MaPs in ENL

The Erythema Nodosum Leprosum International STudy (ENLIST) Group

Methotrexate **a**nd **P**rednisolone **s**tudy
in
Erythema Nodosum Leprosum

Population A – Acute ENL
Population B – Recurrent or chronic ENL

ISRCTN
NCT *(clinicaltrials.gov)*

Version 3 20th November 2018

SPONSOR: London School of Hygiene & Tropical Medicine
FUNDERS: Leprosy Research Initiative 704.16.71
STUDY COORDINATION CENTRE: London School of Hygiene and Tropical Medicine

LSHTM ethics reference: 15762
Trial registration number: NCT03775460

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Funder
Leprosy Research Initiative 704.16.71

This protocol describes the MaPs in ENL study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALERT	All Africa Leprosy, Tuberculosis and Rehabilitation Training (ALERT) Centre
AHRI	Armauer Hansen Research Institute
ALT	Alanine aminotrasferase
AR	Adverse Reaction
AST	Aspartate aminotransferase
BL	Borderline lepromatous leprosy
CI	Chief Investigator
CTA	Clinical Trial Authorisation
DBLM	Danish Bangladesh Leprosy Mission
DLQI	Dermatology Life Quality Index
DSMB	Data and Safety Monitoring Board
ENL	Erythema nodosum leprosum
ENLIST	Erythema Nodosum Leprosum International STudy Group
EESS	ENLIST ENL Severity Scale
FA	Folic Acid
FBC	Full blood count
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
HRQOL	Health Related Quality of Life
IB	Investigator Brochure
ICH	International Council Harmonisation
IMP	Investigational Medicinal Product
LFT	Liver function test
LL	Lepromatous leprosy
LOCF	Last observation carry-forward
LSHTM	London School of Hygiene & Tropical Medicine
MaPs	Methotrexate and Prednisolone studies
MCV	Mean cell volume
MDT	Multi-drug therapy (Rifampicin, dapsone and clofazimine)
MTX	Methotrexate
NFI	Nerve function impairment
QOL	Quality of Life
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPc	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLMI	The Leprosy Mission International
TLMN	The Leprosy Mission Nepal
TLMTI	The Leprosy Mission Trust India
TNF	Tumour necrosis factor
ULN	Upper limit of normal
WBC	White blood cell

KEYWORDS
Leprosy; Erythema Nodosum Leprosum; Methotrexate; Prednisolone: Treatment; leprosy reactions; adverse events

SUMMARY

Methotrexate **a**nd **P**rednisolone **s**tudies in Erythema Nodosum Leprosum study (MaPs in ENL) aims to examinate the effect of methotrexate (MTX) and prednisolone on outcomes for individuals with ENL. The intervention and duration of participation is the same in both populations. Population A will enrol patients who have acute ENL whilst Population B will enrol those with recurrent and chronic ENL. The data for the two groups will be analysed separately because previous studies suggest that their response to treatment may differe. Individuals with chronic and recurrent ENL are more likely to have been on prolonged courses of high doses prednisolone[1].

POPULATION A SUMMARY

TITLE Methotrexate and Prednisolone studies in Erythema Nodosum Leprosum

DESIGN Randomised, double-blind controlled trial

AIMS To determine whether methotrexate and prednisolone is more efficacious than prednisolone alone in the management of **ACUTE** erythema nodosum leprosum

OUTCOME MEASURES

PRIMARY ENDPOINTS:

I. Proportion of individuals who have not required additional prednisolone during the first 24 weeks
II. Proportion of individuals who have not required additional prednisolone during the first 48 weeks

SECONDARY ENDPOINTS:

I. Change in ENLIST ENL Severity Scale score from baseline to the first flare of ENL requiring additional prednisolone
II. Change in patient reported health-related quality of life at 24 and 48 weeks from baseline
III. Proportion of individuals who do not require prednisolone at 60 weeks
IV. Number of flares of ENL per individual requiring additional prednisolone up to 60 weeks
V. The maximum severity of flares of ENL requiring additional prednisolone up to 60 weeks
VI. Time to the first flare of ENL after enrolment
VII. Proportion of individuals with treatment related adverse effects
VIII. Change in patient reported health-related quality of life at 60 weeks from baseline
IX. Proportion of individuals who have not required additional prednisolone in the 60 weeks of the trial

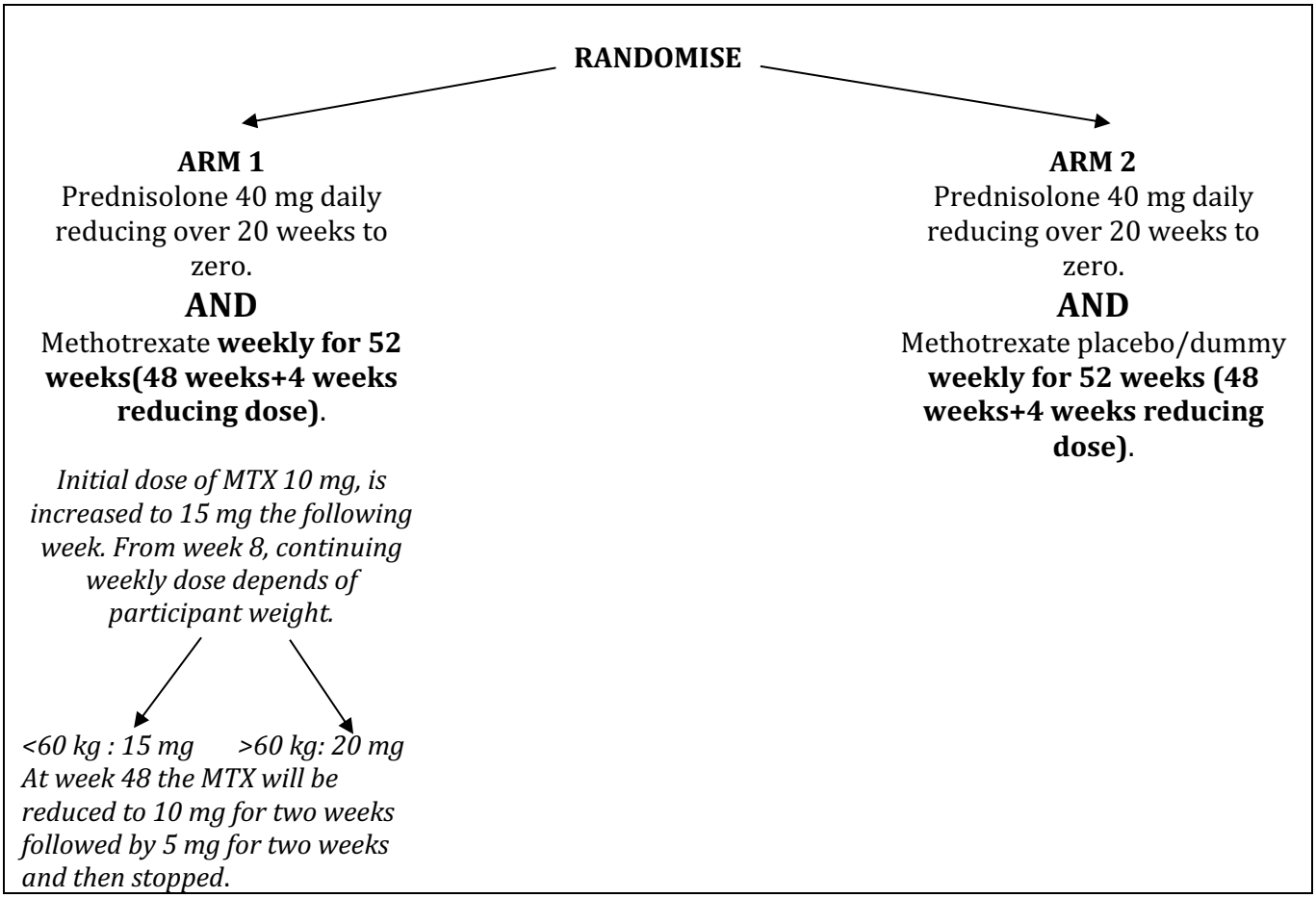
POPULATION Individuals with a confirmed diagnosis of leprosy attending leprosy referral centres.

Case definition of ENL, for the purpose of this study, is: an individual with BL leprosy or LL who develops 10 or more tender papular and/or nodular skin lesions.

NUMBER OF PARTICIPANTS We aim to recruit 150 participants, 75 participants for the control group and 75 participants for the intervention group.

ELIGIBILITY	**Individuals with acute erythema nodosum leprosum**
TREATMENT	Concurrent methotrexate and prednisolone versus prednisolone alone
DURATION	48 weeks of treatment: Arm 1 will take methotrexate for 48 weeks with prednisolone for the first 20 weeks concurrently. Arm 2 will take methotrexate placebo (dummy tablets) for 48 weeks with prednisolone for the first 20 weeks concurrently. Trial duration per participant 60 weeks

REFERENCE DIAGRAM



POPULATION B SUMMARY

TITLE Methotrexate and Prednisolone studies in Erythema Nodosum Leprosum

DESIGN Randomised, double-blind controlled trial

AIMS To determine whether methotrexate and prednisolone is more efficacious than prednisolone alone in the management of **RECURRENT** and **CHRONIC** erythema nodosum leprosum

OUTCOME MEASURES

PRIMARY ENDPOINTS:

I. Proportion of individuals who have not required additional prednisolone during the first 24 weeks
II. Proportion of individuals who have not required additional prednisolone during the first 48 weeks

SECONDARY ENDPOINTS:

I. Change in ENLIST ENL Severity Scale score from baseline to the first flare of ENL requiring additional prednisolone
II. Change in patient reported health-related quality of life at 24 and 48 weeks from baseline
III. Proportion of individuals who do not require prednisolone at 60 weeks
IV. Number of flares of ENL per individual requiring additional prednisolone up to 60 weeks
V. The maximum severity of flares of ENL requiring additional prednisolone up to 60 weeks
VI. Time to the first flare of ENL after enrolment
VII. Proportion of individuals with treatment related adverse effects
VIII. Change in patient reported health-related quality of life at 60 weeks from baseline
IX. Proportion of individuals who have not required additional prednisolone in the 60 weeks of the trial

POPULATION Individuals with a confirmed diagnosis of leprosy attending leprosy referral centres.

Case definition of ENL, for the purpose of this study, is: an individual with BL leprosy or LL who develops 10 or more tender papular and/or nodular skin lesions

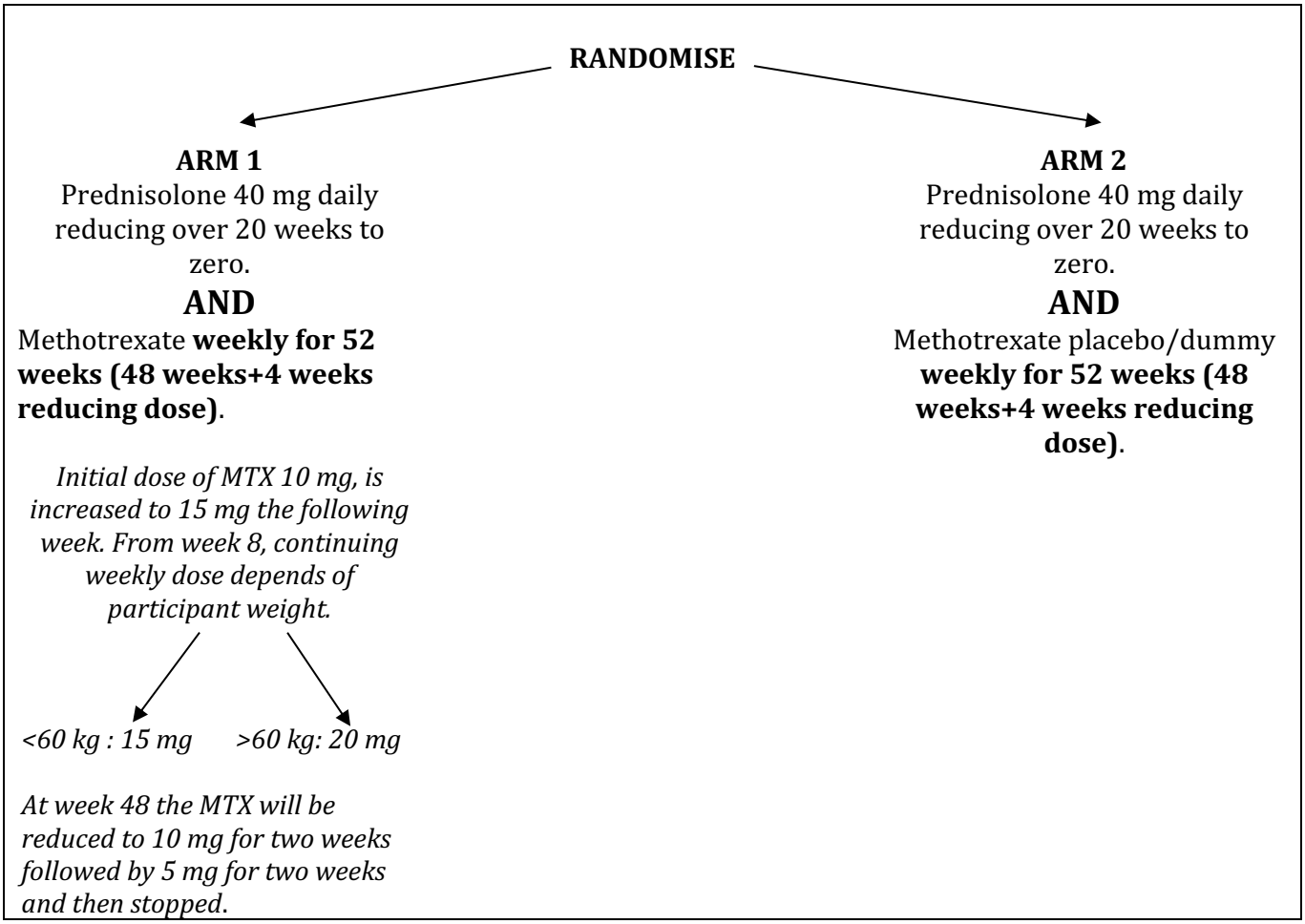
NUMBER OF PARTICIPANTS We aim to recruit 400 participants, 200 participants for the control group and 200 participants for the intervention group.

