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The Leprosy Mission Trust India

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Transforming the treatment and prevention of leprosy and Buruli ulcers in LMICs

PROTOCOL

Comparison of removable off-loading device and routine care to heal plantar ulcers due to leprosy and diabetes in the community: a feasibility plus trial

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1. Summary

1.1 Background

Plantar ulcers are a serious complication in leprosy and diabetes globally resulting in hospitalization, disability, and amputation. Continued pressure over the vulnerable site leads to ulcers and then impedes ulcer healing. Therefore, in addition to removal of infection off-loading the ulcer area is essential to heal the ulcer. The current proposed feasibility plus study is based on removable off-loading walker boot fitted with soft insole which can be easily applied with limited training and may allow the patient to continue their essential daily routine activities. We will test the feasibility and acceptability of using this device and set the scene for a potential trial to test the effectiveness of this device type in reducing ulcer development and ulcer complications in community setting.

1.2 Objectives

Primary objectives (feasibility):

i) Measure adherence rates with the off-loading device versus standard care (provision of footwear with MCR insole).
ii) Observe the acceptability of the device in terms of comfort and acceptability.
iii) Elicit views on a potential randomised control trial with effectiveness outcomes.

Secondary (plus) objectives

i) Set the scene for a future RCT by piloting trial methods and measurements.
ii) To observe ulcer prevalence at baseline
iii) To observe the healing rates in interventions vs control patients

1.3 Design

A community based, randomized feasibility plus trial.

1.4 Study participants

Patients aged 18 years and above with loss of sensation (inability to feel monofilament of 10 grams) and plantar ulcer in the foot due to leprosy or diabetes. Patients with multiple or bilateral ulcers will be included alongside those with just one ulcer.

1.5 Intervention group

Removable walker boot will be applied to off-load the ulcer area(s). This removable nature facilitates daily dressing of the ulcer and monitoring its progress. This also allows patient mobility to carry out essential activities of daily living. The details of the intervention are described below.

1.6 Control group

The current standard of care provided in the community, Micro-cellular rubber footwear.

1.7 Follow-up

The patient will be followed up for 8 weeks and photographs of ulcers will be taken at baseline and after every until the ulcer heals or at 8 weeks, whichever is earlier, to measure the ulcer area and to record the pedometer values.

1.8 Outcomes

The main outcome measures are; 1) Adherence to removable walker boot which will be measured using pedometer; one placed inside the walker boot and second on patient's wrists as a watch/ in pocket. 2) User satisfaction which will be measured using standard questionnaire. 3) Ulcer healing which we will measure the healing of ulcer time to (complete epithelisation of ulcer) and measure the rate of healing both assessed from photographs by masked observers.

1.9 Qualitative interview

User experience on removable walker boot will be explored through semi-structured walking interviews. An estimate of fifteen patients in each site, sampled purposively, will be asked about their experiences of using the device. In the interviews we will seek to elicit reasons for adherence and non-adherence to removable walker.

2 Background

2.1 Problem of plantar ulcers in leprosy and diabetes

Plantar ulcers are a serious complication in leprosy and diabetes globally resulting in hospitalization, disability, and amputation. About 26 million people worldwide annually have a diabetic foot ulcer with another 130 million at risk of diabetic neuropathy.(1) Though the actual burden of ulcers in leprosy is unknown, it is estimated that over 3 million people are living with disability due to leprosy and that 20-50% of patients with peripheral neuropathy due to leprosy will experience ulcers.(2, 3)

The prevalence of diabetes is 8.4% in India(4) and 8.5% in Nepal.(5) These figures are higher than the global prevalence of 6.3%.(6) About one third of diabetic patients develop foot ulcers in their lifetime.(1) While the lifetime incidence of foot ulcers in leprosy is not known, an ongoing cross-sectional study on prevalence of disabilities due to leprosy has shown that over 30% of patients with an anesthetic foot presented with plantar ulcer. Foot ulcers reduce patient mobility, social interaction, and health-related quality of life. The treatment of foot ulcers increases substantial burden on healthcare.(7, 8) Therefore, proper management and expedited healing of foot ulcers is important to limit the burden of ulcer care.

2.2 Challenges in management of plantar ulcers in leprosy and diabetes

The role of pressure on the sole of foot in the pathogenesis of neuropathic plantar ulcer is well established.(9, 10) Continued pressure over the vulnerable site leads to ulcers and then impedes ulcer healing.(11) Therefore, in addition to removing any infection, an effective way to promote healing of ulcers is rest - either complete bed rest, which is rarely possible or, commonly, rest to the affected part using an off-loading method.(11, 12)

The gold standard alternative to rest is use of total contact cast with Bohler irons.(12, 13, 14, 15) The total contact cast method is considered superior as there is a forced compliance since patients cannot remove the cast (16), but is not favored by the patients and clinicians alike. Clinicians find total contact cast unfavorable because of the associated skin abrasions and iatrogenic ulcers. Prolonged use of total contact casts has been associated with muscle atrophy and reduced bone density.(17) A practical problem with the total contact case is that it requires a skilled technician to apply and requires constant monitoring.(18) The expertise is fast disappearing and poorly applied plaster casts will cause more ulcers than they heal.(14, 19) Ulcer specialists and their patients are therefore seeking for a more flexible, less cumbersome method than a total contact cast. These alternatives include 1) Knee high removable off-

loading walker boot, 2) Ankle high removable off-loading walker boot and 3) Footwear with soft insole (micro-cellular rubber) with off-loading provision using orthosis(20).

The advantage of all these removable off-loading methods is that they can be used with minimal training and in community settings. They are less bulky, cause problems in carrying daily routine activities.(21) The main difference between removable and total contact cast is that with the latter, adherence to treatment is the patients choice as they can remove the device, and thus, patient adherence to using these devices has a large impact on healing. Therefore, understanding the factors that influence patients' adherence to using removable off-loading devices is vital to improving the use and effectiveness of off-loading treatments and the healing outcomes for people with plantar ulcers.

