**Study Title:**  Randomised controlled trial to determine the efficacy of thermotherapy in comparison with intralesional meglumine antimoniate to treat cutaneous leishmaniasis in an operational setting in Syria.

**OxTREC Ref:** 42-20

**Date and Version No:** 12 February 2021, Version 2.0

Short title: CL in Syria

|  |  |
| --- | --- |
| **Chief Investigator:** | Hendrik Sauskojus, MPH, Middle East Programme Manager, The MENTOR Initiative, [hendrik@mentor-initiative.net](mailto:hendrik@mentor-initiative.net), +49 1624564516 |
| **Investigators:** | Dr Bob Taylor, MD, FRCP, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, [bob@tropmedres.ac](mailto:bob@tropmedres.ac), +66 2203 6333 ext 6373  Dr Emer Liddy, MD MSc MRCPI, Middle East Regional Health Coordinator, The MENTOR Initiative, [emer@mentor-initiative.net](mailto:emer@mentor-initiative.net) +353896179520  Laura Paris, MSc, Programme Manager Operational Research, The MENTOR Initiative, [laura.paris@mentor-initiative.net](mailto:olivia@mentor-initiative.net), +447583857526  Richard Allan, Director, The MENTOR Initiative, [richard.allan@mentor-initiative.net](mailto:richard.allan@mentor-initiative.net), +44 1444 412171 |
| **Sponsors:** | The MENTOR Initiative |
| **Funder:** | The MENTOR Initiative |
| **Chief Investigator Signature:** |  |

There are no conflicts of interest. The World Health Organization has supplied the thermotherapy devices intended for use in this trial, but no WHO staff have had a hand in designing this study.

**Confidentiality Statement**

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from sponsor, the Investigator Team and members of the Oxford Tropical Research Ethics Committee (OxTREC) and local Ethics Committee, unless authorised to do so.

**TABLE OF CONTENTS**

[1. SYNOPSIS 4](#_Toc41231276)

[2. ABBREVIATIONS 5](#_Toc41231277)

[3. BACKGROUND AND RATIONALE 5](#_Toc41231278)

[3.1. Advantages of thermotherapy in war-torn Syria 6](#_Toc41231279)

[3.2. Rationale for this study 7](#_Toc41231280)

[4. OBJECTIVES AND OUTCOME MEASURES 8](#_Toc41231281)

[5. STUDY METHODS 8](#_Toc41231282)

[5.1. Study sites 8](#_Toc41231283)

[5.2. Study design 9](#_Toc41231284)

[6. PARTICIPANT IDENTIFICATION AND RECRUITMENT 9](#_Toc41231285)

[6.1. Study Participants 9](#_Toc41231286)

[6.2. Inclusion Criteria 9](#_Toc41231287)

[6.3. Exclusion Criteria 9](#_Toc41231288)

[7. STUDY PROCEDURES 10](#_Toc41231289)

[7.1. Recruitment 10](#_Toc41231290)

[7.2. Screening and Eligibility Assessment 10](#_Toc41231291)

[7.3. Informed Consent 10](#_Toc41231293)

[7.4. Randomisation & blinding 11](#_Toc41231294)

[7.5. Baseline Assessments 11](#_Toc41231295)

[7.6. Subsequent Visits 11](#_Toc41231296)

[7.7. Treatment failure 12](#_Toc41231297)

[7.8. Skin scraping & sample handling 12](#_Toc41231298)

[7.9. Discontinuation/Withdrawal of Participants from Study 12](#_Toc41231299)

[7.10. Study duration & definition of End of Study 12](#_Toc41231300)

[7.11. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)/DEVICE Meglumine antimoniate 13](#_Toc41231301)

[7.12. Thermotherapy 13](#_Toc41231302)

[7.13. Storage of IMP 13](#_Toc41231303)

[7.14. Documenting administered study treatment 13](#_Toc41231304)

[7.15. Accountability of the Trial Treatment 14](#_Toc41231305)

[7.16. Concomitant Medication 14](#_Toc41231306)

[7.17. Post-trial Treatment 14](#_Toc41231307)

[8. SAFETY REPORTING 14](#_Toc41231308)

[8.1. Definitions 14](#_Toc41231309)

[8.2. Causality 15](#_Toc41231310)

[8.3. Procedures for Recording Adverse Events 16](#_Toc41231311)

[8.4. Recording and reporting Serious Adverse Events 16](#_Toc41231312)

[8.5. Expectedness 17](#_Toc41231313)

[8.6. SUSAR Reporting 17](#_Toc41231314)

[8.7. Safety Monitoring Committee 17](#_Toc41231315)

[8.8. Development Safety Update Reports 17](#_Toc41231316)

[9. STATISTICS AND ANALYSIS 17](#_Toc41231317)

[9.1. Sample size 17](#_Toc41231318)

[9.2. Description of Statistical Methods 17](#_Toc41231319)

[10. DATA MANAGEMENT 18](#_Toc41231320)

[10.1. Access to Data 18](#_Toc41231321)

[10.2. Data Handling and Record Keeping 18](#_Toc41231322)

[10.3. Handling photographs 19](#_Toc41231323)

[11. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES 19](#_Toc41231324)

