can't read and write, so I had it completed by my children (P13).

"When I asked my son to complete it, I used religious days to help me remember on what days I experienced the attack" (P6).

"We marked it as we remembered, using the religious days was a convenient reminder" (P14).

Finally, a female patient described the excruciating nature of the pain makes it an unforgettable experience, even if the diary could not be marked on the same day-

"The days in which you experience michader could not be forgotten for a year let alone a day" (P3, female).

4.2.6. Reliability study

As described in the methodology (chapter 2), initially, patients and HEWs were trained on symptoms of ADLA and completion of the ADLA diary. In addition, HEWs were trained on measuring foot and leg circumference. The procedure was for patients to report to HPs when they experience acute attacks, HEWs will examine patients and complete the ADLA assessment form with their impression of whether patients were experiencing ADLA attacks.

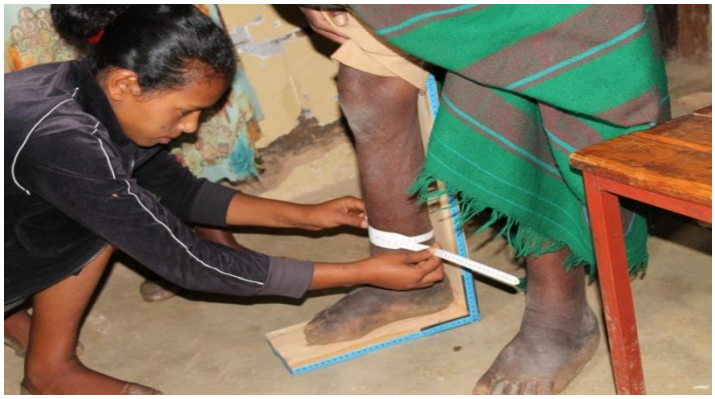


Figure 4.2 Training of a Health Extension Worker (HEW) in northern Ethiopia on disease stage and measurement of foot and leg circumferences during the diary validation study (Photograph by Henok Negussie).

Twenty four males and 20 females participated from the two *kebeles*, 28 from Mislawash and 16 from Sendeba). The participants' age averaged 51 years (range 19-60).

Table 4.1 Socio-demographic characteristics of participants of the reliability study in two *kebeles*.

Variable	Number
Sex	
Male	24
Female	20
Average age (years)	51
Kebele	

Mislawash	28
Sendeba	16

Fever was reported by 15 (94%), pain, increased swelling, and chills by 14 (88%), swollen lymph nodes by 13 (81%), and redness of the affected feet by 12 (75%). Health Extension Workers detected warmth and swollen lymph nodes in 14 (88%) of the patients, tenderness of the feet in 13 (81%) and redness in 8 (50%) of the patients (Table 2).

Table 4.2 Frequencies of ADLA symptoms reported by 16 patients and HEWs clinical assessment.

Presence of							
Symptom	Wound	Swollen lymph nodes	Warm	Redness	Tender	Peeling	ADLA
Freq (%)	6 (38%)	14 (88%)	14 (88%)	8 (50%)	13 (81%)	12 (75%)	13 (82%)
Report of							
Symptom	Increased swelling	Swollen lymph nodes	Fever	Redness	Pain	Chills	ADLA
Freq (%)	14 (88%)	13 (81%)	15 (94%)	12 (75%)	14 (88%)	14 (88%)	16 (100%)

The validity of self-reported ADLA was assessed by calculating the percentage of self-reported ADLA cases that were confirmed to have ADLA by HEWs, i.e. the positive predictive value (PPV), with HEW confirmation as the gold standard (PPV= a/a+b×100, where a=number self-reported and confirmed by HEWs, and b=number self-reported but found not to have ADLA by HEWs). Sixteen completed questionnaires were obtained from HEWs in the two *kebeles*. Of these, 13 self-reported diagnoses were confirmed by the HEWs (PPV=0.81).

4.3. Discussion

This preliminary study indicated that patients, with the assistance of family members, can complete a simple patient-held diary. The local term "michader" could be used to describe the symptoms of ADLA among podoconiosis patients. McPherson *et al* (2005), in their study in Guyana used the culturally understood local description of the symptoms of ADLA 'filarial flares'[51]. Similarly, a study among women in filariasis endemic area in the Dominican republic, episodes of ADLA were referred as "crisis"[141]. The use of a patient completed ADLA diary depicting a 'healthy person working in the field' and 'a sick person in bed' side by side with date and a space to mark under each drawing according to ADLA statuses was found to be acceptable. Although the drawings depicted male patients, female patients equally understood the message. In addition, drawings were not found to be offensive and were not thought to expose patients to ridicule or further stigma from family members or non-affected community members. Further, if trained well, patients could complete the diaries by themselves. Where the elderly and visually impaired are concerned, the assistance of family members and neighbours is to be sought. The exit interviews indicated that 13 out of the 15 diaries were completed by spouses and children. This could be because most patients are illiterate, or have little or no experience using writing materials. These support the need for the involvement of family members such as school-age children[142] and neighbours.

The other important issue raised by participants related to difficulties in completing the diaries on a daily basis. These were mainly due to forgetting to mark after a long day in the farm, or being too tired to remember to mark the diaries. Similarly, when an attack strikes and the patient is incapacitated by severe pain, it is extremely difficult to remember to mark. Not completing diaries could be compensated by repeatedly explaining to patients the importance of marking the diaries as soon as possible (next day), by checking by the study team during Monthly Intervention Visits (MIVs), and using religious days as reminders of start and end dates of event. Studies in other contexts have used different prompts to encourage accurate and regular diary entries and regular interviews to check diaries were being maintained correctly and if any entries had been missed[133]. Comparison of self-reported ADLA events with HEW diagnosis indicated consistency of the

measuring process and that the diary has adequate validity to be employed in the larger investigative study Only 16 diaries were returned, which could be due to problems of understanding as most patients were not used to using writing materials.

4.4. Conclusion

Employing the diary to capture ADLA attack events for the main study was acceptable to participants. In addition, participants found the method feasible; not overly demanding or intrusive in the activities of daily life. Where patients cannot mark the diaries every day, patients should be regularly encouraged to mark as soon as possible. On top of this, regular checking by the study team using religious days as a convenient reminder of start and end dates of attacks should be employed. In addition, during collection of completed diaries at Monthly Intervention Visits (MIVs), Community Podoconiosis Assistants (CPAs) should check accuracy using religious days as reminders. Concerning the elderly and the visually impaired, family members and neighbours could be called upon to assist.

The process of methodological development reported here indicates that data of acceptable reliability could be gathered by drawing on patients' expert knowledge of their disease and symptoms of ADLA (using the local description m*ichader*). The patient-completed diary was recommended as a valuable method for collecting data on ADLA incidents among podoconiosis patients. Accordingly, with some modifications on printing material, the finalized diary was used in the study.

Chapter 5 Incidence and duration of ADLA: baseline and 12 months

5.1. Overview

Recurrent episodes of ADLA are believed to be important role on disease progression as well as risk of further episodes[62]. The frequency and duration of episodes have serious impact on patients' social and economic life. The World Health Organization's Global Program to Eliminate Lymphatic Filariasis (GPELF), in addition to morbidity management and disability prevention, gave increased emphasis on identification and prompt treatment of acute diseases[12]. Accordingly, defining treatment strategies is a necessary preliminary to control and elimination of podoconiosis. The foot care and hygiene management has been shown to reduce the frequency and duration of ADLA episodes, can arrest disease progression in LF [11, 48, 55, 62-64]. Studies in southern Ethiopia also reported decline in DLQI scores associated with the foot care and hygiene intervention, among podoconiosis patients. However, the length of the intervention was shorter in the studies and employed no comparison groups [76, 143]. It is, therefore, crucial to identify the factors associated with the frequency and duration of ADLA. Furthermore, determining the effect of the intervention on the incidence and duration of ADLA and quality of life for period of observation longer than previous studies using a randomized controlled design provides stronger scientific evidence.

This chapter presents the baseline characteristics of participants. First, the trial profile is presented. Then, a description of the number of participants in each Health Post and Health Center is given. Socio-demographic characteristics, shoe ownership, foot washing practices and use of ointment, are given by trial arm. Experience and duration of ADLA, are described followed by clinical aspects: mossy changes, inter-digital lesions and finally social aspects of measurement: Dermatology Life Quality Index (DLQI) are described. Subsequently, changes from baseline to 12 months are presented.

5.2. Results

A total of 1339 patients were recruited, screened and mapped from December 2014 to June 2015. Five hundred fifty-one patients were found to have disease stage 1, 70 did not attend enrolment days, 3 refused consent to participate and 19 patients were excluded for other

reasons. Accordingly, 696 participants; 350 (50.2%) and 346 (49.8%) were randomized to the immediate and delayed intervention groups, respectively (Figure 5.1).

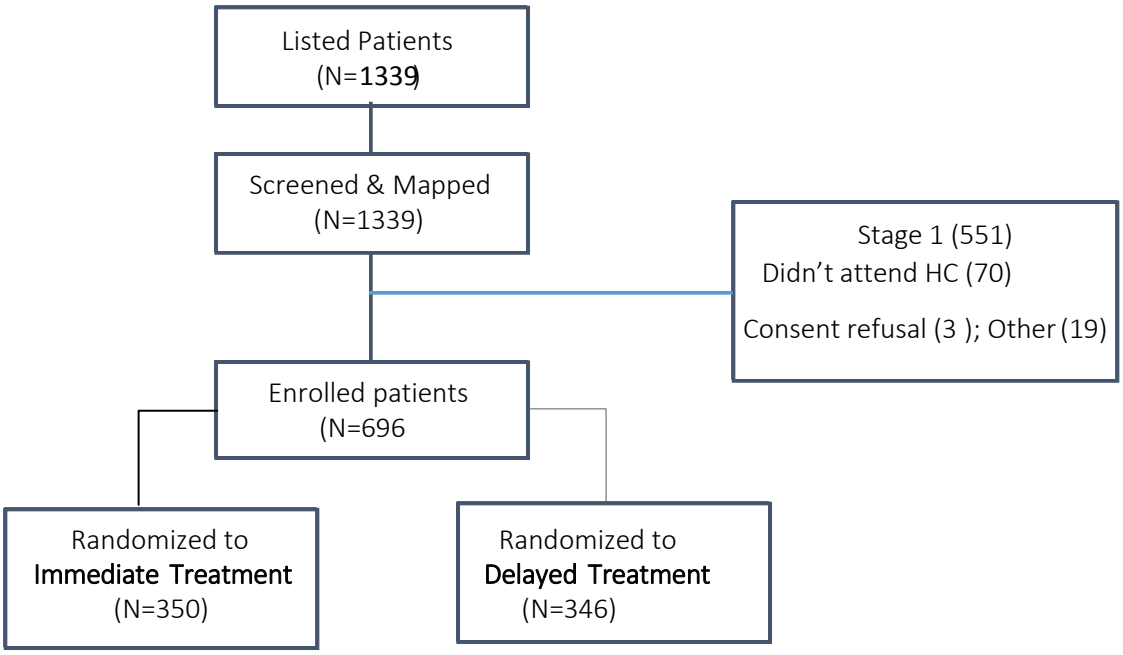


Figure 5.1 CONSORT chart: flow of patients from screening to randomisation.

5.1.1. Baseline characteristics of participants

A total of 696 patients were randomised to the two groups: immediate treatment (n=350) and delayed (n=346). At baseline, participants averaged 50 (range 40-60) and 52 (range 41-65) years of age for immediate and delayed treatment groups respectively. One-hundred-seventy-two (49%) and 164 (48%) in the immediate and delayed groups, respectively, were females and only 66 (19%) in either group had ever attended formal education.

Two hundred nineteen (63%), in the treatment and 231 (67%) in the control group reported owning a pair of shoes, while only 76 (35%) and 64 (28%) from the two groups respectively owned a pair of socks. More than half of the participants in both groups reported having used soap to wash their feet. However, less than 40% of participants had

ever applied any ointment to their feet, 110 (32%) and 128 (38%) from the treatment and control groups, respectively.

Table 5.1 Baseline demographic, foot washing and clinical characteristics of participants.

Characteristics	**Treatment group (n=350)**	**Control group (n=346)**
Age years (median, IQR)*	50 (40-60)	52 (41-65)
Sex (% female)	172 (49)	164 (48)
Marital Status (% married)	226 (65)	226 (66)
Ever attended school (% Yes)	66 (19)	66 (19)
Owned a pair of shoes (%)	219 (63)	231 (67)
Owned a pair of socks (%)	76 (35)	64 (28)
Number of times feet washed past week (< 7) (>= 7)	113 (48) 205 (51)	122 (2) 198 (49)
Washed feet last night (% Yes)	282 (50.4)	278(49.6)
Use soap to wash feet (%)	198 (57)	186 (54)
Use ointment on the feet	110 (32)	128 (38)
Have you ever experienced ADLA? (%)	341 (98)	341 (99)
Total ADLA in past 30 days (median, IQR)	2 (2-3)	3 (2-3)
Average duration (days) of the latest episode (median, IQR)	3 (3-5)	3 (3-5)
Right leg mossy lesions (%)	177 (52)	175 (51)
Left leg mossy lesions (%)	169 (49)	174 (52)
Right leg inter-digital lesions (%)	70 (20)	68 (20)
Left leg inter-digital lesions (%)	76 (22)	82 (24)
Total Dermatology Quality of Life Index: (median and IQR)	21 (14-32)	21 (14-31)

Almost all patients, immediate 341 (98%), delayed 341 (99%) had ever experienced michader. Experiences of michader in the past 30 days at baseline were reported as 2 (range 2-3) and 3 (range 2-3) with an average duration of 3 days (range3-5) in the intervention and control groups respectively.

Over 50% had mossy lesions in either one of the legs. 177 (52%) of patients in the treatment group and 175 (51%) of those in the control group had mossy lesions on the right leg, while 169 (49%) and 174 (52%) had them on the left leg. Fewer than 25% were reported to have inter-digital lesions on either leg. Finally, the median (IQR) scores on the Dermatology Quality Life Index (DLQI), at baseline were 21 (14-32) and 21 (14-31) for the immediate and control groups, respectively (Table 5.1).

5.1.2. Predictors of 30-day ADLA episodes at baseline

A test of association was conducted between the numbers of ADLA episodes in the past 30 days with demographic characteristics at baseline. No significant difference was observed on number of ADLA experiences in the past 30 days and sex (IRR=1.00, p=0.983, 95%CI=-0.90, 1.10), marital status (IRR=-.97, p=0.11, 95%CI=-0.92, 1.00) and school attendance (IRR=0.96, p=0.53, 95%CI=-0.85, 1.08) at baseline. However, the number of ADLA episodes in the past 30 days at baseline were 13% higher among those aged 50 and over (IRR=-1.13, p=0.01, 95%CI=1.05, 1.25).

On the other hand those with stage 3 disease had 39% and 37% higher rate of ADLA than those with stage 2 for the left (IRR=1.39, p=0.02, 95%CI=1.06, 1.81) and right (IRR=1.37, p=0.03, 95%CI=1.04, 1.83), respectively. Those who reported having no inter-digital lesions had significantly fewer episodes at baseline (IRR=0.87, p=0.04, 95%CI=0.76, 0.99). Similarly, those who had wounds on the left foot had a 21% higher rate of ADLA (IRR=1.21, p=0.006, 95% CI=1.05, 1.39) and wounds on the right feet were associated with 20% higher rate (IRR=1.20, p=0.001, 95% CI=1.05, 1.31).

Poisson modeling was conducted for the incidence of ADLA, hygiene practices, presence of wounds and knowledge about the prevention of AD LA episodes at baseline. There was a significant difference in the number of ADLA episodes experienced in the past 30 days

among those who washed their feet once or more a day (seven times and more than seven times in the past week) at baseline. Those who washed more than once had reduced number of episodes in the past 30 days (IRR=0.83, p=0.002, 95% CI=0.74, 0.94). Similarly, compared to patients who did not wash their feet the previous night, those who reported having washed had fewer ADLA episodes in the month preceding baseline (IRR=0.82, p=0.002, 95% CI=0.70,0.96). In addition, a significant difference in the reported number of ADLA episodes was observed in relation to the presence of wounds. Those who had wounds on their feet had about 20% higher rates of ADLA episodes than their counterparts with no wounds. This difference was found to statistically significant (IRR=1.20, p=0.001, 95% CI=1.05, 1.31). An increased number of ADLA episodes was associated with a higher score on the Dermatology Quality Life (DLQI) measure (lower quality of life): patients who scored higher on the DLQI test were found to have a 23% higher rate of episodes in the past 30 days (IRR=1.23, p=0.001, 95% CI=1.11, 1.36). Further, patients who reported knowledge that episodes of ADLA could be prevented had 14% fewer ADLA episodes as those who reported no knowledge, (IRR=0.86, p=0.01, 95% CI=0.77, 0.97) (Table 5.2).

Table 5.2 Number of ADLA episodes in the past 30 days by foot washing practices, presence of wounds, DLQI score, and knowledge about prevention of episodes at baseline.

Number of ADLA past 30 days (n=635)	**Incidence Rate Ratio (IRR)**	**P value**	**95% CI**
Number of times feet washed past week (more than once a day)	0.83	0.002	0.74, 0.94
Having washed feet last night (Yes)	0.82	0.01	0.70, 0.96
Wound (Yes)	1.20	0.001	1.05, 1.31
DLQI score	1.23	0.001	1.11, 1.36
Can episodes of ADLA be prevented (Yes)	0.86	0.01	0.77, 0.97

LR chi2 (5) = 40.06, p=0.0001, Log likelihood = -1152.7083 Pseudo R2= 0.02,

Deviance goodness-of-fit = 524.9917, chi2 (DF=629) p=0.9990
Pearson goodness-of-fit = 662.9696, chi2 (DF=629) p= 0.1686

5.1.3. Predictors of duration of ADLA symptoms

Regarding duration of ADLA symptoms, as severity of the most recent ADLA episode increased, the duration of ADLA symptoms also increased by a factor of 0.30. Those who reported severe episodes were expected to have significantly more days of illness (IRR 1.35, p=0.001, 95% CI=1.2, 1.54). On the other hand, compared to those who reported having wounds, patients who reported no wound involvement had fewer days of illness (IRR=-0.90, p=0.001, 95% CI=-0.81, 0.99) (Table 5.3).

Table 5.3 Association of duration of ADLA symptom (in days) and intensity of the latest episode, presence of lymph node swelling and wounds.

Duration of ADLA symptoms (Days) (n=651)	**Incidence Rate Ratio (IRR)**	**P value**	**95% CI**
Intensity of the latest ADLA episode (Severe)	1.35	0.001	1.2, 1.54
Wound (No)	0.9	0.04	0.81,0.99

Log pseudo likelihood = -1226.6447 Pseudo R2 =0.0096, LR chi2 (DF=2) =23.87, P = 0.0001; Deviance goodness-of-fit = 575.3229, chi2 (DF=648), p= 0.9813, Deviance goodness-of-fit = 544.456, chi2 (DF=598), p = 0.9427. Pearson goodness-of-fit = 653.4451 chi2 (DF=598) p=0.0576

5.1.4. Quality of Life

Table 5.4 shows the results of Poisson regression of DLQI with foot washing practices and intensity of the most recent ADLA. As the intensity of the most recent ADLA increased, the DLQI score also increased. Scores on the DLQI test for participants who reported their most recent ADLA attack to be severe were higher than those who reported their attack to be mild (Log OR=0.13, p=0.001, 95% CI=0.05, 0.21). On the other hand, increasing the number of times the feet were washed to more than seven in the week before baseline was associated with reduced DLQI scores (higher quality of life). Compared to patients who washed their feet once per day, those who washed more than once scored significantly lower (Logs OR=-0.25, SE=0.04, p=0.001, 95%CI=0.30, -0.20). Similarly, DLQI scores of participants who reported having washed their feet the night before baseline were

significantly lower than those who did not (Logs OR=-0.13, SE=0.04, p=0.002, 95%CI=-0.21,-0.05).

Table 5.4 Association of Dermatology Life Quality Index (DLQI) with foot washing practices and intensity of most recent ADLA.

DLQI (n=625)	Coefficient	P value	95%CI
Intensity of latest ADLA	0.13	0.001	0.05, 0.21
Number of times feet washed past week	-0.25	0.001	-0.30,-0.20
Did you wash your feet last night?	-0.13	0.002	-0.21,-0.05

Log pseudo likelihood = -760.97726, Pseudo R2= 0.0094, Wald chi2 (DF, 3) = 122.34 p=0.0001, Deviance goodness-of-fit = 92.13876, chi2 (DF, 621), p =1.0000, Pearson goodness-of-fit = 93.04387, chi2 (DF, 621) p = 1.0000

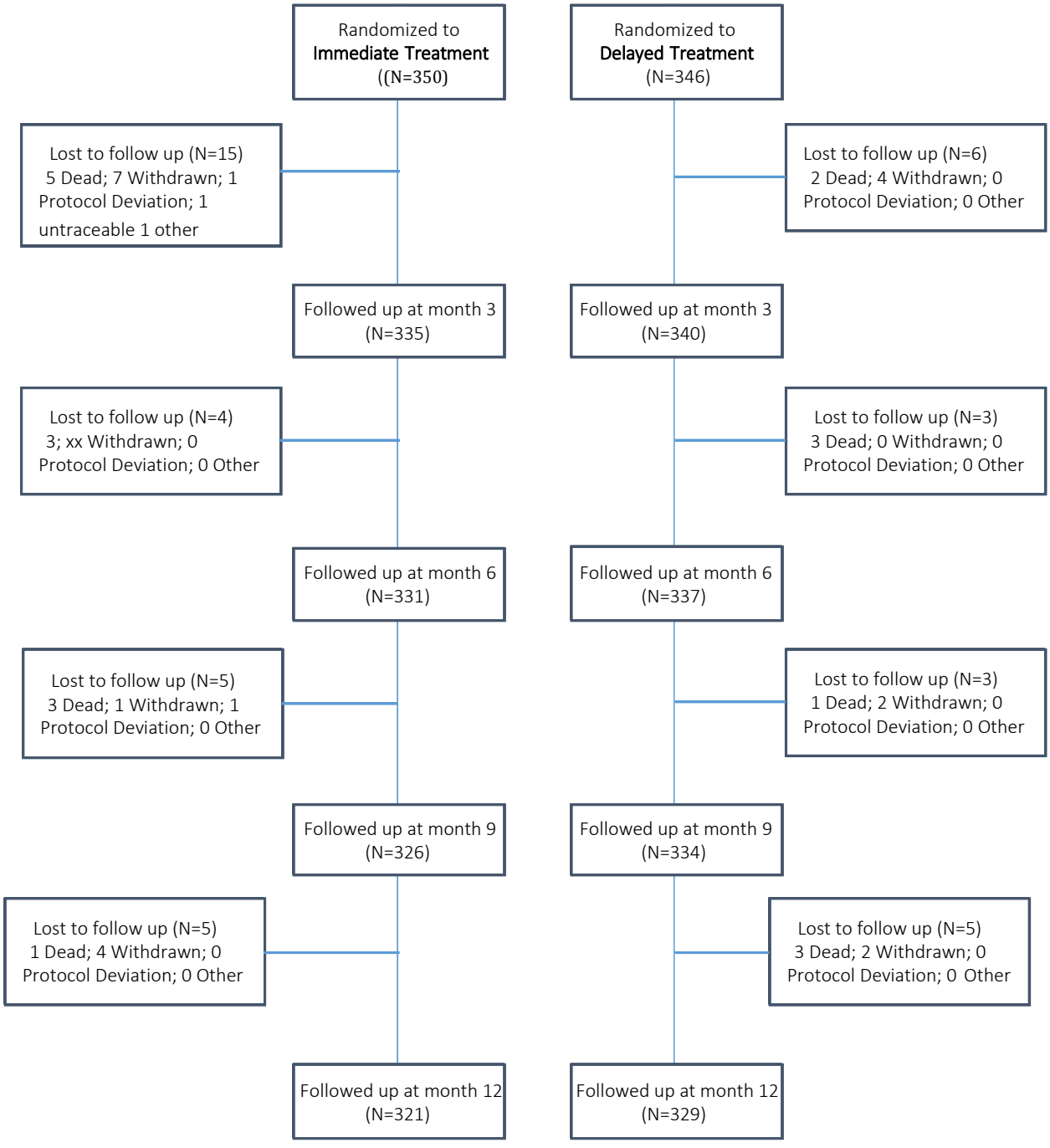


Figure 5.2 CONSORT chart: flow of patients from randomisation to 12 month follow up.