In this study we will generate pilot data to inform a larger clinical trial to evaluate the impact of removable offloading device on adherence and ulcer healing. The current proposed feasibility plus study is based on removable off-loading walker boot fitted with soft insole. This device can be easily applied with limited training and may allow the patient to continue their essential daily routine activities. We will test the feasibility and acceptability of using this device and set the scene for a potential trial to test the effectiveness of this device type in reducing ulcer development and ulcer complications in community setting.

2.3 Current use of off-loading methods to heal plantar ulcers in LMICs

Studies in high income countries show adherence with removable off-loading devices ranging from 28% to 60% (≥80% of daily steps/time) .(22) The situation may be very different in low and middle income countries (LMIC).

We conducted a literature review with the aim of understanding the effectiveness of total contact casts compared to removable off-loading devices for plantar ulcers in patients with diabetes mellitus or leprosy in LMIC. We sought to understand the predictors of adherence to using off-loading devices to heal plantar ulcers to diabetes mellitus or leprosy and any difference in healing rates. Our database search yielded 250 potentially relevant abstracts. These abstracts were reviewed by two researchers. We included 8 studies in the review, 5 randomized control trials; and 3 case series. The majority of the studies identified focused on people with diabetes (n=6)(23, 24, 25, 26, 27, 28) and only one study focused on people affected by leprosy (29) . The final study, a case series,1 included a mixed population of people affected by leprosy, diabetes and meningomyelocele.(30) The majority of the studies (n=5)

used total contact cast (25, 27, 30, 31, 32) as off-loading method and found it to be superior to other techniques (modified ankle foot orthosis (26), removable ankle high cast, (33) and standard dressing (25, 32). Adherence to cast use has been reported to be a major concern but none of the studies measured adherence objectively.(25, 26, 27, 29, 30) None of the studies used removable off-loading devices of the type we propose to test in this study. As a result of difficulties in procurement and support, the great majority of people in LMICs with neuropathic ulcers receive none of the above devices and are provided with footwear with a soft insole of Micro-cellular rubber.

We have an ongoing study on the use of off-loading removable walker boot with soft insole to off-load ulcer area in hospital practice where it is being compared to a total contact cast in patients with non-infected plantar ulcer due to leprosy (Trial registration number: CTRI/2022/06/043568). In this proposed feasibility trial, we want to extend this method to a community where patients with plantar ulcer due to leprosy or diabetes can be treated at home after they are assessed and provided with such a device in a one-off healthcare facility visit prior to initiation of intervention. Our study community is rural where weight bearing is a particular problem because farming is the main occupation.

3 Objectives

Primary objectives (feasibility):

i) Measure adherence rates with the off-loading device versus standard care (provision of footwear with MCR insole).
ii) Observe the acceptability of the device in terms of comfort and acceptability.
iii) Elicit views on a potential randomised control trial with effectiveness outcomes.

Secondary (plus) objectives

i) Set the scene for a future RCT by piloting trial methods and measurements.
ii) To observe ulcer prevalence at baseline.
iii) To observe healing rates in interventions vs control patients (see sample size below to inform size calculations). We have experience in making the above measurements in hospital (34) and the community (35) and the NIHR RIGHT Leprosy INSTIL studies.

4 Methodology

The protocol for the feasibility study has been developed according to SPIRIT guideline and in accordance with recommendations on reporting standards of studies on prevention and management of diabetic foot ulcers.(36)

4.1 Study setting

Community setting in Champa district, Chhattisgarh, India and satellite clinics of Anandaban Hospital in Nepal. Through the ongoing work of the National Institute of Health Research, UK, funded research project working on several projects including cross-sectionals study to estimate the prevalence of ulcers and disabilities due to leprosy and implementation and evaluation of self-care program in Champa district. Through this project we have a cohort of patients with plantar ulcer due to leprosy in the Champa district, Chhattisgarh Champa. They will be screened for eligibility to participate in this feasibility study. In Nepal, we will be linking in with satellite clinics run by TLM Nepal in different provinces such as Anandaban hospital Patan Clinic at Lalitpur, Biratnagar clinic at Koshi Hospital, Biratnagar and Butwal clinic at Lumbini Provincial Hospital, Butwal to identify potential participants.

4.2 Study design

A community based, randomized feasibility plus trial.

4.3 Study population

The study populations will consist of patients with non-complicated plantar ulcer in an insensate foot due to leprosy or diabetes. These ulcers will have no visible infection, no involvement of underlying structures, absence of slough and with sloping and healing edge. They will be screened for eligibility to be included in the study and then informed consent obtained.

4.4 Sample size

We will include 150 people with neuropathic ulcers due to leprosy and diabetes in the study (75 each from India and Nepal). If adherence is 0.5 (50%) then the 95% CIs (n=150) would be 0.42 to 0.58. Any other proportion would provide narrower CIs. We do not anticipate observing a difference in ulcer healing between intervention and control because, given a control healing rate of 70%, the intervention group would have to be 90% to have a 80% power.

4.4.1 **Inclusion criteria**

Patients aged 18 years and above with loss of sensation (inability to feel monofilament of 10 grams) and plantar ulcer in the foot due to leprosy or diabetes. Patients with multiple or bilateral ulcers will be included alongside those with just one ulcer.