[12. ETHICAL AND REGULATORY CONSIDERATIONS 19](#_Toc41231325)

[12.1. Declaration of Helsinki 19](#_Toc41231326)

[12.2. Guidelines for Good Clinical Practice 19](#_Toc41231327)

[12.3. Approvals 19](#_Toc41231328)

[12.4. Participant Confidentiality 19](#_Toc41231329)

[12.5. Expenses and Benefits 20](#_Toc41231330)

[12.6. Reporting 20](#_Toc41231331)

[12.7. Other Ethical Considerations 20](#_Toc41231332)

[13. FINANCE AND INSURANCE 20](#_Toc41231333)

[13.1. Funding 20](#_Toc41231334)

[13.2. Insurance 20](#_Toc41231335)

[14. PUBLICATION POLICY 21](#_Toc41231336)

[15. APPENDIX C: AMENDMENT HISTORY 21](#_Toc41231337)

# SYNOPSIS

|  |  |  |
| --- | --- | --- |
| **Study Title** | Randomised controlled trial to determine the efficacy of thermotherapy in comparison with intralesional meglumine antimoniate (MA) to treat cutaneous leishmaniasis in an operational setting in Syria | |
| **Internal ref. no. (if applicable)** | PAR20002 | |
| **Study Design** | An open randomised controlled non-inferiority treatment trial | |
| **Study Participants** | Patients with cutaneous leishmaniasis presenting at health facilities and leishmaniasis mobile treatment clinics in Idleb governorate, North-West Syria | |
| **Planned Sample Size** | 580 participants, 290/arm | |
| **Planned Study Period** | September 1st 2020 - August 31st 2021 | |
| **Aim** | The study aims to gather evidence on the use of intralesional antimoniates and thermotherapy in Old World cutaneous leishmaniasis in war-torn Syria to inform health policies. | |
|  | **Objectives** | **Outcome Measures** |
| **Primary** | Compare the efficacy of thermotherapy treatment to an IL course of meglumine antimoniate (MA) for the treatment of cutaneous leishmaniasis in Syria. | Complete re-epithelization for ulcerated lesions, and obvious flattening for non-ulcerated lesions measured at 3 months post treatment completion. |
| **Secondary** | Determine tolerability | Adverse events |
|  | Determine leishmania species, genotypes & molecular markers of antimonial resistance | PCR of kinetoplast DNA (species), sequence internal transcriber spacer 2 and cytochrome b genes (genotype), gene expression of e.g. aquaglyceroporin 1, multidrug resistance protein A |

# ABBREVIATIONS

|  |  |
| --- | --- |
| CI | Chief Investigator |
| CL | Cutaneous Leishmaniasis |
| CRF | Case Report Form |
| CUREC | Central University Research Ethics Committee |
| Cytb | Cytochrome B |
| EMRO | Eastern Mediterranean Region |
| GCP | Good Clinical Practice |
| HCW | Health Care Worker |
| HF | Health Facility |
| ICF | Informed Consent Form |
| IDP | internally displaced |
| IL | Intralesional |
| IM | Intramuscular |
| MA | Meglumine Antimoniate |
| MC | Mobile Clinic |
| MORU | Mahidol Oxford Tropical Medicine research unit |
| MRPA | Multidrug resistance protein A |
| MTA | Material transfer agreement |
| NGO | Non-governmental organisation |
| NWCL | New World cutaneous leishmaniasis |
| NWS | North West Syria |
| OR | Odds Ratio |
| OWCL | Old World cutaneous leishmaniasis |
| OxTREC | Oxford Tropical Research Ethics Committee |
| PI | Principal Investigator |
| PIS | Participant Information Sheet |
| SOP | Standard Operating Procedure |
| SSB | sodium stibogluconate |
| vs. | versus |
| WHO | World Health Organization |

# BACKGROUND AND RATIONALE

The current manual for case management of cutaneous leishmaniasis (CL) in the World Health Organization (WHO) Eastern Mediterranean Region (EMRO) advocates the use of thermotherapy treatment or intralesional (IL) pentavalent antimoniates, where the patient has less than four lesions in locations not contra-indicating the use of these treatments. However, there is no clear guidance as to which patients fall within this category and who should be treated with either thermotherapy or IL antimoniates or how health care workers should make this decision.

Parenteral or IL antimoniates are currently the standard treatment option for CL in northern Syria and many other endemic EMRO countries but the availability of thermotherapy (5 ThermoMed devices) is very limited. To the best of our knowledge, 5 devices are available in NWS (all MENTOR supplied) and none in the North East of Syria.

