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

PROTOCOL

Honey Experiment on LeProsy Ulcer (HELP): A Randomised Control Trial of Raw, Unadulterated African Honey for Ulcer Healing in Leprosy

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Contents

1. Study Summary

Background: The germ that causes leprosy can be killed by antibiotics. However, local nerve damage leads to repeated injury and hence recurring and disfiguring ulcers. As a result, patients (and their families) face stigma, social isolation and catastrophic costs.

Our full programme of work under the NIHR Research and Innovation for Global Health Transformation (RIGHT) grant covers:

1) Long-term care and prevention of leprosy ulcers in the community (India, Nepal and Nigeria).

2) A study of patients with a disease called Buruli ulcer (Nigeria only).

3) A clinical trial of ulcer treatment (Nepal only)

4) Sustainability of self-help groups after funding ceases (India, Nepal and Nigeria).

5) Creating a community of applied researchers in leprosy and Buruli ulcer.

This particular protocol is concerned with treatment of leprosy ulcers that are sufficiently severe to require hospital admission. It will take place in Chanchaga leprosy rehabilitation hospital, Minna, Niger state, Nigeria.

Aim: To evaluate the healing properties of raw, undiluted African honey in comparison with Normal saline dressing of leprosy ulcers.

Design: Single centre, comparative, prospective, single blinded, parallel group, 1:1 individually randomised controlled trial.

Participants: Adults admitted to hospital with leprosy ulcer in the range 2-20 cm^2.

Intervention: Raw, undiluted African honey. Controls get dressing change with normal saline.

Main Outcomes: Rate of healing. Percentage wounds healed (re-epithelialization) by up to 84 days.

Sample size: One hundred and thirty consenting participants.

Follow-up: Six months from randomisation.

2. Introduction

2.1. Background

As in diabetes, ulcers in leprosy result from nerve damage and the resulting loss of sensation. Neuropathy in leprosy is caused primarily by inflammatory episodes 'reactions', which occur in 30-50% of leprosy cases in response to live Mycobacterium leprae or persistent cell wall antigens in skin and nerve tissues[1]. Neuritis can develop at any time before, during or even years after leprosy treatment. The combination of loss of sensation and deformities leads to recurrent ulcers and these often present when they are advanced. People afflicted with recurrent ulcers suffer severe consequences in terms of loss of function, loss of earnings and stigma, frequently becoming chronically depressed and withdrawn. This protocol concerns the evaluation of a promising intervention to promote healing for leprosy ulcers.

Leprosy ulcers heal slowly, partly because they are large and/or deep when they present and possibly because the tissues have reduced blood supply due to damage to autonomic nerves. Furthermore, weight bearing and physical activity are often adversely associated with healing rates of plantar ulcers[2] but resting to prevent or heal an ulcer is impractical for many affected people who need to work to earn their living. Improved methods to promote healing are needed in leprosy and the findings would be relevant to other ulcerative conditions, particularly diabetes, where ulcers also result from peripheral nerve damage leading to repeated injury. Recent Cochrane reviews called for higher quality research on ulcer treatment and prevention in leprosy, specifically advocating for randomised controlled trials (RCTs), 'blinding' of outcome measurement and appropriate sample size[3].

2.2. Evidence Before the Study and Need for Trial

The use of honey as a therapeutic agent in treatment of wounds is an ancient practice with the earliest documented report recorded in Edwin Smith papyrus (2600 – 2200 BCE)[4]. Honey is a viscous, supersaturated solution containing sugars, water, amino acids, vitamins, minerals, enzymes, and many other substances which are derived from nectar gathered and modified by honeybee, *Apis mellifera*[5,6]. Studies have shown that honey promotes wound healing, stimulates tissue growth, facilitates debridement and epithelisation, deodourises, reduces oedema and exudates, and possess antimicrobial properties[4,7,8].

In recent times, there is a resurgence of interest in the use of honey for treatment of different kinds of wound as researchers continue to search for improved, cost effective agents of wound healing[6,9]. Several studies have highlighted the importance of honey in wound healing, but have not provided sufficient evidence for the usage of honey in clinical practice. For example, a Cochrane review have reported several studies with unclear outcomes for trials with honey on venous leg ulcers, diabetic foot ulcers, and mixed chronic wounds. Most of the reported studies were considered to be of low quality due to reasons such as imprecision, high risk of bias, and inconsistency. The review suggested high risk of bias in the reports due to non-blinding of study participants and healthcare professionals, and statistical heterogeneity was evident across studies[6].

Although there is sizeable number of reports that shows mixed levels of effectiveness in the use of honey as a topical agent for treatment of different types of wounds, our search through various internet sources revealed a dearth of reports on the use of honey in the treatment of ulcers in leprosy. The main concern

about the use of honey is with regards to the transmission of *Clostridium botulinum* infection. This concern will be addressed as discussed in Section 3.2.4.

2.3. The local site and expertise

The Chanchanga Leprosy Hospital in Minna, Nigeria is a specialist hospital operated by the government of Niger state in collaboration with The Leprosy Mission Nigeria. The hospital was established in 1940 and has two wards, eye and physiotherapy units, theater, laboratory, and dispensary. The hospital is supported by an orthopaedic workshop which is built and managed by The Leprosy Mission Nigeria, which produces assistive devices including wheelchairs, crutches, protective sandals and artificial legs.

A doctor, physiotherapists, and nurses manage leprosy patients in the hospital, including those with severe ulcers. The regular practice for patients with chronic ulcers is soaking of the wounds, cleaning, and dressing with normal saline. Honey is readily available and has been used in some instances, but the usage did not follow any standardized guide and the outcomes were not documented.