4.4.2 Exclusion criteria

Patients with:

- multiple plantar ulcers where largest ulcers cannot be offloaded effectively due to presence of other ulcers
- sign of infection or infected ulcer or with the signs of sinus tracks
- insensitive feet along with orthopaedic conditions in the ankle, knee and hip or limb length discrepancy
- amputation; forefoot and above on the contralateral leg.
- patients who are wheelchair dependent

4.5 Intervention and control group

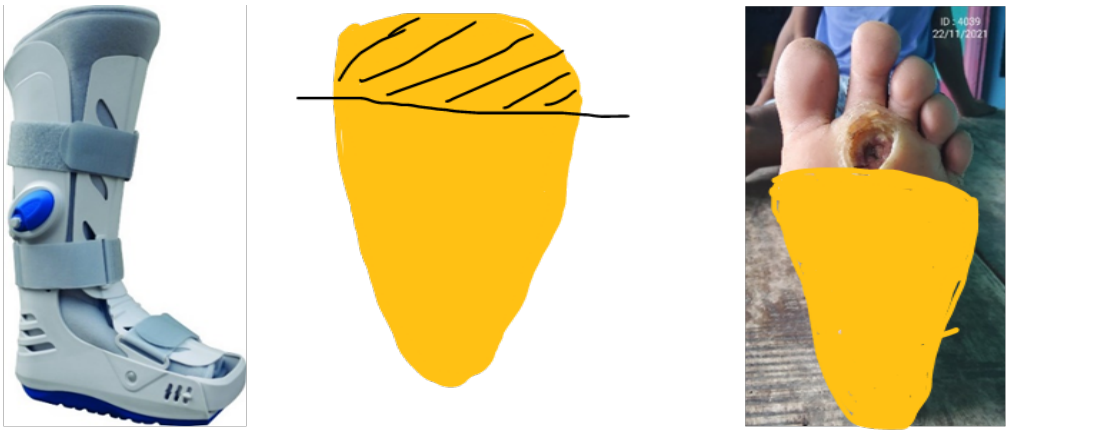
Intervention group: Removable walker boot with a customised insole will be applied to off-load the ulcer area(s). This removable nature facilitates daily dressing of the ulcer and monitoring its progress. This also allows patient mobility to carry out essential activities of daily living. The details of the intervention are described below.

Control group: The current standard of care provided in the community; the Micro-cellular rubber footwear.

Other than the difference in the off-loading methods, the dressings and self-care education provided will be the same between the groups. The dressings will be done by patient themselves or by caregivers who will be provided with required materials and training for dressing. Study participants will receive information on the importance of off-loading to aid ulcer healing, with an emphasis on the need for adherence to the off-loading methods. On completion of the trial, patients in the intervention and control group will be provided with appropriate MCR footwear to prevent recurrence of ulcer.

4.5.1 Description of intervention and control intervention

The Intervention – Removable walker boot: The removable walker is a brace which offers stabilization and immobilization to the foot, ankle and lower leg with comfort which can help in off-loading the ulcer area through pre-cut insole (more details on making of insole is given below). The removable walker boot (Figure 1) works on exactly the same principle as total contact cast(11) in off-loading the ulcer area except that it is removable. The material that covers the leg is soft and facilitates proper fitting with the removable property allows wound inspection, dressing and hygiene. It has a sufficient broad bottom sole promotes natural gait, reduces plantar pressure and at the same time provides stability. The rigid stirrup in both sides provides stability and immobilization to the ankle joint while walking.



1a: Removable walker boot 1b: Soft insole 1c: Cut-out soft insole to off-load

Figure 1: Illustration of removable walker boot with cut out soft insole to offload ulcer area

We will be inserting the insole with a 'pre-cut' (excavated under wound area) for off-loading the ulcer area which will be determined by the health professional based at the healthcare facility. The insole will be made of Ethyl Vinyl Acetate (EVA) polyurethane rubber which is light weight and mechanical property is comparable with Microcellular rubber on distribution of weight across plantar surface of the foot except over ulcer area. The insole will be custom made according to size and shape of the patient's foot and location of ulcer, thereby facilitating the distribution of weight over entire foot, except over ulcer area. The custom-made insole will be fitted inside the removable walker to off-load the ulcer area. We will cut and remove the part of the insole which is directly below the ulcer area to off-load the pressure. For example, if the ulcer is in the first meta-tarsal head, the insole which is directly below the first and part of second MTH will be removed to off-load the ulcer. If the ulcer is in the third MTH, the insole which comes directly in contact with the third MTH and part of second MTH and part of fourth MTH will

be removed to off-load the ulcer. If the ulcer is in the heel, the complete heel part of the insole will be removed to off-load the ulcer. The removable walker is readymade and available in different sizes, which can be fitted for varying length and circumference of the leg. The Velcro straps in the removable walker allows to accommodate varying circumference of the leg. Special attention will be paid to ensure the adherence to wearing of the walker. During the self-care training, we will educate the patients on the importance of adherence to wearing the walker and opening the walker only for dressing changes. On exiting the trial, patients will be provided with appropriate protective (MCR) footwear to prevent recurrence of ulcer.

Immediately after provision of removable walker boot, participants will walk under the supervision of the Physiotherapist until patient feels comfortable while walking. Physiotherapist will look for any imbalance or difficulty while walking and address them if any. The participants will be trained on how to remove and re-apply walker boot to perform ulcer dressing.

Control group: The current standard of care provided in the community; the Micro-cellular rubber footwear (shown in the figure 2).

Figure 2: Standard footwear with Micro-cellular rubber

4.6 Study participants recruitment

In India and Nepal, we will recruit people with ulcers due to leprosy or diabetes. Due to the differing contexts, we shall utilize different context appropriate methods to identify participants. Below, we present our approaches for participant recruitment.