Several studies have been published comparing thermotherapy with parenteral or IL antimoniate against Old and New World CL (OWCL, NWCL). The first study we are aware of was conducted in Guatemala in 1990 and compared parenteral MA to thermotherapy and a placebo group. At 3 months, 73% (16/22) of patients in both the MA and thermotherapy groups were cured, compared to 27% (6/22) in the placebo group.1 In a single arm, observational study in Mexico in 1997, 201 patients with *L. mexicana* NWCL were treated with thermotherapy, curing 90% of the 191 evaluable patients. The authors noted that thermotherapy had proved to be ‘effective and convenient for use in primary health care facilities in Mexico and has many advantages over traditional forms of therapy’.2

The first study of OWCL was a 2005 randomised control trial conducted in Afghanistan, where *L tropica* predominates, which compared IL and intramuscular (IM) sodium stibogluconate (SSB) versus thermotherapy. The odds ratio (OR) for cure with thermotherapy vs. systemic SSB was 2.8 (95% confidence interval [CI], 1.45–5.41), (p = 0.002), but there was no statistically significant difference for thermotherapy vs. IL SSB. The median time to cure was also significantly shorter in the thermotherapy group (median 53 days) versus 75 days in the IL SSG group and >100 days in the IM SSG group, respectively (p= 0.003).3

A retrospective analysis of 360 American soldiers who returned from Iraq with clinically suspected OWCL involved several treatment modalities; although only 27 patients received thermotherapy (ThermoMed device), it was well tolerated and effective.4 A randomised control trial conducted in Iran in 2007, compared four sessions of thermotherapy with 4 injections of IL MA; the cure rate was significantly (p=0.001) higher in the thermotherapy group: 80 vs. 55% in the antimoniate group.5

Another study (2010) of deployed US soldiers in the Middle East with OWCL compared the efficacy and toxicity of systemic SSB with thermotherapy; a similar rate of healing was recorded for both treatments with intention to treat analysis per lesion efficacy at 2 months 59% for SSB and 75% for thermotherapy, (p = 0.053) and per person efficacy 54% for SSB and 48% for thermotherapy (p = 0.78), while the ThermoMed device was better tolerated.7

In another randomized control trial (2012) conducted in Afghanistan, the cure rate of a single treatment with thermotherapy was 82.5% compared to 74% for five sessions of IL MA to treat *L tropica* and was better tolerated.8

In Brazil, a small (n=15) observational trial of thermotherapy-treated NWCL cured 18 of 21 CL lesions without significant toxicity during a 6-month follow-up period; the authors concluded that thermotherapy could be considered as an alternative treatment to antimoniates for localised CL lesions.9 Several studies have also looked at the cost-effectiveness of thermotherapy versus pentavalent antimonials and have concluded that thermotherapy is significantly more cost-effective.10,11

## Advantages of thermotherapy in war-torn Syria

Standard treatment for CL with thermotherapy consists of 1 treatment session; larger lesions may require more applications during the same session to cover the entire lesion area. For patients with several CL lesions, they may be treated during the same treatment session. This is a huge advantage for vulnerable displaced populations who, in Syria, have often had to move several times to seek safety. Moreover, 100% adherence is guaranteed if there is only one treatment session and the ThermoMed device is portable and requires minimal training. Thermotherapy is better tolerated than IL injections and associated with pain at site of application, oozing of lesions and erythema.

IL antimoniates require skilled trained workers and several clinic visits e.g. twice weekly injections x 3-4 weeks, as per EMRO guidelines12. Such treatment is far better suited for stable populations where follow up is more easily achievable. Incomplete IL treatment increases the risk of treatment failure and may increase the risk of drug resistance. The most common IL-associated adverse events are erythema, pain at injection site and secondary infection.13

Thermotherapy is more cost-effective and would obviate the need to import regularly antimoniates from Europe which is a complicated and costly logistical process.

## Rationale for this study

Previous studies comparing thermotherapy with IL antimoniates have mostly been quite small and there are no data from Syria, where security is very volatile and OWCL incidence is high.

Thermotherapy represents a very promising option because of its portability, good cost effectiveness, and ease of use. It also offers the opportunity to reduce reliance on international NGOs and foreign aid programmes and increase local capacity to manage sustainably OWCL.

If shown to be effective in the Syrian context, the results would be widely generalisable, give greater clarity to health care workers on the clinical indications for thermotherapy vs. IL antimoniates and could change policy.