ELIGIBILITY **Individuals with recurrent or chronic erythema nodosum leprosum**

TREATMENT Concurrent methotrexate and prednisolone versus prednisolone alone

DURATION 48 weeks of treatment: Arm 1 will take methotrexate for 48 weeks with prednisolone for the first 20 weeks concurrently. Arm 2 will take methotrexate placebo (dummy tablets) for 48 weeks with prednisolone for the first 20 weeks concurrently.

REFERENCE DIAGRAM



1. INTRODUCTION

1.1 BACKGROUND

Erythema nodosum leprosum (ENL) is an immunological complication affecting individuals with lepromatous leprosy (LL)[2]. ENL affects up to 50% of individuals with LL and approximately 5-10% of borderline lepromatous (BL) leprosy patients [2, 3]. It is estimated that over 50, 000 of the new leprosy patients diagnosed each year are at risk of ENL. ENL may occur before, during or after successful completion of multi-drug therapy (MDT). The inflammatory state of ENL causes significant morbidity and if untreated may cause death. ENL is also associated with severe economic hardship[4]. Patients are treated with corticosteroids and/or thalidomide which are used for prolonged periods of many months or years. Many patients require high doses of corticosteroids to control their disease and this leads to complications and a significant number of deaths associated with long-term use of these drugs [5, 6]. Thalidomide is effective for many individuals with ENL but is not widely available in many countries because of its teratogenic effects. In countries where it is available it is often expensive.

ENL is a multisystem disorder characterised by crops of painful skin lesions, fever, arthralgia, arthritis, osteitis, dactylitis, lymphadenitis, iritis, orchitis and neuritis. A 10 item clinical severity score for ENL, the ENLIST ENL Severity Score (EESS) has been developed and recently validated by the ENLIST Group[7]. The range of scores possible is 0-30. The higher the score the more severe the ENL. A score of 9 or more has

been shown to be associated with more severe ENL. A change in score of 5 resulted in a meaningful difference in severity of ENL for the participants in the validation study.

The histology of ENL lesions classically shows an intense perivascular infiltrate of neutrophils throughout the dermis and subcutis [8]. Tissue oedema and vessels exhibiting fibrinoid necrosis may also be present. ENL has some features of an immune complex mediated disease. Direct immunofluorescence studies have demonstrated granular deposits of immunoglobulin and complement in the dermis in ENL lesions but not in those of uncomplicated LL disease [9]. There is evidence of T lymphocyte and macrophage activation and expression of mRNA for TNFα and interleukin (IL)-12 in the skin [10]. The ratio of CD4:CD8 cells is increased in ENL compared to uncomplicated LL in both cutaneous lesions and the blood [11,12]. High levels of circulating TNFα have been demonstrated in the plasma of individuals with ENL [13]. *In vitro* peripheral blood mononuclear cells from individuals with ENL secrete increased amounts of TNFα following stimulation by *M. leprae* or *M. leprae* antigens compared to individuals with other forms of leprosy [14]. However we do not understand why some individuals develop ENL and others do not[15]. We also do not understand why some individuals have single acute episodes of ENL and others develop chronic forms lasting many years.

The MaPs in ENL trial will be the first to use a validated severity scale of ENL which will represent a major development in evidence based therapeutics for ENL.

There are reports, including a case series, of MTX having a beneficial effect in the management of ENL. [16-18]. However there are no controlled trials of MTX in ENL. The pro-inflammatory cytokine IL-6 has been reported to be increased in the plasma of patients with ENL [19]. Single nucleotide polymorphisms in the *IL-6* gene are associated with the increased circulating levels of IL-6 in Brazilian patients with ENL [19]. Thalidomide has been shown to suppress circulating levels of plasma IL-6 in patients with ENL and reduce it in experimental inflammation in healthy controls[20]. MTX has also been reported to reduce IL-6 levels in patients with psoriasis[21]. Th17 lymphocyte subset has been shown to be expressed in the skin biopsies of patients with ENL before and after treatment with thalidomide[22]. The authors concluded that Th17 cells are involved in the immunopathogenesis of ENL. MTX has been shown to suppress IL-17 release by blood monocytes from patients with rheumatoid arthritis[23].

MTX has been in clinical use since the 1950s. It is affordable and widely available throughout the world and in leprosy endemic countries. Dermatologists and leprologists worldwide are familiar and comfortable with using MTX. It is used to treat immune regulated, TNFα driven inflammatory conditions such as psoriasis and rheumatoid arthritis in doses between 7.5 mg and 25 mg once **weekly**. It has a role in the management of systemic vasculitis and neutrophilic dermatoses, which share some clinical and histopathological similarities with ENL[24, 25]. MTX is also useful in the management of the multi-system disorder Beçhet's disease which is thalidomide responsive as is ENL[26]. In the doses used to treat psoriasis (and those proposed for these studies) MTX depletes the intracellular pool of folate by inhibiting dihydrofolate reductase, thymidylate synthase and other enzymes [27]. Large numbers of patients with moderate to severe psoriasis or rheumatoid arthritis take MTX for many years [28]. The use of prolonged oral MTX therapy in inflammatory conditions is longstanding and has been assessed in a clinical trial of chronic inflammatory demyelinating polyradiculoneuropathy with a total treatment period of 40 weeks at similar doses to those we propose[29].

1.2 RATIONALE FOR CURRENT STUDY

Thalidomide is not available in many leprosy endemic countries (such as Bangladesh, Ethiopia,the Philippines and Malaysia) or is severely restricted (Nepal, Indonesia) because of the risk of teratogenicity. Thalidomide is also associated with adverse effects such as somnolence, nausea, neurotoxicity, dizziness and thromboembolism which may limit its use. The identification of other agents for controlling ENL is a priority[30]. Since the introduction of MDT there have been eight randomised controlled trials involving just 269 individuals (median 33 [range 10-80]) and all were subject to significant methodological issues.

We hypothesise that MTX used in conjunction with prednisolone for ENL will improve the clinical outcomes for patients with ENL. The activation process of MTX within cell is slow and takes up to 27 weeks to reach

a stead state. This explain the delay in clinical response in patients using MTX. Given the slow onset of action of MTX, the most effective treatment of ENL would be an initial 20 week course of prednisolone combine with MTX[31].

Our research question is: do patients with ENL receiving MTX have fewer numbers of exacerbations of ENL and therefore require less additional prednisolone?

The potential benefits are that clinicians would have sound evidence for using MTX in patients with ENL and that outcomes would be improved.

The potential risks are that individuals would experience MTX related adverse events.

For the purposes of the study the case definition of ENL is: an individual with BL leprosy or LL who develops 10 or more tender papular and/or nodular skin lesions.

2. STUDY OBJECTIVES

PRIMARY:

I. To determine whether a 48 week course of methotrexate (and prednisolone) treatment reduces the requirement for additional prednisolone in individuals with ENL at 24 weeks compared to individuals who receive prednisolone alone

II. To determine whether a 48 week course of methotrexate (and prednisolone) treatment reduces the requirement for additional prednisolone in individuals with ENL at 48 weeks compared to individuals who receive prednisolone alone

SECONDARY:

I. To determine whether a 48 week course of methotrexate (and prednisolone) treatment results in a greater change in ENLIST ENL Severity Scale score at 48 weeks, compared to individuals who receive prednisolone alone

II. To determine whether a 48 week course of methotrexate (and prednisolone) treatment results in a greater change in health-related quality of life in individuals with ENL at 48 weeks compared to individuals who receive prednisolone alone

III. To determine whether a 48 week course of methotrexate (and prednisolone) treatment reduces the requirement for additional prednisolone in individuals with ENL, during the study period of 60 weeks, compared to individuals who receive prednisolone alone

IV. To determine whether a 48 week course of methotrexate (and prednisolone) treatment reduces the number of ENL flares in individuals with ENL, during the study period of 60 weeks, compared to individuals who receive prednisolone alone

V. To determine whether a 48 week course of methotrexate (and prednisolone) treatment reduces the severity of ENL flares in individuals with ENL, during the study period of 60 weeks, compared to individuals who receive prednisolone alone

VI. To determine whether a 48 week course of methotrexate (and prednisolone) treatment would increase the proportion of individuals who have not required additional prednisolone during the study period of 60 weeks

VII. To determine whether a 48 week course of methotrexate (and prednisolone) treatment results in fewer adverse effects in individuals with ENL, during the study period of 60 weeks, compared to individuals who receive prednisolone alone

VIII. To determine whether a 48 week course of methotrexate (and prednisolone) treatment results in a greater change in health-related quality of life in individuals with ENL at 60 weeks from baseline, compared to individuals who receive prednisolone alone

IX. To determine whether methotrexate and prednisolone are associated with a prolonged time to the next flare of ENL compared to prednisolone alone

3. STUDY DESIGN

Population A (Acute ENL)
If methotrexate treatment reduces recurrence by 30% (i.e. ENL recurs in 37% rather than 67% as in the published study by Kaur et al[32] then for 90% power with α=0.05 the number of participants required in each arm of this randomised controlled trial is 57[32]. Assuming 20% loss to follow up we require 142 participants. We aim to recruit 150 participants.

Population B (Recurrent/ Chronic ENL)
If methotrexate treatment increases the proportion of patients taking 50% less prednisolone at the end of the study by 20% (assuming that 20% of those taking prednisolone will achieve this target and 40% in the methotrexate group i.e. twice the proportion in the methotrexate arm) then for 90% power with α=0.05 the number of participants required in each arm of this randomised controlled trial is 109. Assuming 20% loss to follow up we require 273 participants. We aim to recruit 400 participants for this study.

This is a randomised, double-blind positive controlled study. A screening log will be kept at all participating centres to ensure that data is captured on all individuals considered for the trial. Block randomisation in groups of four using a table of random numbers will be used. A standard envelope system will be used for allocation concealment. The envelopes will be pre-packed in London. The allocation procedure will be decentralised and operated solely by the chief pharmacist at each site who will keep a separate record of the allocation.

The individuals in the control arm will receive a reducing course of prednisolone for 20 weeks. The individuals in the experimental arm will receive a reducing course of prednisolone for 20 weeks and methotrexate for 48 weeks which will then be reduced to zero over a further four weeks.

Population A 150 participants, 75 in control and 75 in experimental arm
Population B 400 participants, 200 in control and 200 in experimental arm

Multi-centre, multi-country study taking place in leprosy referral centres.

Country	**Centre**	**Centre Lead Investigator**
Bangladesh (Nilphamari)	DBLM Hospital	Dr Benjamin Jewel
Brazil (Rio de Janeiro)	FIOCRUZ	Dr. Jose' Nery
Ethiopia (Addis Ababa)	ALERT Center	Dr Shimelis Doni
India (Mumbai)	Bombay Leprosy Project	Dr Vivek Pai
India (Deli)	TLMTI Deli	Dr Joydeepa Darlong
Indonesia (Surabaya)	Dr. Soetomo Hospital	Dr. Alinda Medhi
Nepal (Kathmandu)	The Leprosy Mission Nepal, Anandaban Hospital	Dr. Mahesh Shah

3.1 STUDY OUTCOME MEASURES

PRIMARY ENDPOINTS:

I. Proportion of individuals who have not required additional prednisolone during the first 24 weeks
II. Proportion of individuals who have not required additional prednisolone during the first 48 weeks

SECONDARY ENDPOINTS:

I. Change in ENLIST ENL Severity Scale score from baseline to the first flare of ENL requiring additional prednisolone
II. Change in patient reported health-related quality of life at 24 and 48 weeks from baseline
III. Proportion of individuals who do not require prednisolone at 60 weeks
IV. Number of flares of ENL per individual requiring additional prednisolone up to 60 weeks
V. The maximum severity of flares of ENL requiring additional prednisolone up to 60 weeks
VI. Time to the first flare of ENL after enrolment
VII. Proportion of individuals with treatment related adverse effects
VIII. Change in patient reported health-related quality of life at 60 weeks from baseline
IX. Proportion of individuals who have not required additional prednisolone in the 60 weeks of the trial

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 PRE-RANDOMISATION OR PRE-REGISTRATION EVALUATIONS

1. Clinical examination
2. Full blood count
3. Blood glucose
4. Renal function including potassium and creatinine
5. Liver function tests: bilirubin and transaminases
6. Urine pregnancy test for women of child bearing potential
7. Hepatitis B serology
8. Hepatitis C serology
9. HIV antibody test
10. ENL Severity Scale

CHEST XRAY SHOULD BE OBTAINED AND REPORTED WITHING 72 HOURS OF RECRUITMENT TO RULE OUT TB AND FIBROSIS, BUT WHERE POSSIBLE BEFORE RANDOMISATION

4.2 INCLUSION CRITERIA

POPULATION A

All of the following six criteria must be met in order for an individual to be eligible (only one of 6a-d need be met):

1. Individuals diagnosed with leprosy complicated by ENL
2. Individuals with **acute** ENL aged 18-60 years old
3. Individuals with **acute** ENL with deteriorating symptoms
4. Individuals with 10 or more tender, papular or nodular ENL skin lesions
5. Individuals with an EESS score of at least 9
6. Individuals with **acute** ENL:

a. On no current anti- ENL treatment

OR

b. **On up to 30mg** per day or equivalent alternative corticosteroid dose

OR

c. On thalidomide or other anti-ENL medication

OR

d. On a combination of prednisolone (up to 30mg) and another anti-ENL medication (thalidomide, clofazimine, azathioprine, pentoxifylline, ciclosporin, minocycline)

Acute ENL is defined as occurring if a patient has either a first episode of ENL less than 24 weeks duration or experiences a second or subsequent episode of ENL which lasts less than 24 weeks and occurs 84 days (ie 12 weeks) or more after stopping treatment for ENL (Adapted from Walker et al).[5]

POPULATION B

All of the following six criteria must be met in order for an individual to be eligible (only one of 6a-d need be met):

1. Individuals diagnosed with leprosy complicated by ENL
2. Individuals with **recurrent or chronic** ENL aged 18-60 years old
3. Individuals with **recurrent or chronic** ENL with deteriorating symptoms
4. Individuals with 10 or more tender, popular or nodular ENL skin lesions
5. Individuals with an EESS score of at least 9
6. Individuals with **recurrent or chronic** ENL:
    a. On no current anti- ENL treatment

    OR

    b. On prednisolone **10-30mg** per day (**inclusive**) or equivalent alternative corticosteroid dose

    OR

    c. On thalidomide or other anti-ENL medication

    OR

    d. On a combination of prednisolone (up to 30mg) and another anti-ENL medication (thalidomide, clofazimine, azathioprine, pentoxifylline, ciclosporin, minocycline)

The difference in the inclusion criteria between the two populations above is section 6b.