4.6.1 Recruitment of patients in India

Patients with neuropathic plantar ulcer will be identified in the community using data collected through the ongoing study on prevalence of disability among people affected by leprosy as part of the larger

project in the Janjgir-Champa district. The district consists of 9 blocks (sub-division of the district) and patients from three blocks will be included in this study. All patients at risk or with ulcer at the time data collection will be re-traced by the research assistant appointed in this project. All those found with neuropathic plantar ulcer will be screened for eligibility to be included in the study. Please see the section 4.7 for randomization and allocation of those eligible patients. The list of patients with diabetes and other non-communicable disease such as hypertension are available at the Health and Wellness centres in the community. There is one Health and Wellness centre for every five Panchayats (each panchayat consists of one or more villages). The appropriate permission will be obtained from state level health authority to obtain this list from the study area. List of patients from all the Health and Wellness centres will be combined to create a list of potential patients. Each patient in the list will be traced by a research assistant employed in this project with the help of local front-line health workers and assessed for presence of neuropathic plantar ulcer. All those found with ulcer will be screened to be included in the study. We will also trace patients with diabetes with ulcer who are not in our line list, and if found, will be included in the study. Please see the section 4.7 for randomization and allocation of those eligible patients.

4.6.2 Recruitment of patients in Nepal

Patients with neuropathic ulcer will be recruited at Anandaban hospital's satellite clinics. Anandaban Hospital is running weekly satellite clinic at Satdobato, Lalitpur and monthly satellite clinic at Lumbini Provincial Hospital, Rupandehi Butwal and Koshi Zonal Hospital at Biratnagar, Morang. Research officer will attend the satellite clinic for screening and enrollment of possible participants. Around 7000 people get outpatient leprosy services at Anandaban Hospital and its satellite clinics of Anandaban Hospital. Six hundred fifty-two people receive outpatient ulcer care yearly at Anandaban Hospital and its satellite clinics.

The people with diabetes will be identified and contacted through local health centers and clinics in Kathmandu Valley and its periphery. Diabetic clinics at different hospitals will be contacted to reach the diabetic patients with foot ulcers due to diabetes.

4.6.3 Randomization and allocation

Participants will be enrolled sequentially, and randomly allocated (1:1) to receive removable walker boot or MCR using the "digital sealed envelope" method resident in a computer. An allocation table will be generated remotely by the trial statistician at the George Institute of Global Health India. A permuted block random method will be used to generate the randomization sequence within each stratum.

Randomly selected blocks of size 2, 4, 6, or 8 will be generated to maintain balance between the numbers allocated to each of the two groups and to ensure allocation concealment. The generated table will be uploaded into the REDCap software to be used for participant enrolment. Access to the allocation table will be restricted. Trial staff in India and Nepal will not have access to the allocation table. When a participant's details are submitted, the trial arm and a unique study number will be assigned and revealed to the local clinician so that the randomized group that the participant is assigned to cannot be altered.

4.6.4 Data collection

Basic demographic and clinical data including co-morbidity conditions associated with ulcer healing will be collected from included patients after obtaining informed consent using (Appendix 3) and documented on tablets. The clinical details will include duration of disease, duration of impairment, duration of current ulcer, ulcer metrics current ulcer, previous history of ulcer, presence of foot deformities at inclusion in the study, self-care practice, vascular condition of the limb (dorsalis pedis pulse rate) and current footwear type/use. Please refer to Appendix 3 For the detailed data collection form.

4.6.5 Main outcome measures

1. **Adherence to removable walker boot**: Adherence will be measured using pedometer; one placed inside the walker boot and second on patient's wrists as a watch/ in pocket. The pedometer will provide data on number of steps taken by patient during the assessment period which will be recorded weekly. We will compare the groups based on their steps per day. In addition, the difference in cumulative steps recorded between the two pedometers will provide a further measure the compliance to walker boot. We will measure the difference in the difference between intervention and control.
2. **User satisfaction**: We will measure the user satisfaction with the off-loading devices using the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0 at complete healing of ulcer or at 8 weeks from recruitment, whichever is earlier.
3. **Ulcer healing**: We will measure the healing of ulcer time to (complete epithelisation of ulcer) and also measure the rate of healing. All observations will be based on 'blind' assessment. The patient will be followed up for 8 weeks and photographs of ulcers will be taken at baseline and after every 2 weeks until the ulcer heals or at 8 weeks, whichever is earlier, to measure the ulcer area. The ulcer will be measured from the photographs taken using the data collection tablets. The ulcer will

be measured by masked observers in another site using the PUSH (Pressure Ulcer Scale for Healing) tool with which we have considerable experience.

The photographs of the ulcer will be taken using standard and uniform method in both the study sites. Photographs will be taken in a well-lit area in a long sitting position with the foot elevated slightly on soft material. The image of the ulcer will be captured by the research assistant standing directly in front of the patient with the camera placed parallel to the affected foot/ulcer.

4.7 Follow-up and study end points

Patients will be followed up weekly for 8 weeks or until ulcer completely heals, whichever is earlier. The complete healing of ulcer will be determined clinically as complete closure of epithelium of the skin which will be photographed for verification. In the event that study participants develop any complications such as worsening of existing ulcer, skin abrasions due to friction or sever swelling to the foot or leg, they may be considered as censored if it affects the wearing of the off-loading device and will not be continued for follow-up. Such patients will be referred to The Leprosy Mission Trust India tertiary hospital at Champa in India and Anandaban Hospital in Nepal for further evaluation and treatment.

4.8 Qualitative study

User experience on removable walker boot will be explored through semi-structured walking interviews. A random sample of patients in the intervention arm of the trial, stratified by gender and age group, will be sampled. Recruitment will be undertaken when the participant joins the trial. The walking interview will be arranged for 2-4 weeks after they receive the walker boots to allow time for the interviewee to experience living with the walker boot. We will recruit until data saturation – estimate fifteen patients from each site. The researcher will arrange to spend up to half a day with each patient. They will be asked to show the researcher around their household and locality as far as they are able to reach without transport and during this walk, explain how use or not of the device affects their ability to undertake daily routines and mobility. They will be asked about their experiences of using the device, challenges they meet in using the device and how they negotiate challenges related to using removable walker boots. They will also be asked about what modifications can be made to improve its effectiveness in off-loading at the same time as to improve adherence. The researcher will audio record the interview and take field notes. Interviews will be transcribed and translated. Fieldnotes will be typed up and

expanded after the walking interview. Data from all sites will be combined for thematic analysis, whilst paying attention to differences in context for interviewees from the different sites.