5.1.5. Changes from baseline in the number ALDA episodes by study group

A total of 321 and 329 participants from the immediate treatment and control groups, respectively, completed the 12 months' follow up (figure 5.2). This section of the chapter presents the results of the impact of the foot care and hygiene intervention on the frequency and duration of ADLA and quality of life measures using DLQI measure after 12 months of intervention. First, comparison of the two arms on overall ADLA events and incidence rates are presented. This is followed by discussion of comparison of the two arms on clinical measures: duration of ADLA symptoms, disease stage, mossy lesions, foot and leg circumferences and inter-digital lesions at 12 month measures.

There were a total of 16,550 episodes of ADLA in the twelve months of observation, within 765.2 person years. The intervention group recorded 7,515 and the delayed group 9,035 episodes within 387.1and 378.1 person years; incidence rates were 19.4 (95% CI 18.9, 19.9) and 23.9 (95% CI 23.4-24.4) episodes per person years respectively (incidence rate ratio (IRR) 0.81 (95% CI 0.69, 0.96, p<0.001).

At 12 months follow up, patients who received the foot care and hygiene intervention had 1614 episodes and the delayed treatment group, 1935 episodes providing incidence rates of 18.5 (95% CI 17.6, 19.4) and 24.5 (95% CI 23.4, 25.6) for the two groups respectively (IRR= 0.76, 95% CI 0.62, 0.93) (p<0.001). Differences in the occurrence of ADLA between the two groups at 12 months follow up were significantly in favour of participants who received the intervention. In other words, at 12 months, patients in the intervention group had a 24% reduced risk of ADLA incidence compared to patients in the delayed group. Similarly, the geometric mean of the total annual duration of symptoms of ADLA for the treatment group (95% CI) was 79 days (95% CI 78, 80), significantly lower than that of the control group at 107 days (95% CI 106, 108) (P<0.001). Similarly, the geometric mean of the duration of ADLA symptoms per episode was 2.1 days (2.0, 2.2) and 2.3 days (2.2, 2.4) for the immediate and delayed groups respectively, also significantly different between the two groups (P<0.001) (Table 5.5).

Table 5.5 Duration of ADLA symptoms, presence of mossy and inter-digital lesions and total DLQI scores at baseline and twelve months follow up among podoconiosis patients.

Duration of ADLA episodes		**Immediate N=350**	**Delayed N=356**	**p-value**
Duration of symptoms of ADLA (days), geometric mean (95% CI)		2.1 (2.0 to 2.2)	2.3 (2.2 to 2.4)	<0.001
Total duration of symptoms of ADLA (days), geometric mean (95% CI)		79 (78 to 80)	107 (106 to 108)	<0.001
Mossy lesions				
Right leg (% Yes)	Baseline	178 (52)	175 (51)	0.94
Left leg (% Yes)		117 (36)	135 (41)	0.20
Right leg (% Yes)	Month 12	102 (32)	138 (42)	0.008
Left leg (% Yes)		102 (32)	133 (41)	0.02
Inter-digital lesions				
Left leg (% Yes)	Baseline	70 (20)	68 (19.8)	0.89
Left leg (% Yes)		77 (22)	82 (24)	0.61
Right leg (% Yes)	Month 12	41 (13)	58 (18)	0.08
Left leg (% Yes)		51 (16)	79 (24)	0.009
Dermatology Life Quality Index				
Baseline		21 (14-32)	21 (14-31)	0.42
Month 12		11 (5-16)	14 (11-19)	<0.001

At 12 months, there was a significant difference in the percentages of mossy lesions in both legs between the two groups in favour of the immediate treatment. One hundred and two of the immediate group (32%) and 138 of the control group (42%) had mossy lesions on the right leg (p= 0.008). Similarly, 102(32%) of the immediate treatment patients compared to 133 (41%) of the control group had mossy lesions on the left leg (p=0.02). Regarding proportion with inter-digital lesions, the baseline measures did not show significant differences between the two groups on right (p=0.89) or the left (p=0.61) legs

Finally, baseline median (IQR) DLQI scores were 21 (14-32) and 21 (14-31), for the immediate and delayed were not different (p=0.42). A decline in DLQI scores from baseline (increase in quality of life) was observed in both groups. At twelve months follow up, scores were 11 (5-16) and 14 (11-19) for the treatment and control groups, a decrease by 10 and 7 points, respectively (p<0.001).

5.2. Discussion

This study was conducted with aim of measuring the impact of a foot care and hygiene intervention on ADLA among podoconiosis patients. Factors associated with number of ADLA episodes experienced at baseline were number of times feet were washed in the past week ($p=0.002$), having washed feet last night ($p=0.01$), presence of wounds ($p=0.001$), scores on DLQI ($p=0.001$) and knowledge about the prevention of episodes ($p=0.01$). Previous studies have indicated the presence of inter-digital lesions and disease stage to be strong risk factors for reported number of ADLA episodes ($p<0.0001$)[59]. However, this study did not find any association between the number of inter-digital lesions and ADLA episodes in the past 30 days at baseline.

On the other hand, duration of ADLA symptoms in days was associated with intensity of the most recent ADLA ($p=0.001$) and with wounds ($p<0.05$). Similar to LF patients, the importance of identification and treatment of any wounds on the legs remains important to prevent subsequent attacks as well as shorten the duration of illness. Similarly, severity of the latest episode experienced was associated with increased DLQI scores ($p=0.001$). On the other hand, increased frequency of foot washing in the past week ($p=0.001$) and having washed feet the last night ($p=0.002$) were both associated with lower DLQI scores (higher quality of life) at baseline.

The significance of foot care and hygiene intervention becomes apparent once comparison between the two arms of the study was made between baseline and 12 months. Differences were seen in the number and duration of ADLA episodes, the number of mossy lesions median DLQI scores.

Compared to patients in the delayed treatment group, podoconiosis patients enrolled in the immediate treatment arm experienced a reduction in Incidence Rata Ratio (IRR) (initially 88%, and 68% at 12 months), consistent with studies in LF [48, 55, 62, 144]. A study in Haiti which assessed the effectiveness of basic lymphoedema management among patients with LF showed a rapid decline in the incidence of ADLA to 31% from earlier levels with a sustained reduction over a period of time[62] .The duration of symptoms of ADLA was significantly lower in the immediate treatment group. Studies investigating the incidence

and duration of ADLA events have used different methodologies. Most studiers recorded patient-reported frequency of episodes for the previous 12 months including episodes per year [51, 53, 59].

Studies have demonstrated that reducing ADLA episodes reduces perceptions of and presence of disability[55]. This study also indicated a reduction in DLQI scores (increase in quality of life) from baseline. Legesse *et al* (2008) validated the DLQI for use among podoconiosis patients and noted lower scores among treated patients [38]. This was also demonstrated in a one year follow up study in southern Ethiopia, which showed a marked reduction in the mean DLQI score from 21.11 at baseline to 6.07 at 12 months ($p<0.001$)[76]. A trial to assess the effectiveness of a new skin regimen on skin hydration in southern Ethiopia also found a reduction in the control group. The control group registered a reduction from 21.61 to 4.12 while the experimental group decreased from 21.07 to 4.12[66]. However, the observed decline ion DLQI scores among control patients may partly be explained by participants' perception of inclusion in the trial which tend to report improvement.

Chapter: 6 Process Evaluation of the RCT

6.1. Overview/ Introduction

Randomised controlled trials (RCTs) are the most rigorous way to evaluate the effectiveness of interventions, regardless of their complexity. Conventional RCTs evaluate the effects of interventions on prespecified health outcomes. Process evaluations within clinical trials ask important questions relevant to their execution and context which often facilitate interpretation of outcome results. They may aim to examine the views of intervention participants, to study how the intervention is implemented, to distinguish between components of the intervention, to investigate contextual factors that may affect an intervention or to study the way effects may vary in subgroups[145-146]. While randomised trials are intended to examine the effectiveness of an intervention, understanding 'what works?', 'for whom?' and 'under what circumstances?' is becoming increasingly more important in order for health service interventions to be useful in informing wider implementation [147-148]. In the trial around which this thesis is based, whether patients are carrying out the intervention at home as intended was assessed every month via self-reported adherence records. However, additional qualitative information assisted interpretation of the adherence information provided, and the trial results.

Pragmatic randomised trials provide high quality ways of investigating evidence of the effectiveness of treatments, interventions, or other aspects of healthcare provision. However, they rarely supply contextual information to explain the trial findings. Conducted within trials, process evaluations yield insights of import to interpret quantitative results [149] and in-depth understanding of the intervention's acceptability in everyday life. This information is important to patients, providers and policy makers if and when the intervention is scaled-up in other contexts[69].

6.2. The hygiene and foot care intervention

The intervention in this trial was podoconiosis lymphoedema management. 'Foot hygiene' comprised soaking feet, washing with soap, rinsing with clean water, drying and application of emollient (Whitfield's ointment). 'Foot care' included supervised use of single-layer, non-elastic bandages for disease stages ≥3; foot and calf exercises; instruction

to practice foot hygiene daily at home; instruction to elevate the foot of the bed or areas slept on; and instruction to use socks and shoes during waking hours (see Table 1). Those randomised to the 'immediate treatment' received the hygiene and foot care intervention immediately after randomisation. Each was allocated one bar of toilet soap (GIV international white) every month, and rate of use monitored at Monthly Intervention Visits (MIVs). In addition, patients were dispensed 40 gm of Whitfield's ointment sufficient for daily application for one month, and were asked to bring used tubes with any remaining ointment to MIVs to monitor usage. Those with stage 3 and greater podoconiosis were each provided with bandages for each affected foot and the condition of the bandages was checked during MIVs.

Table 6.1 Description of the foot care and hygiene intervention.

Time of intervention*	**Intervention**	**Purpose**
Months 1-2: approximately, 1-1:30 hrs.	Monthly Intervention Visits at HPs/HCs led by CPAs Home visits by CPAs and demonstration of treatment and supplying intervention products for the next month.	Provision of bowls, toilet soaps (2 bars of GIV International white), 40g of Whitfield's ointment that lasts for 1 month. For stage ≥3 disease; 2 short-stretch (<80% stretch) bandages, spiral from foot, overlap 50%, continue 8-10cm above the oedema. Demonstration of hygiene and foot care management: Soak for 10 minutes, Wash with soap, Apply emollient, Apply bandages, Elevation & exercises (Ankle rotation exercises. Elevate foot end of sleeping mattress, if used.), Use socks & shoes. Recap of last months' information and demonstration of hygiene and foot care management: Soak for 10 minutes, Wash with soap, Apply emollient, Apply bandages, Elevation & exercises (Ankle rotation exercises. Elevate foot end of sleeping mattress, if used.), Use socks & shoes. Shoes after initial swelling have reduced. Checking adherence to intervention Ensure patients continue performing treatment at home
Month 3: Approximately, 1-1:30 hrs.	Monthly Intervention Visits at HPs/HCs by CPAs and provision of one pair robust, closed shoes & two pairs of socks. Home visits by CPAs and demonstration of treatment and supplying intervention products for the next month	
Months 4-12: Approximately, 1-1:30 hrs.	Monthly Intervention Visits at HPs/HCs and checking of status of feet, shoes, socks and bandages. Completion of adherence forms and checking diaries. Home visits by CPAs and demonstration of treatment and supplying intervention products for the next month	

***During every MIV, adherence forms were completed and diary completion checked

Figure 6.1 Monthly Intervention Visits CPAs demonstrating intervention procedure to patients and checking diary completion (Photograph by Henok Negussie).

6.3. Methods

The methods used for the conduct of process assessment are described in chapter 2, section 2.5.

6.4. Results

A total of 98 participants, 53 females and 45 males, took part in the qualitative study. The majority were over the age of 40 years, married and farmers (Table 6.2).

Table 6.2 Socio-demographic characteristics of participants of the process assessment study.

Characteristic	Number
Sex	
Male	45
Female	53
Age	
18-29	22
30-39	7
40-49	26
50-59	28
60+	15
Marital Status	
Married	76
Widowed	7
Divorced	1
Single	14
Occupation	
Farmer	83
Community Podoconiosis Agent	8
Supervisor	2
Health Extension Worker	3
Woreda Health Office Officer	1
Liquor seller	1

Ten Focus Group Discussions (FGDs) were held with patients and Community Podoconiosis Assistants (CPAs). The role of CPAS in the trial was to lead the Monthly Intervention Visits (MIVs); demonstrate the intervention, check accuracy of diary entries, complete monthly intervention adherence forms and provide next month's intervention supplies. Eighteen In-depth Interviews (IDIs) were conducted with family members, HEWs, CPA supervisors, a *Woreda* Health Office expert, patients who had completed treatment and patients who had voluntarily left the study. Participants from 14 of the 19 *kebeles* in which the RCT was conducted were included (Table 2).

Table 6.3 Data collection activities and number of participants by study *kebeles.*

In-depth Interviews			Focus Group Discussions		
Interviewees	Number	*Kebeles*	*Kebeles*	Number of Participants	Number of FGDs
Family member	5	Genetua, Sendeba	Addisge	8	1
Treatment completed	4	Yewish	Daget	6	1
HEW	3	Sendeba, Shimbrima, Yewish	Enaskay	7	1
CPA Supervisor	2	Debre Markos	Gudalema	8	1
CPA	1	Yewish	Mislawash	8	1
Patient	1	Shimbrima	Jama	8	1
WoHO Officer	1	Amber Zuria	Zinkir	8	1
Voluntary withdrawal	1	Amber Zuria	Zengoba	10	1
			Wonga Nifasam	8	1
			CPA	8	1
Total	18			79	10

6.4.1. Thematic areas

The results of the study are summarised in nine thematic areas: understanding of the intervention and fidelity; reasons for absence from MIVs, feasibility of the intervention, availability of water, assistance from family members, adequacy and quality of intervention products, effectiveness, sustainability, future treatment providers.

6.4.2. Understanding and adherence to the intervention

The majority of patients understood and performed the intervention procedure at home as prescribed in the Monthly intervention Visits. Patients in the study described the intervention sequence accurately although some had appeared to have missed some aspects. CPAs also supported patients' reports of compliance and performing the procedure every day. Reasons for inability to perform the intervention included illness (mainly acute attacks) or fatigue after a long day's work on the farm.

> "They have taught us properly" (P028, patient, male).
>
> "Honestly, we're really following what we're taught…here (at the HP) as well as at home" (P090, patient, male).
>
> "First, we soak our feet, then we wash with soap and clean water, rotate our feet 10 times this way and 10 times that way and move our feet…after that we apply the ointment, put a pillow under our feet and go to bed" (P015, patient, female).
>
> "After soaking our feet with 8 jugs of water, we wash and apply the ointment and put a pillow under our feet when we sleep… since it'll expose to m*ichader* (acute attack) (as the ointment will attract dust), we wash our feet again in the morning…we then wear socks and shoes" (P070, patient, female).
>
> "When I ask them whether they performed the procedure at home daily, over the past month, they reply they had" (P049, CPA, female).
>
> "Some people, as they get very tired after a long day's work…if you ask them in a friendly way, they'll tell you the truth…they say 'as I'll be very tired in the evening, I may sleep without washing my feet'…and others say 'as soon as I get home from

work, I wash my feet before I sleep'…so we can't say every patient will follow the procedure one hundred percent" (P048, CPA, female).

In addition, patients' preferences over the use of warm or cold water for soaking and washing seemed to differ. Some patients preferred warm water for its relaxing effects. However, soaking and washing with cold water was found by many to be more comfortable and to have the effect of cooling the warm feet.

"I started washing with lukewarm water and the swelling began to decrease…I use this experience, but they told us (CPAs, during MIVs) to wash with cold water" (P020, patient, male).

"For me it always starts only when I use warm water, and using warm water is not good…if you soak with cold water (water fit for drinking), it'll reduce your fever…for example, both in town and in rural areas say 'whenever someone has fever pour cold water on them and that reduces the fever'?".

"When we soak our feet up to the ankle in cold water (water fit for drinking) and then thoroughly wash it, it relaxes us…and even it's the cold water that reduces the hotness" (P018, patient, female).

Patients are unable to perform the procedure on a daily basis when they travel to visit relatives, attend religious holidays or marriages. The additional burden of carrying a bowl, shortage of water and patients themselves feeling embarrassed to ask for the water they need for washing were important factors mentioned.

"In many households, water for hygiene purposes is not fetched separate from that used for drinking and cooking…thus, when they travel elsewhere, although they perform the procedure, it may be not be as regularly as it were when they're at home" (P048, CPA, female).

"Recently, a lady who was hospitalized told me 'I didn't wash my feet while in hospital because it was difficult to get water'" (P055, CPA, female).

However, emphasis was placed on the importance of performing the procedure on a daily basis and according to instructions given during the MIVs. When it comes to reports of improvement in the condition, those who failed to perform the intervention on daily basis appeared to be the ones who felt that it made little or no difference.

> "There're some people who say they're are not getting better, the reason being, they're not following the treatment properly. I'm getting better, except for a couple of episodes (acute attacks) recently, I've never been ill…we've benefitted from the treatment" (P035, patient, male).

> "There are some who claim the swelling has not decreased even if it has decreased… who don't properly follow and perform the treatment" (P057, CPA supervisor, female).

6.4.3. Reasons for absence from MIVs

Monthly Intervention Visits (MIVs) were designed to demonstrate the intervention procedure to patients, provide supplies for the coming month and complete adherence forms and received completed ADLA diaries. Where a participant was absent from an MIV, CPAs were to make a home visit and demonstrate the intervention, complete adherence forms and collect the completed diaries. Although absence was not a major problem, despite busy farm work and other hurdles of daily life, some patients did not attend. Reasons mentioned included illnesses (mainly, acute attack), unforeseen situations that needed urgent attention such as the death of a family member, relative or neighbour or urgent farm work; unavoidable religious obligations and attending holy water treatment sites, and physical inability to travel to Health Posts and Health Centres created by being elderly or visually impaired. On the other hand, although not mentioned as a major concern, disdainful relationships with CPAs were also cited as a reason for absence. People in small *kebeles* in rural Gojjam are surrounded by blood relatives, or have lived there for so long that they see other people's children as their own. Consequently, some patients do not take what a young CPA says, or her disapproval, very seriously. However, regardless of the reasons for absence, patients often expressed remorse and were apologetic for their absence.

"If it is harvest time, people may be absent…if there's death of someone nearby "(P022, patient, female).

"People won't be absent unless they're faced with a difficulties…for example, when they're ill or if someone has passed away" (P026, patient, male).

"There is this nun in our village…she was absent because she is not allowed to cross the village borders and the water (local river) on the Sabbath" (P069, patient, female).

"Since I go to their houses to demonstrate the treatment and give them their monthly supplies, they apologize for my trouble…'we had to work, that why we're absent'" (P049, CPA, female).

"I went to assist in a different *kebele* where patients didn't show up repeatedly… since the CPA is from their own *kebele*, she may not disapprove when they're absent…thus, our relations with patients may be a cause for absence sometimes…but, since I went and talked to them, everyone started to attend every month" (P048, CPA, female).

"Everyone in my *kebele* is somehow related; every month, they address me respectfully as 'somebody's daughter, is here'…leave alone to dislike or disobey me …for example, last month a patient had to take his son to Holy Water…when I went to his house and asked him why he didn't show up…he was so embarrassed he wanted to hide from me and he has not been absent since" (P051, CPA, female).

6.4.4. Feasibility

To assess feasibility, participants were asked to take into account the resources they had at their disposal. These included access to and availability of water, adequacy of monthly supplies, perceptions of and assistance from family members, and time to perform the intervention. They were also asked to describe any unanticipated consequences of using the Intervention Products and how easily the intervention could be performed at home. They were asked for feedback on intervention content, delivery and improvements that

need to be considered in the future. In addition, patients who had voluntarily withdrawn from the study were interviewed to establish whether their decision related to aspects of the treatment. Most found the intervention to be easy to understand and perform in everyday life, albeit requiring patients' personal commitment and the assistance of others, for example, as in the case of the elderly and the dependent, especially for fetching and carrying water.

> "The procedure needs a very strong-willed person who can take care of himself everyday…therefore, the treatment is difficult for someone who easily gets bored" (P030, patient, male).
>
> "Surely, it (the treatment) has made a difference…if you ask me what difference…previously my feet had moss which since I started the treatment is now completely gone" (P004, patient, male).
>
> "For me it's not difficult at all…it's in fact easy…I show my friends how they should perform the procedure…I'm comfortable with it, doesn't have any problems, its beautiful" (P031, patient, female).
>
> "We don't have any problem now…we can fetch water…we do the exercise…what can I say, I'm getting much, much better" (P025, patient, male).
>
> "It may be difficult for them to wash everyday…otherwise, the fact that the treatment will make much difference is clearly known…the reason is, it'd be difficult for them to perform the treatment after spending the day working, or at the market…but, they most of the time say the m*ichader* (acute attack) and the swelling has reduced" (P075, CPA, female).
>
> "If these people can't get support, it'd be difficult …even if they can get water for drinking, getting 8 jugs of water every day would be difficult for them…the solution therefore would be to find someone to help them until they get better…for those people who have children, their children should be told to help" (P035, patient, male).

6.4.5. Availability of water

The availability of water was not a concern in most the study *kebeles*. However, where shortage is mentioned, it was either a considerable distance to the source, or water was scarce. When there are extreme shortages of water, yet underground water is believed to exist it is illegal to dig wells. Unaffected community members in some *kebeles* were also said to prevent patients from fetching water for their treatment from communal sources.

> "We don't have shortage of water, there's plenty of water…a tap with two-way faucet has been constructed for us" (P072, patient, male).

> "It is well known that water is abundantly available in *Wonga Nifasam* …it's the water that sustains both man and cattle" (P074, patient, male).

> "Since people say 'you're going to dry out the *kebele's* water source'…I fetch water with Jerry cans from the spring" (P028, patient, male).

> "Digging a well is impossible…the land is very rocky, on the surface as well as underneath…what we use is spring water…our families fetch water for us, if we couldn't" (P082, patient, male).

> "We consider taking care of our feet on the same level as the food we eat and the drink we take…it can't be stopped, it won't be stopped…since this is a treatment, we've to fetch water from wherever it may be…even if it means we've to dig a well ourselves…but, it's prohibited to dig a well around here" (P080, patient, male).

> "I come from where water is very scarce…I'm really suffering…but, what can I do? I've no one to help me…I'm by myself… there're children who sometimes help me fetch water" (P085, patient, female).

6.4.6. Adequacy and quality of intervention products

Although most participants claimed to have performed the intervention at home, shoe-wearing was not consistent. This related to the quality of the shoes provided. First, they were too heavy for long distance walking. Secondly, the material they are made of leather rather than canvas. In addition, the shoes only covered the lower part of the ankle, not

beyond, and inevitably let in soil and were thus deemed unsuitable for farming activities. Gender issues were raised regarding the design of the shoes - most community members thought they were designed for men. This was mentioned as a reason that women did not wearing shoes consistently, in fear of what people might say at church, weddings or other community gatherings. The other dimension for inconsistent shoe wearing was that they exaggerate the swelling and thus expose patients to be singled out as podoconiosis patients. Most patients said the other supplies provided for the intervention were sufficient for a month.

> "One problem we have with shoes is when we wear them on the farm… when we are digging; soil comes into the shoes…on the other hand, since men have experience of wearing shoes, people won't say anything…however, they laugh and make jokes about women saying they're wearing men's shoes…therefore, women don't wear them…so it's better if the model be suitable to women" (P010, patient, male).

> "They are heavy especially when we travel far…we wear them all day within the village…otherwise, they're not a problem" (P016, patient, female).

> "They should be made of canvas…and there should be different styles for men and women…the reason is, since the shoes exaggerate the swelling, they may not wear it…and the leather doesn't easily fit to their feet, so canvas shoes would've been better…a lady came without wearing her shoes today and when I asked her why? she replied 'the shoes are very heavy'" (P075, CPA, female).

> "Women say people laugh at us when we wear this shoe…even the socks itself people ask 'are you wearing men's trousers?'…there're some women who don't wear their shoes when they come to the monthly meetings, because people make jokes about them…and many people gave us this information…I heard this in new *kebeles*…in the old *kebeles*, people are now accustomed to it…there're also people who don't care about what others say 'they can laugh however they want to I'm here to get treated'" (P057, CPA supervisor, female).

> "The ointment we're given is sufficient for a month" (P044, patient, male).

> "We are being given two bars of soap and two tubes of ointment and these are sufficient" (P073, patient, male)

6.4.7. Assistance from family members

The assistance of family members was found to be valuable in several ways. For example, children and spouses helped fetch water, where patients are elderly and dependent, wash feet and help complete acute attack diaries. The importance of this support was stressed among the elderly and those who have no family.