Recurrent ENL is defined as occurring if a patient experienced a second or subsequent episode of ENL occurring between 28 and 84 days of stopping treatment for ENL (Adapted from Walker et al).

Chronic ENL is defined as occurring for more than 24 weeks during which a patient has required ENL treatment either continuously or where any treatment free period had been 27 days or less[5].

4.3 EXCLUSION CRITERIA

Any of the following will result in an individual being excluded from the study:

1. Individuals who were first diagnosed with ENL **more** than **4 years** prior to enrolment
2. Individuals less than 18 years old or older than 60 years
3. Individuals weighing less than 35kg
4. Individuals with 9 or fewer tender, popular or nodular ENL skin lesions
5. Individuals with an EESS score of 8 or less
6. Women of child bearing capacity who decline to use two forms of adequate contraception and men who intent to impregnate his partner during the period of the study.
7. Pregnant or breastfeeding women

8. Individuals with recurrent or chronic ENL who deteriorate on a dose of prednisolone **less** than 10 mg or **more** than 30 mg
9. Individuals who have taken methotrexate by any route for the last 12 weeks
10. Individuals with a hypersensitivity to methotrexate or a recognised contraindication (please see Methotrexate information sheet)
11. Individuals currently diagnosed with Type 1 reaction or Lucio's phenomenon
12. Individuals with the following abnormalities in screening investigations
    - Hemoglobin < 10 g/dL
    - White blood cells < 3.0 x 10^9/l
    - Neutrophils < 1.5 x 10^9/l
    - Platelets < 100 x 10^9/l
    - AST and ALT > 2 times the upper limit of normal range
    - Bilirubin > 5mg/dl (85,5 µmol/l)
    - Hypoalbuminemia <3.5 g/dl
13. Positive serology for HIV, Hepatitis B or C
14. Evidence of tuberculosis or pulmonary fibrosis
15. A history of chronic liver disease or excessive alcohol or illicit substance consumption
16. Individuals with severe inter-current infections, uncontrolled diabetes, active peptic ulcer disease, untreated malignancy
17. Individuals unable to attend regularly for assessment or monitoring

4.4 WITHDRAWAL CRITERIA

Participants will be withdrawn from the study immediately if any of the following occur:

- Clinically significant abnormal laboratory results that preclude continuation of study medication, as determined by the Investigator and/or including any of the following:
    - AST or ALT > 3 × ULN
    - Serum total bilirubin > 3mg/dl × ULN
    - Serum creatinine > 3 × ULN
    - Hemoglobin < 8 g/dL
    - WBC count < 2 x10^9 cells/l
    - Platelet count < 75 x10^9 cells/l
- AEs that preclude continuation of study medication, as determined by the Investigator
- The Investigator believes it is in the best interest of the participant
- The participant or participant's legally acceptable representative requests withdrawal from the study,
- Severe uncontrolled ENL (ie uncontrolled by 60mg/day, which is maximum possible in trial protocol)
- Selection criteria violation was noted after the participant started study drug, and the Investigator determines that the participant should be discontinued.
- Participant becomes pregnant during the study
- Participant is not compliant with study procedures/visits and study drug administration determined by the Investigator
- Participants with a new diagnosis of malignancy (other than successfully treated basal cell carcinoma) during the study will need to be discontinued from the study.
- Participants developing active tuberculosis at any time during the study must be withdrawn from the trial.

If, during the course of the study, the participant must be prematurely discontinued, the procedures outlined for the Early Termination Visit must be completed at that visit or within 2 weeks of the last dose of study drug, and prior to the initiation of another therapy. However, these procedures should not interfere

with the initiation of any new treatments or therapeutic modalities that in the Investigator's opinion are necessary to treat the participant's condition. Following discontinuation of the study drug, the participant will be treated in accordance with the Investigator's best clinical judgment. All attempts must be made to determine the date of last dose and the primary reason for Early Termination. This information will be entered into the appropriate CRF.

At the sponsor's discretion, the entire study may be stopped for any reason. The entire study may be stopped if in the judgment of the Sponsor, the continued exposure to the study medication represents a significant risk to participants. In addition, a site may be discontinued at any time by the Sponsor and all study materials removed. Possible reasons for termination of the study at a site include, but are not limited to:

- Safety concerns based on reported data
- Unsatisfactory enrolment with respect to quantity or quality
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol

In accordance with the informed consent and the Declaration of Helsinki, any participant can refuse to participate or withdraw from the study without giving reasons at any time without any penalty or loss of benefits to which the participant is otherwise entitled. When appropriate, participants may be placed on other conventional therapy when clinically indicated. If the participant withdraws consent, no further evaluations will be performed and no attempts should be made to collect additional data. Data collected up to that point will be held in accordance with the study procedures

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES

Participants will be randomly allocated to one of the two study arms using randomisation tables provided by the statistician. Drugs will be labelled accordingly by the manufacturer. The key will be held by the International Coordinated, Study Manager and PI of each centre and will be broken after the data analysis is completed or earlier for patients with severe events as defined by the protocol.

The packaging of placebo/dummy and prednisolone tablets will be the responsibility of the IC and SM in such a way that random allocation can be effectuated. The key will be held by the IC and SM.

This process will be done as follows:
1. Ordering of 5mg prednisolone tablets.
2.Depending on the participant weight methotrexate tablets must be prepared for each patient, this can be done in weekly pots, which are numbered for randomization by the IC and SM. The same will be done for the placebo/dummy tablets.
3. The drugs thus prepared will be shipped to the various collaborating centres, whereby each centre will receive an equal number of treatments for the two arms of each trial, based on the expected number of study subjects they will be able to take in.
4. If it would be more feasible to prepare the medication at the local level (e.g. due to import restrictions and regulations), the PI can take care of it's preparation and an instruction will be prepared on how to do this. An initial visit of the SM will take care of the randomization.
5. Patients are allocated to the various studies based on predefined criteria, but in each of the studies the local PI will not know which regimen was prescribed to which subject.
6. The key is only broken before the end of the follow-up period for those patients that suffer from complications that could be due to the use of steroids. Breaking the key will be done by the SM and IC in written (by email, on request of a PI).

7. At the end of the follow-up period of 60 weeks, and after the analysis of results in the different arms of the two trials has been finalized, the key will be broken by the IC and SM.

5.2 UNBLINDING

The site receives sealed emergency envelopes for each patient. The envelope contains the information about which treatment is assigned to the participant. The envelope should only be opened by the study site investigator in case of emergency when it is essential for effective treatment of the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat the patient. The PI is to be informed immediately about any unblinding procedure. The documentation of the unblinding must contain the name of the study personnel performing the unblinding, the date of unblinding and the reasons that led to unblinding and has to be reported on the blind break form filed in the investigators site file. The PI will inform the sponsor about any unblinding procedure immediately. AEs or SAEs related to the unblinding have to be appropriately reported.
The investigators are advised not to reveal the study treatment assignment to the site monitor or sponsor personnel. Study medication must be discontinued after unblinding.

6. STUDY MEDICATION

6.1 Methotrexate and prednisolone
Methotrexate placebo/dummy

- Methotrexate is an inhibitor of the enzyme dihydrofolate reductase
- Prednisolone is an oral corticosteroid agent

6.2 Legal status of drug

Methotrexate is licensed for use in the UK and all countries participating in the study. The indications for use in the oral weekly doses being employed are: Crohn's disease, rheumatoid arthritis and psoriasis. Prednisolone is a licensed for use in the UK and all countries participating int the study. The indications for use in ENL are well established and supported by WHO guideline.

6.3 Summary of Product Characteristics (SmPC) or Investigator Brochure (IB)

We will use the following: Methotrexate 2.5mg Tablets - Summary of Product Characteristics (SPC) – eMC (http://www.medicines.org.uk/emc/medicine/22954/SPC) Updated versions will be incoporated into all relevant trial documentation with four weeks of becoming available. The trial manager will ensure the SPC is the most recent every 3 months.

6.4 Drug Storage and Supply

The MTX/placebo/dummy study drug supplies for oral administration must be stored between 15° to 25°C. The controlled storage area should have a temperature-recording device. The site coordinator will advise study subjects regarding an appropriate area for storage of the oral MTX/placebo/dummy.

6.5 Preparation and labelling of IMP

The preparation of IMP will be decentralised and operated solely by the chief pharmacist at each site.

6.6 Dosage schedules/modifications

Time from enrolment	Arm A		Arm B	
	All participants in Arm A will receive an initial dose of MTX 10 mg. The MTX will be increased to 15 mg the following week. Participants weighing less than 60 kg will continue to receive 15 mg of MTX weekly thereafter. Individuals weighing 60 kg or more will receive MTX 20 mg from week 8. At week 48 the MTX will be reduced to 10 mg for two weeks followed by 5 mg for two weeks and then stopped.		**Participants weighing less than 60 kg will receive 6 dummy tablets from week 8. Participants weighing 60 kg or more will receive 8 dummy tablets from week 8.**	
Week	**Methotrexate** (mg/**WEEK**) (MTX tablets will be 2.5 mg)	**Prednisolone** (mg/**day**)	**Prednisolone** (mg/**day**)	**DUMMY** Methotrexate (Number of tablets/**WEEK**)
0	**10**	**40**	**40**	**4**
1	**15**	**40**	**40**	**6**
2	15	35	35	6
3	15	35	35	6
4	15	30	30	6
5	15	30	30	6
6	15	25	25	6
7	15	25	25	6
8	**15/20**	**20**	**20**	**6/8**
9	15/20	20	20	6/8
10	15/20	20	20	6/8
11	15/20	20	20	6/8
12	15/20	15	15	6/8
13	15/20	15	15	6/8
14	15/20	15	15	6/8
15	15/20	15	15	6/8
16	15/20	10	10	6/8
17	15/20	10	10	6/8
18	15/20	5	5	6/8
19	15/20	5	5	6/8
20-47	**15/20**	**0**	**0**	**6/8**
48	10	0	0	4
49	10	0	0	4
50	5	0	0	2
51	5	0	0	2
52-59	**0**	**0**	**0**	**0**

In the event of abnormalities in monitoring investigations the following dosage modifications will be made[33]:

Abnormality	**Action**	**Follow up**
Total WBC count < 3.0 x10^9 cells/l	Withhold MTX	If repeat labs are < 3.0 x10^9 cells/l then withdraw participant
Neutrophils < 1.0 x10^9 cells/l (if available)	Withhold MTX	
Platelets < 100 x10^9 cells/l	Withhold MTX	If repeat platelets are < 100,000/mm3 then withdraw participant
MCV > 105 fl (if available)	Consider withholding dose of MTX; check serum B12, folate and thyroid function tests	
AST and ALT increased by less than two times the ULN	Continue MTX. Repeat LFTs in 2–4 weeks	If LFTs are less than twice ULN continue MTX and monitor again in 4 weeks
AST and ALT greater than 2 but less than or equal to 3 times the ULN	Withhold MTX; Repeat LFTs in 4 weeks Consider other risk factors (including alcohol consumption)	If LFTs are less than twice ULN resume MTX and monitor again in 4 weeks
AST and ALT greater 3 times the normal	Withdrawal from study	Monitor until normal or cause identified
New or increasing dyspnoea or cough	Withhold MTX; repeat chest X-ray	Treat according to investigations
Severe sore throat, abnormal bruising	Withhold MTX; check FBC immediately	Treat according to investigations
Creatinine > 2 × ULN	Withhold MTX. Repeat in 4 weeks	If repeat creatinine > 2x ULN withdraw participant

6.7 Known drug reactions and interaction with other therapies

The interactions are listed below in concomitant medication (section 6.8).

In patients with ENL who may still be taking MDT the **DAPSONE** component must be stopped. This has no significant effect on the anti-mycobacterial effect of MDT and is consistent with WHO policy in individuals unable to take dapsone for other reasons[34]. It is safe to initiate MTX after 24 hs after stopping dapsone.

6.8 Concomitant medication

Medications contraindicated with MTX (absolute contraindication in bold)

Mechanism	Drug
Decreased renal elimination of MTX	Nephrotoxins (e.g., amino-glycosides, cyclosporine)
	Salicylates
	Phenylbutazone
	Sulfonamides
	Probenecid
	Cephalothin
	Penicillins
	Colchicine
	Many NSAIDs (e.g., naproxen, ibuprofen, etc.)
	Omeprazole3
Additive or synergistic toxicity (including any drug inhibiting folic acid pathway)	**Trimethoprim-sulfamethoxazole/co-trimoxazole (BACTRIM)**
	Olanzapine
	Ethanol
	Pyrimethamine
	Triamethamine
MTX displacement from protein binding	**Sulfonamides (DAPSONE)**
	Salicylates
	Probenecid
	Barbiturates
	Phenytoin
	Retinoids
	Sulfonylureas
	Tetracycline
Intracellular accumulation of MTX	Dipyridamole
Hepatotoxicity	**Leflunomide**
	Ethanol
	Retinoids

Prescribers are advised to consult the SPC for MTX for potential drug-MTX interactions prior to prescribing. Participants will be advised to always tell prescribers that they are participating in a clinical trial of MTX and will be given a card to carry with them that they can show to prescribers. Participants will be advised not to take any medication that is not recommended by a study physician.