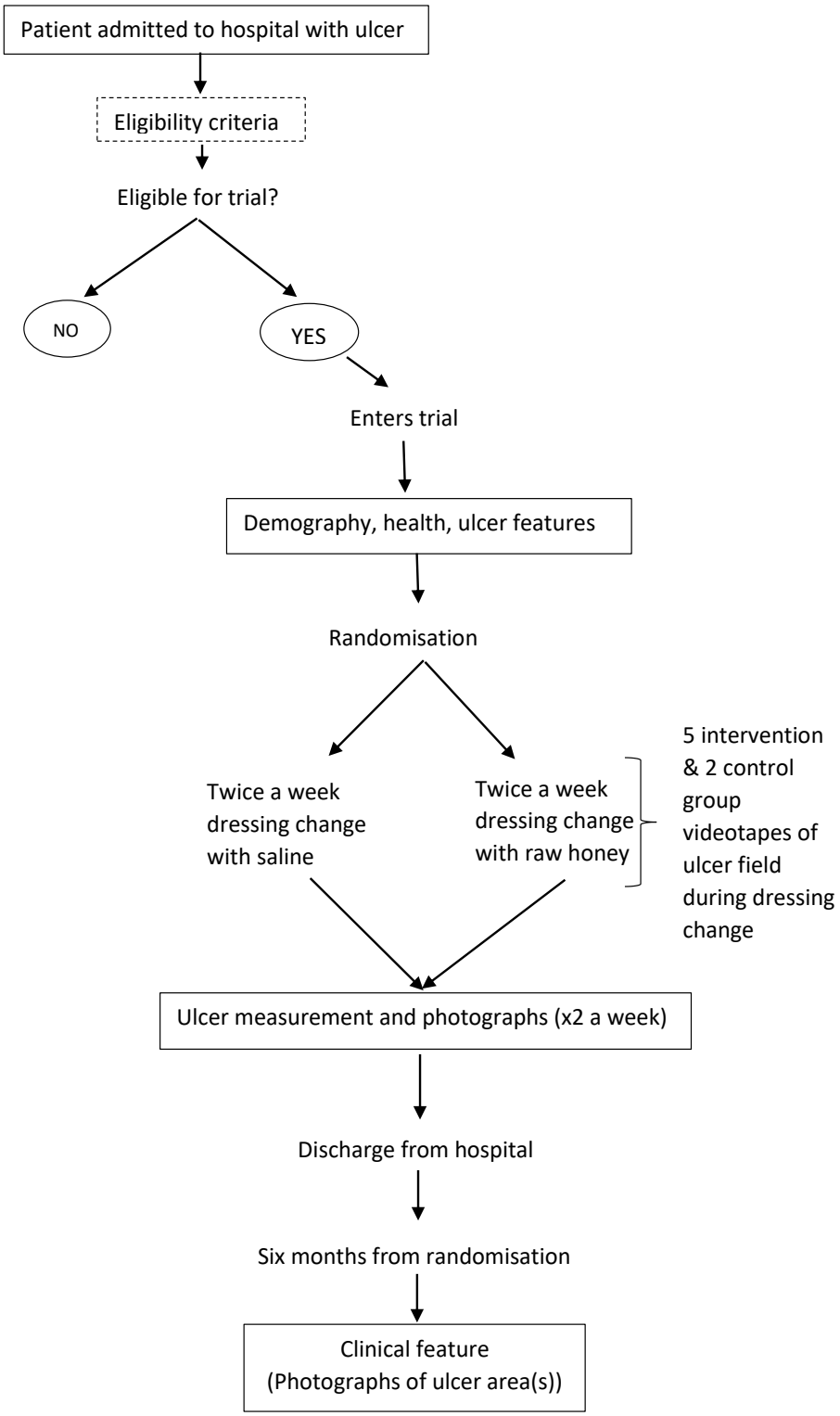
3. Study Design, Methodology, and Analysis

3.1. Research aim

To evaluate the healing properties of raw, undiluted African honey in comparison with normal saline dressing of leprosy ulcers.

3.2. Study design and data collection method (Figure 1)

Fig. 1. Summary of study pathway


Patient admitted to hospital with ulcer
Eligibility criteria
Eligible for trial?
NO
YES
Enters trial
Demography, health, ulcer features
Randomisation
Twice a week dressing change with saline
Twice a week dressing change with raw honey
5 intervention & 2 control group videotapes of ulcer field during dressing change
Ulcer measurement and photographs (x2 a week)
Discharge from hospital
Six months from randomisation
Clinical feature (Photographs of ulcer area(s))

3.2.1. Study setting

The Leprosy Rehabilitation Hospital, Chanchaga, Minna, Niger state. The main study will be preceded by pre-study diligence.

Pre-study diligence

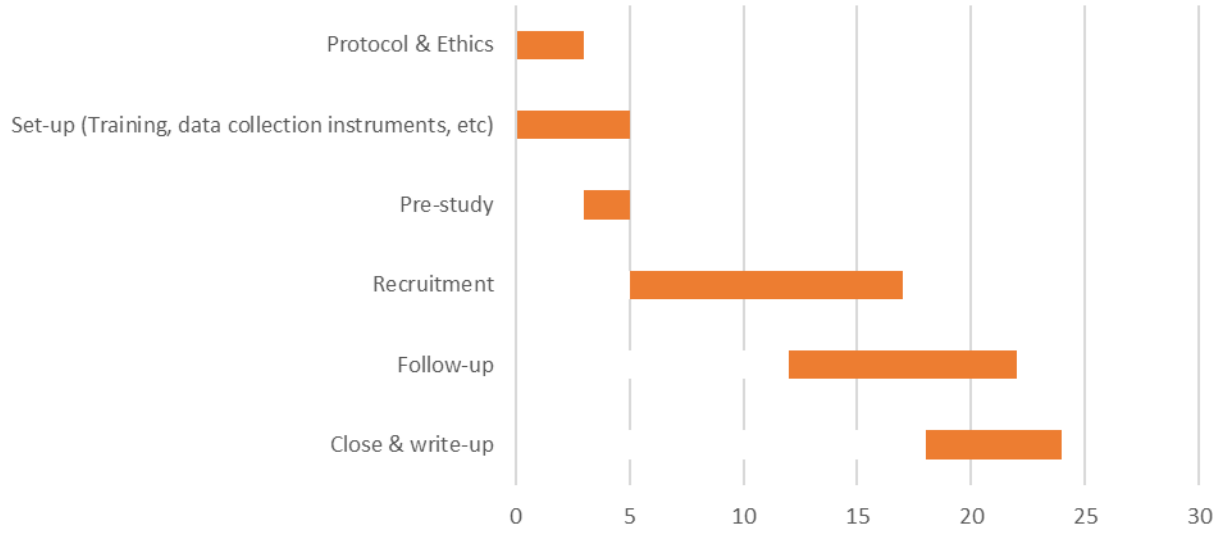
3.2.2. Study design

To ensure proper blinding of the trial, the study will begin with an initial phase where 5 participants will receive honey dressing. A video recording of the first dressing change will be sent to 3 independent assessors. An uninterrupted video-recording will be made from before the dressing is removed until after it has been replaced. Assesors will be asked to reject any inadequate recordings. The independent assessors will be experts in leprosy and diabetes ulcer from Nepal and India.

The assessors will be required to look out for traces of honey residues that might interfere with blind assessment during the second phase of the study. They will also examine for any evidence that removal of honey residue may disrupt delicate healing tissue. If the assessors are able to find traces of honey after the first dressing change, we will consider alternating honey and saline dressings and making weekly observations rather than bi-weekly observations. The second phase which involves randomisation will commence once the independent assessors are satisfied that the dressing change will not leave residues of honey that can be traceable by the blind assessors.

A single centre, prospective, single-'blinded', parallel group, 1:1 individually randomised controlled trial. Study duration is 24 months (maximum) with recruitment starting at month 5 and post-discharge follow-up starting at month 11. The timeline for the trial is shown in Figure 2. We plan to recruit 7-8 patients per month.

Figure 2: Timeline (in Months) for HELP trial (based on most pessimistic estimates)



3.2.3. Eligibility and invitation to participate

The local medically qualified researchers employed on the grant will screen all ulcer admissions. The researchers will complete online eligibility forms in respect of each patient with an ulcer. Consent will be sought by the research fellow from consecutive patients ≥18 years with a foot / leg ulcer of between 2 and 20cm^2 and not requiring surgery (e.g. skin graft). The inclusion criteria are as follows:

1. Patients with a chronic foot ulcer of at least 6 weeks duration due to leprosy neuropathy.
2. ≥18 years of age.
3. Ulcer surface area between 2 and 20 cm^2 inclusive.
4. Ulcer is clean, dry, and free from infection.
5. Patient can provide informed consent.

The wound dressing protocol for HELP study is in Appendix 1.

In the uncommon scenario where a participant has more than one foot ulcer the largest ulcer will be selected as the index ulcer before randomisation, and all ulcers will receive the same treatment (for example, if the participant is in the intervention group all ulcers – not just the one being monitored for the trial – will be treated with honey). Observations will be made on all ulcers but only the largest ulcer will be used in the primary analysis (please see discussion). Eligible patients will be offered entry in the trial at the point where their senior clinician judges them to be suitable for the honey treatment. This point arises once the lesion has been cleared of any debris or infection, typically by 7-10 days after beginning treatment with or without antibiotic and/or debridement.