> "I give him medications like Aspirin and *hareg resa,* when his *michader* (acute attack) starts…when his basin is broken I buy him a new one…me and the other children fetch him water…when he gets ill, we wash his feet" (P063, family member, female).

> "I'm really suffering…but, what can I do? I've no one to help me…I'm by myself… there're children who sometimes help me fetch water" (P085, patient, female).

6.4.8. Perceived impacts of the intervention

The impacts the intervention brought to patients' health, and to economic and social aspects of their lives was clearly indicated in the discussions.

Health: the most important improvement was a decrease in the frequency, duration and/or severity of acute attacks -

> "Previously, I used to have *michader* (acute attack)day-after-day…but now, I have it maybe once a month only…before, we used to lag behind on tasks such as crop gathering, but now we finish at the same time as others…why, because we're healthy" (P010, patient, male).

> "Previously, before I started the treatment, my feet used to peel like potatoes…it was with great difficulty and after a long time, that I could even go to the toilet by myself…but, now even if I get ill, it doesn't keep me in bed…I'm now able to sit down and wash my feet" (P006, patient, female).

> "Before she started the treatment, her feet used to get puffed-up, now that's no more…previously; she used to get ill (acute attack) everyday …she recently got ill, but she got better immediately and the swelling, has decreased very much… wearing shoes helped reduce the swelling" (P061, family member, male).
>
> "I used to be in bed almost every day…it used to make me look like a slaughtered chicken, thrown on the ground…and, only after the skin of my legs got peeled off, skinned over, and brought me back from the dead, that I get better…but, now even if I sometimes get it, it doesn't keep me in bed… it's making a great difference and we're giving thanks" (P005, patient, male).
>
> "Previously, when their michader (acute attack) starts, people used to be in bed for a month…now, they say the michader has reduced (P065, HEW, female).

Economic: similarly, patients who were previously unable to work on and off their farms were reported to have returned to work and to earn a living on a par with their unaffected counterparts.

> "We got healed, we can work and earn a living…there's nothing else" (P028, patient, male).
>
> "Previously, I was unable to work as I wish to…but nowadays, I can do whatever work I want to" (P025, patient, male).
>
> "We don't sit idly like we used to do previously…now, praise to God, we're working" (P044, patient, male).

Social: patients previously faced with humiliation and insults from non-affected community members expressed how these attitudes and remarks had changed. There had been many instances in which patients felt ashamed to mix with people at social and religious events like '*Mahiber*' and '*Senbete*' (terms referring to voluntary and mutual religious gatherings to celebrate a saint's day while feeding the poor, on a rotational basis) and churches and that too has now changed.

“Surely, it (the treatment) has made a difference…people now say ‘look at him jumping around as he wishes’…otherwise, they used to insult us…previously, we used to be insulted as ‘saddle feet’…now people are saying ‘this treatment has benefitted you’” (P004, patient, male).

“My feet that used to be very swollen and used to look like a ripe lemon when the skin is peeled off…now, my feet are soft and people look at my feet…no one would look at it before… previously, people used to tease me about my feet saying ‘look, what kind of leg have you got?’ They think I was born with it…they don’t realize it arrives without warning, like the river Nile…now that we’re better, people say to us ‘this treatment made them humans again’” (P007, patient, female).

“What can we do unless the people stop their manner of speaking? They even used to call us names, very bad names, for example, they say ‘boot feet’…but we didn’t buy the disease with a salt bar…but nowadays, people say ‘you’re getting better’” (P058, patient, female).

“Before, I was unable to go to relatives’ houses, no annual celebrations, no wedding ceremonies and no church…Now I can go as I wish” (P031, patient, female).

“I used to feel uncomfortable myself, because my feet smell bad and the church needs cleanliness…previously, my feet were so swollen people get disgusted and won’t even look at me…but now, I can attend church services, I’ve become equal with my friends” (P045, patient, male).

“It was difficult for us to attend ”*Senbete*” because there was no washing and ointment…because we think and fear it smells (our feet)…we’re afraid to sit among people…but, now we look like newlyweds and since we’re much improved, we can sit among people” (P036, patient, male).

“I joined “*Mahiber*” very recently…before, it’d be very, very difficult to carry this leg and sit there and I used to be ashamed before…now our feet look like that of women and that of newlyweds”(P034, patient, male).

The CPAs agreed with these responses. They confirmed that the condition of patients who strictly followed the intervention as prescribed in the MIV had clearly improved.

> "Those whose swelling has not decreased are those who don't properly follow and perform the treatment procedure…but those who practically followed the treatment clearly tell you their swelling has greatly decreased and the *michader* (acute attack) is decreasing'" (P057, CPA supervisor, female).

> "During the monthly meetings, we go around and ask what difference they've had observed in the past month and most patients tell us 'since we began the treatment, we've not experienced *michader* (acute attack), or the *michader* has reduced" (P056, CPA supervisor, female).

> "Previously, they couldn't work and feed themselves…but, now they say they can work and also thank us…they've understood and accepted that the treatment works and can make a difference" (P053, CPA, female).

> "They tell us 'before we started the treatment, our '*michader* (acute attack) used to last a week or more, but now even if we had it (acute attack), it won't last more than three days. They also tell me, 'we've seen with our own eyes that the swelling is very much reduced'" (P050, CPA, female).

> "A patient, people say, was unable to do any kind of work and was in bed…he told me, since I started the treatment, he said 'I'm much improved and able to go work in the desert and lowlands'…his neighbour added he spends his day tending to the cattle and gathering beans from the field'…there's another lady, much better now she retails onions at Jama market'" (P051, CPA, female).

> "They say when they have disagreements, people call them names such as 'fist foot' …and that previously no one (in the community) allowed them to join '*Senbete*' and '*Iddir'…*for example, there's this man who had huge feet that has all gone, he comes at monthly meetings, takes off his shoes and shows us all and asserts how the treatment is very effective if properly followed' " (P057, CPA supervisor, female).

However, there were patients who were dissatisfied with the intervention. Foot care and hygiene interventions provided by NGOs in other districts are slightly different from that used in the trial, e.g. the addition of bleach to soaking water as an antiseptic. Patients who may have been exposed to such interventions previously may express their dissatisfaction with the intervention provided in the study as they thought the bleach was a medication. Others may also express similar opinions based on the perceived need for antibiotics and pain relief as part of the intervention.

> "There's nothing they've done for me…for me, there's nothing that had improved…Nothing! Not even change the size of a needle hole…I never got better… I used to get treatment at (name of IOCC treatment site removed) and, there's a chemical we used that we measure with a small cup (bleach) that decreased the swelling a little" (P099, treatment completed patient, male).

> "I wash my feet there (during the MIV) and come home…and, I can also wash at home…the cause is sweating and *mitch*…you don't give us tablets to swallow…and if it's only about washing my feet, my question is, can I not wash at home? And, I decided not to come because I can wash at home" (P095, voluntary withdrawal from study, female)

In sum, almost all patients and their families and treatment providers thought the intervention had improved their health, social and economic lives compared to those in the control group and recommended it to be provided for podoconiosis patients throughout Gojjam as well as in other places.

> "It depends on the type of illness…some swell more and with wounds and others ooze therefore, for those with swelling, I think it'll bring change" (P063, family member, female).

> "Since it's helped us, it will definitely help them too…because this treatment has been tested and proven effective, here on us" (P021, patient, male).

> "Of course the treatment has brought change…when we look at other people, even the moss is still there, and their *michader* (acute attack) has not decreased…we're so

much better now and able to come and go as we wish…and, if they get the same treatment, their condition will definitely improve" (P084, patient, male).

With regard to the various components of the intervention, most participants agreed on the combined effect of the whole package. However, some emphasised the importance of washing alone, others on application of the ointment, and still others, on wearing shoes at all times.

"I cannot say this or that separately made a difference" (P063, Family member, female).

"Everything together helped: washing and the ointment and wearing shoes "(P017, patient, female).

"It is because I used everything that I saw a difference...the reason is I've not seen each separately"(P045, patient, male).

"The treatment is very beneficial…the shoes, the ointment, the washing…everything contributed equally…however, if we don't wear socks and shoes, there'd be no change to our condition" (P078, patient, female).

"Wearing shoes is mainly useful…because, if we perform the other procedures but don't wear shoes, it will be meaningless…washing with soap, doing the exercise and applying the ointment each have their own benefits…in general, they've to do everything in the package" (P076, HEW, female).

6.4.9. Sustainability

The main barriers that would hinder patients from continuing to take care of their feet on their own included affordability of the intervention products such as Whitfield's ointment, soap, shoes and socks. The issue of availability of water did not appear to be a concern. The discussions indicated mixed views with some responding that they would do whatever it took to continue, while others were unsure they would continue.

> "Through you, we got our feet back…those of us who've the means, will continue the treatment…however, if it's beyond our means, we'll have to return to our previous condition of despair and illness…if we couldn't afford shoes and soaps, our feet will definitely be dirty" (P084, patient, male).

> "Since we're told the treatment will be stopped…and since we've seen the benefits, we'll continue to struggle to continue…but, as life is very wicked, we may be forced to buy salt instead of soap…so we can't say we'll be able to continue the treatment the way we've been doing so far" (P080, patient, male).

Patients may be too destitute to purchase the required supplies. It can be argued that since patients spend more time taking care of their illness instead of on productive work, when asked whether they would continue treatment in the future, they take account of their resources and make the decision that they would not. However, rural communities spend a lot on festivities and religious holidays. Therefore, in reality the issue at hand is lack of understanding of the importance of the treatment, expressed as a claim of not being able to afford these treatment products.

> "You know what, compared to others these patients are not productive, it is not that they couldn't work, it's simply that they spend much of their time caring for their illness than working…and when you look at it in economic terms, when they say if treatment is stopped we'll also stop, they're taking their assets into consideration…because, they can't afford the treatment supplies, they ask it to be transferred to the health insurance scheme" (P066, WoHO, expert, male).

> "People spend money on many things including festivities several times a year…how can shoes be something unaffordable? When you go to rural areas, most people go barefoot…however; the reason for it is not due to lack of money…but, buying shoes out of their pockets, is something unacceptable, that's their problem…they'd rather make a festivity of some kind and invite people. Therefore, I don't think its lack of money alone, but one of ignorance and lack of awareness" (P056, CPA supervisor, female).

6.4.10. Future treatment providers

When considering structures in which similar treatment should be provided, some suggested approaches like the trial, where CPAs would be employed. As most patients seem to have cultivated a very healthy relationship with the CPAs and are used to receiving their undivided attention, they did not think others would be able to deliver the expected level of attention. In addition, the argument for CPAs to continue providing treatment was also related to creating jobs. Those opposing the Health Post option (which is provision of the lymphoedema management program as an additional service package at Health Post level), typically relate to HEW's being already overwhelmed by heavy workload. On the other hand, others thought the Health Centers to be too far away for patients to travel. Future treatment provision may take experiences from other conditions into account.

> "Here they take care of us with patience and concern…we can't get used to new people…we can't even know what will happen in the future, so should continue as it is" (P021, patient, male).
>
> "It should continue as it is…if transferred to the Health Center, since the majority are too weak (elderly, dependent) to walk all the way to the Health Center, most will not attend…even if it's transferred…as you can see the Health Post was closed (not functional) for the past three months which means the treatment will be interrupted and if interrupted, the disease will come back…therefore, I believe the treatment better be continued in a same way here" (P082, patient, male).
>
> "Better if continued in the same way because Health Extension Workers are very busy" (P064, HEW, female).
>
> "I don't even know what to say about these children (CPAs)…other government employees have taught us about different issues in farmers' associations, but the personal manner of these children is quite…they bend down from their knees to take care of us…I've never seen nor heard of anyone like them" (P021, patient, male).

"I think it's better if the treatment is continued by the girls (CPAs) as it is, because HEWs have a huge workload…even now, I'm just coming in from the field…and it's better if we use/employ those who've completed 10th grade because it also means creating job opportunities…the patient load at the Health Center is also too big, very busy (staff at HC)" (P065, HEW, female).

"If it's given to the Health Extension Workers, it might not be fair, they're very busy…the service delivery unit must be at the Health Center…the community members will register new patients and we continue to treat known patients every month at the HCs…I believe, the responsibility of education and awareness can be given to HEWs. In addition, the task needs ownership and leadership…for example, if the government should not hand it over, similar to MACEPA (Malaria Control and Elimination Partnership in Africa]...if a *kebele* level officer, similar to MACEPA, could be appointed for this (Podoconiosis), it would mean the treatment program and improvements in patients' conditions could be closely monitored…therefore, from the three options, I mentioned, the last option is preferable, that is, patients coming to the HC every month for follow up" (P066, WoHO expert, male).

Finally, most participants indicated their satisfaction with the intervention and recommended it to other patients in other places. Recommendations for future programs included better quality footwear and the addition of antibiotics and analgesics for the treatment of acute attacks–

"The treatment itself is only washing, doesn't have tablets or injections…it'd have been better if these were included in the treatment" (P096, patient, male).

"The rest is getting better, although not completely gone…we get the '*girifat*' (mild form of acute attack) if we're struck by sunray…so give us injections or tablets" (P018, patient, female).

"When I get cold my '*nififit*' (another mild form of acute attack) starts in my legs…but, we're getting better…it (acute attack) can start even when we're wearing

shoes…when we travel far and if when we get struck by sunray…it'd be good if you give us injections and tablets for it" (P017, patient, female).

"The injections should be given when it (acute attack) strikes" (P021, patient, male).

"It'd have been better if you could research and gets us shoes that's better than these…for example, treatment such as injections, would have healed us more…that's my thought, otherwise, I've never used it before (the injection)" (P073, patient, male).

"We never thought of using these treatment even previously… we're getting very much better now if a way could be found, so we can be given treatment for the *michader* in the form of tablets of injections" (P082, patient, male).

6.5. Discussion

This qualitative study demonstrated that implementation of a simple hygiene and foot care intervention in podoconiosis lymphoedema is perceived to reduce the frequency, duration and severity of the most distressing consequences of podoconiosis, acute attacks, thereby improving patients' psychosocial and economic standing. Studies among LF patients in other contexts have described similar physical, psychological, social and economic burden associated with experiences of ADLA [141, 150]. The findings are consistent with studies in other contexts which reported effectiveness of lymphoedema management in reducing acute attacks among patients with LF [48, 53-55, 151]. Discussion with patients, families and providers indicated that after twelve months of participating in the trial, patients could understand and recollect instructions given about the intervention, and perform at home with little difficulty[48]. The intervention was considered to be acceptable, convenient and easy to apply in daily life with minimal side effects. Similar to previous evaluations of the hygiene and foot care intervention in LF [48, 55, 63, 144, 151], the intervention was thought to improve the social and economic lives of podoconiosis patients [75].

On the other hand, shortage of water and affordability of soap, ointment and shoes were mentioned as hindering patients from practicing the intervention treatment as prescribed. Shortage of water, especially during the dry season, was also mentioned by patients to be a

limiting factor for self-treatment in a one-year follow up study of the effectiveness of lymphoedema treatment in southern Ethiopia[76]. The importance of water, sanitation, and hygiene (WASH) is increasingly recognized as essential for the control and elimination of several neglected tropical diseases (NTDs), including trachoma, soil-transmitted helminthes infection, and schistosomiasis [152-153]. Accordingly, plans to scale up the intervention in other contexts should include discussion to identify and remove barriers to access of water for podoconiosis patients. Support to sustain daily self-care including improved access to supplies such as clean water, soap, topical antibacterial and antifungal agents, and oral antibiotics may be challenges that need to be considered[10].

Where compliance with treatment is considered, reasons for non-attendance at treatment days identified included experiencing acute attacks, unforeseen situations that needed urgent attention, unavoidable religious obligations and attending holy water treatment sites, and physical inability to travel to HPs and HCs "Remoteness from a clinic site" was the main reason identified by previous studies for loss to follow up among podoconiosis patients in Amhara region (19), so creation of additional mobile or satellite clinics for lymphoedema treatment should be considered if this is to be incorporated into existing government health care facilities in future. Consistent with studies from Wolaita and Amhara, experiencing acute attacks was found to be the main reason for non-attendance at monthly meetings [154-155].

Regarding future treatment provision, models of delivery need to be considered. The findings of a study which assessed effectiveness of delivery strategies for lymphoedema management in North-Eastern Nigeria indicated that Community Care was the most effective strategy in resource-poor settings. As communities could facilitate care procedures, this will help in reducing stigma and facilitate reintegration of patients. To this effect, teachers and religious leaders could be trained to create support groups, as the majority of communities may be non-literate and thus lack the capacity to register and monitor patients. On the other hand, Health Centres may not encourage the formation of social support groups that are important for lymphoedema management in resource-poor settings. The role of health facilities and personnel would then be limited to training and serving as storage depots for supplies[63]. On the flip side, however, although Community

Care has great potential for lymphoedema management, prescription of antibiotics and analgesics for acute attacks may be difficult using this model. Thus, community management may need to be encouraged alongside routine health services and specialized referral for patients with complicated lymphoedema. Similar to LF management, opportunities for integration of podoconiosis management with other chronic health care programs such as leprosy and diabetes must be explored, together with the possibility that support and education are provided by the public sector of NGOs programs. [55, 156]. Equally important, the effectiveness of incorporation of podoconiosis management at a range of levels of any given state health system, requires further exploration.

6.6. Conclusion

This foot care and hygiene intervention appears acceptable and is reported to bring about health, social and economic improvements in patients' lives. Further, the foot care and hygiene program seems to have empowered some patients to continue self-treatment in the future. Although most will make the effort to continue performing the intervention in the future, whether patients will continue self-treatment once contact with the trial ceases needs further long-term follow up. Future treatment implementation in other contexts should take into account factors that may affect adherence to treatment including availability of adequate, clean water, which will require local discussion regarding water utilization. The need to design high quality footwear should consider the expressed need for gender-specific designs, and making products such as soap and topical ointments affordable to encourage self-treatment, in the future. The roles of health facilities and health personnel, patients, patient associations and the broader community need to be assessed in future research to guide the delivery of treatment services to podoconiosis patients. Once that is determined, there is an urgent need to scale-up the foot care and hygiene intervention nationally to prevent disability and as a morbidity management program to ameliorate the pain and distress of podoconiosis patients.

Chapter 7: Discussion and conclusion

The thesis set out to define ADLA in podoconiosis lymphoedema, apply this definition to estimate the incidence, duration and social impact of ADLA and document the impact of a simple foot hygiene implementation on ADLA. To this effect, quantitative and qualitative methods were applied.

Since the WHO included podoconiosis in its list of Neglected Tropical Diseases (NTDs) in 2011[157], encouraging progress had been made in advocacy, research and policy. A nationwide podoconiosis mapping, which was conducted in 2013, showed that podoconiosis is endemic in 345 districts of Ethiopia with 4% national prevalence. The study indicated that 34.9 million people, 43.8% of the Ethiopian population live in areas where the environment is conducive for the occurrence of podoconiosis[158] and according to a recent estimate by Deribe *et al* (2017) suggests 1,537,963 adults (95% confidence intervals, 290,923-4,577,031 adults) were living with podoconiosis in 2015[31]. Studies have also shown the consequences of podoconiosis including loss of productivity[34] severe stigma[13] and mental distress[159]. Thus, in the national master plan for integrated control of NTDs, podoconiosis has been identified as one of the eight diseases prioritized and a goal has been set to eliminate the disease by 2030[160].

However, unlike Lymphatic Filariasis (LF), there are no published trials on the impact of the foot care and hygiene intervention on ADLA in podoconiosis. This thesis describes work around the first pragmatic randomised controlled trial of podoconiosis lymphoedema management. At present, Non-Governmental Organizations (NGOs) in different regions of the country implement the intervention with varying procedures, intervention packages and duration of treatment. The results of this thesis will inform the implementation of integrated morbidity management for both podoconiosis and LF, providing evidence for acceptability, feasibility and scaling of treatment.

The Rapid Ethical Assessment (REA) provided information on strategies to approach patients in rural Gojjam for participation in this clinical trial. It guided the development of the patient information sheet and consent forms, and mechanisms to improve comprehension of information and encourage continued participation. The diary

acceptability, feasibility and reliability studies showed the local term m*ichader* could be used to describe the symptoms of ADLA. In other LF endemic contexts, local terms have been used to describe the symptoms as 'filarial flares'[51] and crisis[141]. In addition, patients could understand and complete a simple pictorial diary depicting a "sick person in bed" and "a healthy person farming" on a daily basis to provide information on their ADLA experiences. Chapter 5 provided a picture of the health burden that ADLA imposes on patients' lives and comparison of changes in the incidence and duration of ADLA after 12 months of intervention. Chapter 6 reports a qualitative process assessment of the intervention, giving support for the feasibility and effectiveness of the intervention. Patients and treatment providers attested the health, social and economic benefits of the intervention and important contextual aspects that need to be considered if the intervention is to e implemented in other podoconiosis endemic areas. This chapter aims to synthesize the major findings and discuss their interpretation in the light of previous research. It also aims to describe the policy and research implications of the findings.

The REA was conducted to understand strategies to approach communities and prospective participants as well as to develop the study information sheet and consent form, taking into account the context of rural Gojjam and requirements for the conduct of clinical trials stipulated in international ethical guidelines (chapter 3). It indicated the utility of REA specifically when it comes to planning studies in research- *naïve* settings as well as approaching communities with diverse socio-cultural beliefs and expectations. For example, the results revealed the practical importance of holding sensitisation meetings with *woreda*, *kebele* and religious leaders. This helped to cascade information about the trial down to *kebele* and community level and ensure the support and collaboration the study team needed during fieldwork. As Health Extension Workers play a major role as a source of health related information in their respective *kebeles*, employing them to accompany the research team to patients' houses was an appropriate approach. Regarding provision of study information using a health education expert with a thorough understanding of the local culture appeared to have improved comprehension. Further, drawing analogies between concepts used in local agricultural and social organisations and those used in science made explanation about treatment arms, randomisation and delayed

treatment more easily comprehensible. Related to this, using key community members to quell rumors that arose in the course of the trial was advantageous. As participating in and being committed to the trial may require approval of significant others, it is important to allow sufficient time for prospective participants to discuss with their families. A strategy suggested to encourage continued participation of patients in the 'delayed' intervention arm, was to provide small incentives at regular intervals. Accordingly, the findings were employed in the development of the information sheet and consent forms for the main trial. The results provided useful information similar to previous REAs prior to a genetic study among podoconiosis patients in southern Ethiopia[126, 161] and to a study of HPV-serotype prevalence in Northern Ethiopia[112, 162]. A study in Ghana used REA to identify practical issues surrounding the enrollment of paediatric cases in a genetic and genomic study of severe malaria in Ghana[90]. The REA has also provided information on the perception of genetics and genetic research in north western Cameroon[118] and understanding approaches and permission structures for informed consent in rural communities in north western Cameroon[163]. This study therefore, highlighted the utility of REA prior to clinical trials.

Chapter 4 presents the development of a standard case definition for ADLA, and the validation of this measure for use in investigating the impact of foot hygiene on ADLA frequency and duration. The definition was used at baseline and through 12 months of follow up. The diary served as a valid measure to capture ADLA experiences on a daily basis. The comprehension study indicated that the pictorial representation in the diary was acceptable and inoffensive to patients, could easily be understood and be completed by patients themselves, or with the assistance of family members, where the elderly and visually impaired are involved. The positive predictive value (ppv) as indicated by comparison of patients' self report of ADLA with that of health professional diagnosis was 0.81. However, the use of religious days as reminders for patients was recommended. Doing this and asking CPAs to check completion before the diaries were transferred to the field office ensured the collection of reliable and accurate data.

The incidence and duration of ADLA at baseline was described in chapter 5. Almost all patients (98% and 99% in the immediate and delayed groups, respectively) had ever

experienced ADLA attacks, with a median (IQR) ADLA incidence in the past 30 days of 2 (2-3) and 3 (2-3), respectively. This indicated a considerable disease burden in the study population. Associations with the number of ADLA attacks patients experienced in the past 30 days showed the relevance of having washed feet more than 7 times in the past week and having washed the night before baseline - both these were associated with significantly lower number of episodes that month ($p<0.001$). Similarly, knowledge that episodes can prevented was associated with decreased number of episodes ($p<0.01$). On the other hand, presence of wounds in the legs and feet were associated with increased number of attacks by 20% ($p<0.001$). Similarly, absence of inter-digital lesions were associated with fewer episodes ($p<0.05$). These findings indicated the importance of educating patients to prevent, identify and promptly treat wounds and inter-digital lesions in the feet in order prevent recurrent ADLA episodes[47].