6.9 Trial restrictions

Women of childbearing potential must undergo monthly pregnancy testing during the study and agree to use two of the following methods of contraception throughout the study and for 6 months after the last dose of study drug:

- Oral contraceptives;
- Transdermal contraceptives;
- Injectable or implantable methods;
- Intrauterine devices; and
- Barrier methods

Sexually active male subjects (including males who have had a vasectomy) are able to participate in the study if they undertake effective contraception during the study and 6 months after study completion.

6.10 Assessment of compliance

Participants will be counselled on missed doses of medication. The site should question the participant and obtain as much information as possible as to the dosing of the oral MTX/placebo/dummy and prednisolone.

6.11 Name and description of each Non-Investigation Medicinal Product (NIMP)

- Folic acid 5 mg daily for the first 52 weeks of the study except on the day of methotrexate treatment
- Ranitidine 300 mg daily whilst on oral corticosteroids
- Ivermectin 200 microgrammes/Kg body weight daily for two days **OR** albendazole 400 mg twice daily for 3 days at enrolment. Further anti-helminthics can be given at physician's discretion.
- Paracetamol up to a daily maximum of 1 gramme every 6 hours (not to exceed 4g in a 24 hour period)
- Tramadol 50-100 mg every 4-6 hours (not to exceed 400 mg in a 24 hour period)
- Ondansetron 8 mg 2 hours prior to and repeated 12 hours after taking methotrexate if required
- **Osteoporosis prevention therapy (calcium carbonate plus vitamin D3 supplementation and biphosphonates when indicated according availability and guidelines of each centre)**

7. SAFETY REPORTING FOR DRUG TRIALS

7.1 DEFINITIONS

Term	Definition
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. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.
Adverse Reaction (AR)	Any 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 patient 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.
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 brochure (IB) relating to the trial in question.

7.2 CAUSALITY

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related side effects due to the drugs used in this study. The assignment of causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists, the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, both points of view are to be reported.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3 REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given in appendix to aid in the reporting procedures.

7.3.1 Non serious Adverse Reactions (ARs)/Adverse Events (AEs)

All AEs and ARs will be recorded in the CRF.

7.3.2 Serious Adverse Reactions (SARs)/Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information. The CI (for a single-centre trial) or PI (for a multi-centre trial) must record the event with an assessment of seriousness, causality and expectedness.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

7.3.3 SUSARs

All SAEs assigned by the PI or delegate as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Regulatory Authority, in the UK: Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor (or delegate) will inform the MHRA, and the ethics committee of UK-relevant SUSARs within the required expedited reporting timescales (as per LSHTM Standard Operating Procedure for recording, managing and reporting of adverse events for IMP studies).

All SUSARs will be reported assuming the active compound is involved.

In the case of a suspected, unexpected, serious adverse reactions (SUSAR), the staff at the site should:

1. Contact the study coordination centre immediately by phone or email to inform them of the event.
2. Submit a completed SAE form (signed and dated) within 24 hours, together with relevant treatment forms and anonymised copies of all relevant investigations.
3. Submit any additional information promptly upon request.

Contact details for reporting SAEs and SUSARs
Please send SAE forms to: Barbara.de-barros@lshtm.ac.uk
Tel: +442079272316(Mon to Fri 09.00 – 17.00)

8. ASSESSMENT AND FOLLOW-UP

All participants are followed for a total of **60 weeks**. They will be assessed clinically and with monitoring blood tests including a full blood count, renal function and liver function tests. Assessments will be performed weekly for the first three weeks

Day	Week	Methotrexate (mg/WEEK) (MTX tablets will be 2.5 mg)	Prednisolone (mg/day)	Assessments	Investigations	Population A Endpoints*	Population B Endpoints*
1	**0**	**10**	**40**	**1**	Baseline (see section 4.1)		
8	**1**	**15**	**40**	**2**	FBC/Renal/LFT		
15	2	15	35	3	FBC/Renal/LFT		
22	3	15	35				
29	4	15	30	4	FBC/Renal/LFT/ Glucose Urine pregnancy test		
36	5	15	30	-			
43	6	15	25	-			
50	7	15	25	-			
57	**8**	**15/20**	**20**	**5**	FBC/Renal/LFT/ Glucose Urine pregnancy test		
64	9	15/20	20				
71	10	15/20	20	6	FBC/Renal/LFT		
78	11	15/20	20				

85	12	15/20	15	7	FBC/Renal/LFT/ Glucose Urine pregnancy test		
92	13	15/20	15				
99	14	15/20	15				
106	15	15/20	15				
113	16	15/20	10	8	FBC/Renal/LFT/ Glucose Urine pregnancy test		
120	17	15/20	10	-			
127	18	15/20	5	-			
134	19	15/20	5				
141	20	15/20	0	9	FBC/Renal/LFT/ Glucose Urine pregnancy test		
148	21	15/20	0				
155	22	15/20	0				
162	23	15/20	0				
169	24	15/20	0	10	FBC/Renal/LFT/ Glucose Urine pregnancy Test + DLQI+SF-36	**PRIMARY OUTCOME (I)**	**PRIMARY OUTCOME (I)**
176	25	15/20	0				
183	26	15/20	0				
190	27	15/20	0				
197	28	15/20	0	11	FBC/Renal/LFT/ Urine pregnancy test		
204	29	15/20	0				
211	30	15/20	0				
218	31	15/20	0				
225	32	15/20	0	12	FBC/Renal/LFT/Urine pregnancy test		
232	33	15/20	0				
239	34	15/20	0				
246	35	15/20	0				
253	36	15/20	0	13	FBC/Renal/LFT Urine pregnancy test		
260	37	15/20	0				
267	38	15/20	0				
274	39	15/20	0				
281	40	15/20	0	14	FBC/Renal/LFT Urine pregnancy test		
288	41	15/20	0				
295	42	15/20	0				
302	43	15/20	0				
309	44	15/20	0	15	FBC/Renal/LFT Urine pregnancy test		
316	45	15/20	0				
323	46	15/20	0				
330	47	15/20	0				
337	48	15/20	0	16	FBC/Renal/LFT/ Glucose Urine pregnancy	**PRIMARY OUTCOME (II)**	**PRIMARY OUTCOME (II)**

					Test + DLQI+SF-36	**SECONDARY OUTCOMES (I and II)**	**SECONDARY OUTCOMES (I and II)**
344	49	10	0				
351	50	10	0				
358	51	5	0				
365	52	5	0	17	FBC/Renal/LFT Urine pregnancy test		
372	53	0	0				
379	54	0	0				
386	55	0	0				
393	56	0	0	18	Urine pregnancy test** FBC/Renal/LFT (If abnormal at previous visit)		
400	57	0	0				
407	58	0	0				
414	59	0	0				
421	60	0	0	19	Urine pregnancy test** FBC/Renal/LFT (If abnormal at previous visit) +DLQY+SF-36	**SECONDARY OUTCOME (III-VII)**	**SECONDARY OUTCOME (III-VII)**

*Secondary endpoint VIII may occur at any point during the trial.
**Urinary pregnancy test at visit 18 and 19 must be performed in all female participants with childbearing capacity, general advise is to avoid pregnancy for six months after stopping treatment.The other investigations need only be done in individuals who had abnormal results at the previous visit or when there is a clinical indication.

8.1 MANAGEMENT PROCEDURE FOR CLINICAL DETERIORATION

Participants who experience a deterioration should be treated with prednisolone in addition to the study intervention. A participant can receive additional prednisolone more than once or another increase during the additional course, if indicated by a flare.

The indications for additional prednisolone are:

1. A flare or deterioration in ENL
   i. ENL symptoms and/or signs resulting in an increased EESS score to 9 or more
   ii. an increase in EESS score of 5 or more
   iii. Orchitis not responding to conservative management
   iv. Iritis not responding to topical steroids/mydriatics

2. New or a deterioration in NFI
   i. motor impairment - a two grade change in MRC Grade
   ii. sensory impairment - loss of ability to feel 2 g on the hands or 10 g on the feet at three points.

3. Leprosy Type 1 reaction

The amount of additional prednisolone to be used:

Flare or deterioration in ENL

- Individuals requiring additional prednisolone whilst on prednisolone should have a daily regime of 20mg for one week followed by 15mg for two weeks, 10mg for two weeks and 5 mg for three weeks (20/15/15/10/10/5/5/5) *added* to the reducing regime they are currently

taking. **In individuals who have flared at the start of the 15mg part of the steroid intervention regime** the combination of reducing additional prednisolone and the initial prednisolone reducing course would mean that they would stop prednisolone at a dose of 10 mg per day. An additional week of prednisolone 5 mg daily should be prescribed at week 9 for these individuals.

- A flare of ENL in an individual not on prednisolone should be treated with the 20 week regime of the study. Starting at prednisolone 40 mg per day.

New or deterioration in NFI

- Patients experiencing significant NFI associated with ENL should be treated with the 20 week regime used in the study. Starting at prednisolone 40 mg per day.

Leprosy Type 1 reaction

- Participants experiencing a Type 1 reaction should be treated with the 20 week regime of the stydy. Starting at prednisolone 40 mg per day.

8.2 LOSS TO FOLLOW-UP

Any participant not attending their appointed follow up appointment will be contacted by the investigators or their representative.

8.3 TRIAL CLOSURE

The end-of-study is defined as the date of the last subject's last scheduled visit or the actual date of the follow-up contact, whichever is longer.

9. STATISTICS AND DATA ANALYSIS

The primary objectives of the statistical analyses are to evaluate the efficacy and safety of MTX in the treatment of adult participants with chronic or recurrent and acute ENL. The efficacy analysis will be conducted in the intent-to-treat population, safety analysis will be conducted in the safety population. The complete, specific details of the final statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. For the primary analysis of the primary efficacy parameter based on the FA set a last observation carry-forward (LOCF) analysis will be performed. In LOCF analysis the last observation will be carried forward to the last time point for missing assessments of the primary endpoint. The LOCF analysis treats the carried forward data as observed data at the last time point. The remaining study variables will not be imputed.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

10. MONITORING

10.1 RISK ASSESSMENT

Using the MHRA guidelines, this trial has been categorised as 'Type B' = risk somewhat higher than standard care . MTX is marketed and indicated for treatment of diseases such as psoriasis, rheumatoid arthritis, systemic vasculitis, neutrophilic dermatoses and Beçhet's disease, thus, in this trial, is being used for a new indication and presents a risk somewhat higher than standard care. MTX is used to treat immune regulated, TNFα driven inflammatory conditions in doses between 7.5 mg and 25 mg once **weekly**. These immune regulated disorders share close similarities with ENL. There are reports, including a case series, of MTX having a beneficial effect in the management of ENL. MTX safety profile is well characterised. MTX will be compared with placebo. The placebo presents a risk not higher than standard care.

The study is considered to be medium risk based on the adverse effect profile of methotrexate. An assessment of protocols of other clinical trials using methotrexate have been used to ensure the same rigorous standards of monitoring[35, 36].

10.2 MONITORING AT STUDY COORDINATION CENTRE

The conduct of the study will be supervised by trained trial manager from ENLIST group at LSHTM. A trial specific monitoring plan will be established by DSMB. This study will be monitored according to this plan and trial manager will supervise implementation procedures, recruitment and data collection in all participant centres.

10.3 MONITORING AT LOCAL SITE

Coordination within each participating hospital will be through a local Investigator whose responsibility will be detailed in an agreement in advance of starting the trial and will include:

- ensure all necessary approvals are in place prior to starting the trial;
- delegate trial related responsibilities only to suitably trained and qualified personnel;
- train relevant medical and nursing staff who see leprosy patients and ensure that they remain aware of the state of the current knowledge, the trial and its procedures (there are wall charts, pocket summaries and PowerPoint presentations to assist with this);
- agree to comply with the final trial Protocol and any relevant amendments;
- ensure that all patients with ENL are considered promptly for the trial;
- ensure consent is obtained in line with local approved procedures;
- ensure that the patient entry and outcome data are completed and transmitted to the study coordination centre in a timely manner;
- ensure the Investigator's Study File is up-to-date and complete;
- ensure all adverse events are reported promptly to the study coordination centre;
- accountability for trial treatments at their site;
- ensure the trial is conducted in accordance with ICH GCP and fulfils all national and local regulatory requirements;
- allow access to source data for monitoring, audit and inspection;
- be responsible for archiving all original trial documents including data forms for five years after the end of the trial.

11. REGULATORY ISSUES

11.1 ETHICS APPROVAL

Participants will be recruited from six centres: DBLM Hospital, Nilphamari, The Leprosy Mission Bangladesh; Oswaldo Cruz Institute, Rio de Janeiro, Brazil; the ALERT Center, Addis Ababa, Ethiopia; Bombay Leprosy Project, Mumbai, India; The Leprosy Mission Trust Hospitals, India; and Anandaban Hospital, The Leprosy Mission Nepal.

Ethical approval will be obtained by the local research team from the Ethics Committee of the London School of Hygiene and Tropical Medicine; Bangladesh Medical Research Council; Brazilian National Ethical Review Board; AHRI-ALERT Ethical Review Committee; Ethics Committee of the Managing Committee of the Bombay Leprosy Project; and The Leprosy Mission Trust India Ethics Committee; the Nepal Health and Research Council.

Any substantial amendments will not be implemented until a favourable opinion has been granted from the LSHTM Research Ethics Committee (as well as any other applicable regulatory bodies). All correspondence with ethics committees will be filed at LSHTM by the trial management team in the trial management file. Annual progress reports and notification of end of study will be submitted to all of the ethics committees who have granted approval for the study.

11.2 CONSENT

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study.

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained.

The right of the participant to refuse to participate without giving reasons must be respected.

All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

11.3 CONFIDENTIALITY

Any participants' identifiable data collected by the Study Coordination Centre will be stored securely and their confidentiality protected in accordance with the Data Protection Act 2018.

All involved investigators have to confirm that they handle the information strictly in confidence. The process of collecting participant information will comply with the standards for protection of privacy by applicable local/regional/national requirements for patient confidentiality. All records will kept confidential and the patient's name will not be released at any time.