Swabs are taken as a routine, but the interpretation of those swabs is under the control of the clinician. We shall record the result of the (trial) swab taken before randomisation.

3.2.4. The intervention

Raw, unadulterated honey will be sourced from local bee farmers and used as the intervention for this study. The honey samples will be taken to the National Biotechnology Development Institute (NABDA), Abuja for confirmation and microbilogical assessment. The microbial assessment will check for the presence of any microbial contaminant including Clostridial spores. Storage of the honey samples will be done in air tight plastic containers at room temperature, and away from direct sunlight. The honey will be applied topically to the wound during dressing under strict hygienic conditions using sterilized tools and equipment.

In extremely rare cases, honey has been found to be the source of infection with *Clostridium botulinum,* an anaerobic, spore-forming bacteria that releases neurotoxins leading to nerve damage, a disease condition known as botulism. The microbiological assessment will ensure that the honey used in this study is free from *Clostridium* spores. Remarkably, honey has been reported to have unique pH balance that promotes oxygen and inhibits several microbial pathogens.

The treatment will be applied at the time of twice weekly changes of dressings by local trained nurses or paramedics. These dressing changes are part of routine care and will thus apply to the intervention and

control groups. There is no pain from the procedure but dressing changes may take slightly longer for participants in the intervention group. Participants in both groups have twice weekly dressing changes during their hospital stay until ulcers are healed. Any missed sessions will be noted but this will not be treated as a protocol deviation.

3.2.5. The control

The participants in the control group will receive usual care of twice-weekly normal saline dressings only. The clinical care of these participants will otherwise be identical to the intervention participants.

3.2.6. Blinding

Only the North-central Nigerian research team, the database managers in Birmingham, the clinical staff carrying out dressing changes in the room designated for this purpose and participants themselves will be aware of participants' randomly assigned group. Ward staff will not be informed. The assessors in Birmingham will be blinded from the treatment provided for randomly assigned groups.

3.2.7. Activity Measurement

All participants will be invited to wear a pedometer (Model: Mi Smart Band 5, Model: XMSH10HM) on the ankle of their non-affected limb (or non-index case affected limb) which they will wear from the first dressing change until 84 days (the point where cross-over may occur) or discharge, whichever comes first. This will act as a proxy measure of weight bearing and enable us to monitor activity across intervention and control groups and thereby evaluate whether the level of activity is similar across groups.

3.2.8. Baseline data collection

All data will be collected on electronic CRFs using tablets. This will include anonymous data on all patients invited to participate. All electronic case forms (including range and logic checks), photographs, eligibility forms, notices of withdrawal, and notifications of serious adverse events will be available through a menu on the tablet. Details of software and encryption are described in Section 5. The number of people invited will be recorded by research fellows employed in the study but no details or names will be recorded.

Once a person has been consented to participate in the trial (see sections 4.2, 4.3 and 4.4) baseline data will be collected. This will precede randomisation.

Data will be collected onto electronic tablets and the computer program will range check information (see also section 5). Photographs of ulcer will be captured using the methods described in Section 3.2.10. Each participant will be allocated a unique trial number which will be included in all data entry forms and linked to photographs. Level of activity (step count) will be collected daily and monitored across both intervention and control groups until 42 days (the point where cross-over may occur) or discharge, whichever comes first – see analysis below.

3.2.9. End-points

We define two main outcomes relating to ulcer healing, where "healing" is defined as the complete re-epithelialization of the index ulcer. The main end-points will be:

1) Rate of healing based on one observation per week.

2) Time to complete re-epithelisation (up to 84 days).

Secondary end-points:

3) Long-term (6 month) end-points will be:

I. Recurrence of treated ulcer;

II. Appearance of a new ulcer;

III. Anatomical changes in the limb;

Long-term endpoints will be measured at the time of follow up at 6 months from randomisation.

1) Days hospitalised prior to discharge and total (to include any readmission related to leprosy-ulcers) by 6 months.

2) Number of visits to any healthcare facility from discharge to the end of follow-up at 6 months.

Inferences in this study are not based on a null hypothesis significance testing framework, and any conclusions about treatment effectiveness will not be based on "statistical significance", but on a triangulation of available evidence and a consideration of estimated effect sizes across related outcomes. This reflects the appropriate use of p-values as a means of assessing the signal-to-noise rather than to make decisions about whether a treatment is effective, reflected in recent documents such as the ASA's Statement on p-values[10]. For example, we would not declare the trial results null overall if the p-value of proportion healed was non-significantly in favour of the intervention and the rate of healing was significantly in favour of the intervention. Note also that both rate of healing and complete healing (re-epithelialization) are assessed from 'blindly' examined photographs. However, complete healing is also a clinical outcome that a) is not necessarily 'blind' to allocations and b) that might conceivably be a trigger for discharge. We will therefore be alert to any cases discharged before the 'blind' assessor has 'noted complete re-epithelization, and, more specially, the unexpected but not impossible finding of a difference in the population of such cases between groups (see also 6.5).

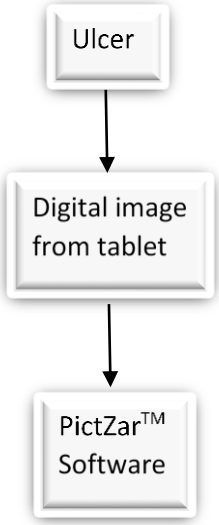
3.2.10. End-point data collection

3.2.10.1. Ulcer measurement

Standardised photographs[11] will be taken twice weekly during in-patient stay dressing changes for participants in both intervention and control groups. Any residual honey will be gently removed with a wet swab.. The photographs will be transferred to the University of Birmingham and the ulcer dimensions measured in (see below). Two observers will be trained to take these measurements. Both observers will be 'blinded' to the treatment allocated to the participant. All photographs from a given participant will be assigned to the observers at random. So that the measurements are not all relegated to the end of the study, they will be made in batches of ten participants reaching completion of their treatments , whichever occurs first. A proportion (20%) of all ulcer photographs will be measured by both assessors to estimate inter-rater reliability. These photographs will be selected at random.

The date at which complete re-epithelisation takes place will be determined by the local clinician. Photographs will be taken at the point of complete re-epithelialization and at the follow up visit.