**References**

1. Navin TR, Arana BA, Arana FE, De Merida AM, Castillo AL, et al. (1990) Placebo-controlled clinical trial of Meglumine Antimoniate (Glucantime) vs. localized controlled heat in the treatment of cutaneous leishmaniasis in Guatemala. Am J Trop Med Hyg 42(1): 43–50.
2. Velasco-Castrejon O, Walton BC, Rivas-Sanchez B, Garcia ME, Lazaro GJ, et al. (1997) Treatment of cutaneous leishmaniasis with localized current field (radio frequency) in Tabasco, Mexico. Am J Trop Med Hyg 57(3): 31–34.
3. Reithinger R, Mohsen M, Wahid M, Bismullah M, Quinnell RJ, et al. (2005) Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by Leishmania tropica in Kabul, Afghanistan: a randomized, controlled trial. Clin Infect Dis 40(8): 1148–154.
4. Willard RJ, Jeffcoat AM, Benson PM, Walsh DS (2005) Cutaneous leishmaniasis in soldiers from Fort Campbell, Kentucky returning from Operation Iraqi Freedom highlights diagnostic and therapeutic options. J Am Acad Dermatol 52(6): 977–987.
5. Sadeghian G, Nilfroushzadeh MA, Iraji F (2007) Efficacy of local heat therapy by radiofrequency in the treatment of cutaneous leishmaniasis, compared with intralesional injection of meglumine antimoniate. Clin Exp Dermatol 32(4): 371–374.
6. Aronson NE, Wortmann GW, Byrne WR, et al. A randomized controlled trial of local heat therapy versus intravenous sodium stibogluconate for the treatment of cutaneous Leishmania major infection. *PLoS Negl Trop Dis*. 2010;4(3):e628. Published 2010 Mar 9. doi:10.1371/journal.pntd.0000628
7. Safi, N., et al. (2012). "Evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Kabul, Afghanistan: a randomized controlled trial." Mil Med 177(3): 345-351.
8. Gonçalves SVCB, Costa CHN. Treatment of cutaneous leishmaniasis with thermotherapy in Brazil: an efficacy and safety study. *An Bras Dermatol*. 2018;93(3):347–355. doi:10.1590/abd1806-4841.20186415
9. Cardona‐Arias, JA, López‐Carvajal, L, Tamayo Plata, MP, Vélez, ID. Cost‐effectiveness analysis of thermotherapy versus pentavalent antimonials for the treatment of cutaneous leishmaniasis. *J Evid Based Med*. 2017; 10: 81– 90. https://doi.org/10.1111/jebm.12245
10. Cardona-Arias JA, López-Carvajal L, Tamayo-Plata MP, Vélez ID. Comprehensive economic evaluation of thermotherapy for the treatment of cutaneous leishmaniasis in Colombia. BMC Public Health. 2018 Jan;18(1):185. DOI: 10.1186/s12889-018-5060-2.
11. Manual for case management of cutaneous leishmaniasis in the WHO Eastern Mediterranean Region, WHO Regional Publications, Eastern Mediterranean Series 35, World Health Organization 2014.
12. Ramalho, D. B., Silva, R., Senna, M., Moreira, H., Pedras, M. J., Avelar, D. M., Saraiva, L., Rabello, A., & Cota, G. (2018). Meglumine antimoniate intralesional infiltration for localised cutaneous leishmaniasis: a single arm, open label, phase II clinical trial. Memorias do Instituto Oswaldo Cruz, 113(9), e180200. https://doi.org/10.1590/0074-02760180200

# OBJECTIVES AND OUTCOME MEASURES

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective** To compare the efficacy of thermotherapy treatment to an IL course of MA for the treatment of cutaneous leishmaniasis at three months post treatment in Syria | Complete re-epithelization for ulcerated lesions, and obvious flattening for non-ulcerated lesions measured. | Photographs of lesions will be taken at diagnosis and at 3 months post treatment completion. |
|  | Coordinate with the technical WHO unit to discuss any modifications to current guidelines and disseminate the amended guidelines to key health partners and their health care staff in the region and incorporate them in trainings on effective CL treatment. | After conclusion of data analysis and sharing of the database. |
| **Secondary Objectives**  Determine tolerability | Adverse events | After data analysis |
| Determine leishmania species, genotypes & molecular markers of antimonial resistance | PCR of kinetoplast DNA (species) for species, sequence internal transcriber spacer 2 and cytochrome b genes (genotype), gene expression of e.g. aquaglyceroporin 1, multidrug resistance protein A | PCR + sequencing analysis will be done after study completion; exact time line unclear at this stage |

The primary outcome of this study will be complete re-epithelialization for ulcerated lesions and obvious flattening for non-ulcerated lesions. This assessment will be done clinically and by taking photographs of each lesion at baseline and at the 3 months follow up appointment.

# STUDY METHODS

## Study sites

The study will take place in Idleb governorate in NW Syria where MENTOR, an international non-governmental organisation (NGO), is currently operating 4 leishmaniasis MCs and supporting 40 HFs with supplies and technical support for treating patients with OWCL. MENTOR has been active in Syria for the past 6 years and continues to be the leading actor working in leishmaniasis control in northern Syria.

The context is challenging with a fluid security situation resulting in regular suspension of operations in certain areas for variable time periods. The population consists of both host community and internally displaced persons (IDPs), housed in camps or within the host community. The IDPs have largely been relocated/displaced from Syrian government held areas in southern Idleb or further south.

MENTOR currently has access to 5 ThermoMed devices (all donated in 2019 by WHO) which can be placed in any of the MENTOR-supported MCs or HFs. MENTOR will select the study MCs and HFs 2 months preceding the study start date based on the security situation, capacity of the HFs to facilitate the study and the OWCL caseload.

## Study design

This is an open randomised, non-inferiority treatment trial with a three-month follow-up.

# PARTICIPANT IDENTIFICATION AND RECRUITMENT

## Study Participants

All patients who present to the 5 selected static health facilities and mobile treatment clinics with CL lesions will be eligible for inclusion in this study if they meet all of the inclusion criteria and none of the exclusion criteria.

## Inclusion Criteria

These are:

* Participant with clinically diagnosed OWCL < 4 cm in size
* Participant is willing and able to give informed consent for participation in the study or
* For children at least 5 years, a parent or guardian gives informed consent on their behalf
* Participant agrees to follow the study processes and attend the follow-up appointment 3 months post treatment completion

## Exclusion Criteria

These are:

* Age < 5 years
* Pregnancy by history
* Lactation
* Lesions
  + on or directly adjacent to lips, eyes/eyelids, nose
  + nose
  + ear
  + fingers/toes
  + close to carotid and jugular vessels in neck
  + antecubital fossa region
  + on volar aspect of wrist joint
* Implantable cardiac devices such as pacemakers
* Metallic implants such as metal plates in skull
* Previous history of treatment to same lesion(s)

# STUDY PROCEDURES

## Recruitment

After the 5 HF or MCs have been chosen, staff working in these facilities/clinics will be trained by MENTOR’s medical coordinator to recruit patients to the study. All participants will be recruited from these facilities.