11.4 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.5 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.6 FUNDING

The Leprosy Research Initiative are funding this study. Participants will be remunerated for out of pocket expenses associated with trial participation. Investigators will not receive any payments but the costs of the trial to their organisations will be covered.

11.7 AUDITS AND INSPECTIONS

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the study. The day-to-day management of the trial will be co-ordinated through the Study Coordination Centre.

13. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Individuals will qualify for authorship if they meet the criteria of the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-

authors-and-contributors.html). Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

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APPENDICES

- Eligibility/Assessment Criteria
- PIS
- Consent form,
- Schedule of procedures/events table
- Safety Reporting Guidelines/Flowchart
- Drugs contraindicated with methotrexate
- ENLIST ENL Severity Scale and User Guide
- Patient reported outcomes (SF-36, DLQI)

Eligibility
Assessment Criteria
Assessment Record

INCLUSION CRITERIA: ALL OF THE FOLLOWING SIX CRITERIA MUST BE MET IN ORDER FOR AN INDIVIDUAL TO BE ELIGIBLE (ONLY ONE OF 6A TO 6D NEED BE MET):

1. Individuals who diagnosed with leprosy complicated by ENL
2. Individuals with ENL aged 18-60 years old
3. Individuals with ENL deteriorating symptoms
4. Individuals with 10 or more tender, papular or nodular ENL skin lesions
5. Individuals with an EESS score of at least 9
6. Individuals with ENL on:
    a. No current anti- ENL treatment
    b. Prednisolone **up to 30mg** per day ***(if ACUTE)*** or
    Prednisolone **10-30mg** (**inclusive**) per day **(if RECURRENT/ CHRONIC)** or equivalent alternative corticosteroid dose

    OR

    c. Thalidomide or other non-steroidal anti-ENL medication

    OR

    d. A combination of prednisolone (up to 30mg) and another non-steroidal anti-ENL medication (thalidomide, clofazimine, azathioprine, pentoxifylline, ciclosporin, minocycline)

EXCLUSION CRITERIA: ***Any of the following will result in an individual being excluded from the study:***

1. Individuals who were first diagnosed with ENL **more** than **4 years** prior to enrolment
2. Individuals less than 18 years old or older than 60 years
3. Individuals weighing less than 35kg
4. Individuals with 9 or fewer tender, popular or nodular ENL skin lesions
5. Individuals with an EESS score of 8 or less
6. Women of child bearing capacity who decline to use two forms of adequate contraception and men who decline to use two forms of adequate contraception
7. Pregnant or breastfeeding women
8. Individuals with recurrent or chronic ENL who deteriorate on a dose of prednisolone **less** than 10 mg or **more** than 30 mg
9. Individuals who have taken methotrexate by any route for the last 12 weeks
10. Individuals with a hypersensitivity to methotrexate or a recognised contraindication (please see Methotrexate information sheet)
11. Individuals currently diagnosed with Type 1 reaction or Lucio's phenomenon
12. Individuals with the following abnormalities in screening investigations
    - Hemoglobin < 10 g/dL
    - White blood cells < 3.0 x 10^9/l
    - Neutrophils < 1.5 x 10^9/l
    - Platelets < 100 x 10^9/l
    - AST and ALT > 2 times the upper limit of normal range
    - Bilirubin > 5mg/dl (85,5 µmol/l)
    - Hypoalbuminemia <3.5 g/dl
13. Positive serology for HIV, Hepatitis B or C
14. Evidence of tuberculosis or pulmonary fibrosis
15. A history of chronic liver disease or excessive alcohol or illicit substance consumption
16. Individuals with severe inter-current infections, uncontrolled diabetes, active peptic ulcer disease, untreated malignancy
17. Individuals unable to attend regularly for assessment or monitoring

	Yes	No
1. Does the patient show any exclusion criteria? If Yes, which one? _____	☐	☐
2. Does the patient have clinical signs of ENL?	☐	☐
3. Does the patient have moderate ENL (EESS score of ≥9) and 10 or more tender, popular or nodular ENL skin lesions?	☐	☐
Has the patient given informed consent?	☐	☐

Is this patient's ENL:

Acute ☐

Acute ENL is defined as occurring if a patient has either a first episode of ENL less than 24 weeks duration or experiences a second or subsequent episode of ENL which lasts less than 24 weeks and occurs 84 days (ie 12 weeks) or more after stopping treatment for ENL.

Or

Recurrent ☐ Chronic ☐

Recurrent ENL is defined as occurring if a patient experienced a second or subsequent episode of ENL occurring between 28 and 84 days of stopping treatment for ENL.

Chronic ENL is defined as occurring for more than 24 weeks during which a patient has required ENL treatment either continuously or where any treatment free period had been 27 days or less.

Participant Information Sheet

***M**ethotrexate **a**nd **P**rednisolone **s**tudy in Erythema Nodosum Leprosum*
MaPs

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.

What is the purpose of the study?
The London School of Hygiene and Tropical Medicine (LSHTM) alongside leprosy specialists from Bangladesh, Brazil, Ethiopia, India, Indonesia and Nepal are conducting research in Erythema Nodosum Leprosum (ENL), which is a severe complication of leprosy. The current treatment of ENL is based on prednisolone, a corticosteroid, which has adverse effects like high blood pressure, weight gain, infections, and diabetes if used for a long time. This is why it is important to find an effective alternative treatment. Methotrexate has been used in many other diseases like psoriasis and rheumatoid arthritis. The side effects of Methotrexate are uncommon and less severe than corticosteroids, it does not cause longterm complications like obesity, diabetes, high blood pressure and osteoporosis.

Why have I been asked to take part?
You have been invited because you were diagnosed with ENL (also known as Type II reaction).

Do I have to take part?
No. It is up to you to decide to take part or no. 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 clinical examination with blood tests that include full blood count, hepatitis B and C, HIV test, liver and kidney functions. We will do a urine pregnancy test for all women of child bearing potential too. A score of the severity of ENL will be performed at this point.
If you meet the study's criteria, and you wish to participate, you will be treated with either prednisolone alone, the normal treatment, or prednisolone plus methotrexate, the treatment we are testing. The treatment will be chosen by chance by a computer. 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 patients 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 prednisolone alone or prednisolone with methotrexate. You won't know which treatment are you receiving and your research team will also not know this. You will be treated properly for ENL.
It is important that you realise that treatment is not always effective and the symptoms can get worse.
If you agree to take part of this study, we will ask you to complete two questionnaires and you will be seen by a member of the research team for the next 60 weeks. The follow up will be similar to a regular ENL treatment, we will ask you to answer the questionnaire again at week 24, 48 and 60. We will also ask you to do blood tests at the beginning of the study and then every week on the first 2 weeks, then every 2 weeks until

3 months, and then monthly until the end of the study. Normally people with ENL are seen every month. Most participants will have only two extra appointments for the purpose of the study.

What will I have to do?

You will be expected to take the medication as directed by your doctors and they will advise you on whether you can continue to take other medication. An important part of this study is the information we gain from the questions we will ask you, examination and laboratory tests. It is important you answer all the questions and attend to the appointments, so that we have a complete set of data for you.

What are the possible risks and disadvantages?

*The current treatment with prednisolone alone already increase the risk of infections and complications like diabetes, high blood pressure and infections, among others. The treatment that we are testing is with an additional **WEEKLY** medication called methotrexate, which has been used for many years to treat conditions, including arthritis and certain types of skin diseases such as psoriasis. Side effects do occur and they are usually reversible when treatment is stopped. Normally, this drug is well tolerated. The most common side effects are: nausea, indigestion and loss of appetite. Other less common side effects are: tiredness, headache, inflammation of the lung, diarrhoea, mouth ulcers and inflammation of the liver. Methotrexate also can affect the blood. MTX cannot be given to pregnant women, if you are pregnant or wish to become pregnant in the next 18 months, you cannot participate in this study. Men should use effective contraception during the study and 6 months after the study completion.*

You should tell the research team about the following symptoms

- *Fever (temperature above 38^0 C), chills and sore throat.*
- *Skin rash*
- *Yellowing of the skin or the white part of the eyes*
- *Bleeding gums, unexpected bruising or bleeding that doesn't stop as quickly as normal*
- *Black "tarry" stools*
- *Chest pain, difficulty breathing or a dry cough that doesn't go away*
- *Severe and continuing diarrhoea, vomiting or stomach pains*
- *Swelling and soreness or ulcers of the vagina*

There may sometimes be side effects that are not listed above. If you notice anything unusual and are concerned then should contact your study team.

What are the possible benefits?

We cannot promise the study will help you but the information we get from the study will help our knowledge and understanding of this research area. ENL is a severe complication of leprosy and all the knowledge we gain in this study will help other patients like you.

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 **(INSERT LOCAL PI INFORMATION)** *If you remain unhappy and wish to complain formally, you can do this by contacting <if LSHTM is the sponsor: Patricia Henley at rgio@lshtm.ac.uk or +44 (0) 20 7927 2626>*

The London School of Hygiene and Tropical Medicine 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. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish, or will continue to be stored for further research.

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 in London **(insert local institution name)** *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 in London, who will store it securely. Your personal details will be kept in a different safe place to the other study information and will be, destroyed within 10 years of the end of the study, stored securely in London.

At the end of the project, the study data will be archived at London School of Hygiene and Tropical Medicine. The data will be made available to other researchers worldwide for research and to improve medical knowledge and patient care. Your personal information will not be included and there is no way that you can be identified.

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 is organising and funding this study?
London School of Hygiene & Tropical Medicine is the sponsor for the research and they have full responsibility for the project including the collection, storage and analysis of your data.

Who has checked this study?
All research involving human participants is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by The London School of Hygiene and Tropical Medicine Research Ethics Committee (<ref:>). The **(insert Local Institution name)** *Ethics Committee has also reviewed the study and have agreed that it is okay for us to ask people to take part.*

What happens when the research study stops?

As a patient with ENL you will continue to be reviewed in the Leprosy clinic as needed, so your follow up will be as normal.
What will happen to the samples I give?

We may use some of the samples collected for future studies. These will be anonymised when stored, and all future research using these samples will be reviewed by an independent ethics committee. Samples may be shipped and stored outside of xxx.

Further information and contact details

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.

MaPs IN ENL: Study number: |_|_|_| Patient Initials: |_|_|_|

Study Center: _____

CONSENT FORM FOR PARTICIPATION IN METHOTREXATE AND PREDNISOLNE STUDIES IN ENL

A. I _____ understand that doctors at _____ and at the London School of Hygiene and Tropical Medicine are involved in research into alternative treatments for leprosy reactions. Erythema Nodosum Leprosum (ENL) is a recurrent condition which can affect patients for many years. This study will look at whether methotrexate and prednisolone is more efficacious than prednisolone alone in the management of acute, recurrent and chronic erythema nodosum leprosum. We are hoping to find a way of reducing the number of ENL attacks and the length of these attacks.

B. The study has been explained to me.

C. I confirm that I am 18 years old or above, and younger than 61 years old.

D. I shall be randomly assigned to a 48 weeks course of either Methotrexate and prednisolone (20 weeks only) or placebo and prednisolone. I agree to take all the tablets that I will be given.

D. I agree to regular review visits, at first fortnightly, then monthly for the duration of my treatment.

E. I also agree to return for follow-up during the course of this study.

F. I understand that I will have to have regular blood tests to monitor for any side effects as I may be at risk of picking up other infections. The maximum amount of blood drawn at any time will be 20ml (this is the equivalent of 4 teaspoons). It is possible that I may experience some side effects as explained on the information sheet and that I will be treated for these freely and appropriately.

G. Some of the samples taken (blood) may be kept in a laboratory for up to 5 years to allow future studies. Please tick the box if you agree to follow up studies to be conducted on stored materials.

□ Yes, I agree □ No, I don't agree

I. Women only: I agree to undergo a pregnancy test, to attend Family Planning and use family planning methods during the period of the study. If I become pregnant I may be withdrawn from the study but will continue on the standard treatment used in pregnancy.
Men only: I agree to use effective contraception during the study and 6 months after study completion.

J. I agree to be tested for HIV via VCT (Voluntary Counseling and Testing). If I am HIV positive I will be excluded from the study but will still receive the standard treatment for leprosy and HIV. HIV testing may be repeated during the study period if clinically indicated.