4.9 Trial analysis plan

The adherence to off-loading devices in the intervention will be based on the number of steps taken by the patient during the assessment period. The mean cumulative steps taken (confidence limits) will be measured using the foot device. We will also measure and compare the difference between wrist and foot between intervention and control. The mean user satisfaction score between the intervention and control group will be tested using t-test. Higher the user satisfaction score indicates greater the satisfaction with the off-loading device. The healing rate between the groups as percentage reduction in the ulcer area per unit time (8 weeks) will be compared between the two groups using methods we have used before. Our statistical philosophy is based on observed standards and confidence/credible intervals and not on hypothesis testing.(34)

5 Governance, Ethics, data collection and security

5.1 Ethics

5.1.1 When will obtain consent?

A local researcher will approach all people identified from line lists available from the ongoing study on the prevalence of disability due to leprosy for leprosy ulcers and local health centres. Those with ulcer due to diabetes will be identified from the line list developed from the combined list from the and local health centres. Except those under 18 years of age, all those with neuropathic ulcers will be included in the study – for instance if a person has difficulty in communicating, they will still be offered entry into the study. People who are willing to participate will be given a Patient Information Leaflet (Appendix 1) to read but consent will be sought after the day when this is provided. If a person cannot read, then they will be assisted in understanding the information in the leaflet. The Patient Information Leaflet (Appendix 1) and informed Consent Form (Appendix 2) will be translated into Hindi and Nepali and back translated according to the WHO methodology.(37)

5.1.2 Who will take consent?

One of the local trained researchers deployed on the grant will offer the person participation in the data collection for the study. The researchers will complete GCP training online and will be included in the delegation log. They will be trained to obtain consent as follows: They will attend a 30 minute talk given by the project manager covering the essence of the Helsinki recommendations (1964 and revisions) (38) and the right to withdraw at any stage (Dr Joydeepa(India), Dr Indra (Nepal), local or Sopna Choudhury(University of Birmingham).

5.1.3 How will we obtain consent?

The forms will be read aloud to people who are illiterate. If they are unable to sign their name using a writing instrument, then they will sign consent by thumb print (or fingerprint if the thumb has been damaged by leprosy). See data management regarding bio-metric data. Screening and the obtaining of informed consent will be evidenced by the completion of an electronic case report form (e-CRF) within the REDCap closed data capture system by staff named on the delegation log. If any person declines to contribute data, then it will be noted that a person has declined but no data will be retained on them. However, reasons for not taking part will be recorded in a place provided on the computer.

5.1.4 Withdrawal

Participants are free to withdraw at any time as explained to people in the information provided. The participant may withdraw in two ways:

1. Does not wish to continue in the intervention, but happy to contribute follow-up data
2. Does not wish to continue to contribute follow-up data

There will be a notice of withdrawal form on the data collection tablet for people in the second group above but people who are in the first group will continue to contribute data but their withdrawal from participation in group activity will be noted.

As this is a feasibility plus trial, there will be no data monitoring committee and no interim analysis. Rather, the study managers will monitor accruing data as a check on quality and so that action may be taken if data are incomplete.

5.2 Protocol amendment

Any protocol amendment will be reported to the Leprosy Mission Trust India and Nepal Health Research Council (NHRC) ethics committee to approve the change.

5.3 Sponsorship

The Leprosy Mission Trust India will be the sponsor.

5.4 Data collection, use and storage

We will adhere to international standards on conducting health research (39). We will ensure that the communities taking part in this research are also those who will see the benefits, and that the privacy of participants are protected. All data (save consent forms) will be collected using tablets (which will also be used to take photographs). Patient facing materials (Information/consent forms) will be translated and back translated according to WHO criteria (e.g. back translation carried out independently of forward translation and results checked independently). Data will be captured and encrypted using the REDCap database at The George institute for Global Health India. We will comply with local regulations governing research:

https://intranet.birmingham.ac.uk/it/documents/public/Information-Security-Policy.pdf and the Indian Council of Medical Research.

All data generated from this study will be classified according to the University of Birmingham Information Security Framework. All data will be collected and stored electronically to eliminate data collection errors, such as contradicting answers, building on our experience under our current NIHR Global Health Research Unit on Improving Health in Slums. Data will be reported on an electronic Case Report Form (eCRF), and all local research staff will be trained to collect data directly onto electronic tablets. Data will be acquired and stored on the REDCap platform with access restricted by passwords at the local site in India and Nepal. Each participant will be allocated a unique study number when they agree to participate which will be used on all documents. REDCap is capable of storing and transferring photographic images.

Range limits and logic checks (e.g., for conflicting responses) will be built into the REDCap form to prevent erroneous data entry. Base-line data from the first ten patients will be cross-checked by the local lead investigator to assure that full and accurate data are collected.

All data will be stored only in backed-up shared network spaces. “Restricted” and “reserved” data files will be encrypted using PGP encryption. The study site in India will create their own unique set of PGP keys to access data locally. For data transmission between study sites and the University of Birmingham the files will be encrypted using the relevant study site public key. Only authorised individuals at each institution will have access to the data. The information collected on REDCap is encrypted on the tablet and sent through a secure link to the server hosted at the George Institute for Global Health.

Once the project has ended, the anonymised trial data will be made available for sharing with all requests being approved by the Chief Investigator. Those accessing the data will abide by the same rules as are applicable throughout the project. Data will be stored for a minimum period of ten years and then reassessed rather than destroyed, as per the local data management policy. During the 10-year post-project period paper data, such as consent forms, will be archived locally in India and Nepal in locked cabinets. Electronic data including photos will be stored in an encrypted archive at the George institute for Global Health India. All electronic data held locally at the investigator site in India will be archived for ten years and then deleted. Should the investigator site wish to access the electronic data, this will be done through the local secure file transfer portal.