From the study start date, all patients matching the study inclusion criteria who present to the 5 facilities/clinics will be briefed regarding the study and explained in detail what the study is intended to assess and how it will be conducted. If they agree to join the study, they will sign the Informed Consent form and then be screened.

## Screening and Eligibility Assessment

All patients will be screened by a history and brief physical examination to ascertain the number and location of lesions.

If the patient is a woman of childbearing age, she will be asked whether she might be pregnant and whether she has any infants that are being breast fed. For children, the age of the child has to be established to be enrolled or excluded.

All patients who are excluded from the study will be offered standard treatment.

## Informed Consent

Before patients are enrolled in the study, they will sign a consent form that clearly states that they take part of their own free will, and, should they wish to no longer participate, the treatment will continue free-of-charge outside of the study and that no disadvantages will arise from their decision to decline study participation or withdrawal, for which also no explanation will be needed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants or a respective caregiver detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time, for any reason, without prejudice to the continuation of the treatment course and future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study.

Written informed consent will then be obtained by means of the participant’s or the respective caregiver’s dated signature and the dated signature of the person who presented and obtained the informed consent.

Each participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. If the patient is not of an age where she/he could give informed consent, a caregiver/guardian will be asked to do so. Age of legal consent in Syria is 15, and as a result all patients less than 15 years of age require informed consent to be taken from a caregiver.

The person who obtained the consent must be suitably qualified, experienced, and authorised to do so by the Chief Investigator. Two Informed Consent forms will be signed. One will remain at the study site and one will be given to the patient.

The consent forms will be collected and transported to MENTOR’s nearest field office and scanned copies will be sent electronically to the main MENTOR office in Gaziantep, eastern Turkey.

## Randomisation & blinding

We will, use a random number table in every study clinic (reproduced from Table XXXIII of Fisher and Yates (1963), following Armitage (1971)). Each patient that enters the clinic for CL treatment and fulfils the requirements of entering the study will be allotted a number from the table, starting at the beginning of a column. If the number is even, he/she will be included in the trial sample and vice versa.

For treatment allocation, we will use sequentially numbered, opaque sealed envelopes (SNOSE) method to randomly allocate treatment. The preparation will follow the instructions given by Doig & Simpson (2005) in their paper “Randomization and allocation concealment: a practical guide for researchers.”, whereby a stack of SNOSE treatment allocation envelopes will be prepared and then a certain number of envelopes will be allotted to each study clinic.

Envelopes will only be opened after the patient is enrolled in the study; this will ensure adequate concealment of treatment allocation. The person opening the envelope will be different to the person recruiting the patient, as per the CONSORT statement (item 10). Rigour will further be enhanced by writing patients’ details on the outside of envelopes (which contain carbon paper), so that the patients’ names are transferred to the sheet of paper with the allocation on before the envelope is opened.

## Baseline Assessments

All patients will have a dermatological assessment at baseline to diagnose whether their lesion is CL or related to a different pathology. For enrolment, the diagnosis of CL will be made clinically; however, all enrolled patients will have a skin scraping from their lesion/s which will be stained with Giemsa solution and examined by light microscopy to confirm diagnosis. This microscopic diagnosis will be conducted at field level within the study time-frame. Enrolled patients whose skin scraping is negative for CL will remain in the study.

Two swabs of the lesion border will be taken and stored for future genetic analysis.

All skin lesions will be photographed and measurement of lesion diameter to the nearest millimetre will be recorded in the Case Report Form (CRF).

## Subsequent Visits

One follow-up appointment will be arranged for all patients at 3 months. Follow-up appointments will be given to patients to attend the HFs or to remain at home on that day to receive the research team.

A follow-up consultation survey form will be completed, which will include information on adverse events that may be related to the treatment experienced by the patient and time to heal in estimated number of days/weeks as recalled by the patient and documented by them through taking a photo, if possible.

All CL lesions will be examined, measured (if unhealed) and photographed.

Participants will also be asked if any other lesions have appeared and if so, they will be referred for standard treatment.

If they do not adhere to this appointment, they will be contacted via phone and asked whether they would prefer to come to the health facility or be visited at home. Participants recruited via mobile clinics will always be followed up at home.

## Treatment failure

If:

* at three months patients’ lesions have not healed or
* before then they notice progression of the lesion/s,

they will be offered cross-over treatment.

This will be easier for patients treated with IL antimoniates, as lesion improvements or a slowly healing lesion can be detected by the research team.

As the treatment with the thermotherapy device only takes one consultation, patients will be told to report if their lesions are not improving to avoid them seeking treatment elsewhere.

## Skin scraping & sample handling

All patients will undergo a skin scraping for microscopic diagnosis. Two swabs per lesion will also be taken and stored for future genetic analysis.