Subsequently, the impact the intervention had in reducing the frequency and duration of ADLA from baseline to 12 months was presented. In addition, the duration of ADLA symptoms at 12 months follow up was significantly different between the two groups ($p<0.001$). The results were in agreement with a number of studies (mostly uncontrolled) on the effectiveness of basic lymphoedema management conducted among LF patients in other contexts [48, 55, 62, 144, 164-166]. In their Haiti study, Addiss *et al* (2010) reported incidence of ADLA before treatment was initiated as 2.1 episodes per year, which eventually decreased to 0.6 episodes per year[62]. Similarly, in their evaluation of the effect of antibacterial soap, Addis *et al* (2011) indicated, although incidence if ADLA was significantly lower in both groups, there were no significant differences between using antibacterial soap and plain soap. Thus, encouraging proper hygiene and skin care with affordable and locally obtainable soap[167].

This study also indicated that at 12 months, the DLQI scores for both groups reduced from baseline (that is, quality of life increased). Scores for the immediate treatment ranged from 5-16 (median 11) while the control scores ranged from 11-19 (median 14) and the two-sample Wilcoxon rank-sum test indicated the difference was significant ($p<0.001$). A small follow up study (n=27) among podoconiosis patients in southern Ethiopia reported a 10 point reduction in DLQI scores and mean decrease 15.04 ($p<0.001$). Legesse and Davey

(2008) reported a significant difference in DLQI between treated and treatment-naïve patients in southern Ethiopia ($p<0.001$). Although the study established the feasibility, reliability and validity of the Amharic DLQI, using a cross-sectional design it was difficult to clarify whether the differences in DLQI scores between new and treated patients were due to the intervention[143]. A small RCT to evaluate a new skin regimen in southern Ethiopia (n=193) followed up patients for three months. In the three month follow up period the mean DLQI experimental group reduced from 21.07 to 7.97 to 4.06 to 3.94 and in the control group from 21.61 to 8.83 to 4.59 to 4.12. However, this difference was not significant ($p=0.907$)[66]. Another small study using the DLQI among LF patients in Guyana showed improvements in DLQI scores for all patients as well as acute attack rates [64]. The observed rapid decline in DLQI scores could be related to a rapid reduction in severity of ADLA as a result of the foot care and hygiene intervention which in turn lead to improved ability to perform activities of daily life. It could also be due to improved awareness of the disease and understanding of how to manage the illness. Also cited are morale building by health personnel and other staff [64, 66] and monthly group meet with other patients which creates a platform for discussion which act as a moral force to perform the foot care and hygiene intervention as prescribed.

However, no other RCTs in podoconiosis have measured impact on ADLA of a foot care and hygiene intervention. Thus, comparison with studies of the same condition is not possible. It should be noted that use of a comparison group has not been possible in several earlier studies in LF (12, 13) and podoconiosis (16) for ethical and logistic reasons. Reduction in ADLA episodes and other clinical outcomes reported over the study periods may have occurred regardless of the intervention. The present trial provides stronger scientific evidence of the effectiveness of the foot care and hygiene intervention for lymphoedema resulting from both LF and podoconiosis. In addition, the fact that we were able to collect prospective information on ADLA episodes allowed more accurate calculation of ADLA.

Clinical changes were observed in relation to mossy lesions and inter digital lesions. At 12 months, the difference in the presence of mossy lesions was significant in the right and left feet (102 (32%) vs 138 (42%), and 102 (32%) vs 133 (41%), for the treatment and control groups, respectively, $p<0.001$ and $p<0.02$). Sikorski *et al* (2010) reported that the presence

of mossy lesions at 12 months was not different between the new and treated patients (p=0.375)[76]. Similarly, the presence of inter digital lesions in the left leg for the treatment group were significantly different (15 (16%) vs 79 (24%), p<0.001). McPherson *et al* (2005) indicated that the number of inter digital lesions strongly predicts the frequency of ADLA episodes within the past year[51]. Accordingly, as podoconiosis is highly endemic in Ethiopia[31], every effort should be made scale up the intervention to other areas.

As the first exploration into patients' perceptions of the intervention and its components, results also showed that the foot care and hygiene intervention was acceptable to podoconiosis patients, their families and treatment service providers. This study added a process evaluation dimension recommended by MRC[80] but often not undertaken in other trials[168]. Qualitative studies can shed light on subtleties of benefits of intervention as well as challenges patients may face in the future[151]. The intervention was found to be simple, easy to conduct at home with minimal difficulty and to bring about health, social and economic improvements in patients' lives. A report of experiences of community-based lymphoedema management in Odisha State, India, indicated similar findings [151]. Evaluations of similar programs have demonstrated improvements in acute episodes[144] and productivity[55]. Accordingly, the adverse health, and socioeconomic consequences of podoconiosis may be ameliorated by introducing this simple treatment.

Access to treatment was an issue: Health Centres are far from some villages and are difficult to reach, particularly for the elderly and visually impaired. Participants of the process assessment also mentioned HEWs' workload as a major concern making the HP as a less preferable option. This brings another option suggested by participants; conducting treatment in a similar setting as this study was conducted, that is, employing CPAs. Previous studies in northern Ethiopia have indicated the relationship between long distance walking and ADLA episodes[56]. Thus, future large scale implementation in other contexts should take into consideration distance from treatment sites, availability of water and policies regarding water utilization, addressing gender differences in designing high quality footwear and socks, and ensuring availability, affordability and quality of treatment products. It should also be noted that the *pros* and *cons* of the various models need to be

evaluated to select the optimal mode of treatment delivery in the future. Studies have argued in favour of incorporating care into existing government health care systems or establishing mobile clinic sites for the purpose[154]. However, others have suggested once the training needs of communities and community leaders is achieved, a minimal role should be allocated to health facilities such as procurement, storage and distribution of supplies [63]. Further, possibilities for integration with other chronic health care programs such as leprosy and diabetes as well as part NGOs can play in support and education must be explored[55, 156, 169-170].

7.1. Limitations of the studies

The studies in this thesis have several limitations. The diary return rate for the validation study was very small (16/52) and most were completed by family members. This could be due to low literacy levels and lack of experience using writing materials. Accordingly, the accuracy of diary entries of some patients (especially the elderly and visually impaired) might have been affected. However, following the suggestions of participants in the validation study, patients in the trial were advised to seek the assistance of school children and neighbours. In addition, patients were consistently trained during all MIVs, and CPAs checked accuracy of completion using religious days as reminders of start and end dates and corrected diaries accordingly before transferring to the field office. In addition, during quarterly follow up visits, experiences of ADLA were recorded by recall, as back up. The study also required patients to accurately answer questions during follow up visits. However, being included in the study by itself might have positively biased responses (Hawthorne effect) in some questionnaires. For example, scores on DLQI measures showed a decline (improved quality of life) in participants in the control group. This could be explained in the intensity of follow up. RCTs with more intensive follow-ups may result in higher Hawthorne effect than those with minimal follow up. This study had four follow up periods in 12 months, which would be considered minimal follow up[171].

Prior to the study, visits to the nearest service providers indicated that there was little experience in sharing treatment items even among members of the same household. In addition, those waiting their turn for treatment at IOCC clinics, did not attempt to buy their

own supplies even though they saw the treatment materials provided. To minimise the effects of contamination, if more than one potential participant lived in the same household, one was selected using a lottery method [57].

Another issue is individual variation in conducting the intervention. The intervention was delivered following a Standard Operating Procedure (SOP) and CPAs in each *kebele* were trained at the outset followed by refresher trainings at regular intervals with the investigator making regular supportive visits. These were, in general to ensure procedures specified in the SOPs are followed. However, variations might have occurred among CPAs, for example, in delivering health education messages, and timing of MIVs and home visits. However, as a pragmatic trial, such variations in real life settings are to be expected[172].

Regarding the Rapid Ethical Assessment described in chapter 3, participants from the community were identified by Health Extension Workers (HEWs), which might have introduced selection bias - HEWs selecting people they know. Further, this might result in social desirability bias-as participants were selected by HEWs based on knowledge of being trusted to provide "the right answers". However, every effort was made to include a productive group by varying locations/*kebeles* (maximum variation). Connected to this, participants of focus groups indicated there would be no reason for podoconiosis patients to refuse participation in the trial. This might be due to the fact that communities in the area have little or no experience participating in research and thus misunderstood the project as a treatment/service provision, instead of research. Accordingly, the difference between the two concepts was clarified to the satisfaction of participants before enrollment and in the information sheet given.

In the process evaluation study, mixed (male and female) FGDs were conducted. This might have prevented women from freely discussing their views. However, analysis of the first few FGDs did not support such concerns as men and women discussed freely. In addition, an individual independent of the trial team led the discussions, which provided more freedom for participants and intervention providers to reflect on and discuss positive as well as negative aspects of the intervention. Including more patients who had completed participation might have shed more light on issues of continued self-treatment in the

future. Only a few appeared for the focus groups and interviews. Attempts to reach the six patients, who had left the study voluntarily, were in vain. The reasons for leaving the study included: leaving the study area permanently, personal reasons (such as death of family members), and geographical remoteness of patients' homes. Including them in the process assessment might have helped understand their reasons for withdrawing. Among those who voluntarily left the study, two were interviewed and gave unfulfilled requests for tablets or injections to be included in the treatment as a reason for withdrawal. This disillusionment over the mundane nature of the hygiene treatment, and the lack of injectable medication, has been reported to be a reason for discontinuation in other settings[173]. Finally, conducting analysis in the language of interview minimizes loss of meaning during translation. However, interviews in this study were conducted in Amharic and analysis was done in English.

7.2. Key conclusions

This thesis is based on a practical approach to the preparation and conduct of a RCT to measure the incidence, duration and social impact of ADLA with significant practical and policy implications. The REA proved to be handy and practical in identifying approaches to communities with little experience in research. This inexpensive and quick approach is not beyond the financial costs required to conduct some studies. In support of prior studies which provided evidence on the importance of the REA, it was proved to be a useful tool in rural Gojjam in the context of preparing and launching a RCT among podoconiosis patients. It undoubtedly may provide contextual information if conducted prior to similar studies in other settings, in the future.

The preliminary studies proved the patient-completed diary to be a valuable approach for collecting prospective data on ADLA incidents among podoconiosis patients in northern Ethiopia. The local term "*michader*" describes the symptoms of ADLA was understandable to patients in rural Gojjam. The practical implication of this could be put to use in future intervention programs, for example, as a tool to monitor improvement in the incidence and duration of ADLA once treatment had been initiated. However, cost implications of

designing and regular printing as well as patient acceptability of the contents of the diary may need to be evaluated in other contexts.

Regarding disease burden, the fact that almost all patients had experienced ADLA in the past 30 days, speaks for itself. At baseline, the more frequently feet were washed, the absence of wounds in the legs and favorable knowledge that ADLA could be prevented were significantly associated with reduced number of episodes in the past 30 days. These were also found to be associated with lowered scores on the DLQI test. Combined with findings that after 12 months of follow up, patients who received the foot care and hygiene intervention had significantly lower incidence and duration ADLA as well as reduced DLQI scores compared to the controls ($p<0.001$), it indicated the effectiveness of the hygiene intervention among podoconiosis patients. Organisations implementing the foot care and hygiene intervention in Ethiopia were observed to vary in their use of intervention products such as soap: toilet, laundry or herbal soaps. However, NGOs providing podoconiosis prevention and treatment services should be encouraged to adopt the treatment package as a safe, affordable and uniform package. This could be mandated by the NaPAN or the FMoH.

Findings of the process assessment also indicated the benefits of the intervention in reducing the number and duration of episodes as well as improving social standing of patients. From the process assessment it also appears that patients prefer treatment near where they live. Health Centres seem to be far from remote villages and difficult to reach particularly for the elderly and visually impaired. On the other hand, the fact that the HEWs are already overburdened with many packages appears to make the HP as a less preferable option. This brings another option suggested by participants, conducting treatment in a similar setting as this study was conducted. That is, employing CPAs. However, the full aspect of the feasibility of these options *vis-à-vis* other formats of integration need to be assessed carefully for several reasons including compliance with treatment. Speaking of compliance with treatment, if there is anything that could be said regarding future treatment provision in other contexts, it may be that attention should be given to concerns regarding availability of and unrestricted access to water, local availability and affordability of treatment products and the all too important gender differences in designing footwear.

7.3. Dissemination of results of the study

The study proposal had been presented nationally and internationally. The poster presentation was awarded the Global Health Trials competition to attend the Royal Society of Tropical Medicine and Hygiene Annual Meeting in Oxford, UK, in September 2014. In addition, in 2015, poster was presented at National Health Professional workshops at Jimma and Haramaya universities in Ethiopia. The results of all the studies were presented at a national workshop held on 25 May 2017 in Addis Ababa. This was a platform for all NGOs implementing the treatment and prevention programs, researchers and the academic community.

Figure 7.1 National level study results dissemination workshop, 24 May, 2017, Addis Ababa, Ethiopia (Photograph by Henok Negussie and Yonatan Baka).

Similarly, in June 2017, the main quantitative and qualitative findings were presented in Amharic language at the study site. A total of 44 participants attended the half-day workshop: representatives of East and West Gojjam Zone Health Department, *woreda* administration, health, education, agriculture, social affairs, government communication and youth and women's offices, selected participants of the study, *kebele* and religious leaders, CPAs and DCs and their supervisors.

Figure 7.2 *Woreda* (district) level study results dissemination workshop, Amhara Regional State, East Gojjam Zone, Aneded *woreda*, 10 June, 2017 (Picture by Henok Negussie and Abebe Kelemework).

7.4. Capacity building in clinical trials

As the study was the first clinical trial in the zone and in view of limited or no experience in clinical research, a capacity building initiative was considered appropriate. Accordingly, in collaboration with and funded by Global Health Trials, a three-day "Essential Clinical Research Skills: A skills sharing workshop" was conducted at Debre Markos University, from 15-17 June, 2015. The objective of the workshop was to introduce essential clinical research skills and help establish a network among university faculties to share skills and knowledge about running clinical research using available resource and academic staff. Accordingly, topics of discussion of the training included: level of evidence, introduction to clinical trials rationale, research question, aim (PICOT method) design and classification of clinical research, with emphasis on pragmatic randomized controlled trials (this study used as an example), study population, site, outcomes, data collection and analysis, ethical issues in RCTs. Other faculty at the university covered data management using STATA software, English for academic writing. The workshop was attended by over 90 faculty members from different departments.

Figure 7.3 Capacity building: training on essential skills in clinical research, Debre Markos University, Ethiopia, 15-17 June, 2015 (Photograph by Thomas Addissie).

8. Author contributions

As a basis for the measurement of the impact of the intervention on the frequency and duration ADLA and on quality of life, I led a multidisciplinary team, to conduct two preliminary studies; the Rapid Ethical Assessment and the design and testing of a patient-completed ADLA diary for acceptability, feasibility and reliability. In the REA, I designed the study, led the field team during data collection, transcription of interviews and focus groups, coding and analysis of the data. I designed the diary, conducted the acceptability and feasibility interviews and focus groups, trained HEWs on ADLA diary, collected and analyzed the reliability data. For the main RCT, I participated in the design of the study, development and translation of the data collection instruments. I developed Standard Operating Procedures (SOPs), and study logs, was responsible for the delivery of the intervention, reporting of Adverse Events (SAEs) and collection of adherence data. While the baseline analysis, association and Poisson regression were conducted by the author, the follow-up data were analyzed by statisticians from Kilifi Clinical Trials Facility (KCTF, KEMRI-Wellcome Trust). Finally, I designed and led the process evaluation study, developed and translated the interview and focus group guides and led the field work and translation of transcripts, coding of data. I entered and analyzed the data.

References

1. Davey G, Gebrehanna E, Adeyemo A, Rotimi C, Newport M, Desta K:**Podoconiosis: a tropical model for gene-environment interactions?** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2007, **101:** 91-96.
2. Price EW, Bailey D:**Environmental factors in the etiology of endemic elephantiasis of the lower legs in tropical Africa.** *Trop Geogr Med* 1984, **36:** 1-5.
3. Fuller LC:**Podoconiosis: endemic nonfilarial elephantiasis.** *Curr Opin Infect Dis* **18:** 119-122.
4. Price EW, Henderson WJ:**The elemental content of lymphatic tissues in barefooted people in Ethiopia, with reference to endemic elephantiasis of the lower legs.** *Trans R Soc Trop Med Hyg* 1978, **72:** 132-136.
5. Molla YB, Wardrop NA, Le Blond JS, Baxter P, Newport MJ, Atkinson PM, Davey G:**Modelling environmental factors correlated with podoconiosis: a geospatial study of non-filarial elephantiasis.** *International Journal of Health Geographics* 2014, **13:** 1-12.
6. Price EW:**A possible genetic factor in non-filarial elephantiasis of the lower legs** *Ethiop Med J* 1972, **10:** 87–93.
7. Price EW:**The association of endemic elephantiasis of the lower legs in East Africa with soil derived from volcanic rocks.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1976a, **70:** 288-295.
8. Ayele FT, Adeyemo A, Finan C, Hailu E, Sinnott P, Burlinson ND, Aseffa A, Rotimi CN, Newport MJ, Davey G:**HLA Class II Locus and Susceptibility to Podoconiosis.** *N Engl J Med* 2012, **366:** 1200-1208.
9. Davey G:**Podoconiosis, non-filarial elephantiasis and lymphology.** *Lymphology* 2010, **43:** 168-177.
10. Addiss DG, Brady MA:**Morbidity management in the Global Programme to Eliminate Lymphatic Filariasis: a review of the scientific literature.** *Filaria Journal* 2007, 19.
11. Kerketta A, Babu B, Rath K, Jangid P, Nayak A, Kar S:**A randomized clinical trial to compare the efficacy of three treatment regimens along with footcare in the morbidity management of filarial lymphoedema.** *Tropical Medicine & International Health* 2005, **10** 698–705
12. Ichimori K, King JD, Engels D, Yajima A, Mikhailov A, Lammie P, Ottesen EA:**Global programme to eliminate lymphatic filariasis: the processes underlying programme success.** *PLoS neglected tropical diseases* 2014, **8:**
13. Tora A, Franklin H, Deribe K, Reda AA, Davey G:**Extent of podoconiosis-related stigma in Wolaita Zone, Southern Ethiopia: a cross-sectional study.** *SpringerPlus* 2014, **3:** 647.
14. Yakob B, Deribe K, Davey G:**Health professionals' attitudes and misconceptions regarding podoconiosis: potential impact on integration of care in southern Ethiopia.** *Trans R Soc Trop Med Hyg* 2010, **104:** 42-47.
15. Price EW:**The elephantiasis story.** *Trop Dis Bull* 1984, **81:** R1-R12.
16. Gail D:**Recent advances in podoconiosis.** *Annals of Tropical Medicine & Parasitology 377–382 (2009)* 2009, **103**
17. Wanji S, Tendongfor N, Esum M, Che J, Mand S, Tanga C, Enyong P, Hoerauf A:**Elephantiasis of non-filarial origin (podoconiosis) in the highlands of north-western Cameroon.** *Annals of Tropical Medicine & Parasitology* 2008, **102:** 1-12.
18. Eid R, Sharma D, Smock W:**Podoconiosis in Rural Tanzania.** *Am J Trop Med Hyg* 2016, **95:** 1.

19. Dwek P, Kong LY, Wafer M, Cherniak W, Pace R, Malhamé I, Simonsky D, Anguyo G, Stern E, Silverman M:**Case Report and Literature Review: Podoconiosis in Southwestern Uganda.** *International Journal of TROPICAL DISEASE & Health* 2015, **9:** 1-7.
20. Ruiz L, Campo E, Corachan M:**Elephantiasis in Sao Tome and Principe.** *Acta Trop* 1994, **57:** 29-34.
21. Oomen AP:**Studies on elephantiasis of the legs in Ethiopia.** *Trop Geogr Med* 1969, **3:** 97-113.
22. Desta K, Ashine M, Davey G:**Prevalence of podoconiosis (endemic non-filarial elephantiasis) in Wolaitta, Southern Ethiopia.** *Trop Doct* 2003, **33:** 217-220.
23. Kloos H, Kello AB, Addus A:**Podoconiosis (endemic non-filarial elephantiasis) in two resettlement schemes in wetster Ethiopia.** *Tropical Doctor* 1992, **22:** 109-112.
24. Animut A:**The burden of non-filarial elephantiasis in Ethiopia.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2007, **101:** 1173-1174.
25. Tekola Ayele F, Alemu G, Davey G, Ahrens C:**Community-based survey of podoconiosis in Bedele Zuria woreda, west Ethiopia.** *International health* 2013, **5:** 119-125.
26. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G:**Podoconiosis in East and West Gojam Zones, northern Ethiopia.** *PLoS Negl Trop Dis* 2012, **6:** e1744 doi:1710.1371/journal.pntd.0001744.
27. Geshere Oli G, Tekola Ayele F, Petros B:**Parasitological, serological and clinical evidence for high prevalence of podoconiosis (non-filarial elephantiasis) in Midakegn district, central Ethiopia.** *Tropical medicine & international health : TM & IH* 2012, **17:** 722-726.
28. Alemu G, Tekola Ayele F, Daniel T, Ahrens C, Davey G:**Burden of podoconiosis in poor rural communities in Gulliso woreda, West Ethiopia.** *PLoS neglected tropical diseases* 2011, **5:** e1184.
29. Deribe K, Brooker SJ, Pullan RL, Sime H, Gebretsadik A, Assefa A, Kebede A, Hailu A, Rebollo MP, Shafi O, et al:**Epidemiology and individual, household and geographical risk factors of podoconiosis in Ethiopia: results from the first nationwide mapping.** *The American journal of tropical medicine and hygiene* 2015, **92:** 148-158.
30. Deribe K, Cano J, Newport MJ, Golding N, Pullan RL, Sime H, Gebretsadik A, Assefa A, Kebede A, Hailu A, et al:**Mapping and Modelling the Geographical Distribution and Environmental Limits of Podoconiosis in Ethiopia.** *PLoS Negl Trop Dise* 2015, **9:** e0003946.
31. Deribe K, Cano J, Giorgi E, Pigott DM, Golding N, Pullan RL, Noor AM, Cromwell EA, OsgoodZimmerman A, Enquselassie F, et al:**Estimating the number of cases of podoconiosis in Ethiopia using geostatistical methods [version 1; referees: awaiting peer review].** *Wellcome Open Res* 2017, **2:78 (doi: 10.12688/wellcomeopenres.12483.1):**
32. Tekola F, HaileMariam D, Davey G:**Economic costs of endemic non-filarial elephantiasis in Wolaita Zone, Ethiopia** *Tropical Medicine & International Health* 2006, **11:** 9
33. Alemu G, Tekola Ayele F, Daniel T, Ahrens C, Davey G:**Burden of podoconiosis in poor rural communities in Gulliso woreda, West Ethiopia.** *PLoS Negl Trop Dis* 2011, **5:**
34. Tekola F, Mariam DH, Davey G:**Economic costs of endemic non-filarial elephantiasis in Wolaita Zone, Ethiopia.** *Tropical medicine & international health : TM & IH* 2006, **11:** 1136-1144.
35. Yakob B, Deribe K, Davey G:**High levels of misconceptions and stigma in a community highly endemic for podoconiosis in southern Ethiopia.** *Transactions of the Royal Society of Tropical Medicine & Hygiene* 2008, **102:** 439.
36. Tora A, Davey, G., Tadele, G.:**A Qualitative Study on Stigma and Coping Strategies of Patients with Podoconiosis in Wolaita Zone, Southern Ethiopia.** *International health* 2011,
37. Yakob B, Deribe K, Davey G:**High levels of misconceptions and stigma in a community highly endemic for podoconiosis in southern Ethiopia.** *Trans R Soc Trop Med Hyg* 2008, **102:** 439-444.
38. Henok L, G D:**Validation of the Dermatology Life Quality Index among patients with podoconiosis in southern Ethiopia.** *Br J Dermatol* 2008, **159:** 903-906.