5.5 Study organization and management

5.5.1 Study management group

The Study Management Group (SMG) includes individuals at the University of Birmingham, The Leprosy Mission Trust India and The Leprosy Mission Nepal who are responsible for the day-to-day management of the trial. This will include the Chief Investigator for the whole study (Prof Richard Lilford), local Investigator in India (Dr Joydeepa Darlong) and Co-Principal Investigator (Mr Karthikeyan Govindasamy), local Investigator in Nepal (Dr Indra Napit), Project Manager (Mr Dilip Shrestha) for overall study and local Project Manager, lead methodologists and patient representatives. The Study Management Group will meet monthly by teleconference, but this may be more frequent if deemed necessary by the members. The role of the Study Management Group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

5.5.2 Monitoring and oversight

The trial will be overseen by the clinical trials unit at George Institute for Global Health. They will provide overall supervision of the trial and will ensure that it is conducted in accordance with the principles of

good clinical practice and relevant regulations. They will review the safety and efficacy data during the active phase of the trial handbill advice on the continued recruitment of trial participants. They will meet by teleconference and the team will consist of a trial manager, statistician and data manager.

5.2.3 Summary of staff training

All current site staff in India and Nepal have undertaken Good Clinical Practice Training and new appointees to the trial will be required to complete online training. Staff will be trained to seek patient consent (as outlined in 5.1.2).

5.6 Dissemination and Publication

The results of the study will be reported to collaborators of this study. Equal credit will be given to those who have collaborated in the trial.

The findings will be shared with the patients and communities through the networks of The Leprosy Mission Trust India and The Leprosy Mission Nepal who have extensive experience in working with the patient communities. We shall also present our work at local and international conferences.

Tools we will use to disseminate our research output include: bite-sized research reports in lay format; publication in peer reviewed international journals; public announcements in LMICs; policy briefings; print and online media; the director's news blog (680+ subscribers); institutional and social media accounts and websites.

5.7 Gantt Chart

	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Ethics Approval																				
Recruitment of staff																				
Training of staff																				
Line listing & tracing (DM) and leprosy patients																				
Recruitment of patients																				
Intervention																				
Follow-up																				
Qualitative interview																				
Data cleaning																				
Analysis																				
Report writing & Publication																				
Contingency																				

Ethics section:

SECTION 2

Risk and benefits	**What are the potential risks to the participants? Consider social and emotional risks as well as more obvious physical risks.**
	There are no additional risk associated with participating in the study. The treatment method of removable walker works the same way as total contact cast which has been in practice for ulcer care in leprosy. Patients may develop skin abrasion due to ill-fitting walker boots. However, removable walkers used in this study is considered safe as it comes with soft inner lining to prevent skin abrasions. We expect that application of removable cast in the community will help ulcer heal faster without requiring for hospital admission.
	What is your risk management plan?
	If patient develops skin abrasions, we will discontinue the removable walker boot and patient will be called to hospital for medical care which will be as per standard protocol of the Leprosy Mission Trust India hospital in Champa.
	What will be the compensation for unexpected risks?
	There are no compensation planned for expected risks.
	What are the potential benefits to the participants?
	In routine care micro-cellular rubber footwear is provided for patients with insensitive foot irrespective of presence of ulcer. The treatment provided in this study are standard care for ulcer management in leprosy. Regular monitoring of ulcers and feedback to patient will help in healing of ulcers.
Safety and other controls	**Does this study involve invasive or hazardous procedures, ionizing radiation or hazardous substances (including radiological imaging, vein puncture, or intimate physical examination)?**
	No
Informed consent	**What will be the procedure for seeking informed consent from research participants? How will "research", "randomization", "risks and benefits" be explained?**
	Potential study participants will be provided with the printed information sheet (see appendix 1). Adequate time will be given for patient to read and take decision. In case patient is unable to read, project staff will read and explain to the patient. The decision to participate in the study will voluntary.
	What will be the procedure for seeking informed consent from parents/guardians etc of research participants who are children, mentally/physically challenged? How will assent be obtained from these research participants?
	Children less than 18 and those with mental health issues will be excluded from the study as they will not be able to follow the instructions and keep the removable walker boot on for the required period.

	How will it be made clear that participants are under no compulsion to participate and may withdraw at any time without jeopardizing any service delivery or their relationship with the researcher?
	Decision to participate in the study is completely voluntary. Point of entry into study is when patient presents with non-infected ulcer. If patient decides not to join the study, they will continue to get the routine care without any compromise (self-care & Micro-cellular rubber footwear) for their insensitive feet and ulcer as per standard practice.
	Provide a copy of plain language statement and informed consent form in English and local language.
	Patient information sheet and informed consent is provide in the Appendix 1 and 2. It has been translated into Hindi which will be given to study participants.
	Details of proposed compensation and reimbursement of incidental expenses.
	No compensation and reimbursement will be provided.
	Statement of probable ethical issues and steps taken to tackle the same.
	We do not envisage any specific ethics issues at this stage. If any issues arise during the study will be brought to the ethics committee for the approval.
Potential conflict of interest	None.

Confidentiality, ownership and storage of data and dissemination plans	
Confidentiality	
The raw data collected will be locked and protected	Agree
The electronic data will be pass-word protected	Agree
Ownership and storage of data	
The data collected during the research will be stored and maintained by TLMTI principal investigator. The other principal investigators will have a copy of the data	Agree
All the principal investigators will be responsible for the safety of the data.	Agree
The data collected will be an intellectual property of TLMTI and it should be submitted to TLMTI after submission of thesis/publications	Agree
Publication plans	
All the principal investigators with mutual agreement will publish articles / reports	Agree

TLMTI will be acknowledged appropriately in thesis/publications from the study	Agree
Potential conflict of interest: None:	
Dissemination of research findings	
How will the results be disseminated?	
The results of the study will be reported to collaborators of this study. Equal credit will be given to those who have collaborated in the trial.	
What information will be fed back to the participants and/or participating organization?	
The findings will be shared with the patients and communities through the networks of The Leprosy Mission Trust India and The Leprosy Mission Nepal. Both the organization have an extensive experience in working with the patient communities. We shall also present our work at local and international conferences.	