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

L. 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.

M. 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.

N. 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.

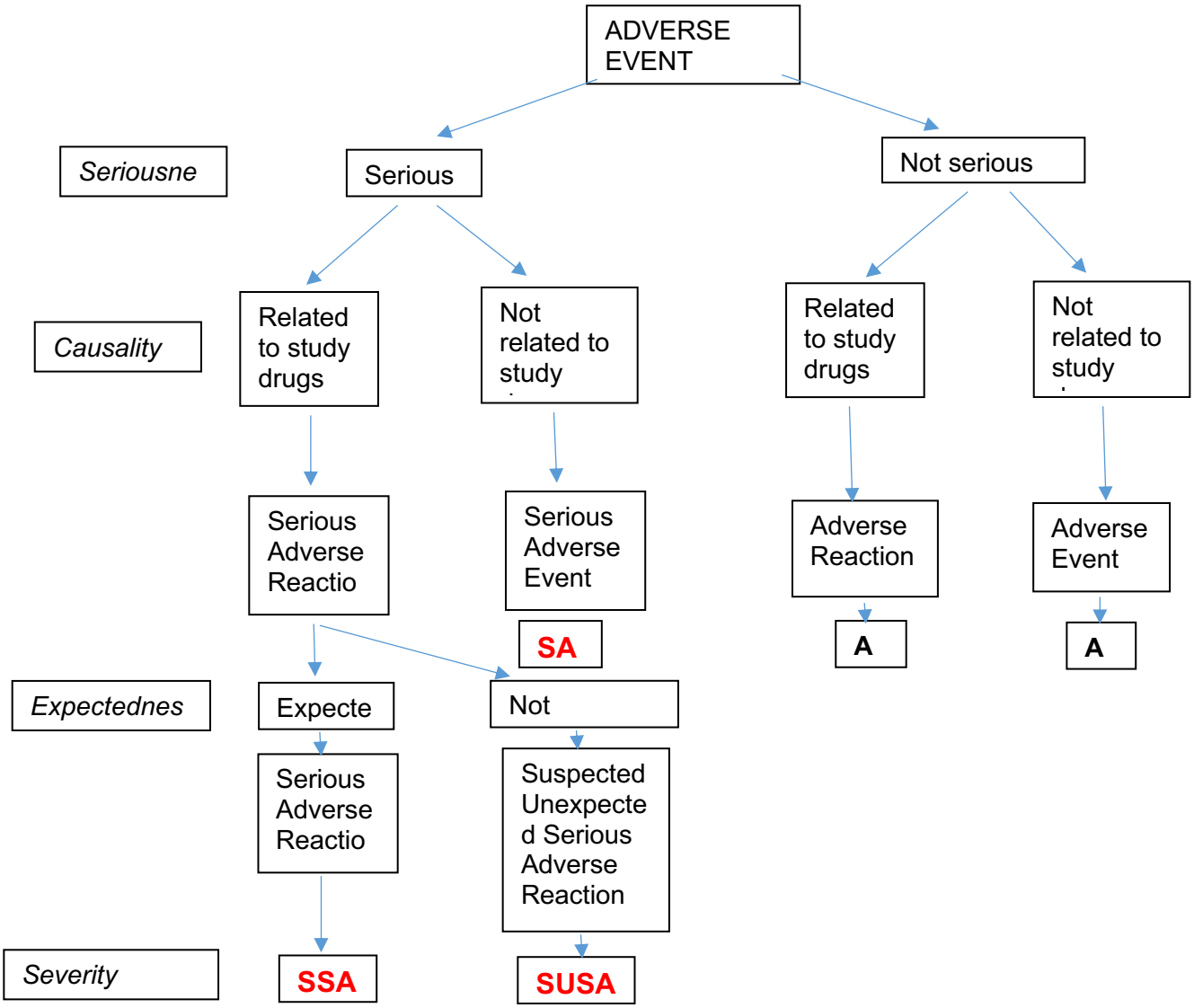
	Printed Name	Signature	Date
Patient	_____	_____	____/_____/20___
Witness	_____	_____	____/_____/20___
Doctor	_____	_____	____/_____/20___

PROCEDURES TABLE

Day	Week	Assessments	Investigations	Population A Endpoints	Population B Endpoints
1	0	1	Baseline		
8	1	2	FBC/Renal/LFT		
15	2	3	FBC/Renal/LFT		
29	4	4	FBC/Renal/LFT/glucose Urine pregnancy test		
57	8	5	FBC/Renal/LFT/glucose Urine pregnancy test		
71	10	6	FBC/Renal/LFT/glucose		
85	12	7	FBC/Renal/LFT/glucose Urine pregnancy test		
113	16	8	FBC/Renal/LFT/glucose Urine pregnancy test		
141	20	9	FBC/Renal/LFT/glucose Urine pregnancy test		
169	24	10	FBC/Renal/LFT/glucose Urine pregnancy test + DLQI+ SF36	**Primary Outcome**	**Primary Outcome**
197	28	11	FBC/Renal/LFT/ Urine pregnancy test		
225	32	12	FBC/Renal/LFT/ Urine pregnancy test		
253	36	13	FBC/Renal/LFT/ Urine pregnancy test		
281	40	14	FBC/Renal/LFT/ Urine pregnancy test		
309	44	15	FBC/Renal/LFT/ Urine pregnancy test		
337	48	16	FBC/Renal/LFT/ Urine pregnancy test + DLQI+ SF36	**Primary Outcome And Secondary Outcome**	**Primary Outcome And Secondary Outcome**
365	52	17	FBC/Renal/LFT/ Urine pregnancy test**		
393	56	18	FBC/Renal/LFT/ (if abnormal at previous visit) Urine pregnancy test		
421	60	19	FBC/Renal/LFT/ (if abnormal at previous visit) Urine pregnancy test** + DLQI+ SF36	**Secondary Outcome**	**Secondary Outcome**

** Urinary pregnancy test at visit 18 and 19 must be performed in all female participants with childbearing capacity. The other investigations need only be done in individuals who had abnormal results at previous visit or when there is a clinical indication.

SAFETY REPORT FLOWCHART



AR and AE: record in notes and CRF
SAE and SSAR: report to sponsor immediately
SUSAR: expedited reporting!

Methotrexate Information Sheet

Concurrent drug therapy issues

STOP DAPSONE IN MDT!!!!

Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

- Hepatotoxic agents: Use caution when used with other hepatotoxic agents (azathioprine, retinoids, sulfasalazine).
- Mercaptopurine: Methotrexate may increase the levels and effects of mercaptopurine; may require dosage adjustments.
- Nephrotoxic chemotherapy: Use with caution in osteosarcoma patients treated with high-dose methotrexate in combination with nephrotoxic chemotherapy (eg, cisplatin).
- NSAIDs: Do not administer NSAIDs prior to or during high dose methotrexate therapy; may increase and prolong serum methotrexate levels. Doses used for psoriasis may still lead to unexpected toxicities; use with caution when administering NSAIDs or salicylates with lower doses of methotrexate for RA.
- Proton pump inhibitors: Concomitant use of proton pump inhibitors with methotrexate (primarily high-dose methotrexate) may elevate and prolong serum methotrexate levels and metabolite (hydroxymethotrexate) levels (based on case reports and pharmacokinetic studies). May lead to toxicities; use with caution.
- Vaccines: Immunization may be ineffective during methotrexate treatment. Immunization with live vaccines is not recommended; cases of disseminated vaccinia infections due to live vaccines have been reported.
- Vitamins: Vitamins containing folate may decrease response to systemic methotrexate; folate deficiency may increase methotrexate toxicity.

Drug-drug interactions:

Acitretin: May enhance the hepatotoxic effect of Methotrexate. *Risk X: Avoid combination*

Alitretinoin (Systemic): May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bile Acid Sequestrants: May decrease the absorption of Methotrexate. *Risk C: Monitor therapy*

Cephalothin: May diminish the therapeutic effect of Methotrexate. *Risk C: Monitor therapy*

Chloramphenicol (Ophthalmic): May enhance the adverse/toxic effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ciprofloxacin (Systemic): May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CycloSPORINE (Systemic): May increase the serum concentration of Methotrexate. This may result in nausea, vomiting, oral ulcers, hepatotoxicity and/or nephrotoxicity. Methotrexate may increase the serum concentration of CycloSPORINE (Systemic). This may result in nephrotoxicity. *Risk D: Consider therapy modification*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dexketoprofen: May increase the serum concentration of Methotrexate. Management: Concurrent use of dexketoprofen with methotrexate doses of 15 mg/week or more is inadvisable. Use with lower methotrexate doses should only be performed with caution and increased monitoring. *Risk D: Consider therapy modification*

Diethylamine Salicylate: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Methotrexate. Methotrexate may enhance the adverse/toxic effect of Dipyrone. Specifically, the risk for agranulocytosis and pancytopenia may be increased. *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Eltrombopag: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. *Risk C: Monitor therapy*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Foscarnet: May enhance the nephrotoxic effect of Methotrexate. *Risk X: Avoid combination*

Fosphenytoin-Phenytoin: Methotrexate may decrease the serum concentration of Fosphenytoin-Phenytoin. Fosphenytoin-Phenytoin may increase the serum concentration of Methotrexate. Specifically, fosphenytoin-phenytoin may displace methotrexate from serum proteins, increasing the concentration of free, unbound drug.*Risk C: Monitor therapy*

Gemfibrozil: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. See separate drug interaction monographs for agents listed as exceptions. *Risk C: Monitor therapy*

Ibrutinib: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Leflunomide: Methotrexate may enhance the adverse/toxic effect of Leflunomide. Particular concerns are an increased risk of pancytopenia and/or hepatotoxicity. *Risk C: Monitor therapy*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. Management: Avoid the use of lenograstim 24 hours before until 24 hours after the completion of myelosuppressive cytotoxic chemotherapy. *Risk D: Consider therapy modification*

LevETIRAcetam: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Lipegfilgrastim: Antineoplastic Agents may diminish the therapeutic effect of Lipegfilgrastim. Management: Avoid concomitant use of lipegfilgrastim and myelosuppressive cytotoxic chemotherapy. Lipegfilgrastim should be administered at least 24 hours after the completion of myelosuppressive cytotoxic chemotherapy. *Risk D: Consider therapy modification*

Loop Diuretics: Methotrexate may diminish the therapeutic effect of Loop Diuretics. Loop Diuretics may increase the serum concentration of Methotrexate. Methotrexate may increase the serum concentration of Loop Diuretics. Management: Monitor for increased methotrexate and/or loop diuretic levels/toxicity with concomitant use of these agents and monitor for decreased therapeutic effects of loop diuretics. Methotrexate and/or loop diuretic dose reductions may be necessary. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Mipomersen: May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nitrous Oxide: May enhance the adverse/toxic effect of Methotrexate. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Nonsteroidal Anti-Inflammatory Agents: May increase the serum concentration of Methotrexate. Management: Alternative anti-inflammatory therapy should be considered whenever possible, especially if the patient is receiving higher, antineoplastic doses of methotrexate. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Penicillins: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.).*Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.).*Risk C: Monitor therapy*

Pidotimod: Immunosuppressants may diminish the therapeutic effect of Pidotimod. *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Probenecid: May increase the serum concentration of Methotrexate. Management: Avoid concomitant use of probenecid and methotrexate if possible. If used together, consider lower methotrexate doses and monitor for evidence of methotrexate toxicity. *Risk D: Consider therapy modification*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May increase the serum concentration of Methotrexate. *Risk C: Monitor therapy*

Pyrimethamine: May enhance the adverse/toxic effect of Methotrexate. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Salicylates: May increase the serum concentration of Methotrexate. Salicylate doses used for prophylaxis of cardiovascular events are not likely to be of concern. *Risk D: Consider therapy modification*

Sapropterin: Methotrexate may decrease the serum concentration of Sapropterin. Specifically, methotrexate may decrease tissue concentrations of tetrahydrobiopterin. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SulfaSALAzine: May enhance the hepatotoxic effect of Methotrexate. *Risk C: Monitor therapy*

Sulfonamide Antibiotics: May enhance the adverse/toxic effect of Methotrexate. Management: Consider avoiding concomitant use of methotrexate and either sulfamethoxazole or trimethoprim. If used concomitantly, monitor for the development of signs and symptoms of methotrexate toxicity (eg, bone marrow suppression).*Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tegafur: Methotrexate may enhance the adverse/toxic effect of Tegafur. *Risk C: Monitor therapy*

Teriflunomide: May increase the serum concentration of OAT3 Substrates. *Risk C: Monitor therapy*

Teriflunomide: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. *Risk C: Monitor therapy*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Theophylline Derivatives: Methotrexate may increase the serum concentration of Theophylline Derivatives. *Risk C: Monitor therapy*

Tofacitinib: Methotrexate may enhance the immunosuppressive effect of Tofacitinib. Management: Avoid the use of tofacinib in combination with potent immunosuppressive methotrexate-containing regimens. *Risk C: Monitor therapy*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Trimethoprim: May enhance the adverse/toxic effect of Methotrexate. Management: Consider avoiding concomitant use of methotrexate and either sulfamethoxazole or trimethoprim. If used concomitantly, monitor for the development of signs and symptoms of methotrexate toxicity (e.g., bone marrow suppression). *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Methotrexate may enhance the adverse/toxic effect of Vaccines (Live). Methotrexate may diminish the therapeutic effect of Vaccines (Live). Management: Low-dose methotrexate (0.4 mg/kg/week or less) is not considered sufficiently immunosuppressive to create vaccine safety concerns. Higher doses of methotrexate should be avoided. *Risk D: Consider therapy modification*

Food Interactions

Methotrexate peak serum levels may be decreased if taken with food. Milk-rich foods may decrease methotrexate absorption. Management: Administer without regard to food.

ENLIST ENL Severity Scale (EESS)
User Guide

ENLIST ENL Severity Scale

Pain Rating - Visual Analogue Scale (Ensure line is 100 mm long)

How severe is your pain today? Mark the line below with an **X** to indicate how bad you feel your pain is *today*

No Pain _____ **Worst possible Pain**

	ITEM	SCORES				
		0	1	2	3	SCORE
1	**VAS – Pain (mm)**	0	1-39	40-69	70-100	
2	**Fever** (in **°C**)	None (37.5 or less)	No fever now but history of fever and/or chills in last 7 days	37.6-38.5	38.6 or higher	
3	**Number of ENL skin lesions**	None	1-10	11-20	21 or more	
4	**Inflammation of ENL skin lesions**	Non tender	Redness	Painful	Complex	
5	**Extent of ENL skin lesions**	0	1-2 regions	3-4 regions	5-7 regions	
6	**Peripheral oedema**	None	1 site of Hands or Feet or Face	2 sites	All three sites (Hands and Feet and Face)	
7	**Bone pain**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	
8	**Inflammation of Joints and/or digits due to ENL**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	
9	**Lymphadenopathy due to ENL**	None	Enlarged	Pain or tenderness	Pain or tenderness in 2 or more groups	
10	**Nerve tenderness due to ENL**	None	Absent if attention distracted	Present even if attention distracted	Patient withdraws limb on examination	
	TOTAL					

User Guide for ENLIST ENL Severity Scale

The score for each item should be **added** together to obtain the ENLIST ENL Severity Scale score. **Mild ENL** is categorised as an ENLIST ENL Severity Scale of **8 or less**.

The **Minimal Important Difference** of the ENLIST ENL Severity Scare is **5**.