39. Tora A, Davey G, Tadele G:**A qualitative study on stigma and coping strategies of patients with podoconiosis in Wolaita zone, Southern Ethiopia.** *International health* 2011, **3:** 176-181.
40. Tekola F, Bull S, Farsides B, Newport M, Adeyemo A, Rotimi C, Davey G:**Impact of social stigma on the process of obtaining informed consent for genetic research on podoconiosis: a qualitative study.** *BMC Med Ethics* 2009, **10:** 13.
41. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G:**Patients' perceptions of podoconiosis causes, prevention and consequences in East and West Gojam, Northern Ethiopia.** *BMC Public Health* 2012, **12:** 1-7.
42. Mousley E, Deribe K, Tamiru A, Tomczyk S, Hanlon C, Davey G:**Mental distress and podoconiosis in Northern Ethiopia: a comparative cross-sectional study.** *International health* 2015, **7:** 16-25.
43. Bartlett J, Deribe K, Tamiru A, Amberbir T, Medhin G, Malik M, Hanlon C, Davey G:**Depression and disability in people with podoconiosis: a comparative cross-sectional study in rural Northern Ethiopia.** *International health* 2016, **8:** 124-131.
44. Tekola F, Ayele Z, Hailemariam D, Fuller C, Davey G:**Development and testing of a de novo clinical staging system for podoconiosis (endemic non-filarial elephantiasis).** *Tropical medicine & international health : TM & IH* 2008, **13:** 1277-1283.
45. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G:**Patients' perceptions of podoconiosis causes, prevention and consequences in East and West Gojam, Northern Ethiopia.** *BMC Public Health* 2012, **12**
46. Price EW: **Endemic elephantiasis: early signs and symptoms and control.** *Ethiop Med J* 193, **21:** 243-253.
47. Dreyer G, Addiss D, Gadelha P, Lapa E, Williamson J, Dreyer A:**Interdigital skin lesions of the lower limbs among patients with lymphoedema in an area endemic for bancroftian filariasis.** *Tropical Medicine and International Health* 2006, **11:** 7.
48. Suma TK, Shenoy RK, Kumaraswami V:**Efficacy and sustainability of a footcare programme in preventing acute attacks of adenolymphangitis in Brugian filariasis.** *Tropical Medicine and International Health* 2002, **7:** 3
49. Olszewski WL:**Episodic dermatolymphangioadenitis (DLA) in patients with lymphedema of the lower extremities before and after administration of benzathine penicillin: a preliminary study.** *Lymphology* 1996, **29:** 126.
50. Dreyer G, Medeiros Z, Netto MJ, Leal NC, de Castro LG, Piessens WF:**Acute attacks in the extremities of persons living in an area endemic for bancroftian filariasis: differentiation of two syndromes.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1999, **93:** 413-417.
51. McPherson T, Persaud S, Singh S, Fay M, Addiss D, Nutman T, Hay R:**Interdigital lesions and frequency of acute dermatolymphangioadenitis in lymphoedema in a filariasis-endemic area.** *British Journal of Dermatology* 2006 **154:** 933–941.
52. McPherson T, Michael PF, Singh S, Penzer R, Hay R:**Health Workers' agreement in clinical description of filarial lymphoedema.** *Am J Trop Med Hyg* 2006, **74:** 500-504.
53. Addiss DG, Louis-Charles J, Roberts J, LeConte F, Wendt JM, Milord MD, Lammie PJ, Dreyer4 G:**Feasibility and Effectiveness of Basic Lymphedema Management in Leogane, Haiti, an Area Endemic for Bancroftian Filariasis.** *PLoS neglected tropical diseases* 2010, **4:** 1-8.
54. Jullien P, Someb JdA, Brantusc P, Bougmad RW, Bambad I, Kyelemd D:**Efficacy of home-based lymphoedema management in reducing acute attacks in subjects with lymphatic filariasis in Burkina Faso.** *Acta Tropica* 2011, **120s:** S55-S61.
55. Budge PJ, Little KM, Mues KE, Kennedy ED, Prakash A, Rout J, Fox LM:**Impact of Community-Based Lymphedema Management on Perceived Disability among Patients with Lymphatic Filariasis in Orissa State, India.** *PLoS neglected tropical diseases* 2013, **7:** 1-11.

56. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G:**Podoconiosis in East and West Gojam Zones, northern Ethiopia.** *PLoS Negl Trop Dis* 2012, **6:** e1744.
57. Negussie H, Kassahun MM, Fegan G, Njuguna P, Enquselassie F, McKay A, Newport M, Lang T, Davey G:**Podoconiosis treatment in northern Ethiopia (GoLBet): study protocol for a randomised controlled trial.** *Trials* 2015, **16:** 307.
58. Alemu G, Ayele FT, Daniel T, Ahrens C, Davey G:**Burden of Podoconiosis in Poor Rural Communities in Gulliso woreda, West Ethiopia.** *PLoS Negl Trop Dis* 2011, **5:** 6.
59. Dreyer G, Addiss D, Gadelha P, Lapa E, Williamson J, Dreyer A:**Interdigital skin lesions of the lower limbs among patients with lymphoedema in an area endemic for bancroftian filariasis.** *Tropical Medicine and International Health* 2006, **11:** 1475–1481.
60. Brantus P:**Ten years of managing the clinical manifestations and disabilities of lymphatic filariasis.** *Annals of tropical medicine and parasitology* 2009, **103 Suppl 1:** S5-10.
61. Wiseman V, Conteh L, Matovu L, :**Using diaries to collect data in resource-poor settings: questions on design and implementation.** *Health Policy Plan* 2005, **20** 394-404.
62. Addiss D, Louis-Charles J, Roberts J, LeConte F, Wendt J, Milord MD, Lammie P, Dreyer G:**Feasibility and Effectiveness of Basic Lymphedema Management in Leogane, Haiti, an Area Endemic for Bancroftian Filariasis.** *PLoS Negl Trop Dis* 2010, **4(4): e668. doi:10.1371/journal.pntd.0000668:**
63. Akugn OB, Badakib JA:**Management of adenolymphangitis and lymphoedema due to lymphatic filariasis in resource-limited North-eastern Nigeria.** *Elsevier* 2010 **Acta Tropica 120S:** S69-S75.
64. McPherson T:**Impact on the quality of life of lymphoedema patients following introduction of a hygiene and skin care regimen in a Guyanese community endemic for lymphatic filariasis: A preliminary clinical intervention study.** *Filaria J* 2003, **2:** 1.
65. Sikorski C, Ashine M, Zeleke Z, Davey G:**Effectiveness of a Simple Lymphoedema Treatment Regimen in Podoconiosis Management in Southern Ethiopia: One Year Follow-Up.** *PLoS Negl Trop Dis* 2010, **4:** 1-5.
66. Brooks J, Ersser S, Cowdell F, Gardiner E, Mengistu A, Matts P:**A Randomised Controlled Trial to evaluate the effect of a new skin care regimen on skin barrier function in those with podoconiosis in Ethiopia.** *The British journal of dermatology* 2017, **Accepted Author Manuscript. doi:10.1111/bjd.15543:**
67. Mengitsu B, Shafi O, Kebede B, Kebede F, Worku DT, Herero M, French M, Kebede B, Mackenzie C, Martindale S, et al:**Ethiopia and its steps to mobilize resources to achieve 2020 elimination and control goals for neglected tropical diseases: Spider webs joined can tie a lion.** *International health* 2016, **8:** i34-i52.
68. Budge PJ, Little KM, Mues KE, Kennedy ED, Prakash A, Rout J, Fox LM:**Impact of Community-Based Lymphedema Management on Perceived Disability among Patients with Lymphatic Filariasis in Orissa State, India.** *PLoS Negl Trop Dis* 2013, **7:** 1-11.
69. Rapport F, Storey M, Porter A, Snooks H, Jones K, Peconi J, Sánchez A, Siebert S, Thorne K, Clement C, Russell I:**Qualitative research within trials: developing a standard operating procedure for a clinical trials unit.** *Trials* 2013, **14:** 1-8.
70. Central Statistical Agency:**Population and Houseing Census Report. CSA Addis Ababa Ethiopia, 2007.**
71. Central Statistical Agency, ICF:**Ethiopia Demographic and Health Survey (2011).** *CSA and ICF International, Calverton, Maryland, USA* 2012,
72. Federal Democratic Republic of Ethiopia:**Health Sector Strategic Plan (HSDP-III)** *Planning and Programming Department, Federal Ministry of Health, Addis Ababa; 2009/10*

73. Tekola F, Bull S, Farsides B, Newport M, Adeyemo A, Rotimi C, Davey G:**Tailoring consent to context: designing an appropriate consent process for a biomedical study in a low income setting.** *PLoS Negl Trop Dis* 2009, **3:** e482.
74. Bull SJ, Farsides B, Tekola FA:**Tailoring information provision and consent processes to research contexts: the value of rapid assessments.** *J Empir Res Hum Res Ethics Int J* 2012, **7:** 37-52.
75. Tomczyk S, Tamiru, A., Davey, G.:**Addressing the Neglected Tropical Disease Podoconiosis in Northern Ethiopia: Lessons Learned from a New Community Podoconiosis Program.** *PLoS neglected tropical diseases* 2012, **6(3): e1560. doi:10.1371/journal.pntd.0001560:**
76. Sikorski C, Ashine M, Zeleke Z, Davey G:**Effectiveness of a simple lymphoedema treatment regimen in podoconiosis management in southern ethiopia: one year follow-up.** *PLoS Negl Trop Dis* 2010, **4:** e902.
77. Negussie H, Addissie T, Addissie A, Davey G:**Preparing for and Executing a Randomised Controlled Trial of Podoconiosis Treatment in Northern Ethiopia: The Utility of Rapid Ethical Assessment.** *PLoS Negl Trop Dis* 2016, **10(3): e0004531:**
78. Molla YB, Tomczyk S, Amberbir T, Tamiru A, Davey G:**Podoconiosis in East and West Gojam Zones, Northern Ethiopia.** *PLoS Neglected Tropical Diseases* 2012, **6:** e1744.
79. Peterson RL, Tran M, Koffel J, Stovitz SD:**Statistical testing of baseline differences in sports medicine RCTs: a systematic evaluation.** *BMJ Open Sport & Exercise Medicine* 2017, **3:**
80. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J:**Process evaluation of complex interventions: Medical Research Council guidance.** *BMJ : British Medical Journal* 2015, **350:**
81. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M:**Developing and evaluating complex interventions: the new Medical Research Council guidance.** *Bmj* 2008, **337:**
82. **NVivo* 11 Pro for Windows. Avialable from: www.qsrinternational.com**

83. Brandt MA: **Racism and research: the case of the Tuskegee Syphilis Study.** *Hastings Center Reports* 1978, **8:** 21-29.
84. Rothman D:**Ethical and social issues in the development of new drugs and vaccines.** *Bulletin of the New York Academy of Science* 1987, **63:** 557-568.
85. **The Nuremberg Code (1947).** *Bmj* 1996, **313:** 1448.
86. Council for International Organizations of Medical Sciences (CIOMS):**International Ethical Guidelines for Biomedical Research Involving Human Subjects.** *Geneva, Switzerland* 2002,
87. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (NCPHSBBR):**The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research** *Washington, DC: Department of Health, Education and Welfare* 1979,
88. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: **ICH harmonized tripartite guideline. Guideline for good clinical practice E6. ICH 1996.** *Avialable: http://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guidelinepdf*
89. World Medical A:**World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.** *JAMA* 2013, **310:** 2191-2194.
90. Tindana P, Bull S, Amenga-Etego L, de Vries J, Aborigo R, Koram K, Kwiatkowski D, Parker M:**Seeking consent to genetic and genomic research in a rural Ghanaian setting: A qualitative study of the MalariaGEN experience.** *BMC Medical Ethics* 2012, **13:** 1-12.

91. Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, JC JCB, al. e:**Ottawa Ethics of Cluster Randomized Trials Consensus Group. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials.** *PLoS Med* 2012, **9(11):** e1001346.
92. del Carmen MG, Joffe S:**Informed Consent for Medical Treatment and Research: A Review.** *The Oncologist* 2005, **10:** 636-641.
93. Tam NT, Huy NT, Thoa LTB, Long NP, Trang NTH, Hirayama K, Karbwang. J:**Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta analysis.** *Bull World Health Organ* 2015, **93:** 186–198H.
94. Shiono YN, Zheng Y-F, Kikuya M, Kawai M, Ishida T, Kuriyama S, Ohuchi1 N:**Participants' understanding of a randomized controlled trial (RCT) through informed consent procedures in the RCT for breast cancer screening, J-START.** *Trials* 2014, **15:** 1-10.
95. Chappuy H, Bouazza N, Minard-Colin V, Patte C, Brugieres L, Landman-Parker J, Auvrignon A, Davous D, Pacquement H, Orbach D, et al:**Parental comprehension of the benefits/risks of first-line randomised clinical trials in children with solid tumours: a two-stage cross-sectional interview study.** *BMJ Open* 2013, **3:** 1–10.
96. Bergenmar M, Molin C, Wilking N, Brandberg Y:**Knowledge and understanding among cancer patients consenting to participate in clinical trials.** *Eur J Cancer* 2008, **44:** 2627–2633.
97. Brezis M, Israel S, Weinstein-Birenshtock A, Pogoda P, Sharon A, Tauber R:**Quality of informed consent for invasive procedures.** *Int J Qual Health Care* 2008, **20:** 352–357.
98. Krosin MT, Klitzman R, Levin B, Cheng J, Ranney ML:**Problems in comprehension of informed consent in rural and peri-urban Mali, West Africa.** *Clin Trials* 2006, **3:** 306-313.
99. Manafa O, Lindegger G, IJsselmuiden C:**Informed consent in an antiretroviral trial in Nigeria** *Indian J Med Ethics* 2007, **4:** 26-30.
100. Saidu Y, Odutola A, Jafali J, Ogundare O, Worwu A, Sey G, Thomas V, Stanley-Batchilly E, Afolabi M, Idoko O, et al: **Contextualizing the Informed Consent Process in Vaccine Trials in Developing Countries.** *J Clinic Res Bioeth* 2013, **4:**
101. Bhutta ZA:**Beyond informed consent.** *Bulletin of the World Health Organization* 2004, **82:** 771-777.
102. Bioethics NCo:**The Ethics of Research Related to Healthcare in Developing Countries.** *London, England: Nuffield Foundation* 2002,
103. Krogstad DJ, Diop S, Diallo A, Mzayek F, Keating J, Koita OA, Touré YT:**Informed Consent in International Research: The Rationale for Different Approaches** *Am J Trop Med Hyg* 2010, **83:** 743-747.
104. Kengne-Ouafo J, Nji T, Tantoh W, Nyoh D, Tendongfor N, Enyong P, Newport M, Davey G, Wanji S:**Perceptions of consent, permission structures and approaches to the community: a rapid ethical assessment performed in North West Cameroon.** *BMC Public Health* 2014, **14:** 1026.
105. Shaibu S:**Ethical and cultural considerations in informed consent in Botswana.** *Nurs Bioeth* 2007, **14:** 503–509.
106. Ezeome ER, Marshall PA:**Informed consent practices in Nigeria.** *Dev World Bioeth* 2009, **9:** 138-148.
107. Lobato L, Bethony JM, Pereira FB, Grahek SL, Diemert D, Gazzinelli MF:**Impact of gender on the decision to participate in a clinical trial: a cross-sectional study.** *BMC Public Health* 2014, **14:** 1-9.
108. Tekola F, Bull S, Farsides B, Newport M, Adeyemo A, Rotimi C, Davey G:**Impact of social stigma on the process of obtaining informed consent for genetic research on podoconiosis: a qualitative study.** *BMC Med Ethics* 2009, **10:** 1-10.
109. Appelbaum P, Roth L, Lidz C:**The therapeutic misconception: informed consent in psychiatric research.** *Int J Law Psychiatry* 1982, **5:** 319–329.

110. Jonas A, Kengne-Ouafo, Millardb J, Njic T, WilliamTantohd, Nyohe D, Tendongfora N, Enyong P, Newport M, Davey G, Wanji S:**Understanding of research, genetics and genetic research in a rapid ethical assessment in north west Cameroon.** *International health* 2015, **doi:10.1093/inthealth/ihv034:** 1-7.
111. Abay S, Addissie A, Davey G, Farsides B, Addissie h:**Rapid Ethical Assessment on Informed Consent Content and Procedure in Hintalo-Wajirat, Northern Ethiopia: A QualitativeStudy.** *PLoS ONE* 2016, **11(6): e0157056. doi:10.1371/journal. pone.0157056:**
112. Abay S, Addissie A, Davey G, Farsides B, Addissie T:**Rapid Ethical Assessment on Informed Consent Content and Procedure in Hintalo-Wajirat, Northern Ethiopia: A Qualitative Study.** *PLoS ONE* 2016, **11:** e0157056.
113. Kamuya D, Marsh V, Molyneux S:**What we learned about voluntariness and consent: incorporating "background situations" and understanding into analyses.** *Am J Bioeth* 2011, **11:** 31-33.
114. S.R B, :**Reflections and recommendations on research ethics in developing countries.** *Soc Sci Med* 2002, **54:** 1131-1141.
115. Lidz CW, Appelbaum PS, Grisso T, Renaud M:**Therapeutic misconception and the appreciation of risks in clinical trials.** *Soc Sci Med* 2004, **58:**
116. Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G:**Informed consent: how much and what do patients understand?** *American journal of surgery* 2009, **198:** 420.
117. Hyder AA, Rattani A, Krubiner C, Bachani AM, Tran NT: **Ethical review of health systems research in low- and middle-income countries: a conceptual exploration.** *Am J Bioeth* 2014, **14(2):** 28–37.
118. Kengne-Ouafo JA, Millard JD, Nji TM, Tantoh WF, Nyoh DN, Tendongfor N, Enyong PA, Newport MJ, Davey G, Wanji S:**Understanding of research, genetics and genetic research in a rapid ethical assessment in north west Cameroon.** *International Health* 2015,
119. Nijhawan L, Janodia M, Bhat M, Udupa N, Muddukrishna BS, Bairy KL, Musmade PB:**Informed consent: Issues and challenges.** *Journal of Advanced Pharmaceutical Technology & Research* 2013, **4:** 135-140.
120. Bhan A, Majd M, Adejumo A:**Informed Consent in International Research: Perspectives from India, Iran and Nigeria.** *Medical Ethics* 2006, **3**
121. Abdel-Messih IA, El-Setouhy M, Crouch MM, Earhart KC:**Developing Cultural Competence and Overcoming Ethical Challenges in the Informed Consent Process: An Experience from Egypt** *Journal of Research Administration* Fall 2008, **39** 33-40.
122. Bower P, Brueton V, Gamble C, Treweek S, Smith C, Young B, Williamson P:**Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities.** *Trials* 2014, **15:** 399.
123. Bull SJ, Farsides B, Tekola Ayele F:**Tailoring information provision and consent processes to research contexts: the value of rapid assessments.** *J Empir Res Hum Res Ethics* 2012, **7:** 37–52.
124. Bhutta Z:**Beyond informed consent.** *Bulletin of the World Health Organization* 2004, **82:** 771-777.
125. Bull SJ:**Consent to research in a Gambian context: legal, social and ethical issues** *PhD Thesis Kings College, London* 2007,
126. Tekola F, Bull S, Farsides B, Newport MJ, Adeyemo A, Rotimi CN, Davey G:**Impact of social stigma on the process of obtaining informed consent for genetic research on podoconiosis: a qualitative study.** *BMC Med Ethics* 2009, **10:** doi:10.1186/1472-6939-1110-1113.
127. Addissie A, Davey G, Newport MJ, Addissie T, MacGregor H, Feleke Y, Farsides B:**A mixed-methods study on perceptions towards use of Rapid Ethical Assessment to improve informed**

consent processes for health research in a low-income setting. *BMC Medical Ethics* 2014, **15:** 2-12.
128. Bull SJ:**Consent to research in a Gambian context: legal, social and ethical issues (PhD thesis).** *London Kings College* 2007,
129. Addissie A, Davey G, Newport M, Farsides B, Feleke Y:**FEASIBILITY OF RAPID ETHICAL ASSESSMENT FOR THE ETHIOPIAN HEALTH RESEARCH ETHICS REVIEW SYSTEM.** *Ethiop Med J* 2015, **53**
130. Council for International Organization of Medical Sciences (CIOMS):**International Ethical Guidelines for Biomedical Research Involving Human Subjects. Avenue Appia 20, CH1211 Geneva 27, Switzerland: CIOMS, c/o WHO: 2002.**
131. (OPRS) OftPoRS:**Informed Consent in Human Subjects Research.** *University of Southern California,https://oprsuscedu/files/2013/04/Informed-Consent-Booklet-4413pdf* 2013,
132. Commission USNBA:**Ethical and policy issues in international research: clinical trials in developing countries: Volume I: Report and Recommendations of the National Bioethics Advisory Commission.** 2001,
133. Wiseman V, Conteh L, Matovu F:**Using diaries to collect data in resource-poor settings: questions on design and implementation.** *Health Policy and Planning* 2005, **20:** 394-404.
134. Garber M, Nau D, Erickson S, Aikens J, Lawrence J:**The concordance of self-report with other measures of medication adherence: a summary of the literature.** *Medical Care* 2004, **42:** 649–652.
135. Landgren B, Collins A, Csemiczky G:**Menopause transition: annual changes in serum hormonal patterns over the menstrual cycle in women during a nine-year period prior to menopause.** *Journal of Clinical Endocrinology and Metabolism* 2004, **89:** 2763–2769.
136. Gibson J:**Why does the Engel method work? Food demand, economies of size, and household survey methods.** *Oxford Bulletin of Economics and Statistics* 2002, **64:** 341-359.
137. Parkin D, Rice N, Jacoby A, Doughty J:**Use of a visual analogue scale in a daily patient diary: Modelling cross-sectional time-series data on health-related quality of life.** *Social Science and Medicine* 2004, **59:** 351-360.
138. Johnson J, Bytheway B:**An evaluation of the use of diaries in a study of medication in later life.** *International Journal of Social Research Methodology* 2001, **4:** 183-204.
139. Stinson JN, Huguet A, McGrath P, Rosenbloom B, Soobiah C, White M, Coburn G:**A qualitative review of the psychometric properties and feasibility of electronic headache diaries for children and adults: Where we are and where we need to go.** *Pain Research & Management : The Journal of the Canadian Pain Society* 2013, **18:** 142-152.
140. Burcu A: **A comparison of two data collection methods: Interviews and questionnaires.** *Hacettepe Univ J Educ* 2000, **18:** 1-10.
141. Person B, Addiss D, Bartholomew LK, Meijer C, Pou V, Gonzálvez G, van den Borne B:**A qualitative study of the psychosocial and health consequences associated with lymphedema among women in the Dominican Republic.** *Acta Tropica* 2007, **103:** 90-97.
142. Grosh M, Glewwe P:**Designing household survey questionnaires for developing countries: lessons from 15 years of the Living Standards Measurement Study.** *Washington, DC: The World Bank* 2000,
143. Henok L, Davey G:**Validation of the Dermatology Life Quality Index among patients with podoconiosis in southern Ethiopia.** *Br J Dermatol* 2008, **159:** 903-906.
144. Mues KE, Deming M, Kleinbaum DG, Budge PJ, Klein M, Leon JS, Prakash A, Rout J, Fox LM:**Impact of a Community-Based Lymphedema Management Program on Episodes of Adenolymphangitis (ADLA) and Lymphedema Progression - Odisha State, India.** *PLoS neglected tropical diseases* 2014, **8:** e3140.