Figure 3: Ulcer capture and measurement process

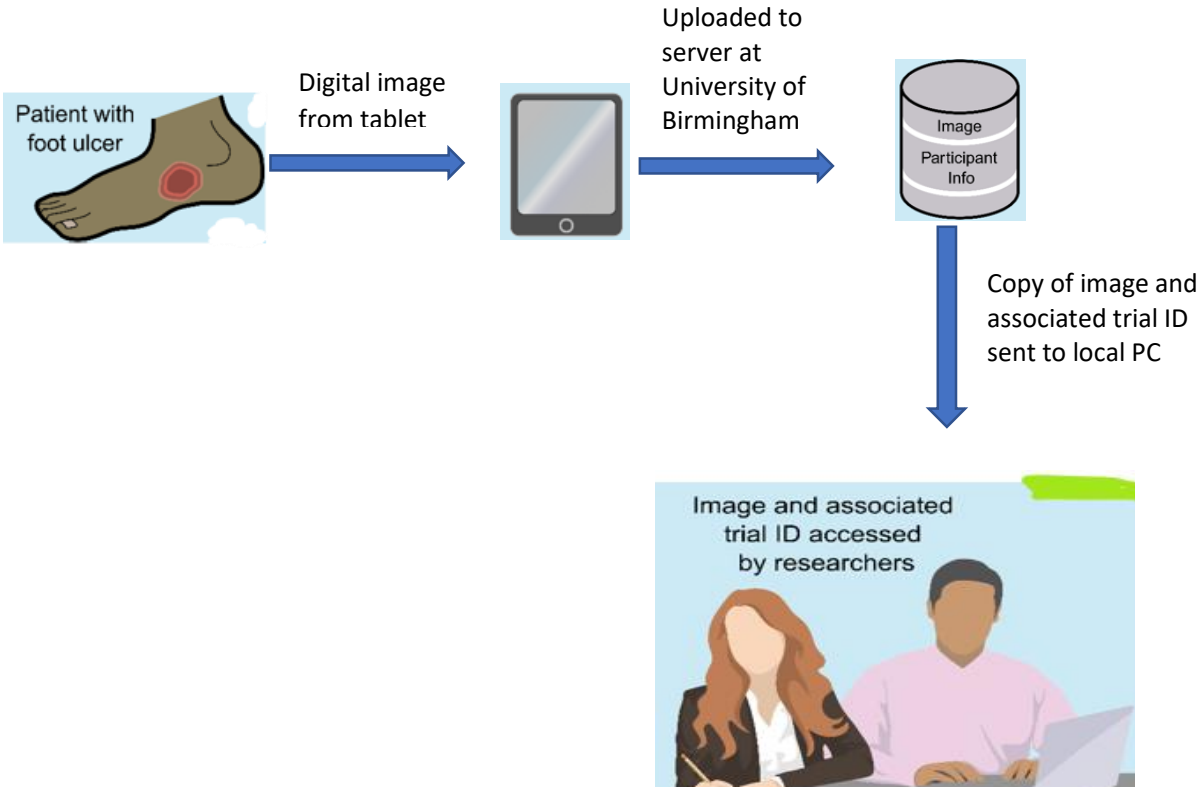


Digital Tablet

All measurements will use a photograph taken using the in-built camera in the tablet devices (Samsung Galaxy Tab S7). The photographs will be taken perpendicular to the ulcer. For calibration purposes, a 3cm size clean paper ruler with date and participant's trial identification number will be placed in the photograph frame above or below the ulcer but at the level of the skin. The photograph will be evaluated digitally by the designated observer in Birmingham using the PictZar™ Digital Planimetry Software[12] with an electronic PUSH Tool (National Pressure Injury Advisory Panel (NPIAP) at https://npiap.com/page/PUSHTool). The observer will delineate an area of interest by manually 'painting' the ulcer area with colour using a computer mouse. The software will then calculate the ulcer dimensions based on this profile.

All observations will be made 'blind' to treatment allocation. The 'closed loop' ulcer assessment process is shown in Figure 4. The changes in surface area can then be determined between each observation using three methods of assessment (Figure 4). Where an index ulcer heals into multiple smaller ulcers, the surface area of all ulcers within the original index ulcer site will be recorded in cm^2.

Figure 4: Ulcer assessment process



Photographic data are collected at each dressing change – twice per week. The research fellow will record data at each of these dressing changes by completing a form on the electronic tablet. The type of treatment administered (i.e. intervention or control) will be recorded so that adherence to allocated treatment can be observed. A short clinical form will also be completed at each dressing change to record the clinical appearance of the wound (e.g. any residual exudate or honey noted) and the time taken to complete the dressing change (from the start of opening the wound bandage to the end of re-bandaging).

We shall develop a new method of photograph supervision as a further quality control process. Seven dressing changes (five intervention and two controls selected at random) will be video-taped targeting the ulcer site and the tapes will then be analysed independently (i.e. at University of Birmingham) to include 'stills' taken at the discretion of the independent off-site observer (research fellow), and analysed using the PictZar software analysis method only (see above). This novel method, along with our approach to 'blinded' assessment, is discussed further elsewhere[12]. We shall also take a video of the treatment as it is applied in the intervention arm of the trial in five of these seven cases, for quality assurance purposes. A separate form, available on the tablet will be used to record any adverse event (Section 3.2.12).

The proportion of ulcers healed at up to 84 days is a study end point (see Section 3.2.9). The majority of participants will be discharged at this point. They will either return to hospital for a follow-up appointment, or a home visit will be made by the local research fellow.

3.2.10.2. Activity measurement

Level of activity (step count) will be collected daily (Appendix 2) and monitored across both intervention and control groups up to 84 days .

3.2.10.3. Follow-up

The date of discharge will be noted along with participant contact details, address and contact details for at least one family member. The participants will be routinely contacted every three months post discharge from the hospital. The treated ulcer area will be examined and photographed. The researcher will take photographs of the ulcer area (healed in the majority of cases). The dates covering any re-admissions will be recorded. The photographs will be obtained by the methods described above.

3.2.10.4. Withdrawal and consent

If any patient discontinues participation (see Section 4), then the date and reason will be recorded, using a Trial Withdrawal/Exit Form on the tablet.

As stated, data will be collected directly onto forms resident on electronic tablets. The forms that record clinical data will be recorded in English – clinical demographic data. However, 'patient and participant-facing' forms will be translated into Hausa. Consent forms that we translate will be back-translated by a separate person according to the WHO standard.

Researchers in Nigeria will be trained in obtaining consent as described in section 4.

3.2.11. Concomitant illness and medication

Details of any concomitant illness or medication (present at start of the trial) will be recorded at trial entry (see Section 3.2.6). If the change influences the participant's eligibility to continue in the trial, the local chief investigator will be informed and a decision to continue with the intervention will be made in the participant's best interest (please see also Withdrawals – Section 4.5).

3.2.12. Safety report/adverse event

An adverse event is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with the treatment.

We will follow the Birmingham Clinical Trials Unit (BCTU) Standard Operating Procedure on safety reporting and adverse events. Dr Sunday Udo who will lead the trial in North-central Nigeria and will be responsible for recording all Adverse Events (AEs) and reporting any Serious Adverse Events (SAEs) to the the University of Birmingham within 24 hours of the research staff becoming aware of the event. A SAE Form will be available on the tablets used to collect data and we will maintain a database of all safety / adverse events. The forms will be reviewed by the Trial Management Group which meets monthly and if required, also by the Project Manager. The Trial Steering Committee will periodically review all safety data and liaise with the Independent Data Monitoring Committee regarding any safety issues.

Any deaths will be reported to the Sponsor irrespective of whether the death is related to the disease progression, the intervention or an unrelated event. Only deaths that could plausibly be caused by the intervention will be reported to the Sponsor immediately.

3.2.13. End of trial

The end of trial will be 6 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The trial will be stopped prematurely if:

1. Mandated by the Ethics Committees.
2. Following recommendations from the Independent Data Monitoring Committee.
3. Funding for the trial ceases.

The Research Ethics Committees will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early. The Research Ethics Committee will be provided with a summary of the clinical trial report within 12 months of the end of trial. A copy of the End of Trial Notification as well as the summary report will also be sent to the sponsor.

3.2.14. Randomisation

Participants will be enrolled sequentially and randomly allocated (1:1) to undergo honey treatment or usual care with normal saline using a "digital sealed envelope" method[13]. An allocation table will be generated remotely by the trial statistician at The University of Birmingham to allocate participants in a 1:1 ratio at the level of the individual over the course of the trial. A random number generator will be used to generate a random sequence of the numbers between 1 to N inclusive. A permuted block randomisation method will be used by randomly selecting blocks of size 2, 4, 6, or 8 in order to maintain balance between the numbers allocated to each of the two groups. 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 Nigeria 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 randomised group that the participant is assigned to cannot be altered.