SCALE ITEM	NOTES
1. VAS Pain	Instruct the patient to point to the position on the line to indicate how much pain they are **currently** feeling. The far left end indicates 'No pain' and the far right end indicates 'Worst possible pain'. Take the measurement (in **mm**) using a ruler from the **LEFT** end of the line to the centre of the cross. **Ensure that the line when reproduced from this document is 100 mm long**.
2. Fever	Take temperature (in **°C**) using a thermometer. If the temperature is **GREATER** than 37.5°C the patient has a fever. If it is less than or equal to 37.5°C the patient scores 0 for this item UNLESS they give a history of having had a fever in the last 7 days in which case they score 1. The cause of the fever does not need to be established.
3. Number of ENL skin lesions	***Note: only skin lesions due to ENL are to be considered for this item.***
4. Inflammation of ENL skin lesions	***Note: only skin lesions due to ENL are to be considered for this item.*** The term complex refers to the following type of skin lesions: vesicular, bullous, pustular, erythema multiform-like, panniculitis, necrotic, ulcerated. ***If the participant fulfils criteria for more than one score then the highest scoring criteria should be used***. For example if there are red ENL skin lesions and some are ulcerated or vesicular or pustular then the patient scores 3 because "complex" lesions are present.
5. Extent of ENL skin Lesions	***Note: only skin lesions due to ENL are to be considered for this item.*** The separate regions are: a) Head and neck b) Left upper limb c) Right upper limb d) Torso –front (including genitals) e) Torso back (including buttocks) f) Left lower limb g) Right lower limb
6. Peripheral oedema due to ENL	The three sites to be considered are the face, hands and feet. Both feet count as one site. Both hands count as one site. Oedema thought to be due to treatment such as corticosteroids or thalidomide should not be counted.
7. Bone pain	Bone pain is distinct from pain or tenderness of the joints. It is most usually elicited by palpation of the subcutaneous border of the tibia.
8. Inflammation of joints and/or digits due to ENL	***Note: only joint inflammation due to ENL are to be considered for this item.*** Inflammation of the joint will be present if there is any of the following: pain or tenderness, redness, swelling or heat. It them must be determined if any of these are sufficiently severe to meet the criteria of the scores. If more than one joint is affected the most severely affected joint is used to determine the score.

9. Lymphadenopathy due to ENL	The lymph node groups to be examined are: a) Head and neck (including the supraclavicular fossae) b) Axillary c) Inguinal ***Note: Lymph node groups on the different sides of the body are separate for example: left axillary and right axillary. Therefore there are 6 lymph node groups for the purposes of the scale.***
10. Nerve tenderness due to ENL	Any peripheral or cutaneous nerve tenderness due to ENL is to be considered. If the participant fulfils criteria for more than one nerve then the highest scoring nerve should be used. ***The most severely affected nerve should be used. Where the examiner suspects that neuropathic pain is being elicited then this should be disregarded.***

Definitions of "complex" skin lesions

Bulla is defined as a visible accumulation of fluid within or beneath the epidermis more than 0.5cm
Erythema multiform-like lesions are atypical ENL lesions resembling those of erythema multiform and include macular, papular or urticarial lesions, as well as the classical iris or 'target lesions'.
Panniculitis inflammation of the subcutaneous adipose tissue.
Pustule an accumulation of free pus.
Target lesions are defined as less than 3 cm in diameter and have three or more zones, usually a central area of dusky erythema or purpura, a middle paler zone of oedema and an outer ring of erythema with a well-defined edge.
Ulceration a break in the epithelial surface (the epidermis in the skin).
Vesicle is defined as a visible accumulation of fluid within or beneath the epidermis 0.5cm or less in diameter.

CASE REPORT FORM

Start Date: (dd/mm/yyyy) __ __ / __ __ / __ __ __ __

Visit #		Date due dd/mm/yyyy	Date done dd/mm/yyyy	Extra notes	Initials of Dr
1	Base line - day 1			SF36 and DQIL	
2	Day 8 - week 1				
3	Day 16 - week 2				
4	Day 29 - week 4				
5	Day 57 - week 8				
6	Day 71 - week 10				
7	Day 85 - week 12				
8	Day 113 - week 16				
9	Day 141 - week 20				
10	Day 169 - week 24			**End point assessment +**SF36 and DQIL	
11	Day 197 - week 28				
12	Day 225 - week 32				
13	Day 253 - week 36				
14	Day 281 - week 40				
15	Day 309 - week 44				
16	Day 337 - week 48			End of TX –0 SF36 and DQIL	
17	Day 365 - week 52				
18	Day 393 - week 56				
19	Day 421 – week 60			End of Study – SF36 and DQIL	
	Unscheduled review				
	Adverse Events				
	Study Termination				

Part 1: Registration/Enrolment

- **PATIENT CONSENT**

Have the participant read and consent to participate in this study? **YES** ☐ **NO** ☐

Have the participant received the patient information sheet? **YES** ☐ **NO** ☐

- **PATIENT CONTACT DETAILS**

Name:
Address:
Contact numbers (best time to be contacted):
Date of birth:
Study Participant number:

Sex: **M** ☐ **F** ☐

- **HISTORY AT REGISTRATION**

Assessment at baseline Day 1 **Today's Date (*dd/mm/yyyy*):** _ _/ _ _ / _ _ _ _
Assessment done by: _____

Leprosy History and treatment

Classification (Ridley- Jopling): 1. BL ☐ 2. LL ☐

Mean Bacterial Index at time of diagnosis: |_|.|_| Date: _ _ / _ _/ _ _ _ _ N/A ☐

Mean most recent Bacterial Index: |_|.|_| Date: _ _ / _ _/ _ _ _ _ Pending ☐
MDT Start Date: _ _ / _ _/ _ _ _ _

Current MDT status: 1. On MDT ☐ 3. Not on MDT ☐

Reaction History and treatment:

Is this the first episode of ENL the patient has ever had? 1. Yes ☐ 2. No ☐
If yes: How long has he had symptoms of ENL (in months)? |_|_|_|
If no: How long ago was the last ENL episode (in days): |_|_|_|
When did the last ENL treatment end: _ _ / _ _/ _ _ _ _ (if more than 84 days ago, count as acute ENL)

How many months of ENL reactions in total? |_|_|_|

Duration of this ENL flare (in days): |_|_|_|

Is the patient on ENL treatment: 1. Yes ☐ 2. No ☐
If yes: When was it started: _ _ / _ _/ _ _ _ _
If no: When was it stopped: _ _ / _ _/ _ _ _ _

Prednisolone:

How long has the participant been on prednisolone (in days)?
What is the current daily dose of prednisolone in (0-30)mg? |_|_|
When was the last dose taken? Date: ___/___/_____

Any other anti- ENL treatment (drug name/ dose /length of treatment):

_____
_____

Medical History

Diabetes	1. Yes ☐	2. No ☐
Hypertension	1. Yes ☐	2. No ☐
Tuberculosis	1. Yes ☐	2. No ☐
History of chicken pox	1. Yes ☐	2. No ☐
Alcohol intake	1. Yes ☐	2. No ☐

If other, specify: _____

Current medications:

	1. Yes	2. No	Generic name
1. Analgesia	☐	☐	_____
2. Anti-inflammatory	☐	☐	_____
3. Antibiotics	☐	☐	_____
4. Antihypertensive	☐	☐	_____
5. Antifungal	☐	☐	_____
6. Diabetic control	☐	☐	_____
7. Ophthalmological	☐	☐	_____
8. Psychiatric medication	☐	☐	_____
9. Other	☐	☐	_____

If other, specify: _____

Known allergies: 1. Yes □ 2. No □
Specify: _____

Is the patient on any contra-indication 1. Yes □ 2. No □
(DAPSONE, SULFONAMIDE ANTIBIOTICS, TRIMETHOPRIM)

Women: Child-bearing capacity: 1. Yes □ 2. No □

Date of 1st day of last menstruation: ___/___/____

Contraception used or planning to use:

- **BASELINE QUESTIONNAIRE**

Ask the patient about the following complaints:

	Yes	No
Fevers		
Cutaneous (including nails) fungal infections		
Infections		
Infected ulcers		
Recent tuberculosis diagnosis		
Night sweats		
Nausea		
Jaundice		
Dyspepsia		
Gastric pain requiring antacid		
Gastrointestinal bleeding/ Melena		
Vomiting		
Diarrhoea		
Ulcers in the mouth		
Moon face		
Anorexia		
Weight lost >5kg in 3 months		
Weight gain		
Nocturia, polyuria, polydipsia		
Hypertension BP> 160/90 on 2 separate readings at least 1week apart		
Other rashes		
Hair loss		
Pruritus		
Acne		
Peripheral oedema		
Shortness of breath		
Chronic cough		
Chest pain		
Easy bruising/Haematoma		
Dizziness		
Headaches		
Convulsions		
Psychosis or other mental health problems		
Recent fractures		
Menorrhagia		
Amenorrhea		
Corner Glaucoma		
Corneal ulcer		
Cataract		

Any other symptoms: _____

- **EXAMINATION AT REGISTRATION**

Baseline Physical Examination Day 1

I. Vital signs

Temp (°C) |_|_|. |_|	Pulse (b/min) |_|_|_|	B.P. (systolic/ diastolic) |_|_|_| /|_|_|_|

II. Weight: |_|_|_|.|_|**kg** **Height:** |_|_|_| **cm**

III. General examination

	1.Normal	2.Abnormal	If abnormal specify
Pallor			
Jaundice			
Eyes			
Mouth			
Head and neck			
Lymph nodes			
Skin (non leprosy)			
Lungs			
Heart			
Abdomen			
Liver			
Spleen			
Ext Genitalia (male)			

Does the patient have?	1. Yes	2. No
1. Orchitis	☐	☐
2. Painful or red eyes	☐	☐

IV. Leprosy Examination

i. <u>Nerves</u> - signs and symptoms of neuritis (recent = less than 6 months)

Name of nerve	Motor symptoms –weakness (√ if yes)			Sensory symptoms – numbness (√ if yes)		
	Normal	Abnormal	Duration in wks if abn	Normal	Abnormal	Duration in wks if abn
R Facial				N/A	N/A	
L Facial						
R Ulnar						
L Ulnar						
R Median						
L Median						
R lat popliteal						
L lat popliteal						
R Post Tibial	N/A	N/A				
L Post Tibial	N/A	N/A				

CONFIRM YOU HAVE SEEN AND ATTACHED VMT/ST FORM □

I. ENLIST ENL Severity Scale

Day 1

Pain Rating - Visual Analogue Scale (Ensure line is 100 mm long)

How severe is your pain today? Mark the line below with an **X** to indicate how bad you feel your pain is *today*

No Pain _____ **Worst possible Pain**

	ITEM	SCORES				
		0	1	2	3	SCORE
1	**VAS – Pain (mm)**	0	1-39	40-69	70-100	
2	**Fever** (in **°C**)	None (37.5 or less)	No fever now but history of fever in last 7 days	37.6-38.5	38.6 or higher	
3	**Number of ENL skin lesions**	None	1-10	11-20	21 or more	
4	**Inflammation of ENL skin lesions**	Non tender	Redness	Painful	Complex	
5	**Extent of ENL skin lesions**	0	1-2 regions	3-4 regions	5-7 regions	
6	**Peripheral oedema**	None	1 site of Hands or Feet or Face	2 sites	All three sites (Hands and Feet and Face)	
7	**Bone pain**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	
8	**Inflammation of Joints and/or digits due to ENL**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	
9	**Lymphadenopathy due to ENL**	None	Enlarged	Pain or tenderness	Pain or tenderness in 2 or more groups	
10	**Nerve tenderness due to ENL**	None	Absent if attention distracted	Present even if attention distracted	Patient withdraws limb on examination	
	TOTAL					

- **INVESTIGATIONS –Physician to complete BASELINE – DAY 1**
  Laboratory tests (record results)

	Date taken dd/mm/yyyy	Result	Normal values
FBC	--/--/----	Hb: |__|__|.|__| g/dl WCC: |__|__|__|__| x 10^9 cells /l Plt: |__|__|__| cells/mm^3 MCV |__|__|__| fl	
Renal function	--/--/----	Creat: |__|__|.|__|__| mg/dl K+: |__|__|.|__| mmol/l Urea |__|__|.|__|__| mg/dl	
Blood sugar	--/--/----	Glucose |__|__|__|.|__|__| mg/dl	
LFT	--/--/----	Alk phos |__|__|__| u/l AST (SGOT) |__|__|__| u/l ALT (SGPT) |__|__|__| u/l Bilirubin |__|__|__| mg/dl Albumin |__|__|__| g/dl	
HIV	--/--/----	1. Positive |__| 2. Negative |__|	
Hep B -HbsAg	--/--/----	1. Positive |__| 2. Negative |__|	
Hep C antibody	--/--/----	1. Positive |__| 2. Negative |__|	
Pregnancy test (urine)	--/--/----	1. Positive |__| 2. Negative |__|	Advise re contraception options
Skin biopsy	--/--/----	1. LL |__| 2. BL |__|	
Slit skin smear	--/--/----	|__|__|__|__|__|__|	Mean BI |__|.|__|
Chest Xray	--/--/----	1. Normal |__| 2. Abnormal |__|	
Other investigations			

- **MEDICATION TO BE PRESCRIBE Baseline – Day 1**

CONFIRM THAT PATIENT IS NOT ON DAPSONE ☐

Non-intervention medications:

	1. Yes	2.No	Dosage/ time
1. Folic acid - 5mg od x 52 weeks (6 days a week- not on day of MTX)	☐	☐	_____
2. Ivermectin – 200mcg/kg od x2d	☐	☐	_____
Or Albendazole 400mg bd x3d	☐	☐	_____
3. Ranitidine	☐	☐	_____

4. Paracetamol max 4g/d	☐	☐	_____
5. Calcium	☐	☐	_____
6. Vitamin D	☐	☐	_____
7. Ondansetron	☐	☐	_____
8. Contraception	☐	☐	_____
9. Tramadol	☐	☐	_____

****EXTRA MEDICATION PRESCRIBED TODAY**:**

_____

_____

_____

COMPLETE PHARMACY CARD AND SEND PATIENT TO PHARMACY

Check SF 36 and DLQI have been completed

Patient aware of next review date

PART 2: FOLLOW UP

AT EACH REVIEW AND UNPLANNED VISIT, THE FOLLOW FORM MUST BE COMPLETED:

Insert the relevant day number: Day |__|__|__|

Visit #: **Date:** _ _ / _ _ / _ _ _ _

Physician to complete history and examination and ensure lab results are entered
Physician to complete adverse event form if necessary
Ensure correct physiotherapy form and QoL questionnaires are attached to PRF
After each visit:

1. **Mark off visit on page 1**
2. **Write in date of next planned visit on page 1**
3. **Tell Investigator about completed patient review in order to transfer data to CRF**

- **HISTORY**

Compared to the last review, does the patient feel:

1. Better ☐
2. Somewhat better ☐
3. Same ☐

4. Somewhat worse ☐

5. Worse ☐

Were last set of bloods satisfactory as per trial protocol 1. Yes ☐ 2. No ☐

Has the patient taken all study medication? 1. Yes ☐ 2. No ☐

Any relevant new history:

_____

_____

_____

Any new additional medications including steroids, dapsone-free MDT and analgesia

Drug, dose and reason starting	Date started dd/mm/yyyy	Ongoing treatment Yes or No
1.	/ /	
2.	/ /	
3.	/ /	

Does the patient complain of any of the following (new since last visit?)