145. Campbell NC, Murray E, Darbyshire J, Emery J, Farmer A, Griffiths F, Guthrie B, Lester H, Wilson P, Kinmonth AL:**Designing and evaluating complex interventions to improve health care.** *Bmj* 2007, **334:** 455-459.
146. Hawe P, Shiell A, Riley T:**Complex interventions: how "out of control" can a randomised controlled trial be?** *BMJ : British Medical Journal* 2004, **328:** 1561-1563.
147. Nanyonjo A, Nakirunda M, Makumbi F, Tomson G, Kallander K, in SSG:**Community acceptability and adoption of integrated community case management in Uganda.** *The American journal of tropical medicine and hygiene* 2012, **87:** 97-104.
148. Peterson S:**Assessing the scale-up of child survival interventions.** *Lancet* 2010, **375:** 530-531.
149. Lutge E, Lewin S, Volmink J:**Economic support to improve tuberculosis treatment outcomes in South Africa: a qualitative process evaluation of a cluster randomized controlled trial.** *Trials* 2014, **15:** 236.
150. Akogun OB, Akogun MK, Apake E, Kale OO:**Rapid community identification, pain and distress associated with lymphoedema and adenolymphangitis due to lymphatic filariasis in resource-limited communities of North-eastern Nigeria.** *Acta Tropica* 2011, **120:** S62-S68.
151. Cassidy T, Worrell CM, Little K, Prakash A, Patra I, Rout J, Fox LM:**Experiences of a Community-Based Lymphedema Management Program for Lymphatic Filariasis in Odisha State, India: An Analysis of Focus Group Discussions with Patients, Families, Community Members and Program Volunteers.** *PLoS neglected tropical diseases* 2016, **10:** e0004424.
152. Stocks ME, Ogden S, Haddad D, Addiss DG, McGuire C, Freeman MC:**Effect of water, sanitation, and hygiene on the prevention of trachoma: a systematic review and meta-analysis.** *PLoS Med* 2014, **11:** e1001605.
153. Grimes JE, Croll D, Harrison WE, Utzinger J, Freeman MC, Templeton MR:**The relationship between water, sanitation and schistosomiasis: a systematic review and meta-analysis.** *PLoS neglected tropical diseases* 2014, **8:** e3296.
154. Campion A, Tamiru A, Tsegay G, Davey G:**Reasons for loss to follow-up of patients with podoconiosis in the Amhara Region, northern Ethiopia.** *International health* 2015, **7:** 367-373.
155. Tora A, Davey G, Tadele G:**Factors related to discontinued clinic attendance by patients with podoconiosis.** *BMC public health* 2012, **12:** 1-7.
156. Stillwaggon E, Sawers L, Rout J, Addiss D, Fox L:**Economic Costs and Benefits of a Community-Based Lyphedema management Program for Lymphatic Filariasis in Odisha State, India** *The American journal of tropical medicine and hygiene* 2016, **doi:10.4269/ajtmh.16-0286:**
157. Davey G, Bockarie M, Wanji S, Addiss D, Fuller C, Fox L, Mycoskie M, Gruin M, Tsegaye A, Ayele FT, Newport M:**Launch of the International Podoconiosis Initiative.** *The Lancet* **379:** 1004.
158. Deribe K, Cano J, Newport MJ, Golding N, Pullan RL, Sime H, Gebretsadik A, Assefa A, Kebede A, Hailu A, et al:**Mapping and Modelling the Geographical Distribution and Environmental Limits of Podoconiosis in Ethiopia.** *PLoS Neglected Tropical Diseases* 2015, **9:** e0003946.
159. Mousley E, Deribe K, Tamiru A, Davey G:**The impact of podoconiosis on quality of life in Northern Ethiopia.** *Health and quality of life outcomes* 2013, **11:** 122.
160. Federal Democratic Republic of Ethiopia Ministry of Health:**Ethiopia National Master Plan For Neglected Tropical Diseases. Addis ababa, Ethiopia. Avialable at http://ntdenvision.org/resource/ethiopia_national_master_plan_for_neglected_tropical_diseases. Accessed on 13 July 2017.**
161. Tekola F, Bull SJ, Farsides B, Newport MJ, Adeyemo A, Rotimi CN, Davey G:**Tailoring consent to context: designing an appropriate consent process for a biomedical study in a low income setting.** *PLoS neglected tropical diseases* 2009, **3:** e482.

162. Addissie A, Abay S, Feleke Y, Newport M, Farsides B, Davey G:**Cluster randomized trial assessing the effects of rapid ethical assessment on informed consent comprehension in a low-resource setting.** *BMC medical ethics* 2016, **17:40:**
163. Kengne-Ouafo JA, Nji TM, Tantoh WF, Nyoh DN, Tendongfor N, Enyong PA, Newport MJ, Davey G, Wanji S:**Perceptions of consent, permission structures and approaches to the community: a rapid ethical assessment performed in North West Cameroon.** *BMC Public Health* 2014, **14:** 1026.
164. World Health Organization:**Lymphatic filariasis: Progress of disability prevention activities.** *Wkly Epidemiol Rec* 2004, **79:** 417-424.
165. Chandrasena TN, Premaratna R, Nilanthi RRd:**Lymphoedema management knowledge and practices among patients attending filariasis morbidity control clinics in Gampaha District, Sri Lanka.** *Filaria Journal* 2004, **3:**
166. Shenoy R, Kumaraswami V, Suma T, Rajan K, Radhakuttyamma G:**A double-blind, placebo-controlled study of the efficacy of oral penicillin, diethylcarbamazine or local treatment of the affected limb in preventing acute adenolymphangitis in lymphoedema caused by brugian filariasis.** *Ann Trop Med Parasitol* 1999, **93:** 367-377.
167. Addiss DG, Michel M-C, Michelus A, Radday J, Billhimer W, Louis-Charles J, Roberts JM, Kramp K, Dahl BA, Keswick B:**Evaluation of antibacterial soap in the management of lymphoedema in Leogane, Haiti.** *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2011, **105:** 58-60.
168. O'Cathain A, Thomas KJ, Drabble SJ, Rudolph A, Hewison J:**What can qualitative research do for randomised controlled trials? A systematic mapping review.** *BMJ Open* 2013, **3:**
169. Engelman D, Fuller LC, Solomon AW, McCarthy JS, Hay RJ, Lammie PJ, Steer AC:**Opportunities for Integrated Control of Neglected Tropical Diseases That Affect the Skin.** *Trends in parasitology* 2016, **32:** 843.
170. Walsh V, Little K, Wiegand R, Rout J, Fox LM:**Evaluating the Burden of Lymphedema Due to Lymphatic Filariasis in 2005 in Khurda District, Odisha State, India.** *PLoS neglected tropical diseases* 2016, **10:** e0004917.
171. McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P:**The Hawthorne Effect: a randomised, controlled trial.** *BMC Medical Research Methodology* 2007, **7:** 30.
172. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K:**A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers.** *Canadian Medical Association Journal* 2009, **180:** E47-E57.
173. Tsegay G, Wubie M, Degu G, Tamiru A, Cooper M, Davey G:**Barriers to access and re-attendance for treatment of podoconiosis: a qualitative study in northern Ethiopia.** *International health* 2015, **7:** 285-292.

8. Appendices

Appendix 1. Ethical clearance: RGEC, Brighton and Sussex Medical School

BSMS Research Governance & Ethics Committee (RGEC)

brighton and sussex medical school

Chair: Professor Kevin Davies

Deputy Chair: Professor Bobbie Farsides

Ethical approvals

Brighton and Sussex Medical School

Medical Teaching Building

University of Sussex

Falmer

Brighton

BN1 9PX

01/08/2013

Dr Gail Davey
Brighton and Sussex Medical School
Medical Teaching Building
University of Sussex
Falmer
Brighton
BN1 9PX

Dear Dr Davey

Full Study Title:	**GoLBet: Randomised controlled trial of podoconiosis treatment in Northern Ethiopia (GoLBet - Gojjam Lymphoedema Best Practice Trial - means 'leg' or 'strength' in Amharic)**
R&D Ref No. :	**13/107/DAV**

I am writing to inform you that the Brighton and Sussex Medical School Research Governance and Ethics Committee (RGEC) Sub-Panel which met on **25th July 2013** has now assessed your application and granted **Provisional Research Governance Approval** to proceed with the above named project.
The Committee granted Provisional Governance Approval to proceed with the rapid ethical assessment on the following basis:

- Please could the researchers clarify the local ethical approval status for this project – has approval been obtained?

Following clarification of the above, please could the researchers inform the Committee of the outcome of the rapid ethical assessment and submit copies of the Consent Form and Participant Information Sheet drafted for the study to the Committee for our records.

Yours sincerely

Professor Kevin Davies

Chair of the BSMS Research Governance and Ethics Committee

Appendix 2 Ethical clearance: CHS, Addis Ababa University, Ethiopia

ANNEX 3
Form AAUMF 03-008

IRB's Decision

Meeting No: 056/2014 Date (D/M/Y): January 9,2014
Protocol number: 071/13/SPH Assigned No.....

Protocol Title: *GoLBet: Randomized control trial of podocnosis in Northern Ethiopia*		
Principal Investigators:	Dr. Gail Davey / Dr. Fikre Enquoselassie	
Institute:	College of Health Science , School of Medicine	
Elements Reviewed (AAUMF 01-008)	☐ Attached	☐ Not attached
Review of Revised Application ☐ Yes ☐ No	Date of Previous review:	
Decision of the meeting:	■ Approved ☐ Approved with Recommendation ☐ Resubmission ☐ Disapproved	

I. Elements approved- 1. Protocol Version No. .....
2. Protocol Version Date.....
3. Informed consent Version No. .....
4. Informed Consent Version Date .....

II. Obligations of the PI-
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 10 days of the event
4. End of the study, including manuscripts and thesis works should be reported to the IRB

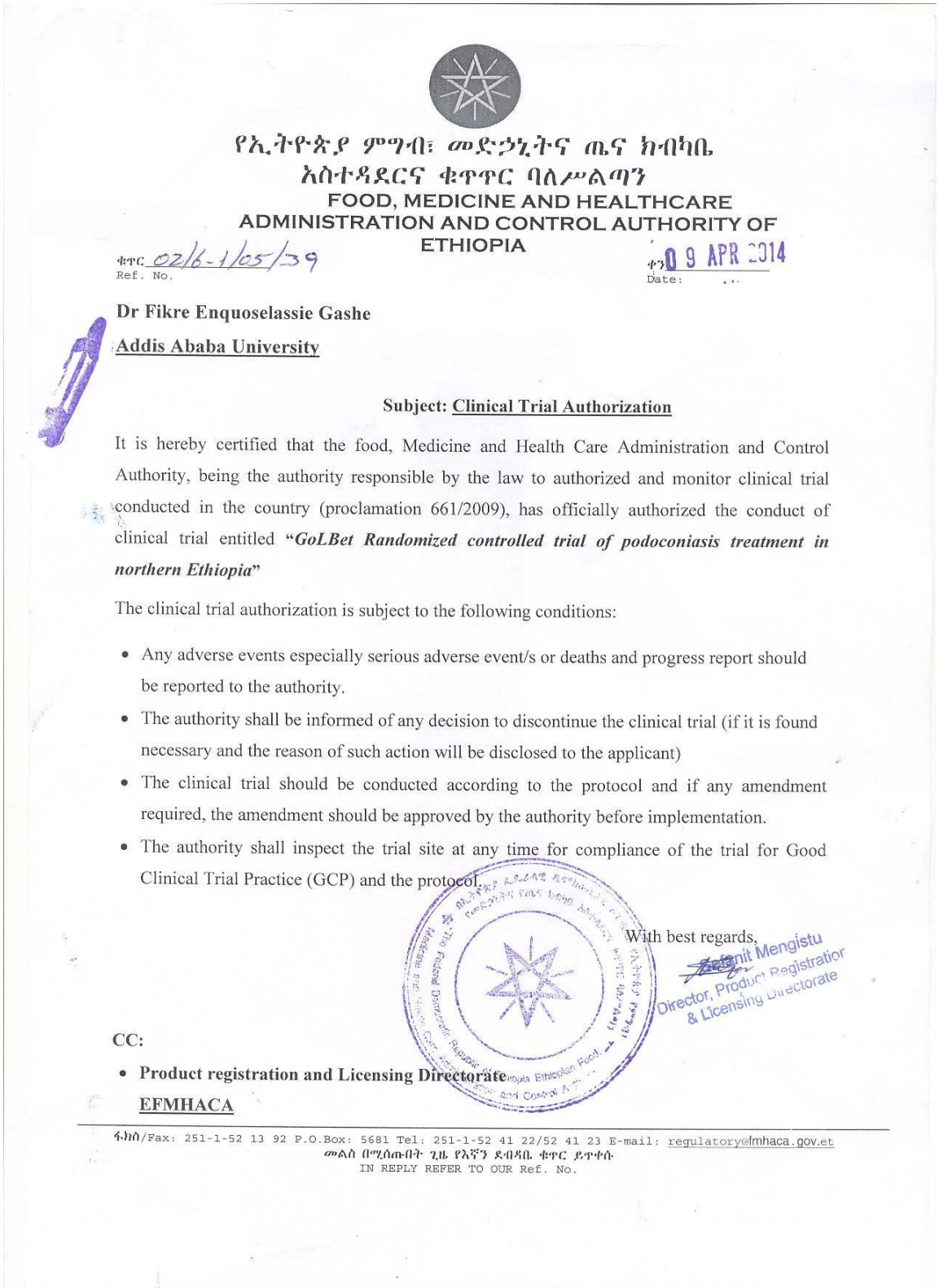
III. **TO ESTM** ■

Institution Review Board (IRB) Approval: Period from
Follow up report expected in 3 Months ___ 6 months ____ 9 months__√___one year____

Chairperson, IRB
Dr. Yimtubezenash W/Amanuel
Signature
Date: 12/01/14

Associate Director of Research and Technology Transfer
Signature _____
Date _____

Appendix 3 Ethical clearance: FMHACA, Ethiopia



የኢትዮጵያ ምግብ፣ መድኃኒትና ጤና ክብካቤ
አስተዳደርና ቁጥጥር ባለሥልጣን
FOOD, MEDICINE AND HEALTHCARE
ADMINISTRATION AND CONTROL AUTHORITY OF
ETHIOPIA

ቁጥር Ref. No. 02/6-1/05/39

ቀን Date: 09 APR 2014

Dr Fikre Enquoselassie Gashe

Addis Ababa University

Subject: Clinical Trial Authorization

It is hereby certified that the food, Medicine and Health Care Administration and Control Authority, being the authority responsible by the law to authorized and monitor clinical trial conducted in the country (proclamation 661/2009), has officially authorized the conduct of clinical trial entitled ***"GoLBet Randomized controlled trial of podoconiasis treatment in northern Ethiopia"***

The clinical trial authorization is subject to the following conditions:

- Any adverse events especially serious adverse event/s or deaths and progress report should be reported to the authority.
- The authority shall be informed of any decision to discontinue the clinical trial (if it is found necessary and the reason of such action will be disclosed to the applicant)
- The clinical trial should be conducted according to the protocol and if any amendment required, the amendment should be approved by the authority before implementation.
- The authority shall inspect the trial site at any time for compliance of the trial for Good Clinical Trial Practice (GCP) and the protocol.

With best regards,

Director, Product Registration & Licensing Directorate

CC:

- **Product registration and Licensing Directorate**
  EFMHACA

ፋክስ/Fax: 251-1-52 13 92 P.O.Box: 5681 Tel: 251-1-52 41 22/52 41 23 E-mail: regulatory@fmhaca.gov.et

Appendix 4 Ethical clearance: NRERC, MoST, Ethiopia

በኢትዮጵያ ፌዴራላዊ ዴሞክራሲያዊ ሪፐብሊክ
የሳይንስና ቴክኖሎጂ ሚኒስቴር
The Federal Democratic Republic of Ethiopia
Ministry of Science and Technology

ቁጥር 3.10/ቅ94/06
Ref. No.
ቀን 25/10/06
Date

To: Addis Ababa University, College of Health Sciences

Addis Ababa

Re: GoLBet-randomised controlled trial of podoconiosis treatment in northern Ethiopia.

Dear sir/Mr./s/Dr.

The National Research Ethics Review committee (NRERC) has reviewed the aforementioned project protocol in an expedited manner. We are writing to advise you that NRERC has granted

Full Approval

To the above named project, for a period of **one year (June 29, 2014- June 28, 2015).** All your most recently submitted Documents have been approved for use in this study. The study should comply with the standard international and national scientific and ethical guidelines. Any change to the approved protocol or consent material must be reviewed and approved through the amendment process prior to its implementation. In addition, any adverse or unanticipated events should be reported within 24-48 hours to the NRERC. Please ensure that you submit progress report once in a four month and annual renewal application 30 days prior to the expiry date.

We, therefore, request your esteemed organization to ensure the commencement and conduct of the study accordingly and wish for the successful completion of the project.

With regards,

Yohannes Sitotaw

Secretary of NRERC

Cc _ Dr Fikre Enquselassie (PI)

ማነጋገር ቢያስፈልግዎ
You may Contact

ፖ.ሳ.ቁ. P.O.Box 2490
አዲስ አበባ ኢትዮጵያ Addis Ababa, Ethiopia E-mail most@ethionet.et
ስልክ Tel. 251-011-4-674353 Web site:-http://www.most.gov.et
ፋክስ Fax +251-011-4-66 02 41

Appendix 5 Purchase approval for Intervention Products: FMHACA, Ethiopia

ቁጥር 02/9/30/1/122
Ref.No.
ቀን 03 ሚያዚያ 2006
Date

የኢትዮጵያ የምግብ፣ የመድኃኒትና ጤና ክብካቤ
አስተዳደርና ቁጥጥር ባለሥልጣን
FOOD MEDECINE AND HEALTH CARE ADMINISTRATION
AND CONTROL AUTHORITY OF ETHIOPIA

ለአዲስ መደኃኒት ፋብሪካ ኃ/የተ/የግ/ማ

አዲግራት

ጉዳዩ፡ ትብብር እንዲደረግላቸው ይመለከታል፡፡

የዓለማቀፍ ኦርቶዶክስ ክርስትያን ተራድኦ የተባለ መንግስታዊ ያልሆነ ድርጅት በምስራቅ ጎጃም ዞን የተለያዩ ወረዳዎች የገዘሆኔ በሽታ መከላከልና ህክምና ስራዎች የሚውል white field ointment (Bensalic-Benzoic Acid 6 %+ Salicylic Acid 3% ,20 gm Ointiment ለመግዛት ስለፈለገ በአቶ ሄኖክ ንጉሴ ግዢ ለማከናወን እንዲችሉ የትብብር ደብዳቤ እንዲፃፍላቸው በቁጥር IOCC/L/036/2014 በቀን 23/08/06 ዓም በተፃፈ ደብዳቤ ጠይቀውናል፡፡

በዚህ መሠረት ከላይ የተገለፀው መደሀኒት ብዛት 16800 ቱዩብ እንዲገዙ የተፈቀደ ስለሆነ የክምችታችሁ ሁኔታና የሌሎች ተጠቃሚዎች ፍላጐት ግምት ውስጥ በማስገባት ትብብር እንዲደረግላቸው እናሳስባለን፡፡

ከሠላምታ ጋር

መሐሪ ብርሃነ

የኢንስፔክሽንና ሰርቬይላንስ ዳይሬክቶሬት ዳይሬክተር
Director, Inspection & Surveillance Directorate

ግልባጭ፣

➢ ለኢንስፔክሽንና ቅኝት ዳይሬክቶሬት
ኢ.ም.መ.ጤ.አ.ቂ.ባ

ፋክስ/Fax:251-11-552 13 92 P.O.Box: 5681 Tel: 251-11-552 41 22/552 41 23 E
www.fmhaca.gov.et

Appendix 6. Discussion schedule: Rapid Ethical Assessment

Rapid Ethical Assessment (REA) draft FGD Guide
Community members

INTRODUCTION:

Ground rules for discussion

In order to have a useful discussion the moderator explains the ground rules of the discussion.

- We would like all participants to remain throughout the discussion. However, if you feel like interrupting the discussion, please inform us and leave. You will not be faced with any form of harm by deciding not to participate. But, we would like to inform you that your participation today will greatly contribute to the study.
- We would like to remind you speak one at a time according to moderator's permission.
- However, we would appreciate full participation from all of you and like to hear all your stories and experiences.
- We encourage all of you to speak your mind freely.
- We would like to inform you that we respect the views of all of you during the discussion. There is no RIGHT or WRONG answer to our questions. Accordingly, participants should respect and refrain from criticizing the views of other participants.
- We expect all of you to keep others' opinions secret by avoiding talking about the discussion, once finished.

NOTE:

Moderator: make sure to do a <u>tour de table</u> to ensure and encourage all participants have a chance to add to points raised.

Co-facilitator: take comprehensive notes if permission to audio-tape session denied at anytime and/or equipment failure. **Make sure the recorder is working properly and deal with any unforeseen situations during the discussions.**

Make sure participant/ seat mapping is done.

Discussion questions:

1. To begin our discussion, can you tell me a bit about your background? Probe:
    - Education/ Training?
    - How long have you lived in Aneded *woreda*, East Gojjam zone?
    - How do you describe your current occupation/work?

Moderator will explain particular interest in the PROCESS of consent **for a randomized controlled trial podoconiosis treatment in northern Ethiopia.** Consent should happen prior to someone agreeing to participate and once they have done so continually until the end of the study. We are trying to understand how best design approach to the consent process from communities' perspectives…

1.1. We are interested in consent in the context of a trial (a study that lasts for a year) regarding the treatment of podoconiosis in northern Ethiopia. Do you know if community members in Aneded *woreda* have been asked to give consent to participate in a research before? If yes, (can you describe what the study was about?) Probe:

- In your opinion what are prevailing attitudes in communities in Aneded *woreda* towards consenting for a study/research?
    - How do people feel if asked to consent to participate in a study unusual, surprising, and valued? How?
- If asked to participate in a research, do you think people affected by podoconiosis in the community can reach the decision to participate/decline on their own?). If not why not?
- How would you explain the norm of decision-making about important situations such as participating in a study in this community?
    - What are the most preferred methods of decision-making to provide consent to participate in a study? (E.g. would participants want time to discuss information about the study with family members and relatives before deciding to participate?)
        - How long do you think it would take families to decide to take part in the study?
    - What roles do heads of families, family members and other relatives have in the decision-making process about an individual's participation in a study?
        - What roles do women in the families have in decision-making?
    - What about significant other people (e.g. neighbors, community and religious leaders?)
        - What about women in the community?
    - How do community elders respond when children (e.g. as young as 16 years of age) speak out in their presence?
    - To what extent does an adolescent (e.g. as young as 16 years of age) feel personally empowered to agree to participate in an activity?

- In your opinion how should we approach to have a better understanding of how to approach individuals affected by podoconiosis in recruiting prospective participants?)
    - (e.g. local government officials, healthcare providers, community leaders, community members) Why? How can they assist in understanding about approaching the community/individuals to be involved?
- If anyone has to be involved in the decision-making process, how should they be involved? E.g. discussions with them before approaching individuals. How?
    - Who should be approached first, second and so on for the consent process? In what order should the different groups and individuals you mentioned above should be approached? Why? (E.g. heads of families followed by individuals??)
    - Which aspects of the study must be explained for prospective participants' consent to be considered appropriately informed?

- In your opinion what is the best way to approach podoconiosis patients for participation in the trial?
    - What do you think is the role of local intermediaries like the IOCC podoconiosis project in Debre Markos (local institutions such as 'iddirs', '*mahibers'* church etc) in supporting comprehension of the purpose of the trial? How?
    - What about fieldworkers e.g. from agriculture office healthcare workers (in HCs) in Andeded *woreda* who might have worked with podoconiosis patients/ potential participants over time in recruiting participants for the trial?
- From your experience living in Aneded *woreda*, what are the most respectful ways to approach different groups (communities, individuals etc) to ask consent for a study? (E.g. the importance of introducing oneself and making general discussion before discussing about the study) Probe:
    - How can relationship with the prospective participants be best developed?
- In your opinion, would consenting to participate in the trial in any way harm participants/ podoconiosis patients? (E.g. would it fuel stigma) How?
    - What do you recommend as a strategy to minimize any further stigma to prospective participants?
- What ways do you suggest for research team to identify issues (questions) that may arise about the study during consent process?
    - How can the interests and concerns of the podoconiosis patients in the community (health or non-health) be best understood?
    - How can the issues be addressed? (e.g., regular meetings to address frequently asked questions or frequently expressed concerns). Explain how it may work?

2. Knowledge about research

How would you describe community members in Aneded *woreda* understanding of what research is?

Probe:

- Are there any positive and negative myths exist about research?
- How does community understand the difference between research Vs treatment, (research Vs Aid)?
- In your opinion what factors may contribute to misunderstandings?
    - How can understanding be promoted? Explain means to address misconceptions

3. Now, let's discuss a bit more about your previous experiences in participating in research in this community?

- Have you or anyone you know in your community been asked to participate in research before?? If yes, explain what happened?
    - How was information about the study provided? (Verbal, written information sheets, group information provision/ community discussions/community sensitization etc). How did you go about it?
- Were you asked to consent to participate? If yes, please explain the process?
- What information was given about the study during the consent process? Probe:
    - Understanding the difference between treatment and research? How?
    - Right to decline participation without negative consequences such as being denied healthcare to which they are otherwise entitled at any health care facility/ government health facilities. How?
    - Right to choose whether or not to participate?

- Understanding the extent of individual benefits that may be gained by agreeing to participate.
- Privacy and confidentiality of information? What was said?

- What is the preferred mode for giving consent (signed or verbal??) why?