3.2.15. Pre-specified sub-group

We will collect demographical and clinical information. After careful consideration, we have decided not to pre-stratify (see 3.2.14).

3.2.16. Planned analyses and reporting of results

Data will be collected on tablets using REDCap by local fieldworkers. Ulcer dimensions obtained off-site (i.e. in Birmingham) will be used to derive the outcomes in the primary analyses (see below).

3.2.16.1. Time to healing

Time to healing will be analysed using a Cox proportional hazards model with and without adjustment for baseline characteristics (trial ulcer area and participants' age) allowing for right-censoring. For the rate of healing we will define the outcome ulcer size in cm2 at each time point and include in the model time

since admission, treatment status, and their interaction. We will analyse this model using a linear mixed-effects model with participant-level random effects and both with and without adjustment for participant characteristics. Given there are multiple primary outcomes (two outcomes, with and without adjustment, for three types of ulcer assessment) we will adjust reported p-values for multiple testing using a stepdown method, which provides an efficient means of controlling the family-wise error rate[14]. We will derive the approximate distributions of the test statistics to perform the stepdown procedure using a permutation test approach, by simulating 10,000 re-randomisations of the individuals[15].

3.2.16.2. Measurements

Measurements are based on the tablet based cameras (see Figure 3The images are calibrated digitally by reference to a measurement ruler in the frame. The areas (cm^2) are then generated within the software package.

We will pre-specify only one sub-group analysis based on ulcer size (cm^2) at baseline above or below the median value at baseline.

We will measure inter-rater agreement where appropriate (interclass correlation coefficients) and will describe variance within and between methods. In the (extremely unlikely) event that some participants go home before complete healing according to the blind assessor and that rate differs between groups, a sensitivity analysis would be applied to this end-point.

One formal interim analysis is planned (see withdrawal and interim analysis, Section 4.5).

We will analyse by intention to treat. In the event that more than 10% of control participants cross-over from one arm to another, we will consider performing a complier average causal effects analysis to the 84 day outcome. If participants withdraw from the intervention, data will still be collected and analysed providing the participant agrees (see Section 4.5).

3.2.16.3. Activity measurement

We will also compare average daily step count between treatment and control groups as a simple difference in means (t-test). Since one group may stay longer in hospital than the other and since there may be an interaction between rate of healing and step count, we will compare step counts over periods pre-set at 7, 14 and 42 days.

3.2.16.4. Reporting

The trial will be reported in line with the CONSORT (Consolidated Standards of Reporting Trials) Standards[16, 17].

3.2.17. Sample size

Sample size is based on the two primary outcomes: rate of healing and time to complete re-epithelialization. We expect at least 70% of ulcers to heal within 84 days with standard care (according to a recent study of neuropathic ulcers, over half due to leprosy[18]. Further, assuming that the intervention will increase this proportion to 90% and hazards are constant and proportional, for a two-sided test of the hazard ratio with a type I error of 5% and statistical power of 80% and a 1:1 allocation ratio, 40 individuals are required in each group. Patients tend to stay in hospital until ulcers are healed but we aim for 50 participants per group to allow for a small number of drop-outs. We will, of course, have much greater precision in comparing the rate of healing since this outcome is on a continuous scale and measured

repeatedly. We take a conservative approach and base the sample size calculation on the main outcome and model with lower efficiency to ensure an adequate sample size for all main outcomes since our inferential approach is not based on statistical significance but on a consideration of effect sizes and a comparison and triangulation of the totality of evidence. We are not concerned particularly of being "overpowered" or of a problem of multiple comparisons, but on ensuring a sufficient sample size to estimate clinical effectiveness to a reasonable degree of precision.

4. Ethics and Informed Consent

4.1. Summary

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) Guidelines. It will also comply with all applicable UK legislation and Standard Operating Procedures for University of Birmingham Sponsored Studies.

All data will be stored securely and held in accordance with General Data Protection Regulations 2018 (GDPR) and the Data Protection Act 2018. Ethical approval in Nigeria will be gained in-line with the National Health Research Ethics Committee Act.

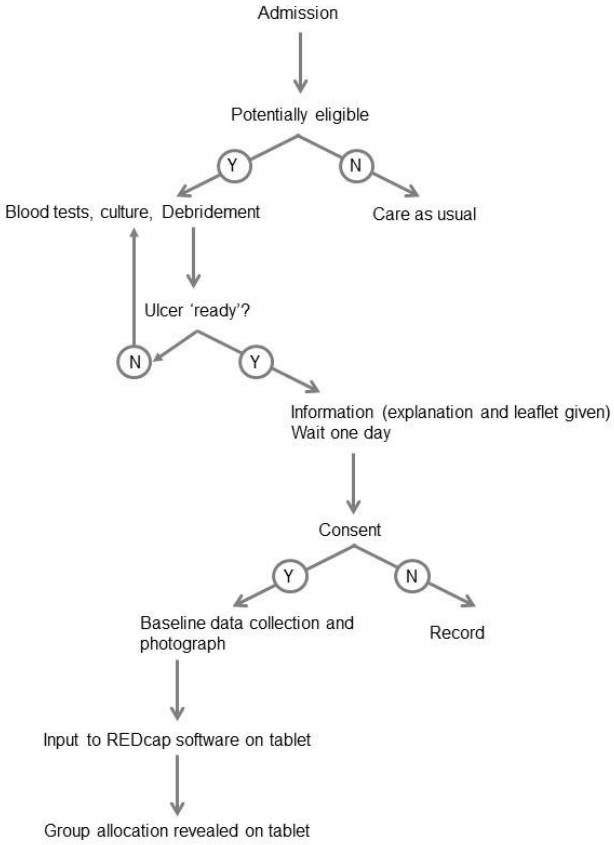
The trial will not over-ride the obligations of clinicians to provide optimal care for their patients. Clinical equipoise applies to the honey treatment for reasons stated above. A single interim analysis will be carried out (as described in Section 4.5). If the treatment is found to be effective (as described in Section 4.5) then the trial will be stopped. At this point control participants will be offered the honey treatment as will new patients admitted with ulcers.

Participants in the control group will be offered the intervention treatment if their ulcer remains unhealed. We will establish an Independent Data Monitoring Committee (IDMC) to oversee safety and efficacy data, which will meet at a set-point during the recruitment phase of the trial (see below).

4.2. When will consent be obtained?

A local researcher will screen all admissions to the facility for eligibility. Eligible patients will be given a Participant Information Leaflet (Appendix 3) to read and consent will be sought after the day when this is provided via the Consent Form (Appendix 4), once eligibility has been confirmed by the researchers and Principal Investigator. This sequence is represented in Figure 5.

Figure 5. Representation of enrolment and consent process



The Participant Information Leaflet and Consent Form will be translated into Hausa and back translated according to the WHO methodology as stated above[18].

4.3. Who will take consent?

One of the local clinically-trained researchers deployed on the grant will offer the patient participation in the trial. The researchers will all complete GCP training online and will be included in the delegation log. They will be trained to obtain consent as follows:

1) They will attend a 30 minute talk given by the chief investigators covering the essence of the Helsinki recommendations (1964 and revisions)[19] and the right to withdraw at any stage.

2) They will then discuss the issues concerned with the chief investigators and also at least two representatives drawn from the leprosy community.