A SOP will be written that describes the process of skin scraping using the method recommended by WHO EMRO12.

The swabs will be securely stored before being analysed after study completion at a suitable laboratory in a third country. At this point, there are several options including, MORU in Thailand, Iran, South Korea, and the UK. All applicable regulations will be followed for the export of samples from Syria and a Material Transfer agreement (MTA) will be signed between MENTOR and the laboratory.

## Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time, without having to provide an explanation as to why they wish to withdraw, and without having to fear that their treatment will be stopped or that there will be any negative impact on future health care services.

In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

* Pregnancy
* Ineligibility (either arising during the study or retrospectively having been overlooked at screening). This will be dependent on the treatment, as certain exclusion criteria are based on possible adverse effects arising as a result of the combination of treatment and exclusion criterium
* Significant non-compliance with treatment regimen or study requirements
* Withdrawal of Consent

The reason for withdrawal (if given) will be recorded in the Case Report Form.

## Study duration & definition of End of Study

The proposed start date for this project is September 1st 2020 with a proposed end date of June 30th 2021.

The duration of the study is expected to be 10 months: a 2-month set-up before first participants are recruited, 6 months during which the study will run (including the 3-month follow-up period), and 2 months after all data has been collected to allow for data analysis. It is therefore expected that all patients will be recruited to this study in a 3-month period.

## INVESTIGATIONAL MEDICINAL PRODUCT (IMP)/DEVICE Meglumine antimoniate

IL MA will be infiltrated around the OWCL lesions. There is no set dose so the volume of MA varies depending on the size of the lesion, but generally varies between 1 and 5mls. MENTOR will follow the WHO EMRO guidelines which state that each lesion should be injected twice per week for 3-4 weeks until complete cure is reached.

When injecting, the angle of the needle should be max 5-10 degrees to ensure injection into the dermal layer. 3-4 injection sites, 0.5 to 1cm outside the border of the lesion, should be chosen. These 3-4 injection sites should be at roughly equal distance from one another around the circumference of the lesion. Injection of the drug into the intradermal layer should cause blanching and slight swelling of the skin.

MA is manufactured by Sanofi Aventis, France. It will be purchased and imported into Syria by MENTOR.

## Thermotherapy

The device used in this study – ThermoMed Model 1.8 (Thermosurgery Technologies, Inc., Inc, Phoenix, AZ) - has received both Food and Drug Administration (FDA) and WHO approval for use in treatment of CL and is already in use by MENTOR in NWS.

Standard treatment for CL with thermotherapy consists of 1 treatment session with application of the ThermoMed device for a duration of 30 seconds at a selected heat of 50 degrees Celsius to each treated area. Larger lesions may require more than 1 application during the same session to cover the entire lesion area. For smaller lesions 1 application of the ThermoMed device will suffice.

For patients with several CL lesions, all lesions may be treated during the same treatment session. No further treatment sessions are required. Further information regarding the device can be found in the ThermoMed User Manual which can be supplied by MENTOR.

## Storage of IMP

According to the manufacturer’s guidelines, MA should be stored at a temperature of between 15 and 30 degrees Celsius. MENTOR ensures that all of its supported health facilities have adequate storage facility to ensure that the medication which we donate for treatment of leishmaniasis can be stored according to manufacturer guidelines. The health facilities which will be included in this study will therefore have this capacity.

The MA that is used in MENTOR’s mobile clinics is stored in a cool box which is connected to a power source within the vehicle. The cool box also contains a thermometer to accurately record the temperature. Outside of the day-time working hours of the mobile clinics, both the thermotherapy device and the MA are stored in MENTOR’s warehouse which is temperature controlled to ensure that drugs are stored according to manufacturer guidelines. MENTOR’s logistics department conduct regular temperature checks in the warehouse each day and also have a device installed which records daily minimum and maximum temperature.

## Documenting administered study treatment

Both treatments are administered on site by a health care worker; therefore, the number of administered treatments will be recorded. Thermotherapy requires only 1 treatment session. A typical course of IL MA is 6-8 injections over a 3-4-week period – depending on lesion size and response to treatment.

Every time the patient attends, IL MA volume will be recorded.

At the end of the study, the total number of IL MA sessions and volume used will be calculated.

We will analyse the total number of IL MA treatments administered in a logistic model to determine factors associated with cure at 3m.

## Accountability of the Trial Treatment

A study log will be maintained by the chief investigator (CI), detailing the distribution of MA to the HFs and MCs. This will list the drug batch number, expiration date, the amount of drug distributed to each HF or MC each week, how much is used each week, how much remains at the end of each week, how much remains at the end of the study and how much is damaged or thrown away.

The study log will also contain information about each ThermoMed device, listing which device is located at each HF and MC. Each device is labelled with a MENTOR Asset ID number to identify it.

## Concomitant Medication

There are no contraindicated concomitant medications in this trial.

## Post-trial Treatment

There will be continued provision of MA beyond the trial period at all study locations. Should thermotherapy be proven to be as effective as or better than MA injections, MENTOR will advocate for a wider uptake of this treatment option. However, there is a limited supply of thermotherapy devices. Therefore, access to thermotherapy cannot be universally available within our network beyond the trial period.