	Yes	**No**
Fevers		
Cutaneous (including nails) fungal infections		
Infections		
Infected ulcers		
Recent tuberculosis diagnosis		
Night sweats		
Nausea		
Jaundice		
Dyspepsia		
Gastric pain requiring antacid		
Gastrointestinal bleeding/ Melena		
Vomiting		
Diarrhoea		
Ulcers in the mouth		
Moon face		
Anorexia		
Weight lost >5kg in 3 months		
Weight gain		
Nocturia, polyuria, polydipsia		
Hypertension BP> 160/90 on 2 separate readings at least 1week apart		
Other rashes		
Hair loss		
Pruritus		
Acne		
Peripheral oedema		
Shortness of breath		
Chronic cough		

Chest pain		
Easy bruising/Haematoma		
Dizziness		
Headaches		
Convulsions		
Psychosis or other mental health problems		
Recent fractures		
Menorrhagia		
Amenorrhea		
Corner Glaucoma		
Corneal ulcer		
Cataract		

Any other symptoms**:**

_____

_____

Do you want to report an adverse event? **1. Yes ☐** **2. No ☐**

IF YES FILL IN ADVERSE EVENT FORM

- **PHYSICAL EXAMINATION**

I. Vital signs

Temp (°C) |__|__|. |__|	Pulse (b/min) |__|__|__|	B.P. (systolic/ diastolic) |__|__|__| /|__|__|__|

II. Weight: |__|__|__|.|__|kg

III. General examination

	1.Normal	2.Abnormal	If abnormal specify
Pallor			
Jaundice			
Eyes			
Mouth			
Head and neck			
Lymph nodes			
Skin (non leprosy)			
Lungs			
Heart			
Abdomen			
Liver			
Spleen			
Ext Genitalia (male)			

Does the patient have?	1. Yes	2. No
1. Orchitis	□	□
2. Painful or red eyes?	□	□

IV. Leprosy Examination

ii. <u>Nerves</u> - signs and symptoms of neuritis (NEW = SINCE LAST REVIEW)

Name of nerve	Motor symptoms –weakness (√ if yes)			Sensory symptoms – numbness (√ if yes)		
	Normal	Abnormal	Duration in wks if abn	Normal	Abnormal	Duration in wks if abn
R Facial				N/A	N/A	
L Facial						
R Ulnar						
L Ulnar						
R Median						
L Median						
R lat popliteal						
L lat popliteal						
R Post Tibial	N/A	N/A				
L Post Tibial	N/A	N/A				

CONFIRM YOU HAVE SEEN AND ATTACHED VMT/ST FORM □

I. ENLIST ENL Severity Scale

Pain Rating - Visual Analogue Scale (Ensure line is 100 mm long)

How severe is your pain today? Mark the line below with an **X** to indicate how bad you feel your pain is *today*

No Pain _____ **Worst possible Pain**

ITEM		SCORES				
		0	1	2	3	SCORE
1	**VAS – Pain (mm)**	0	1-39	40-69	70-100	
2	**Fever** (in **°C**)	None (37.5 or less)	No fever now but history of fever in last 7 days	37.6-38.5	38.6 or higher	
3	**Number of ENL skin lesions**	None	1-10	11-20	21 or more	
4	**Inflammation of ENL skin lesions**	Non tender	Redness	Painful	Complex	
5	**Extent of ENL skin lesions**	0	1-2 regions	3-4 regions	5-7 regions	
6	**Peripheral oedema**	None	1 site of Hands or Feet or Face	2 sites	All three sites (Hands and Feet and Face)	
7	**Bone pain**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	

8	**Inflammation of Joints and/or digits due to ENL**	None	Present on examination but does **not** limit activity	Sleep or activity disturbed	Incapacitating	
9	**Lymphadenopathy due to ENL**	None	Enlarged	Pain or tenderness	Pain or tenderness in 2 or more groups	
10	**Nerve tenderness due to ENL**	None	Absent if attention distracted	Present even if attention distracted	Patient withdraws limb on examination	
	TOTAL					

- **INVESTIGATIONS – Physician to complete**

Laboratory tests (record results)

	Date taken dd/mm/yyyy	Result	Normal values
FBC	--/--/----	Hb: |__|__|.|__| g/dl WCC: |__|__|__|__| x 10^9 cells /l Plt: |__|__|__| cells/mm^3 MCV |__|__|__| fl	
Renal function	--/--/----	Creat: |__|__|.|__|__| mg/dl K+: |__|__|.|__| mmol/l Urea |__|__|.|__|__| mg/dl	
Blood sugar	--/--/----	Glucose |__|__|__|.|__|__| mg/dl	
LFT	--/--/----	Alk phos |__|__|__| u/l AST (SGOT) |__|__|__| u/l ALT (SGPT) |__|__|__| u/l Bilirubin |__|__|__| mg/dl Albumin |__|__|__| g/dl	
HIV	--/--/----	1. Positive |__| 2. Negative |__|	
Hep B -HbsAg	--/--/----	1. Positive |__| 2. Negative |__|	
Hep C antibody	--/--/----	1. Positive |__| 2. Negative |__|	
Pregnancy test (urine)	--/--/----	1. Positive |__| 2. Negative |__|	Advise contraception options
Skin biopsy	--/--/----	1. LL |__| 2. BL |__|	
Slit skin smear	--/--/----	|__|__|__|__|__|__| _|	Mean BI |__|.|__|
Chest Xray	--/--/----	1. Normal |__| 2. Abnormal |__|	
Other investigations			

Have you checked the previous set of blood results? **1. Yes** ☐ **2. No** ☐

Do you wish to fill an adverse effect form? **1. Yes** ☐ **2. No** ☐

MEDICATION TO BE PRESCRIBED

CONFIRM THAT PATIENT IS NOT ON DAPSONE ☐

Has the patient taken all study medication? **1. Yes** ☐ **2. No** ☐

Non-intervention medications:

	1. Yes	2.No	Dosage/ time
1. Folic acid - 5mg od x 52 weeks (6 days a week- not on day of MTX)	☐	☐	_____
2. Ranitidine	☐	☐	_____
3. Paracetamol max 4g/d	☐	☐	_____
4. Calcium	☐	☐	_____
5. Vitamin D	☐	☐	_____
6. Ondansetron	☐	☐	_____
7. Contraception	☐	☐	_____
8. Tramadol	☐	☐	_____

***EXTRA MEDICATION PRESCRIBED TODAY*:**

_____

_____

Do you wish to prescribe additional prednisolone? **1. Yes** □ **2. No** □

If prescribing additional prednisolone please indicate reason:

4. A flare or deterioration in ENL ☐
   - i. ENL symptoms and/or signs resulting in an increased EESS score to 9 or more
   - ii. an increase in EESS score of 5 or more
   - iii. Orchitis not responding to conservative management
   - iv. Iritis not responding to topical steroids/mydriatics

5. New or a deterioration in NFI ☐
   - iii. motor impairment - a two grade change in MRC Grade
   - iv. sensory impairment - loss of ability to feel 2 g on the hands or 10 g on the feet at three points.

6. Leprosy Type 1 reaction ☐

Dose of additional steroid prescribed as per protocol

- Individuals requiring additional prednisolone whilst on prednisolone should have a daily regime of 20mg for one week followed by 15mg for two weeks, 10mg for two weeks and 5 mg for three weeks (20/15/15/10/10/5/5/5) *added* to the reducing regime they are currently taking. **In individuals who have flared at the start of the 15mg part of the steroid intervention regime (week 7)** the

combination of reducing additional prednisolone and the initial prednisolone reducing course would mean that they would stop prednisolone at a dose of 10 mg per day. An additional week of prednisolone 5 mg daily should be prescribed at week 9 for these individuals.

- A flare of ENL in an individual not on prednisolone should be treated with the 20 week regime of the trial. Starting at prednisolone 40 mg per day.
- Patients experiencing significant NFI associated with ENL should be treated with the 20 week regime used in the trial. Starting at prednisolone 40 mg per day
- Participants experiencing a Type 1 reaction should be treated with the 20 week regime of the trial. Starting at prednisolone 40 mg per day

COMPLETE PHARMACY CARD AND SEND PATIENT TO PHARMACY

Check QoL questionnaires have been completed if week 24/48 and 60 (or visit 10, 16 and 19)

Patient aware of next review date

PART 3: ADVERSE EVENTS

AT EACH REVIEW AND UNPLANNED VISIT, THE FOLLOW FORM MUST BE COMPLETED IF THERE IS AN ADVERSE EVENT TO BE RECORDED:

Insert the relevant day number: Day |__|__|__|

Visit #: **Date:** _ _ / _ _ / _ _ _ _

Record any adverse events here:

Type of adverse event	Serious y/n	Date of onset
		_ _ / _ _ / _ _ _ _
		_ _ / _ _ / _ _ _ _

Comments on management of adverse events:

_____

_____

Did the patient require hospital admission? 1.Yes ☐ 2. No ☐

If admitted was a SERIOUS ADVERSE EVENT FORM filled in?

1.Yes ☐ 2. No ☐

Was the DSMB notified? 1.Yes ☐ 2. No ☐

What action was taken?

_____

_____

WHEN FINISHED:

COMPLETE PHARMACY CARD AND SEND PATIENT TO PHARMACY

PART 4: STUDY TERMINATION

Insert the relevant day number: Day |__|__|__|

Visit #: **Date:** _ _ / _ _ / _ _ _ _

Termination date: ___/___/___

	1.Yes	2. No
1. Did the patient complete the full course of medication?	☐	☐
2. Did the patient receive additional Prednisolone?	☐	☐

If so, how many weeks (in total) did the patient receive Prednisolone? _____

3. Did the patient report for all examinations after treatment?

Week 48	☐	☐
Week 52	☐	☐
Week 56	☐	☐
Week 60	☐	☐

4. If the patient did not complete the medication or the follow-up, select the reason:

☐ Subject did not return for clinic visit

☐ Protocol violation (specify) _____

☐ Subject refused study procedure(s): _____

☐ Voluntary withdrawal

☐ Illness (specify): _____

☐ Death: ___/___/___ (date)

☐ Other reason (specify): _____

Comments:

_____

_____

I have reviewed the contents of this case report form and found it to be complete and accurate.

Investigator's signature: _____ Date: _ _/_ _ / _ _ _ _

36- Item Short Form Survey Instrument (SF-36)
RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

1. Excellent	☐
2. Very good	☐
3. Good	☐
4. Fair	☐
5. Poor	☐

2. **Compared to one year ago**, how would you rate your health in general now?

1. Much better now than one year ago	☐
2. Somewhat better now than one year ago	☐
3. About the same	☐
4. Somewhat worse now than one year ago	☐
5. Much worse now than one year ago	☐

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot.	Yes, limited a little	No, not limited at all
3. Vigorous activities, **such as running, lifting heavy objects, participating in strenuous sports**			
4. Moderate activities, **such as moving a table, pushing a vacuum cleaner, bowling, or playing golf**			
5. **Lifting or carrying groceries**			
6. **Climbing** several **flights of stairs**			
7. **Climbing** one **flight of stairs**			
8. **Bending, kneeling, or stooping**			
9. **Walking** more than a mile			
10. **Walking** several blocks			
11. **Walking** one block			
12. **Bathing or dressing yourself**			

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the amount of time **you spent on work or other activities.**		
14. Accomplished less **than you would like**		
15. **Were limited in the** kind **of work or other activities**		
16. **Had** difficulty **performing the work or other activities (for example, it took extra effort)**		

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional** problems (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the amount of time **you spent on work or other activities.**		
18. Accomplished less **than you would like**		
19. **Didn't do work or other activities as** carefully **as usual**		

20. During **the past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

1. Not at all ☐
2. Slightly ☐
3. Moderately ☐
4. Quite a bit ☐
5. Extremely ☐

21. How much **bodily** pain have you had during the **past 4 weeks**?

1. None ☐
2. Very mild ☐
3. Mild ☐
4. Moderate ☐
5. Severe ☐
6. Very Severe ☐

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

1. Not at all ☐
2. A little bit ☐
3. Moderately ☐
4. Quite a bit ☐
5. Extremely ☐

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks…**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. **Did you feel full of pep?**						
24. **Have you been a very nervous person?**						
25. **Have you felt so down in the dumps that nothing could cheer you up?**						
26. **Have you felt calm and peaceful?**						
27. **Did you have a lot of energy?**						
28. **Have you felt downhearted and blue?**						
29. **Did you feel worn out?**						
30. **Have you been a happy person?**						
31. **Did you feel tired?**						

32. During the **past 4 weeks**, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

1. All of the time ☐
2. Most of the time ☐
3. Some of the time ☐
4. A little of the time ☐
5. None of the time ☐

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. **I seem to get sick a little easier than other people**					
34. **I am as healthy as anybody I know**					
35. **I expect my health to get worse**					
36. **My health is excellent**					

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DERMATOLOGY LIFE QUALITY INDEX

DLQI

Date:

Study ID: Score:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ⇨ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all Not relevant	☐ ☐ ☐ ☐ ☐

7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes	☐
		No	☐
		Not relevant	☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot	☐
		A little	☐
		Not at all	☐
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
		Not relevant	☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
		Not relevant	☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
		Not relevant	☐

Please check you have answered EVERY question. Thank you.