3) They will then simulate the consent process at least twice where public representatives of the Trial Steering Committee will act as patient 'surrogates'.

4.4. How will consent be obtained?

The forms will be read aloud to people who are non-literate. If they are unable to sign their name using a writing instrument then they will sign consent by thumb print (or finger print 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 and on the delegation log.

4.5. Withdrawal, interim analysis and cross-over

Participants are free to withdraw at any time and clinicians must act in each participant's best interest. The participant may withdraw in two ways:

1. Withdraws from the randomised intervention but continues to be followed-up.
2. Withdraws from the trial as a whole (no further follow-up data collected).

There will be a notice of withdrawal form on the data collection tablet. This will record the participant preference as above, along with any cross over e.g. a control participant who receives the intervention.

An interim analysis will be conducted when at least 49 (three eights of the target) have been followed up for a minimum of 42 days. The rationale for this analysis is the detection of a 'penicillin like' benefit or statistically significant negative effect of the treatment on either primary outcome. The statistical methods will be as specified above. A statistical threshold of 0.01, one-sided, (0.02 two-sided) will be used for either primary outcome. If either threshold is exceeded, or if the Independent Data Monitoring Committee (IDMC) has other concerns, then the Trial Steering Committee will be advised accordingly (see Independent Data Monitoring Committee below). If the IDMC wishes to meet again before trial conclusion they will be able to do so. Only the trial statistician and the Independent Data Monitoring Committee will see the 'unblinded' data, unless the Trial Steering Committee are informed.

If the trial is stopped early for a large benefit by the Trial Steering Committee, then any participants currently in the control group and with unhealed ulcers will be offered the honey treatment. Likewise, when the trial is complete, any participants in the control arm with unhealed ulcers will be offered the honey treatment if this is efficacious. New patients will be offered honey treatment since this is in line with the rationale for the trial. If a control participant has withdrawn from the study, then like any other patient, they will be eligible for honey treatment.

4.6. Protocol amendment

Any protocol amendment will be reported to the Trial Management Committee to approve the change. The amendment will be sent to the sponsor to confirm substantiality and then to REC for approval. This will be reported to NHREC as well.

4.7. Indemnity

The Leprosy Mission Nigeria is pursuing a non-negligence insurance for the study in Nigeria. The insurance process will be finalized before the study begins.

4.8. Sponsor

The Leprosy Mission Nigeria, a legal entity in Nigeria will act as the sponsor for this study.

5. Data Collection, Use and Storage

We will adhere to international standards on conducting health research[20]. We will ensure that the communities taking part in this research are also those who will see the benefits, and that the rights and wellbeing of participants are protected. We will obtain ethical approval for all studies carried out in this research programme in both the UK (University of Birmingham's Science, Technology, Engineering and Mathematics (STEM) ethics committee) [https://intranet.birmingham.ac.uk/it/documents/public/Information-Security-Policy.pdf] and the National Health Research Ethics Committee in Nigeria www.nhrec.net

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 and University of Birmingham research staff will be trained to collect data directly onto electronic tablets (section 3.2.8). Data will be acquired and stored on the REDCap platform with access restricted by passwords at both the University of Birmingham and the local site in Nigeria. Each participant will be allocated a unique study number when they agree to participate (and before randomisation), which will be used on all documents. A master list linking a trial participant number to their identity (name) will be retained by the hospital securely in a locked filing cabinet. This is necessary so that the notes of any person who withdraws consent for data storage can be removed. The trial participant master list will be stored separately from patient lists and the trial data. In summary, we will collect data as outlined in Table 1. 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. Baseline data from the first ten participants will be cross-checked by the local lead investigator to assure that full and accurate data are collected. Please see also Section 3.2.10 and 3.2.16.

Table 1: Data sources and time points for data collection

Data type[+]	When	Comment
Baseline data	Following consent. Dated.	Initiates the electronic Case Report Form (CRF). Unique number allocated.
Ulcer photographs	Standardised methods	Photographs captured by tablets and included in CRF of participant
Randomisation	Post consent, post base-line, data collection	Update CRF with allocated group, i.e. the group allocation

		is now added – intervention or control.
Ulcer healing parameters	Photographs taken at each dressing change.	Analysed by observers 'blind' to treatment allocation at University of Birmingham using PictZar then entered and CRF updated.
Video tape	Video tapes of 7 cases	Analysed in Nigeria and results transferred to Birmingham. Analysed at University of Birmingham and CRF updated.
Appearance of ulcer	Dressing change, 2x per week	Update CRF.
Activity	Pedometer readings collected daily and the total recorded at each dressing change and at the end of inpatient stay on the discharge form.	CRF Step counts compared over periods pre-set at 7, 14 and 42 days.
Discharge	Ulcer status (usually 'healed').	Include 'comments' section.
Post discharge follow-up	6 months post randomisation	Completed by local researcher.
Withdrawal from study form	Clinical features at time. Reason for withdrawal.	Special form to update CRF.
Serious Adverse Event	Recorded on appropriate form	Dr Sunday Udo informed and reports to Project Manager and Sponsor.

[+]All dated

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 Nigeria 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 University of Birmingham. Videos too large to transfer on REDCap and other information classified as reserved or restricted will be downloaded onto a secure hospital computer at the field site in Nigeria, encrypted (using PGP) and transferred to the Birmingham server. Only the trial manager and designated statisticians in the trials unit will have access to the data prior to the primary data analysis. Subsequent studies (e.g. of methodological interest – see 3.2.16) will be carried out and we will encourage Dr Udo and his team to lead or participate in these analyses. We cannot envisage any reason for 'un-blinding' since this study is single 'blinded'.

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 University's research data management policy. During the 10 year post-project period paper data, such as consent forms, will be archived locally in Nigeria in a locked cabinet. Electronic data including photos and videos will be stored in an encrypted archive at the University of Birmingham. All electronic data held locally at the investigator site in Nigeria will be archived for at least 10 years then deleted. Should the investigator site wish to access the electronic data, this will be done through the Birmingham secure file transfer portal.

Full and detailed information relating to data collection, use and storage is included in the data management plan.

6. Trial Organisation and Management

The Leprosy Mission Nigeria is the study sponsor and will oversee the study process in Nigeria. The University of Birmingham will house the data securely and perform quality checks on the data in line with the approved trial Monitoring Plan. A research fellow to the grant will devote 50% effort to the trial and will report to the Chief Investigator.

6.1. Trial management group

The Trial Management Group (TMG) includes individuals at the University of Birmingham and the Leprosy Hospital Chanchaga, The Leprosy Mission Nigeria 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), Principal Investigator in North-central Nigeria (Dr Sunday Udo), Project Manager for overall study and local Project Manager in North-central Nigeria, lead methodologists and patient representatives. The Trial Management Group will meet monthly by teleconference, but this may be more frequent if deemed necessary by the members.

The role of the Trial 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.

6.2. Trial steering committees

The Trial Steering Committee (TSC) provides overall supervision of the trial and will ensure that it is being conducted in accordance with the principles of Good Clinical Practice and other relevant regulations. The Trial Steering Committee will have oversight of the trial. It will send its report to the overall RIGHT programme steering committee, but the Trial Steering Committee will have the final say with the running of the trial itself. The Committee will meet either face to face or via teleconferencing. Meetings will be scheduled for before enrolment and following each meeting of the Independent Data Monitoring Committee and then during the analysis phase or more often if required. Specific tasks of the Trial Steering Committee include:

- Approval and sign-off of the trial protocol and any protocol amendments.
- Resolve any problems brought to it by the research group or study sponsor.
- Provide advice to the researchers on all aspects of the trial.
- Review recruitment, data collection, data completeness and protocol deviations.
- Review recommendations from the Independent Data Monitoring Committee (IDMC), and help with decision-making that follows on from the recommendations of the IDMC.