# SAFETY REPORTING

## Definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.  The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.  All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:   * results in death * is life-threatening * requires inpatient hospitalisation or prolongation of existing hospitalisation * results in persistent or significant disability/incapacity * consists of a congenital anomaly or birth defect.   Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.  NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out:   * in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product * in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question. |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

## Causality

The relationship of any adverse events which occur to the trial medication will be determined by the MENTOR’s regional health coordinator who is a medically qualified doctor. Such a relationship will be determined according to the following definitions:

**Related**: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

## Procedures for Recording Adverse Events

All AEs occurring during the trial that are observed by the Investigator / a resident and trained medical professional or reported by the participant, will be recorded on the CRF, whether or not attributed to trial medication. All participants will be asked about adverse events at each treatment consultation and at follow-up appointment.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary. AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

MA is a drug which has been marketed for the treatment of CL since 1946. The side effect profile for parenteral MA has been well established and documented. In this study, IL MA will be administered and, because there is no systemic absorption, is associated with local toxicity, namely, secondary bacterial infection, erythema, pain at injection site, oedema and pruritis. MENTOR will monitor for signs of secondary bacterial infection and will treat early with topical antibacterial ointment if this develops.

Treatment of CL with thermotherapy using the ThermoMed device is also standard practice now in many parts of the world with many published papers as listed above outlining its application and treatment outcomes since 1990. Along with MA it is now also included as a treatment option for CL in the WHO regional guidelines. This treatment involves external application of heat only.

The most common adverse events associated with thermotherapy are pain at site of application, oozing of lesion and erythema.

## Recording and reporting Serious Adverse Events

All serious AEs occurring during the study, from the time of the first treatment is administered to the time of the 3-month post final treatment follow-up appointment, will be recorded on the SAE form, whether or not related trial treatment. This form will be completed by MENTOR’s research medical officer who is a qualified doctor.

The following information will be recorded: description of event, date of onset and end date, assessment of relatedness to trial medication, other suspect drug or device and action taken.

All participants will be given a phone number for MENTOR’s research medical officer and asked to make contact in the event that they become very unwell and/or require hospitalisation. MENTOR’s staff will also enquire specifically about possible SAEs at the 3-month post treatment follow up appointment.

As soon as the HF or MC staff become aware that there is a SAE that might be related to study treatment, they will inform immediately the research medical officer who in turn will gather the necessary clinical details, fill out the SAE form and send it to the inform the:

* MENTOR medical coordinator, Dr Hareth Issa, dmc.s@mentor-initiative.net
* Bob Taylor, bob@tropmedres.ac

In addition, MENTOR’s research medical officer will enquire weekly about any other SAEs recorded / detected by the study MCs and HFs, fill out the SAE from, and send it to three named individuals above.

SAE summaries will also be sent to MENTOR’s regional health coordinator for review.

All SAEs will be managed and followed up as clinically indicated i.e. until the SAE has resolved or is considered stable.

## Expectedness

If there is a treatment-related SAE that is a known complication, it is considered an expected SAE. An unexpected treatment-related SAE is one that has not been described before for a given treatment and this meets the definition of a SUSAR.

## SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authorities in Syria and other parties, as applicable.

For fatal and life-threatening SUSARS, this will be done within 7 calendar days after the CI is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

## Safety Monitoring Committee

Because this is a low-risk study with two recommended, well known, low toxicity treatments, an independent monitoring committee is not needed.

## Development Safety Update Reports

These will only be produced if requested by the ethics committees or regulatory authorities.

# STATISTICS AND ANALYSIS

## Sample size

The sample size was calculated based on non-inferiority. Based on field experience in Syria, we assume a 3-month IL MA cure rate of 90%, a non-inferiority margin of 7.5%, a one-sided alpha of 0.025 and a power of 80%. Adding 15% loss to follow-up, the sample size will be 290 participants per arm with parasitologically confirmed CL, 580 in total.

Because the parasitological diagnosis will be made after patient recruitment, the total number of recruited patients will exceed 580. Given the skill of the research team at clinical diagnosis, we expect this number to be relatively small. We seek ethical permission to recruit up to 700 patients.

## Description of Statistical Methods

The analysis will be performed according the intention-to-treat (ITT) principle.

Patients wrongly randomised or lost to follow-up will be excluded from ITT analysis. For efficacy, only subjects with a parasitological (skin scrape and/or PCR) diagnosis will be included. For the safety evaluation, patients will be included if had their thermotherapy and, for the AM arm, received at least one injection of IL MA.

The differences in patient characteristics between excluded vs. included patients will be assessed. If there are clinically important differences, a worst-case scenario outcome analysis will be also be done, in which all excluded: (i) IL MA patients will be considered cured, and (ii) thermotherapy patients considered treatment failures.

The 3-month cure rate will be compared using chi squared or Fisher’s exact test, as appropriate. These will also be used for comparing proportional data.

Continuous data (e.g. lesion size) between two groups will be analysed by the unpaired t-test, transforming the data, as needed.

A binomial logistic regression model will also be used to assess factors affecting cure.

All analyses will be two sided and p value of <0.05 is considered statistically.

# DATA MANAGEMENT

## Access to Data

Direct access will be granted to authorised representatives from the sponsor and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.