6. Appendix

6.1 Appendix 1: Patient Information Sheet

Study title: Comparison of removable off-loading device and routine care to heal plantar ulcers due to leprosy and diabetes in the community: a feasibility plus trial

Introduction

We would like to invite you to take part in a research study. Joining the study is entirely up to you. Before you decide, you need to understand why the research is being done and what it would involve. One member of our team will go through this information sheet with you and answer any questions you may have. Ask questions if anything you read or hear is not clear or you would like more information. Please feel free to talk to others about the study if you wish. Take time to decide whether or not to take part.

Who is organizing and funding the study?

The study is being organized by The Leprosy Mission Trust India and The Leprosy Mission Nepal in collaboration with the University of Birmingham, UK. The study is funded by the UK National Institute for Health Research.

What is the purpose of the study?

Leprosy ulcers are not caused by the leprosy germ but by loss of sensation leading to repetitive injury. As a result, patients (and their families) face stigma, social isolation as well as a lot of economic burden. Also, about one third of diabetic patients develop foot ulcers in their lifetime.

The purpose of our research study is to trial the use of a removable walker boot versus standard care, which is footwear with MCR insole. We will look at adherence to wearing the removable walker boot to off-load the ulcer area. We will observe the acceptability of the device in terms of comfort and acceptability.

Why have I been asked to take part?

You have been invited to take part because you have an ulcer due to leprosy or diabetes.

Do I have to take part?

No. It is up to you to decide if you want to take part or not. If you do not want to take part, that is ok.

We will discuss the study together and give you a copy of this information sheet. If you agree to take part, we will then ask you to sign a consent form.

What will happen to me if I take part?

If you are willing to take part in this study, we will first ask you to sign a consent form which is your indication that you understand the study and agree to take part.

We will then issue you with a unique study identification number to ensure that any details we collect remain confidential and secure.

If you agree to take part in this study, you will be provided with the off-loading walker boot or MCR footwear to help heal ulcer. You will also be trained on self-care practice by social mobilizer/staff employed in this project and you will be asked questions about your hand and foot impairments and take photo of the foot. We may ask you in more detail about your experience on using the off-loading device.

What will I have to do?

You will be expected to take part in self-care teaching by social mobilizer, individual interviews, and to answer questions about the impairments and foot ulcers. You need to put-on off-loading boot on your foot with an ulcer for 8 weeks, or until the ulcer heals, and need to do dressing of you the ulcer. We may ask you to show us how you practice self-care.

What information will be collected?

Only your name will be collected. However, the information you give will be anonymised and only ever be viewed by your unique identification number. We will keep this information separate from other information.

During the interview, you are expected to share information about your disability details, foot impairments in particular and ulcer details if present. We will take the picture of your both feet. The picture will not have any personal identification details except the unique identification number.

What will happen to information collected about me?

All information collected about you will be kept private. Only the study staff and authorities who check that the study is being carried out properly will be allowed to look at information about you. Data may be sent to other study staff at University of Birmingham, but this will be anonymised. This means that any information that includes your name and address will be removed so that you cannot be recognized.

Anything you say during the interview will have names of people and places removed. We may use direct quotations in the reports or publications from the study, but they will not be linked to you. All the data will be securely stored in safe place.

The collected data may also be used for future research following approval by an independent Research Ethics Committee and subject to your consent at the outset of this research project.

For further information, please refer to the University of Birmingham Research Privacy Notice which is available here: https://www.birmingham.ac.uk/privacy/index.aspx or by contacting the Information and Data Compliance Team at dataprotection@contacts.bham.ac.uk.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. You can also contact Dr Joydeepa Darlong, The Leprosy Mission Trust India E-mail: joydeepa.darlong@leprosymission.in; Dr. Indra Bahadur Napit, Tel: +977-9851136027, email: indran@tlmnepal.org, investigators of this study for any queries. If you remain unhappy and wish to complain formally, you can do this by contacting Professor Richard Lilford, University of Birmingham UK, r.j.lilford@bham.ac.uk

Can I change my mind about taking part?

Yes. You can withdraw from the study at any time. You just need to tell your research fellow that you do not want to be in the study anymore. Information collected may still be used.

What will happen to the results of this study?

The study results will be published in a medical journal so that other people can learn from them. Your personal information will not be included in the study report and there is no way that you can be identified from it.

Who has reviewed the study?

All research involving human participants is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the University of Birmingham's Science, Technology, Engineering and Mathematics (STEM) ethics committee (ERN_), The Leprosy Mission Trust India ethics committee and Nepal Health Research Council (NHRC ERB_).

Who should I contact if I want further information?

Dr Joydeepa Darlong, The Leprosy Mission Trust India E-mail: joydeepa.darlong@leprosymission.in

Dr. Indra Bahadur Napit, The Leprosy Mission Nepal E-mail: indran@tlmnepal.org

Professor Richard Lilford, University of Birmingham, r.j.lilford@bham.ac.uk

****Thank you for taking time to read this information leaflet. If you think you will take part in the study please read and sign the consent form. ****

6.2 Appendix 2: Informed consent form

Study title: Comparison of removable off-loading device and routine care to heal plantar ulcers due to leprosy and diabetes in the community: a feasibility plus trial

Name of Investigator (s): Dr Joydeepa Darlong, The Leprosy Mission Trust India; Dr. Indra Bahadur Napit, The Leprosy Mission Nepal, and Professor Richard Lilford, University of Birmingham, UK

I _____ understand that researchers from The Leprosy Mission Trust India, The Leprosy Mission Nepal and representatives at University of Birmingham are involved in a study regarding evaluation of the use of removable walker boot versus standard MCR footwear for the treatment of ulcers. Part of this study involves talking to people who have had ulcers. You are being invited to take part in an individual interview, disability assessment and consent to take picture of your feet.