Members of the Committee are listed at the start of this document.

6.3. Independent data monitoring committee (IDMC)

Safety and efficacy data will be supplied, in strict confidence, for review by the Independent Data Monitoring Committee during the active phase of the trial. The Committee will be asked to give advice on

whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The Committee will meet either face-to-face or by teleconferencing. An emergency may also be convened if a safety issue is identified. The IDMC will escalate any issues and recommendations to the Trial Steering Committee who will make decisions based on these recommendations. The IDMC members are listed at the start of this document.

6.4. Patient and community advisory group

The North-central Nigeria project hub will have a Patient and Community Advisory group that will meet quarterly and be engaged in all stages of the research. We will also feedback the results of the trial to patients via hospital staff who see patients on a daily basis.

6.5. Summary of staff training (see also Section 4)

All current site staff in Nigeria 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 previously (section 4.3).

We will create a data management manual for use to guide online data collection and entry systems and data security. Dr Samuel Watson (data manager) will train all local staff in Nigeria.

6.6. Finance

This study is funded by the UK National Institute for Health Research (NIHR) Research and Innovation for Global Health Transformation (RIGHT) programme.

6.7. Assessment and management of risk

The assessment and management of risk will be guided by the policy which outlines the roles and responsibilities of staff, how risks are identified, assessed and mitigated. Each risk is assessed using two key metrics; likelihood of occurrence and impact on the programme. Using this assessment each risk is assigned a risk rating which is colour coded for severity and included on a risk register. Actions to mitigate the risk will be identified and noted within the risk register and discussed as a regular agenda item at the Trial Management Group meetings (see Section 6.1) to ensure proper management of risk.

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group and Trial Steering Committee based on the trial risk assessment which may include on site monitoring. Throughout the protocol we discuss our plans for monitoring and quality assurance.

7. Dissemination and Publication

The results of the trial will first be reported to trial collaborators. The main report will be drafted by the trial coordinating team and the final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK and Nigeria. Equal credit will be given to those who have wholeheartedly collaborated in the trial.

We shall also feedback results to patients and communities through hospital staff who see patients on a daily basis. The Leprosy Mission has extensive experience in working with local communities and we will draw on their experience and networks to engage patients and communities within our research.

We will present our work at conferences such as the annual conference of the Neglected Tropical Disease, NGDO Network of which The Leprosy Mission is a member, Health Systems Global Conference and the International Leprosy Congress in 2022.

Tools we will use to disseminate our research output include: bite-sized research reports in lay format; public announcements in communities in LMICs; policy briefings; print and online media; the director's News Blog (680+ subscribers); institutional and professional social media accounts and websites. These forums will alert interested parties to our work, and also allow them to communicate with us.

8. Discussion

We gave thought to the question of multiple foot ulcers that are present in approximately 20% of cases. We considered within patient randomization but were dissuaded by the need for simplicity to complete the trial within time and the likely imbalance given the considerable differences across and within patients in the number, size and condition of the ulcers. This heterogeneity also dissuaded us from measuring the total ulcer area across all ulcers as our primary outcome measure.

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Appendix 1

Wound dressing protocol for HELP study at Leprosy Referral Hospital Chanchaga

If Patients fulfil the inclusion criteria and offer to enrol them in the study.

Screening and consent taking:-

1. Participant admitted to hospital.
2. Check the blood pressure, send blood sample for complete blood count and other serological (HIV, Hepatitis B, Hepatitis C) and biochemical (fasting blood sugar) checks. Note down all parameters.
3. Send ulcer swab for culture to lab and check for any microbial growth and their antibiotic sensitivity. Irrigate wound with normal saline before taking swab.
4. After receiving the reports, screen the participants for eligibility using REDcap and record size of ulcer- length, breadth, depth and area in cm/cm^2 using measurement scale.
5. If participant is eligible and willing to take part in the trial, take informed consent.
6. The patients should have the details of the procedure explained to them on the first day and written consent should be provided the following day with signature or fingerprints.
7. Randomize patients using REDCap online randomization process.

Randomization:

All participants will be allocated into 2 groups according to computer generated randomisation schedule:

1. Twice a week dressing with normal saline (Control group)
2. Twice a week dressing with Honey (Intervention Group)

Wound Preparation for both Control and Intervention Groups:

1. Fill out the participant e-CRF (case report form) into REDCap.
2. Record time as hour: minutes so that we can calculate the time taken for dressing change. It should be the duration of time from opening the dressing until closing the wound with bandaging.
3. Clean the wound with normal saline through irrigation to remove all exudates.

4. Wound debridement - remove the devitalized tissue and fibrin membrane surrounding the ulcer by careful debridement (marginal resurfacing) of the wound. Clean the wound with normal saline. Ulcer debridement is not recommended at every dressing change.

5. Take photographs perpendicular to wound with a labelled (Participant Identification Number and Date) 3cm ruler at the level of the skin and calculate measurements using PUSH tool, and record these locally. Record the wound- length, breadth, depth and surface area in cm/cm^2. Measurements should not be recorded in REDCap software by the Nigeria team, as wound assessment will be performed by the team at University of Birmingham blind to intervention status. Where an index ulcer heals into multiple smaller ulcers, the surface area of all ulcers within the original index ulcer site will be recorded in cm^2.

Honey Application to the Wound for Intervention Group:

1. Filter the honey into sterile container using sterile polypropylene 0.5 micron filter cloth.

2. Prepare clean dry gauze and soak with the filtered honey. Apply the honey-soaked gauze directly on the wound

3. Cover the wound with sterile Vaseline gauze and apply sterile dry gauze on it, close wound with bandaging. Apply liquid paraffin to the surroundings of the wound if the foot skin is dry. Convince the participants to avoid weight bearing at the wound site. There is no need of dressing every day. Record the total time taken for dressing change as hour: minutes.

4. Open the wound after 3-4 days as per twice a week dressing schedule. Clean the wound with normal saline, dry it with gauge, and do not rub the wound. Take photographs, note down the measurement of wound size and depth.

Normal Saline Wound dressing for Control Group:

Wound preparation procedure is same as mentioned above.

1. Perform irrigation with 50-100 ml Normal saline depending on the size of the ulcer. Apply normal saline gauge over the wound area and cover with sterile Vaseline gauze. Apply sterile dry gauze over it and close wound with bandaging. Apply liquid paraffin to the surroundings of the wound if the foot skin is dry. Convince the participants to avoid weight bearing at the wound site. There is no need of dressing every day. Record the total time taken for dressing change as hour: minutes.

2. Open the wound after 3-4 days as per twice a week dressing schedule. Repeat the Normal saline dressing as mentioned above. Do not rub the wound surface. Take photographs, note down the measurement of wound size and depth.

Implement following to all participants in both Intervention and Control groups-

Provide a glass of energy drink to participants every time after dressing change.

Add Iron tablets (200 mg BD), folic acid (5 mg OD), Vitamin C (500 mg BD) and Multivitamins (1 tab BD) to the participant's medication list during admission period.