4. Information to be provided during consent processes

- In your opinion, what fundamental aspects of the study/trial would you say should be explained to participants during the consent process? (What aspects of the trial are likely to be of most interest to prospective participants to know)? Probe:
  - Expected benefits of the research? Why?
  - About the researchers/ who the researchers are, organizations involved? Why?
  - The purpose of the study/ why the study is proposed? Why?
  - How confidentiality of information will be maintained? Why?
  - Information on how to distribute/ feedback about study findings to the community? Why?
    - How would the community prefer to receive information about the findings of the study? E.g. meetings between study/trial team and participants/ patient associations to discuss research findings? Why?
    - What about a simplified/lay report in Amharic distributed to participants? If yes, what information should be included? Why?
- Information on where, how and who to seek for further information about the trial, if necessary? (providing contacts details of researchers/organizations etc)
- Information about how issues raised by participants during/after recruitment would be considered in the consent?

4.1. Means of providing information

In your opinion, how would the community prefer to receive information about information about the study/ trial?

- **Form in which information is provided (**e.g., verbal/ conversation, information sheets to them, media/pictorial presentations) Why?
- **Who should provide the information at which stage** during the consent process (fieldworkers, researchers, or others)
- Who should be **involved in community/group meetings as part of the consent process?**
  - Community/ religious leaders, *Kebele* leaders (people from the *woreda* administration) etc.

- In your opinion, what are the prevailing beliefs about of podoconiosis within the community that will be relevant to explaining the purposes of the trial? Probe: causes and management…
- How do you see the role of written information among communities in Aneded (populations with low literacy?) in understanding information about the study?
  - Would having information sheets explaining about the study to refer to if they have queries, as the trial progresses be useful? How?
  - Would asking family members or others to read information sheets to them be embarrassing or compromises the privacy of podoconiosis patients participating in the study? Why?

5. Constraints on voluntariness and their effects on decision-making

5.1. In your opinion, what reasons could be expected for podoconiosis patients to prefer/refuse participating in the study? (What motivates people in communities to take part in a study or decline to take part?). Probe:

- Understanding/ misunderstanding about the differences between free health care/ treatment, and research? Prompt more explanation.
- What might put them off from participating? How?
- Understanding/misunderstandings about likelihood of individual benefit from the research? How?
- What about the level of simplicity in which information is given?
- Do you think the where consent for participation is taking place will affect decision to participate/refuse (e.g. seeking consent at home) How?

5.2. In your opinion, which aspects of the study/ trial are likely to be more difficult for prospective participants to understand? (Also ask for field workers?)

- Randomization to different groups? Why?

5.3. What local narratives exist within the community to explain random allocation to treatment and control groups for participants? (E.g. lotteries or agricultural analogies). Probe:

- Can you think of techniques to promote understanding of reason why only some receive treatment and others should wait for a year before getting treatment among participants?
- How can the benefit of participating in the trial be explained? (E.g. for delayed treatment group?)

Concluding questions:

- Are there any other issues we should have raised about the consent process that we have not and you'd like to discuss?
- In addition to what we discussed so far, is there anything you would like to add?

Thank You!

Appendix 7. Discussion guide: ADLA diary acceptability and feasibility studies

We plan to use a "michader diary" among podoconiosis patients in a larger study. Before that, we would like to have your opinions on it. Each page contains 7 boxes under each image representing days of the week to be completed every day (only a brief explanation). We'll ask your opinions on different aspects of the diary. Please look at the diaries while we discuss.

1. To begin with our discussion, in your opinion is it acceptable to use a diary like this to describe experiences of michader among Podo patients? If not please explain why? Probe:
2. Are the texts in the instruction to complete the diary readable? Understandable?
    2.1. What about the texts in the image and date indicators?
3. Now let's discuss about the two images. What do you understand the images as representing? Probe:
    3.1. Are the images clear/ visible?
    3.2. Do you think podo patients (men, women & young people) can easily understand the images? If not what aspects are not understandable?
    3.3. Are images acceptable in describing michader among podo patients (men, women & young people) in your community?
    3.4. Do you think images may be embarrassing if seen by other non-podo affected people in the community? Why?
    3.5. Do you think images could be offensive to podo patients in anyway? Why?
4. Are the date indicators (religious days) clear? Probe:
    4.1. Are the religious days we used relevant in your community (Gojjam)?
5. Do you think the size of the diary is convenient? E.g. to be kept at home? Probe:
    5.1. Do you think it can be safely kept at home without being damaged?
    5.2. Can you suggest anything that would minimise damage?
6. [2]In your opinion, what do you think about patients being able to complete the diary every day? Probe:
    6.1. Can you suggest anything to make it easier to remember to fill out the diary daily?
    6.2. How easy/difficult would it be to complete the michader diary daily?
    6.3. How much of a bother would it be to complete the diary daily? E.g. interfering with patients' daily work? Explain more.
    6.4. Do you think podo patients can complete the diary on their own? If not why?
    6.5. Would you recommend we use the diary in a study among other podo patients? If not why not?
7. What difficulties do you think podo patients will experience in completing the dairy daily?

[2] Questions 5-7 will also be asked on feasibility aspect at exit interview? May be a close ended or rating?

8. What suggestions do you have to improve the diary?

Thank you for participation!

Feasibility Study Exit Interview items

	Items	**Rating**			
1	How easy was it to remember to fill out the michader diary daily?	Very Hard =1	Hard =2	Easy=3	Very easy=4
2	How much of a bother was it to fill out the diary daily?	Very bothersome=1	Moderately bothersome=2	A Minor bother=3	No bother at all=4
3	How would you rate the way michader diary looked?	Very good=1	Good=2	Fair=3	Poor=4
4	Would you consider recommending it to be used with other patients?	Yes =1	Not sure-2	No=3	

5.what difficulties did you experience in completing the diary?_____
_____
_____

6. What suggestions do you have to improve the dairy?_____
_____
_____

7. Did anyone else help you complete the diary? If so, what is their relationship to you (son/daughter/spouse…)?_____
_____

Appendix 8. Standard Operating Procedures: Intervention and diary

Standard Operating Procedure Intervention

1. **Introduction/Purpose**

There will be two study arms in this study: the intervention arm that will continue with daily intervention and the delayed treatment arm that will begin intervention after one year follow up. The hygiene and foot care intervention comprises use of soap, Whitfield ointment, bandages, sock and shoes. This SOP outlines the study intervention procedures including training of the patients, evaluations and documentation.

2. Responsibility

This SOP applies to Community Podoconiosis Assistants (CPAs) who have been delegated the task of conducting monthly intervention visits, and to the Trial Co-ordinator who will oversee how they are done.

3. **Abbreviations**

- CPAs-Community Podoconiosis Assistants
- ICF - Information and Consent Form
- PI - Principal Investigator: the person overall responsible for the conduct of a study at a research site
- SOP – standard operating procedure: detailed, written instructions to achieve uniformity of the performance of a study specific consent procedures
- SSP - Study Specific Procedures
- TC-Trial Co-ordinator

4. **Materials for Monthly Intervention Meetings/ visits**

- Bowl
- Water
- Toilet soap (GIV)
- Whitfield's ointment (30gm for 1 month)
- Bandages (2 short stretch bandages per affected leg)
- Tape (to secure bandages)
- Black pen
- Compliance form
- AE form
- IP dispensary log
- Appointment cards
- Clipboard
- Gloves

5. **Procedure for Monthly Intervention Meetings**

- Greet patients/participants.
- Recap Information and Education given at the previous monthly meeting.
- Demonstrate treatment procedure again.
- Record compliance to date and record brief reasons for non-compliance.
- Solicit Adverse Events related to treatment (use format below).
- Check quantities of supplies used, issue a further month's treatment supplies.
- Note down any ointment left over.
- Arrange next appointment and instruct patients to come for monthly meeting.
- Check forms: adverse event, compliance, IP dispensary logs etc. for completeness.
- Allow time for patients to ask questions or raise concerns they may have.
- Dispose off any waste according to facility's practices and leave venue/area tidy.
- Note patients absent from monthly meeting and visit them at home the next day and deliver same intervention at home.

5.1. **Procedure for demonstrating intervention**

5.1.1. Demonstrate how to soak and wash feet in a basin of clean, cool water for 10 minutes.
5.1.2. Ask patients to wash with soap onto hands, and clean the leg from top of swelling downwards including between toes.
5.1.3. Show them how to rinse with clear water, and dry thoroughly between the toes with a clean cloth or towel (each patient will have their own lean clothes and towels for drying).
5.1.4. While the foot is drying, ankle rotation and tip toe exercises will be demonstrated.
5.1.4.1. Demonstrate to the patients how to perform toe points, ankle circles and calf raises. Instruct them to be doing the exercises 2-3 times per day and elevation of the leg whenever possible
5.1.5. Demonstrate how much of Whitfield's ointment to apply and how to do it sparingly.
5.1.6. If swelling is predominantly soft, rather than nodular show the patients how to apply the bandage from foot upward.
5.1.7. Instruct the patients to be elevating the foot at the end of mattress by 10-15cms using stone, wood or pillow.
5.1.8. Remind patients to be washing both legs like this daily, even if only one leg is affected.
5.1.9. Reinforce importance of wearing shoes at all waking hours with clean socks whenever shoes worn

5.2. Procedure for recording compliance and reasons for non-compliance

5.2.1. Ask the patients the number of days in the past month that they have followed procedure as prescribed.
5.2.2. Enquire also the number of days they have not done according to prescription.
5.2.3. Ask them the reasons for non compliance (if any): record as described and use direct enquiry:
   1) Beginning to feel better/treatment no longer necessary Yes ☐ No ☐
   2) Lack of understanding of procedure Yes ☐ No ☐
   3) Run out of supplies at home Yes ☐ No ☐
   4) Lack of time Yes ☐ No ☐
   5) *Provide feedback on compliance and set/encourage correct use by participants using patients who followed procedure accurately as models/examples. Advice the patients to customize intervention timing to individual needs (as long as it remains daily).

5.3. Procedure for enquiring about Adverse Event/ Experience

5.3.1 Ask each patient the following question: "Have you felt different in any way since the last time we met here while using Whitfield's ointment?"

5.3.2 If the patients have experienced any event, fill in an **Adverse Event form** and report events to the Trial Co-ordinator the same day (maximum of 12 hours)[3]

5.4. Procedure for checking quantities of supplies used and replenishing

5.4.1. While at the clinic, assess the usage of each supply and the need for replenishment as follows:

1. Soap: check the rate of use (how often).
2. Whitfield's ointment: check if there is any remaining ointment in the tube at each monthly meeting, and record if there is excess ointment.
    - Any excess ointment observed Yes ☐ No ☐
3. Bandages: check condition of bandages at each monthly meeting and replace as required. Replace if bandage is torn.
    - Needs replacement Yes ☐ No ☐
4. Shoes and Socks: observe condition of shoes and socks and ask the patients. Needs replacement? Yes ☐ No ☐
    - Make a note for replacement at the next visit

5.4.3 Supply each patient with supplies for the next month. Document in the dispensing log how much of what has been supplied to each patient

5.5 Procedure for *setting* the next appointment

5.5.1 The next appointment for monthly meeting should be set exactly on the same days of the week each month. This will be minus two days from previous month's meeting date.

5.5.2Religious holidays will be used as landmarks and a reminder for the exact appointment dates for patients.

5.5.3 Appointment for next meeting should not be delayed more than 2 days.

5.5.4. Fill in follow up information and appointment card indicating the next scheduled meeting day (see annex)

6. Ensuring quality of the monthly group meeting process

a. The study team will ensure that the monthly group meeting process is being adhered to by ensuring that forms are completed and signed, by conducting supervisory visits, and through regular meetings with CPAs. Intervention meetings will be overseen by the Trial-Co-ordinator.
b. Adherence to procedures described in this document will be assessed during monitoring and follow-up visits.
c. Patients' understanding of what monthly meetings and the intervention entail will be continuously assessed through recapping the previous session before the next is delivered, and during follow up visits.

[3] A separate form

d. Community Podoconiosis Assistants (CPAs) will be encouraged to understand the scientific aspects of the study and the rationale behind the procedures stated in the study protocol.
e. CPAs will ensure they have adequate supplies of necessary materials, will prepare venues before any monthly intervention meeting, will ensure the safety of patients and the confidentiality of information shared, and will discuss issues related to procedures and problems encountered in detail with the Trial Co-ordinator.

References

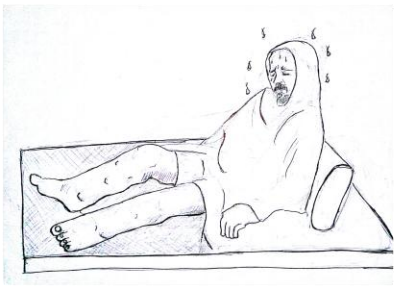
GoLBet final version protocol

Annexes

Document control:

Appendix 9. Patient completed ADLA diary

የምችአደር ማስታወሻ



የወሩ ቀናት ምች አደር አላመመኝም ምች አደር አምኛል

19/06/2007	×	
20/06/2007		×
21/06/2007		×
22/06/2007		×

የጉልበት ጥናት ዉጤት ስርጭት ወርክሾፕ፣ ሰኔ 2009

Patient name: _____

Study Number: |__||__||__|

Instructions for completing the michader diary

Dear GoLBet participant:

The following instruction is to help you to record your michader diary:

1. Please complete the michader diary for all days of the month.
2. On each of the following page, there're two drawing: of a person 'experiencing michader' and 'not experiencing michader'.
3. We would like you to identify your michader experience with one of the two drawings as **'I'm experiencing michader' or 'No I'm not experiencing michader'** by placing a mark **'✓'** under the column below each drawing for the appropriate day. For example, if you experience Michader on Yekatit 1 (Lideta), place a mark on the box corresponding to Yekatit

1 under **'I'm experiencing michader'**. Similarly, if you're not experiencing Michader on Yekatit 1 place a mark on the box corresponding to Yekatit 1 under **'I'm not experiencing michader'.**

4. Once you completed a page go to the next page which represents the second week of that month and so on.
5. When you complete all the pages, we'll give you another diary for the next month.
6. Please record your experience of michader or not every day (before you go to bed).

Note

- The diary and instructions were translated into Amharic
- To minimize error, CPAs wrote days of the month during each MIV before handing out fresh diaries. Thus, patients need to complete their experiences of ADLA.

Appendix 10. Clinical Assessment form: reliability of reporting ADLA study

Dear Health Worker: please complete the following questionnaire for all podoconiosis patients reporting acute attacks 'm*ichader*'.

Clinical questionnaire for podoconiosis patients with acute attacks

Clinical Assessment	Right Leg	Left leg
01. What stage is the Lymphoedema?	2 3 4 5	2 3 4 5
02. Lower leg circumference (cms)		
03. Foot circumference (cms)		
04. Are there any wounds?	Y N	Y N
05. Are inguinal lymph nodes enlarged?	Y N	Y N
06. Do legs feel warm?	Y N	Y N
07. Is leg tender to touch?	Y N	Y N
08. Is there redness of the leg/foot?	Y N	Y N
09. Is skin of legs peeling?	Y N	Y N

General symptoms

For the following please circle 'Y' if patient reports and 'N' if patient does not report symptoms

10. Does patient report increased swelling of leg/foot?	Y N	Y N
11. Does patient report pain in leg/foot?	Y N	Y N
12. Does patient report redness of leg/foot?	Y N	Y N

13. Does patient report enlarged groin lymph nodes? Y N Y N

14. Does patient report painful groin lymph nodes? Y N Y N

15. Does patient report fever (‘*Tikusat*’)? Y N Y N

16. Does patient report chills (*‘Birrd’*) Y N Y N

Your diagnosis:

17. Is patient having an acute attack/michader currently? Y N
18. If the answer is ‘NO’, what is your alternative diagnosis and reasons for this?
    diagnosis_____

Name of HEW:_____Signature:_____Date:|__||__|/|__||__|/|__|__|__|__|

Day Month Year

Appendix 11. Information sheet and consent form

Study Title: Randomized controlled trial of podoconiosis treatment in northern Ethiopia

Lay Title: A study of the treatment of podoconiosis in northern Ethiopia

Introduction: My name is ……. I work for the International Orthodox Christian Charities (IOCC-Ethiopia). We are asking your permission for you to participate in a research study. Before you decide whether to take part, it is important for you to understand what participation in the study will involve. Please take time to read this information sheet or listen carefully while it is being read out to you and further discuss with your family and relatives if you wish to. The information you’re about to receive was prepared based on discussions we had with researchers/experts at IOCC, DMU, Aneded *Woreda* Health Office, *Kebele*, religious and community leaders, podoconiosis affected and non-affected men and women in different *Kebeles* in Aneded to identify the best ways to provide information about the study preferred by the community. Please ask us if there is anything that is not clear or if you would like more information.

Your illness: As you remember you were examined by our research team on our recent visit to your home. We found you to meet the preliminary criteria for participation in the study. Depending on the stage of the disease, NGOs in different parts of the country provide treatment and prevention services. IOCC-Debre Markos provides such services in different *woredas* in East Gojjam Zone. Treatment services include a package of foot hygiene, skin care, bandaging, exercises and use of socks and shoes.

What is IOCC? The International Orthodox Christian Charities (IOCC-Ethiopia) is a NGO working in different areas including the prevention and treatment of podoconiosis. IOCC Debre Markos project was established in 2010 and since then, is working in different *Woredas* in East Gojjam Zone. The services include information and education on podoconiosis, providing wound care and treatment supplies through regular treatment/ patient meetings and forming patient associations.

E12What is GoLBet study about? IOCC in collaboration with University of Sussex in the UK, Addis Ababa University, and Kilifi Clinical Trial Facility in Kenya, is trying to learn more about the effectiveness of the treatment of podoconiosis. Experience from NGOs so far has shown the current treatment for podoconiosis to work and to be safe. However, more research is required to test the effectiveness the treatment. Unlike projects which are mainly focused on provision of prevention and treatment services, the GoLBet study is mainly focused on finding out evidence about the effectiveness of the current treatment and make it widely available in the future for everybody's benefit. The trial/ study site is in Aneded *woreda*, East Gojjam zone, Amhara Region.

Study Procedures

How are participants selected? As it is impossible to enroll in the study everyone with podoconiosis, patients aged 18 years and older will be drawn based on carefully defined selection criteria. This will also make sure that study findings can be applied to patients in other areas.

How are patients allocated to study arms? Assume the *woreda* agriculture office wanted to check the effectiveness of a new fertilizer in terms of providing yield and making the soil fertile before giving the fertilizer to all farmers in the *woreda*. The Agriculture office selected plots from farmers who volunteer to take part, spread the fertilizer only on some plots selected and not on the others. Then, a year later they compared the yield of plots with the new fertilizer with those without it. Based on this comparison, the agriculture office would either provide the fertilizer to all farmers or would not. Similarly, the GoLBet will test the effectiveness of the treatment of podoconiosis on patients who are willing to take part in the study by assigning them into one of two study groups: 'immediate' treatment', or 'delayed treatment'. Those in the 'immediate' treatment group will receive treatment immediately for a year while those in delayed treatment will be offered the same treatment a year later. This will help us find out if there is any difference between the two groups by closely watching the progress of everyone in this study. A total of 680 patients (340 in each arm) will participate in the study with duration of one year participation in the study for any given patient. The decision on which any person gets to be allocated to which group will be decided by a system based on chance, not by anyone in the research team. Study numbers we give for individual patients who meet the selection criteria will be fed into a computer which will make allocation based a lottery method. This will be done by experts at Kilifi Clinical Trial facility in Kenya.

What will participating involve? If you agree to participate, first we'll first need to check whether the type of your leg swelling is one transmitted by mosquitoes. For this, we'll take a small sample of blood, 2 drops from your finger tip. We will give a unique number to identify patients in lieu of their names. In addition, we'll take your picture to provide you with a study identification card. This will help

professionals in health centers and hospitals to know you're participating in the GoLBet study as you visit them for different health concerns. Then, you'll be asked to respond to study questionnaires and assigned (by a lottery method) to one of the two study arms. Patients in the immediate treatment arm are required to attend a monthly intervention meeting at their nearest Health Post/Health Centre. We will visit you at home for follow up every three months for about 90 minutes. Every day, we will also ask all patients to record whether they experienced michader or not in a diary we'll provide. It's very important that diaries are completed accurately, and we need to check your diary entries regularly. All participants are also to report any condition they experience as a result of using the study treatment products to the study team using the telephone number dedicated for the purpose.

Are there risks or disadvantages to me of participating in the study? Our priority for every participant is his/her well-being. The treatment products we plan to use has been shown to be safe and thus we do not expect any reaction. However, we'll be monitoring everyone very closely and in the unlikely event of any harm related to using the products, we'll ensure you get treatment for your condition. Please follow instructions we give you about storage and use of treatment products. Taking blood from your finger tips causes a small amount of pain, but the amount taken is too small to affect your health. There are no expenses for participating in the study. Follow up visits may take some of your time (about 90 minutes). If any information becomes available that may be relevant to your willingness to continue participation, we'll inform you immediately. In addition, if for any reason investigators think you would benefit from leaving this trial, they will recommend this to you.

Are there any benefits to me of participating in the study? By taking part in the study (in both arms) you get access to treatment /care and close observation during the trial. In addition, your participation will help us provide evidence on the effectiveness of the treatment for policy formulation at national and international levels that'll benefit a large number of people suffering from podoconiosis in other places. We also think this will create employment opportunities for young people in the study *Kebeles* who'll be part of the study team.

What happens if I refuse to participate? All participation in the study is essentially on voluntary basis. You are free to decide if you want to take part. If you decide not to participate, you can do so without any penalty. In addition, even if you do agree to participate first, you can change your mind at any time and withdraw from the study. This will not in any way interfere with the way you interact/communicate with HPs/HCs, *Kebele* leaders and affect your right to receive health care and other services you've been getting so far or in the future. However, your participation and remaining in the study will greatly contribute to the objectives of the study.

Where can I get alternative treatment? The IOCC Podoconiosis project in Debre Markos provides prevention and treatment services. Many patients in the project *woredas* of East Gojjam Zone have benefited from the services. A potential problem you may face is a long waiting period (a year or more) before getting the services.

Who will have access to my information? All information we collect about you during the course of the study will be kept in securely locked cabinets and on a password protected computer database in the

project office at IOCC- Debre Markos and is strictly confidential. Only a few people closely concerned with the research will be able to view your information. For example, the study monitors, and regulatory authorities will be granted access to your documents for verification of procedures followed in the study in such a way that does not violate your right to confidentiality of information. We hope to share the results of the study with government and non-government organizations as well as study participants in workshops and in the form of written reports. However, any information that can identify individual participants will remain confidential. By signing this form you're authorizing such use.

What happens to the blood sample? Your name will not be used to label blood samples we collect; instead a unique code/number will be used for investigators to able to link samples to individual participant. The blood test will be done at the site on the same day you gave the sample. And, once the results of the test are known, the sample will be disposed of.

What if I have any questions? You may ask any of our staff at any time. If you wish more information you can contact individuals on the addresses given below.

Who has allowed this research to take place? Ethics committees at University of Sussex in the UK, Addis Ababa University, Ministry of Science and Technology and Federal Ministry of Health in Ethiopia have looked carefully at this work and agreed that the research is important, that it will be conducted properly and participants' safety and rights have been respected.

Who is organizing and funding the research? The research is supported by the University of Sussex who will pay for any treatment or compensation in the unlikely event of any injury resulting from the study investigational product, and organized jointly by researchers in Ethiopia, Kenya and the UK.

Your understanding of the information we gave you about the study

Do you understand information we gave you about the study? 1. YES_____ 2. NO_____ (place a check mark ✓ on option that applies). (Record response on Informed Consent Log) If the answer is **YES**:

Please describe what you understand in your own words. Ask contents of the information sheet: **study procedure, risk/benefits, privacy, voluntary participation, and understanding of how to get further information** (e.g. if you've queries about the study or your participation, where do you find additional information?)

Do you've any questions on the information we gave you about the study?

1. YES_____ 2. NO_____ place a check mark (✓) on option that applies. If **YES**, the person seeking consent will answer the question or ask assistance from Trial Co-ordinator/designee but will record the question raised/ answer provided in a separate form we'll prepare for the purpose.

IOCC Consent Form

Study Title: **Randomized controlled trial of podoconiosis treatment in northern Ethiopia**

I, _____ (name of patient) have had the research explained to me. I have understood all that has been read about the study: procedures, what is expected from me as participant, risks/benefits, privacy and voluntary participation and had my questions answered satisfactorily. I put my signature/thumbprint as a sign of expressing my willingness to participate in the study based on information provided to me and that I was not in any way coerced into participating in the study.