I consent to be approached for more detailed interview and taking photographs of hands and feet with impairments.

I consent to be asked to be observed undertaking self-care.

The study has been explained to me and I understand what is expected of me.

I confirm that I am 18 years old or above.

I understand that once my data has been incorporated with others, it might not be possible for it to be withdrawn, though every attempt will be made to extract my data, up to the point of publication.

I understand that my name will not be revealed in any published material concerning this study.

I agree that my data can be used in reports, publications, conferences, and training events,

I agree that my data can be used for further research in future. YES/NO*

Please delete as appropriate. Please note that participants may say 'NO' to this question and still take part in the study. I understand that I can leave the study at any time for any reason, and I will still receive support and care for my condition.

I have received enough information about the study in a language I understand. I have had the opportunity to discuss it and ask questions, and those questions have been answered to my satisfaction.

I agree to take part in the study.

Printed Name & Signature (or fingerprint) Date

Name of Patient _____

Signature/Fingerprint _____ _____/_____/20____

Name of Witness _____

Signature/ Fingerprint _____ _____/_____/20____

Name of Researcher_____

6.3 Appendix 3: Data collection form

Case / Patient record form (CRF)

A. Demographic data

1. Patient ID (study number): ……..
2. Randomization number: ……..
3. Group: Intervention / Control
4. Age: …….. In years
5. Gender: Male / Female / Third gender
6. Village/Area name: ……..
7. Block: ……
8. Residence: Rural / Urban
9. Height in cm: ……
10. Weight in kilograms: ……..
11. Education level (number of years of education completed): ……..
12. Employment: Farming / Employed / self-employed or own business / labourer / student / house wife / unemployed / unable to work due to disability
13. Family Income per month in INR: ……..
14. Marital status: Single / Married / divorced / widowed

B. Clinical data

Leprosy only

15. Duration of leprosy in months: ……
16. Sensory loss (unable to feel 10 grams of monofilament): Yes / No
17. Sensory loss: Right / Left / Both
18. Duration of foot impairment in months: ……
19. EHF score (for leprosy only): …… Foot (EHF) score: ……..

Diabetes only

20. Type of diabetes: Type I / Type II
21. Duration of diabetes in months: ……..
22. Glycaemic control: ……..
23. Dorsalis Pedis Pulse: ……

Limb details *(information about the foot in which the index ulcer is present)*

24. History of previous ulceration: Yes / No
25. History of previous amputation (minor such as toe): Yes / No
26. Sub-talar alignment: Neutral / Supinated / Pronated
27. Claw toes: Yes / No

Ulcer details

28. Number of active ulcers:
29. Location of index ulcer: right foot / left foot
30. Site of the index ulcer: fore foot / mid foot / heel
31. Ulcer recurrence: First / second / third / fourth / fifth / more than five times
32. Duration of the Index ulcer in months: ……..
33. Presence of infection in the index ulcer: Present / Absent
34. Exudate in the index ulcer: None / Mild / Moderate / Copious
35. Photograph taken: Yes / No
36. Ulcer metrics - baseline: Length in cm: …….
37. Ulcer metrics – baseline: Width in cm: …….
38. Co-morbidities: Yes / No If Yes, specify: …….

Pedometer recordings:

Variable	1st week	2nd week	3rd week	4th week	5th week	6th week	7th week	8th week
Date								
Pedo. – 1 (Off-loading device)								
Pedo. – 2 (in hand)								

Follow-up assessment

39. Ulcer metrics during follow-up:

	At 2nd week	At 4th week	At 6th week	At 8th week Or At complete healing of ulcer
Date				
Photograph taken	Y/N	Y/N	Y/N	Y/N
Length in cm				
Width in cm				
Adverse events related to ulcer	Y/N	Y/N	Y/N	Y/N
If yes, specify				
Adverse events related to device	Y/N	Y/N	Y/N	Y/N
If yes, specify				

User satisfaction with off-loading devices

(at completion of 8 weeks or complete healing of ulcer)

Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0

1	2	3	4	5
not satisfied at all	not very satisfied	more or less satisfied	quite satisfied	very satisfied

ASSISTIVE DEVICE ***How satisfied are you with,***	
1. the **dimension**s (size, height, length, width) of your assistive device? *Comments*:	1 2 3 4 5
2. the **weight** of your assistive device? *Comments*:	1 2 3 4 5
3. the **ease in adjusting** (fixing, fastening) the parts of your assistive device? *Comments*:	1 2 3 4 5
4. how **safe and secure** your assistive device is? *Comments*:	1 2 3 4 5
5. the **durability** (endurance, resistance to wear) of your assistive device? *Comments*:	1 2 3 4 5
6. how **easy** it is to use your assistive device? *Comments*:	1 2 3 4 5
7. how **comfortable** your assistive device is? *Comments*:	1 2 3 4 5
8. how **effective** your assistive device is (the degree to which your device meets your needs)? *Comments*:	1 2 3 4 5

6.4 Appendix 4: Qualitative interview guide

After explaining the purpose of the walking interview and informed consent open ended questions will be asked to explore their lived experiences of using the off-loading device and facilitators and barriers to use of such devices.

The walking route will be no more than in and around the home or other place where participant performs daily routine activities.

- What is your experience on using this off-loading device?
- What made you to wear this device continuously (at least while walking)
    - Explain all reasons that made you to wear this device.
- What are the difficulties that you faced while using this device?
    - Explain the individual difficulties you faced
- How easy or difficult for you to do your essential routine activities with device on
- Would you suggest any modifications to improve the effectiveness of the device to heal ulcer at the same time improve adherence to it

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