Record of Activity Measurement (Steps count) using Pedometer:

Explain the use of the pedometer to both intervention and control group participants. Participants should wear their pedometer on the ankle of the non-affected limb (or non-index limb if both feet have ulcers) after the first dressing change. Collect activity measurements (step count) daily and record the total number of steps taken at each dressing change and at the end of inpatient stay, on the discharge form. REDCap will automatically calculate the cumulative sum of total steps at the end.

Post wound healing care and Follow up:

1. If the wound is completely epithelialized before 70 days after enrolment, check for the consistency of tissue at wound site. Take a photo with PUSH tool tablet camera of whole foot. Apply Vaseline gauge at healed wound site and liquid paraffin around it, then apply Plaster of Paris (PoP) cast with window at healed wound site for 2-4 weeks until the healed ulcer site will have matured tissue.

   Participants will be discharged from hospital after POP application. They can be transferred to Self-Care Unit until the PoP will be removed out or can be sent to their home. The POP should be removed after 2-4 weeks.

2. After removal of PoP, train the participants for self-care and prevention of disability.

3. Consult footwear staff to design protective footwear.

4. Discharge the participants from Self-Care Unit and ask them to come at six months from randomisation for follow up evaluation.

5. At follow up check condition of foot and record any recurrence or new ulcer at same foot.

6. Take photographs with PUSH tool at follow-ups.

7. If any complications or adverse events are seen during admission period, please inform the Principal Investigator or RIGHT Research Staff.

Appendix 2

Pedometer Log:

Participants ID:

Date of Enrollment:

Hospital ID:

S. no.	Date (DD/MMM/YYYY)	Time of data record	Steps	Information filled by
01.				
02.				
03.				
04.				
05.				
06.				
07.				
08.				
09.				
10.				
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39.				
40.				

Total steps=……..

Appendix 3

Honey Experiment on LeProsy Ulcer (HELP): A Randomised Control Trial of Raw, Unadulterated African Honey for Ulcer Healing in Leprosy

Participant Information Sheet

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 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 organising and funding the study?

The study is being organised by The Leprosy Mission Nigeria 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. Treatment consists of keeping the ulcer clean and fresh and also applying wet bandages regularly – dressing changes. You will currently have these dressing changes every 3 or 4 days.

The purpose of our study is to test a new method that may help the ulcer to heal faster. This treatment is done while you have your dressing changed. We will use honey to dress the wound for some of you while others will receive normal saline dressing on their wounds. The selection of participants for the honey or normal saline dressing will be done randomly. Honey is being used for wound dressing for centuries but this time, we want to do it as a registered trial.

At present, this treatment appears to be very safe, although we do not know if it works. This study only looks at ulcers on the feet or legs and not anywhere else.

Why have I been asked to take part?

You have been invited because you have ulcer in your foot.

Do I have to take part?

No. It is up to you to decide to take part or not. If you don't want to take part, that's ok. Your doctor will still care for you and your decision will not affect the quality of care you receive.

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.

Then you will be evaluated, do an interview and physical examination of your ulcer in your foot. If you meet the study's criteria, and you wish to participate, you will receive dressing with normal saline or with honey. The treatment will be chosen by chance by a computer so that half of the people in the trial get the normal saline (control group) and the other half get the honey (intervention group). It is really important that the two groups for this study have a similar mix of patients in them. Having a similar mix means that we know that if one group of participants does better than the other, it is very likely to be because of the treatment and not because there are differences in the types of patients in each group. You will have an equal chance of receiving either normal saline dressing or honey dressing. If you get enrolled in the study you will be asked to wear a pedometer on the ankle of non-affected limb. This is to monitor your movement during the hospital admission period from the first dressing change to discharge. It is important that you realise that treatment is not always effective. If you agree to take part of this study, we will ask you to complete different questionnaires. You will be called for follow-up six months after randomisation for the trial.

What will I have to do?

You will be expected to be admitted in hospital during the treatment period. You have to answer the entire questions asked to you. This will help us to gather information about you and your progress during the study period.

What information will be collected?

Only simple information about you, your treatment for your ulcer and how it affects you will be collected. This will include your name, but you will only ever be viewed by your participant number. We will keep this information separate from your address.

We will also take photographs of your ulcer every time you have your dressing changed to see how well it is healing. These photographs will only ever be viewed by your participant number. We may also make video of your dressing change.

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 about you which leaves the hospital/surgery/clinic will have your name and address removed so that you cannot be recognised.

Your doctor will send some details about you to the study team at university of Birmingham, who will store it securely. Your personal details will be kept in a different safe place to the other study information and will be kept for at least 10 years after study completion. All the data will be securely stored in safe place.

The collected data may also be used for future research, including impact activities following review and 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. Sunday Udo who is the principal investigator 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

The study holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you may be eligible to claim compensation.

Can I change my mind about taking part?

Yes. You can withdraw from the study at any time. You just need to tell your doctor that you don't want to be in the study anymore. Your doctor will still care for you.

You can withdraw from treatment but keep in contact with us to let us know your progress. Information collected may still be used.

This would not affect the care you receive. If the intervention proved effective, you will be eligible to receive it if you develop a new ulcer or if your ulcer has not healed or recur.

What will happen to the results of this study?

The study results will be published in a medical journal so that other doctors 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 University of Birmingham's Science, Technology, Engineering and Mathematics (STEM) ethics committee.

Who should I contact if I want further information?

Dr Sunday Udo, TLM Nigeria, Tel: +234 8090850600,

email: sundayudoTLMN@gmail.com

Professor Richard Lilford, University of Birmingham, UK 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.*****

Appendix 4

CONSENT FORM

Title of Project: **Honey Experiment on LeProsy Ulcer (HELP): A Randomised Control Trial of Raw, Unadulterated African Honey for Ulcer Healing in Leprosy**

Name of Researcher(s): Dr Sunday Udo, TLM Nigeria and Professor Richard Lilford, University of Birminigham, UK

A. I _____ understand that doctors at the Leprosy Referral Hospital Chanchaga and at University of Birmingham are involved in research into alternative treatments methods for leprosy ulcers. This study will look at whether honey is more beneficial than normal saline dressing in healing foot ulcer or not. We are hoping to prove efficacy of new treatment method for healing leprosy ulcer.

B. The study has been explained to me.

C. I confirm that I am 18 years old or above.

D. I shall be randomly assigned to a normal saline dressing group or honey dressing group. There is equal chance of getting either normal saline dressing or honey dressing.

E. I agree to have photographs and videos taken during the ulcer dressing.

F. I agree that my collected data be used for further research in future*.

*Please note that participants may say 'NO' to this question and still take part in the study.

G. I can decide to leave the study at any time for any reason and will still receive other treatment from the hospital for my condition.

H. I understand that my name will not be revealed in any published material concerning this study. I understand that my notes will be treated with maximum confidentiality and will only be accessed by staff directly involved in the Study or the monitors of the Study.

I. I have received enough information about the study in a language I understand. I had the opportunity to discuss it and ask questions, and my questions have been answered to my satisfaction. I understand that participation is voluntary and that I am free to withdraw my

consent at any time. I freely consent to participate in this research study and to allow treatment and tests to be performed on me as explained.

J. I understand that I can be requested anytime to terminate my participation in the trial if the need arises. I will be given full explanation of the reason and will still receive standard treatment.

K. I agree to take part in the study.

Printed Name & Signature (or finger print) Date

Name of Participant _____

Signature/Finger Print _____ _____/_____/20____

Name of Witness _____

Signature/ Finger Print _____ _____/_____/20____

Name of Researcher_____

Signature _____ _____/_____/20____