## Data Handling and Record Keeping

MENTOR’s well-established main data collection tools for information recording from patients will be used:

* patient registration books
* ID cards
* Enrolment log
* Case record form

The enrolment log will contain the patient’s name and contact details and will be kept separate to all other study documentation and under strict lock and key.

The patient registration book will be used to record clinic visits and basic clinical information and serves as the patients’ medical record. The patient registration book will remain at the HF or MC and the patients will bring their ID card for every visit so they can be identified correctly.

The case record form will be used to collect all study-related data and will not include the patient’s name; it is a source document.

Scanned copies of the CRF and the patient registration book will be sent to MENTOR’s data department for data entry and cleaning. When the final database is considered clean, it will be locked and data analysis conducted by MENTOR.

The paper CRFs will be stored according to sponsor’s requirement unless local regulations require a longer timeframe.

All study data will be entered into the statistical software Stata 16.

Patient confidentiality will be assured by only using the unique patient ID on all study documents and databases.

## Handling photographs

Photographs of the lesions will also be taken using a dedicated mobile phone at study enrolment and at the 3-month follow-up visit. At least two good quality photos will be taken one with and one without the ID number.

Photographs will be sent to MENTOR’s medical coordinator and for safe storage and back up. These photographs will be kept by MENTOR and MORU so the morphologies can be correlated with the species identified by genetic testing from the swabs.

Permission will be sought to keep these photographs in perpetuity for academic purposes and possibly for inclusion in peer-reviewed publications.

At study end, all photographs will be sent to specialists to review blinded the photographs to determine the study primary outcome.

All photographs will be deleted from the HCW or research officer’s phone immediately after sending to the medical coordinator.

# QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with relevant regulations and standard operating procedures.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and all co-investigators are familiar with the contents of the Declaration of Helsinki.

## Guidelines for Good Clinical Practice

The Chief Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice. GCP training will be included at the prestudy training. Mentor will set up a system of monitoring of study conduct, CRF completion, source document verification, and database accuracy.

## Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to OxTREC and local ethics governing bodies, including district health offices, committees for written approval, as per local requirements.

Should there be amendments to the protocol, the above parties will be informed and provide approval before proceeding. This will be especially the case when approaching and discussing changes with the local governing bodies.

## Participant Confidentiality

All patients that enter the study will be kept anonymous and only identified by a unique ID number on all study documents, in electronic databases as well as during statistical analysis. This will be made clear to the participant. All paper documents will be stored in a locked cupboard, only accessible to the field coordinator and authorised personnel.

Data clerks hired for cleaning and sorting data will sign a confidentiality agreement to highlight the importance of not sharing with third parties. The study will also comply with the UK Data Protection Act 2018, which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

## Expenses and Benefits

No participants will be paid for their time as they are receiving free treatment. For those treated at the mobile clinics, follow-up appointments will be conducted at their homes, and, therefore, no travel costs are incurred by the participant. Patients treated at HFs will be asked to return for their follow-up appointments. If they fail to do so or express the wish to the followed-up at home, MENTOR staff will visit them at their homes.

## Reporting

MORU will submit an Annual Progress Report to OxTREC and the local EC on the anniversary of the date of approval of the study and an End of Study Report to OxTREC and local EC within 12 months of completion of the study.

## Other Ethical Considerations

This is a low risk study using two recommended treatments.

Thermotherapy, which has very limited availability in Syria, will be compared to the local standard, IL MA. It has been shown to be as effective or superior to IL injections in other trials. Therefore, no participant will receive a treatment known to be inferior to IL MA. Moreover, should one treatment fail, participants will be switched over to the other treatment.

In addition, cutaneous leishmaniasis does not discriminate against anyone based on sex, age, occupation or income, and as such a portion of patients will belong to the wider group of generally vulnerable people. As OWCL is usually highly visible, there is no added stigma to being in this trial.

The treatments will be offered in both health facilities as well as mobile clinics, which are able to reach even those who are particularly vulnerable and may not have ready access to health care services. All services will be free of charge, which allows for everyone to have access to the services regardless of their vulnerability status.

# FINANCE AND INSURANCE

## Funding

MENTOR uses existing funds to conduct the study.

The Wellcome Trust part funds Dr. Bob Taylor though it core grant (220211) to the Mahidol-Oxford Tropical Medicine Research Unit research programme.

## Insurance

The MENTOR Initiative maintains essential insurances and health authority agreements for its work in Syria and will ensure all due care and provision as needed, in the event of a patient suffering any harm as a direct result of their involvement in the therapeutic study.

# PUBLICATION POLICY

The data generated in this study belongs to the study group as a whole. The final database will be shared amongst the site PIs and key members of the research team.

The database may be shared with investigators not directly involved in this study but only after the main paper has been published and following MENTOR policies on data sharing. The database will only be shared if future publications are not compromised.

If WHO fund this study, it will have full access to all generated data and will be acknowledged in any publication as the main funding agency.

The criteria for authorship will be consistent with the international guidelines (<http://www.icmje.org/#author>).

# APPENDIX C: AMENDMENT HISTORY

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol Version No.** | **Date issued** | **Author(s) of changes** | **Details of Changes made** |
|  |  |  |  |  |