☐ **(Yes please tick✓)** I **agree to participate in this research**

☐ **(Yes please tick✓) I agree to blood samples being taken**

☐ (**Yes [please tick✓) I agree I can withdraw at any time**

I understand that I can change my mind at any stage and it will not affect me in any way.

Participant's signature: _____ **Date**: |__||__|/|__||__|/|__|__|__|__|

Day Month Year

Participant's name (print):_____ **Time**: |__||__|

Hr Min

I certify that I have followed the study SOP to obtain consent from the participant. S/he apparently understood the nature and the purpose of the study and consents to participate in the study. S/he has been given opportunity to ask questions which have been answered satisfactorily.

Trial Co-ordinator/Designee signature: _____ **Date**: |__||__|/|__||__|/|__|__|__|__|

Day Month Year

Trial Co-ordinator/Designee name (print): _____**Time**: |__||__|

Hr Min

Only necessary if the patient cannot read:

I *attest that the information concerning this research was accurately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Witness' signature: _____ **Date**: |__||__|/|__||__|/|__|__|__|__|

Day Month Year

Witness' name: _____**Time:** |__||__|

Hr Min

*A witness is a person who is independent from the trial or a member of staff who was not involved in gaining the consent.

Thumbprint of the patient as named above if they cannot write: _____

A SIGNED COPY OF THIS SHEET MUST BE GIVEN TO PARTICIPANT.

THANK YOU FOR TAKING PART IN THIS STUDY!

Appendix 12. Data Collection Instrument: Baseline and 12 months

GoLBet Study Number: |__|__|__|__|	**GoLBet Enrollment Number** |__|__|__|__|

GoLBet: Randomised controlled trial of podoconiosis treatment in northern Ethiopia
Case Record Forms Version 3 October 22, 2013

BASELINE: | | | / | | | / | 2 | 0 | 1 | 4 |

Time (hh:mm) |__||__||__||__| **Interviewer's Initials:** |__||__||__|

For Field Use (data collector and supervisor) and Office Use (data entry clerks)

	Collected by	**Supervised by**	**Checked by**	**Entered by**
Initials	|__|__|__|	|__|__|__|	|__|__|__|	|__|__|__|
Date	Day |__|__|	Day |__|__|	Day |__|__|	Day |__|__|
	Month |__|__|	Month |__|__|	Month |__|__|	Month |__|__|
	Year|__|__|__|__|	Year|__|__|__|__|	Year|__|__|__|__|	Year|__|__|__|__|
Signature				

DATA COLLECTION ACTIVITY FLOW CHART

ACTIVITY	SCREENING	ENROLLMENT	MONTH 3	MONTH 6	MONTH 9	MONTH 12
Preliminary evaluation against the inclusion and exclusion criteria	X					
Potential willingness to take part in the trial	X					
Record geographic coordinates	X					
Provide information about the study		x				
Full Informed Consent		x				
Final inclusion and exclusion criteria once more, including ICT test		X				
Eligible patients Identified		X				
Provide information about the study		X				
Data collection on socio-demographic		X				X
Data collection on Economic		X		X		X
Data collection on ADLA (recall)		X	X	X	X	X
Data collection on SAEs			X	X	X	X
Data collection on DLQI		X	X	X	X	X
Data collection on WHO-DAS II		X				X
Data collection on Stigma scale		X				X
Data collection on Clinical stage		X		X		X
Data collection on Mossy lesions		X		X		X
Data collection on Foot & Leg Circumference		X		X		X
Data collection on Inter-digital lesions		X		X		X
Data collection on preventive behavior		x				
Data collection on adherence			X	X	X	X

INSTRUCTIONS FOR HANDLING AND COMPLETING CASE REPORT FORM

- Please use only black ball points to complete CRFs
- Only GoLBet data collectors should write on these CRFs
- Please fill the header in each page

- Data correction: Cross out the mistake (mistake has to remain readable), write the correction alongside together with your initials and date of correction. In case of non-self-explanatory mistakes, please add the reason for correction. Do not use type write correction fluid (Tipp-Ex)

E.g. (DD/MM/YYYY) ~~2~~ 4 / 0 3 / 2 0 1 6

1 MMK

- In open boxes/numeric fields please enter

Numbers **4** **9** Or ticks 

- Always enter digits **right aligned** and fill **open spaces** to the left with **zeroes**

- Please write **0** **4** | **9** mark data which could not be recorded as follows: **Cross out boxes** and **"NOT DONE"** on the side

- Date: Day. Month. Year: (GC)

0 **4** / **0** **3** / **2** **0** **1** **6**

Date **Month** **Year**

- Please enter initials in the following order: First letter of the first name, First letter of the middle name, First letter of the surname

M **M** | **K**

- Please do not omit to date and sign the pages where required.

SECTION ONE: ENROLLING AND ELIGIBILITY CHECK

GoLBet INCLUSION CRITERIA:	YES	NO
1.1. WRITTEN FULL INFORMED CONSENT OBTAINED	☐	☐
1.2. AGE AT LEAST 16 YEARS OLD	☐	☐
1.3. DIAGNOSIS OF AT LEAST STAGE 2 PODOCONIOSIS (EITHER LEG)	☐	☐
1.4. NEGATIVE ICT TEST	☐	☐
1.5. NOT PLANNING TO LEAVE THE STUDY AREA DURING THE NEXT 12 MONTHS	☐	☐

ALL MUST BE YES TO BE ELIGIBLE

GoLBet EXCLUSION CRITERIA:

1.6. ALREADY UNDERTAKING SELF-TREATMENT

COMPARABLE TO THE INTERVENTION

1.7. WITH NODULAR DISEASE PREVENTING
USE OF SHOES

1.8. WITH COMPLEX WOUNDS

1.9. WITH HISTORY OF ALLERGIC REACTION TO

TREATMENT MATERIALS

1.10WITH MENTAL HEALTH OR LEARNING DISORDER

AFFECTING ABILITY TO ADHERE WITH TREATMENT

1.11. WITH PHYSICAL DISABILITY BEYOND PODOCONIOSIS

PRECLUDING ATTENDANCE AT GROUP SESSIONS

1.12. WITH DISEASE/DISORDER TO AFFECT ABILITY TO SELF-TREAT

ALL MUST BE NO TO BE ELIGIBLE

DATE AND TIME OF CONSENT: Date |__|__|/|__|__|/|__|__|__|__| Time|__|__|:|__|__|

SECTION TWO: SOCIO-DEMOGRAPHIC DETAILS

2.1 **Date of birth** |__|__|/|__|__|/|__|__|__|__| ***(DD/MM/YYYY)***

2.2 **How old are you now? In completed years**|__|__| Years

2.3 **Record sex as observed.** 1=Male **2=**Female

2.4 **Location of the patient: *Kebele*** _____ ***Village/Got***_____

2.5 What is current **religion**? Select the single best options

1=Orthodox Christian =Muslim Other

If other religion, specify…. _____

2.6 **Ethnicity** **1=**Amhara 2=Other

If other ethnicity, specify…. _____

2.7 What is your current **marital status**? Select the single best option. ***Indicate code:* |__|**

1. Never married
2. Currently married

3. Divorced
4. Separated
5. Widowed
6. Cohabiting
7. Prefer not to say

2.8 Have you ever attended school? Yes ☐ No ☐

2.9 If attended school, what is the highest grade of school you completed? ***Indicate code:*** **|__|**

1. Informal education
2. Primary (1-6)
3. Secondary (7-12),
4. TVET/TTC
5. College/diploma
6. University
7. Other

If other highest level of school completed, specify…. _____

2.10 How many years in all did you spend studying in school, college or university? **|__|years**

2.11 Which describes your **main work status** best? ***Select the single best options. Indicate code:*** **|__|**

1. Paid worker such as daily laborer
2. Self-employed such as your own business or farming
3. Non-paid worker such as volunteer or charity
4. Keeping house/home maker
5. Student
6. Retired
7. Unemployed (health reasons)
8. Unemployed (other reasons)
9. Other

If other occupation, specify…. _____

SECTION THREE: SOCIO-ECONOMIC DETAILS

3.1 Have you participated in farming in the last week?

Yes ☐ No ☐

If no skip to 3.3

3.2 How many days and hours per day do you normally spend in farming activities in past week?

|__||__| Number of days

|__||__| Number of hours per day

3.3 Have you participated in non-farming activities for the last week?

Yes ☐ No ☐

If no skip to 3.5

3.4 How many days and hours per day do you normally spend in non-farming activities in the past week?

|__||__| Number of days

|__||__| Number of hours per day

3.5 Have you participated on domestic for the last week?

Yes ☐ No ☐

If no skip to 3.7

3.6 How many days and hours per day have you normally spent in domestic activities in the past week?

|__||__| Number of days

|__||__| Number of hours per day

3.7 Have you taken leisure in the last week?

Yes ☐ No ☐

If no skip to 3.9

3.8 How many days and hours per day have you normally spent in leisure activities in the past week?

|__||__| Number of days

|__||__| Number of hours per day

3.9 Average household monthly income. ***Indicate code:*** |_____|

1= Less than 1,000 **2=**1,000-3,999 **3=**4,000-9,999 **5**=10,000-19,999 **6=**Greater than 20,000 **7**=do not know

SECTION FOUR: USE OF SHOES

4.1 Have you ever owned a pair of shoes? Yes ☐ No ☐

If *'No' skip to* ***section FIVE***

4.2 Have you ever owned a pair of socks? Yes ☐ No ☐

4.3 How old were you when you first owned a pair of shoes? |__|__| Years

4.4 How many of the years since this have you had a pair of shoes? ***Indicate code:*** |__|

1. All the years.
2. Almost all the years.
3. More than half of the years.
4. About half of the years.
5. Less than half of the years.
6. Almost none of the years.
7. none of the yea

4.5 When you own a pair of shoes, how often do you wear them? ***Indicate code:*** |__|

1. More than 5 days per week
2. 2-5 days per week
3. Every week, but less than 2 days per week
4. Less often than weekly

4.6 On the days you wear shoes, how much of the day do you wear shoes? ***Indicate code:*** |__|

1. All day
2. More than half the day
3. About half the day
4. Less than half the day
5. Only a few hours

SECTION FIVE: FOOT WASHING PRACTICES

5.1 Can you get enough water for general household use (such as drinking, cooking, washing clothes, bathing etc)

Yes ☐ No ☐

5.2 Can you get enough water for washing your feet?

Yes ☐ No ☐

*If 'Yes' skip to **question number 5.4 of this section***

5.3 If 'No' what is the problem?

Seasonal shortage ☐ Distance from source too far ☐ other ☐

If other problem, specify…. _____

5.4 Did you wash your feet last night?

Yes ☐ No ☐

5.5 How many times in **THE PAST MONTH** did you wash your feet? |__|__| **Number of times**

5.6 Do you use soap to wash your feet?

Yes ☐ No ☐

*If 'No' skip to **question number 5.9***

5.7 What type of soap did you use? ***Indicate code:*** |__|

1. Laundry soap
2. Toilet soap
3. Any soap available

5.8 How many times in **THE PAST MONTH** did you wash your feet with soap? |__|__| **Number of times**

5.9 Over the last month, have you put any ointment on your feet?

Yes ☐ No ☐

5.10 If yes, how many times per week on average? |__|__| **Number of times**

5.11 **OBSERVE**: How is interviewee's feet? ***Indicate code:*** |__|

1. Clean and intact
2. Dirty
3. Cracked
4. Dirty and cracked

SECTION SIX: HISTORY OF SWOLLEN LEGS (PODOCONIOSIS)

6.1 How old were you when you first noticed your legs were swollen? |__|__| **years**

6.2 Have you ever sought any treatment? Yes ☐ No ☐

If 'No 'skip to the next section

6.3 If yes to question number 6.2, how old are you when you sought treatment? |__|__| **years**

6.4 If yes to question number 6.2, where did you go to get treatment?

Traditional practitioner/healer ☐

Health facility (hospital/health centre) ☐

☐

Other

If other treatment facility/healer exists, specify…. _____

SECTION SEVEN: ACUTE ATTACK (ADLA)

7.1 Have you ever experienced 'm***ichader'***?'

Yes ☐ No ☐

If 'No', skip to ***Section 8***

7.2 How many m*ichader* attacks did you experience in **the last 30 days**? |__|__| **number of attacks**

7.3 On average how long did the most recent m***ichader*** last? |__|__| **number of days**

7.4 How long did you have to stop working/going to school when you experienced the most recent m***ichader***?

|__|__| **number of days**

7.5 How would you describe the INTENSITY of the latest m*ichader* you experienced?

1. Mild ☐ **2.** Moderate ☐ ***3.*** Severe ☐

7.6 What symptoms do you experience when you have a m*ichader* attack? (Multiple answers possible) Do not read out the choices.

Indicate code: |__|
Indicate code: |__|
Indicate code: |__|
Indicate code: |__|

1. Fever
2. Chills or rigor
3. Red, hot legs
4. Increased swelling of the legs
5. Peeling of the skin on legs
6. Swollen inguinal lymph nodes (*Frintit*)
7. If other symptoms exist, specify…. _____

7.7 Can episodes of m*ichader* be prevented?

Yes ☐ No ☐

SECTION EIGHT: CLINICAL ASSESSMENT

Q.N		RIGHT LEG	Q.N		LEFT LEG
R8.1	Stage	**1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐	L8.1	Stage	**1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐
R8.2	Moss	**Yes** ☐ **No** ☐	L8.2	Moss	**Yes** ☐ **No** ☐
R8.3.1	Lower leg circumference	|__|__|**cm** **Record the circumference**	L8.3	Lower leg circumference	|__|__|**cm** **Record the circumference**
R8.3.2	Foot circumference	|__|__|**cm** **Record the circumference**	L8.3.2	Foot circumference	|__|__|**cm** **Record the circumference**
R8.4	Wound	**Yes** ☐ **No** ☐	L8.3.3	Wound	**Yes** ☐ **No** ☐
R8.5	Type	**1.Water bag** **2. Nodular** **3. Mixed** ***Indicate code:*** |__|	L8.5	Type	**1.Water bag** **2. Nodular** **3. Mixed** ***Indicate code:*** |__|
R8.6	Inguinal nodes	**Normal** ☐ **Enlarged** ☐	L8.6	Inguinal nodes	**Normal** ☐ **Enlarged** ☐

R8.7	Inter-digital entry lesions	**Yes** ☐	**No** ☐	L8.7	Inter-digital entry lesions	**Yes** ☐	**No** ☐
	EVIDENCE OF ACUTE ATTACK				**EVIDENCE OF ACUTE ATTACK**		
R8.8	Fever	**Yes** ☐	**No** ☐	L8.8	Fever	**Yes** ☐	**No** ☐
R8.9	Red legs	**Yes** ☐	**No** ☐	L8.9	Red legs	**Yes** ☐	**No** ☐
R8.10	Tender legs	**Yes** ☐	**No** ☐	L8.10	Tender legs	**Yes** ☐	**No** ☐
R8.11	Swollen lymph nodes(firntit)	**Yes** ☐	**No** ☐	L8.11	Swollen lymph nodes(firntit)	**Yes** ☐	**No** ☐

Section Nine: Dermatology Life Quality Index (DLQI)

11.1	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
11.2	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
11.3	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.4	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.5	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.6	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.7	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
11.7.1	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
11.8	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.9	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
11.10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Appendix 13. Discussion guide: Process assessment study

INTRODUCTION:

Ground rules for discussion

In order to have a useful discussion the moderator explains the ground rules of the discussion.

- We would like all participants to remain throughout the discussion. However, if you feel like interrupting the discussion, please inform us and leave. You will not be faced with any form of harm by deciding not to participate. But, we would like to inform you that your participation today will greatly contribute to the study.
- We would like to remind you speak one at a time according to moderator's permission.
- However, we would appreciate full participation from all of you and like to hear all your stories and experiences.
- We encourage all of you to speak your mind freely.
- We would like to inform you that we respect the views of all of you during the discussion. There is no RIGHT or WRONG answer to our questions. Accordingly, participants should respect and refrain from criticizing the views of other participants.
- We expect all of you to keep others' opinions secret by avoiding talking about the discussion, once finished.

NOTE:

Moderator: make sure to do a <u>tour de table</u> to ensure and encourage all participants have a chance to add to points raised.

Co-facilitator: take comprehensive notes if permission to audio-tape session denied at anytime and/or equipment failure. **Make sure the recorder is working properly and deal with any unforeseen situations during the discussions.**

Make sure participant/ seat mapping is done.

1. The intervention
    a. Understanding, attitudes and perceptions towards the intervention
        i. Knowledge of sequence of intervention (as described in MIVs)
        ii. How difficult/easy is the intervention procedure to understand? Explore:
        iii. Reaction to the intervention (acceptability)
    b. Feasibility
        i. How do you see the acceptability of the treatment procedure?
        ii. Can the treatment be conducted at home without difficulty?

iii. Given the resources, time and commitment of patients to what extent can the treatment be performed at home? (Barriers to implementing the intervention at home)
    1. Access/availability of water? Distance from source?
    2. Time to perform treatment?
    3. Adequacy monthly supply of IPs? What?
    4. Perceptions of and assistance from family members? Neighbours? How?
    5. Experiences of unintended and/or unanticipated consequences of using the IPs? Please explain more?

iv. Adherence
    1. Is the treatment procedure clear, logically sequenced? If not what is unclear?
    2. In what sequence do you perform the treatment? Time of day?
    3. What are the main factors that affect the performance of the treatment as described?
    4. What are the main reasons patients fail to attend MIVs?
    5. What are the main reasons for patients not to complete their diaries?

2. Satisfaction with the way the intervention was delivered: Overall satisfaction with MIVs followed by unpacking the different components?
    i. Procedure? Washing, exercise, shoes, socks (as a whole)?
    ii. ADLA diary completion
    iii. Adequacy of IPs/ supplies?
    iv. Contextual factors
        1. Distance from HP (HC)
        2. Dates MIVs are delivered? Why?
        3. Interaction with study team? How?
3. Perceived impacts of the intervention
    a. Do you think the treatment works? How? Why?
        i. Health (frequency of ADLA?) Explain to what extent comparing with no intervention?
        ii. Social (improvements in family or other relationships, increased ability to work, ability to care for relatives, etc.)? How?

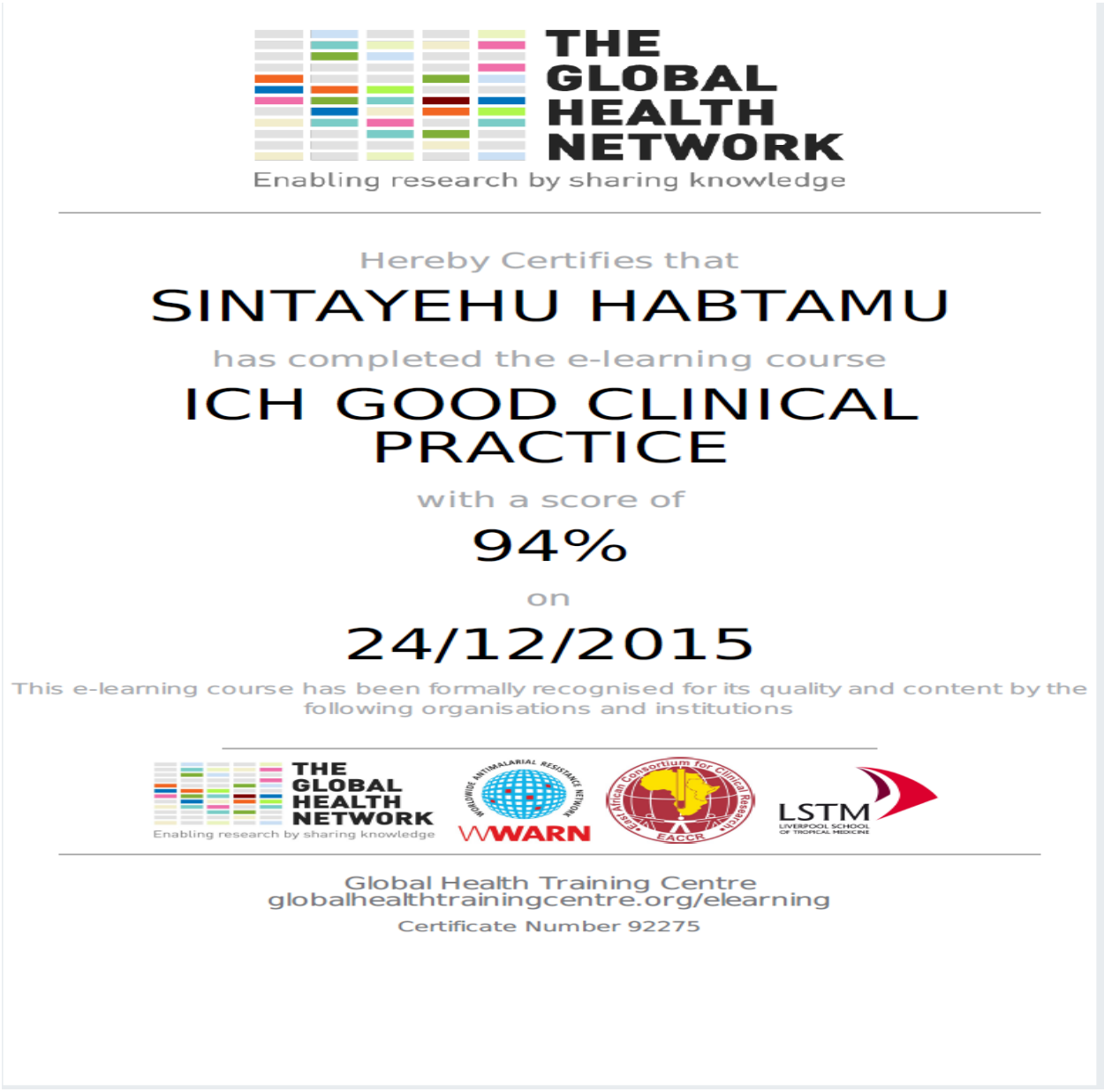
iii. Do you think participating in the intervention may increase stigma (for example, by marking you out as having podo?) how?

b. Would you recommend the intervention to podo patients in other places? Why?

4. Likely implications of the intervention for translation into policy and practice in East and West Gojjam, Amhara region and beyond? (stakeholders; CPAs, Supervisors)
    a. Would you recommend the intervention to podo patients in other places? Why?
    b. What aspects of intervention would be difficult/easy to implement? Why?
5. Training and conducting MIVs
    a. Do you think your training has provided you with sufficient skills to conduct intervention? Explore:
        i. Providing health education? How/Why?
        ii. Completing adherence sheet? How/Why?
        iii. Checking diaries for accuracy? How/Why?
    b. What aspects of the MIV do you find most difficult? Why?
        i. Providing health education? How/Why?
        ii. Completing adherence sheet? How/Why?
        iii. Checking diaries for accuracy? How/Why?
        iv. Fetching water for washing and disposing used water?
    c. Can CPAs from other places be recruited and trained to conduct the intervention?
    d. What should be improved for CPAs in other places to deliver intervention successful?
6. Are there any points we should have raised about the intervention that we missed and you think should've been raised/discussed?

Thank you for participating in this very important study!

Appendix 14. ICH-GCP certificates: sample



THE GLOBAL HEALTH NETWORK

Enabling research by sharing knowledge

Hereby Certifies that

SINTAYEHU HABTAMU

has completed the e-learning course

ICH GOOD CLINICAL PRACTICE

with a score of

94%

on

24/12/2015

This e-learning course has been formally recognised for its quality and content by the following organisations and institutions

THE GLOBAL HEALTH NETWORK

Enabling research by sharing knowledge

WWARN

EACCR

LSTM

LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Global Health Training Centre
globalhealthtrainingcentre.org/elearning

Certificate Number 92275

Note: all fieldworkers including the Author and statisticians have received certificates

Appendix 15. Paper 1

Negussie H, Kassahun MM, et asl (2015). **"Podoconiosis treatment in northern Ethiopia (GoLBet): study protocol for a randomised controlled trial."** *Trials* **16:** 307.

Appendix 16. Paper 2

Negussie H, Addissie T, Addissie A, Davey G (2016). "Preparing for and Executing a Randomised Controlled Trial of Podoconiosis Treatment in Northern Ethiopia: The Utility of Rapid Ethical Assessment." PLoS Negl Trop Dis 10(3): e0004531.

Appendix 17. Paper 3

Negussie H, Addissie T, Addissie A, Davey G (2017). (Under co-author review) "Process evaluation of a randomized controlled trial to test the effectiveness of a simple foot care and hygiene intervention in podoconiosis lymphoedema: a qualitative study in northern Ethiopia"

Appendix 18. Pictures from fieldwork