

CnT1R and CnENL

PROTOCOL/ STANDARD OPERATING PROCEDURES

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Physician review

Pharmacy

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Transport allowance provided  
All results gathered and attached to PRF  
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Adverse events  
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## *Ciclosporin studies Protocol/ SOP*

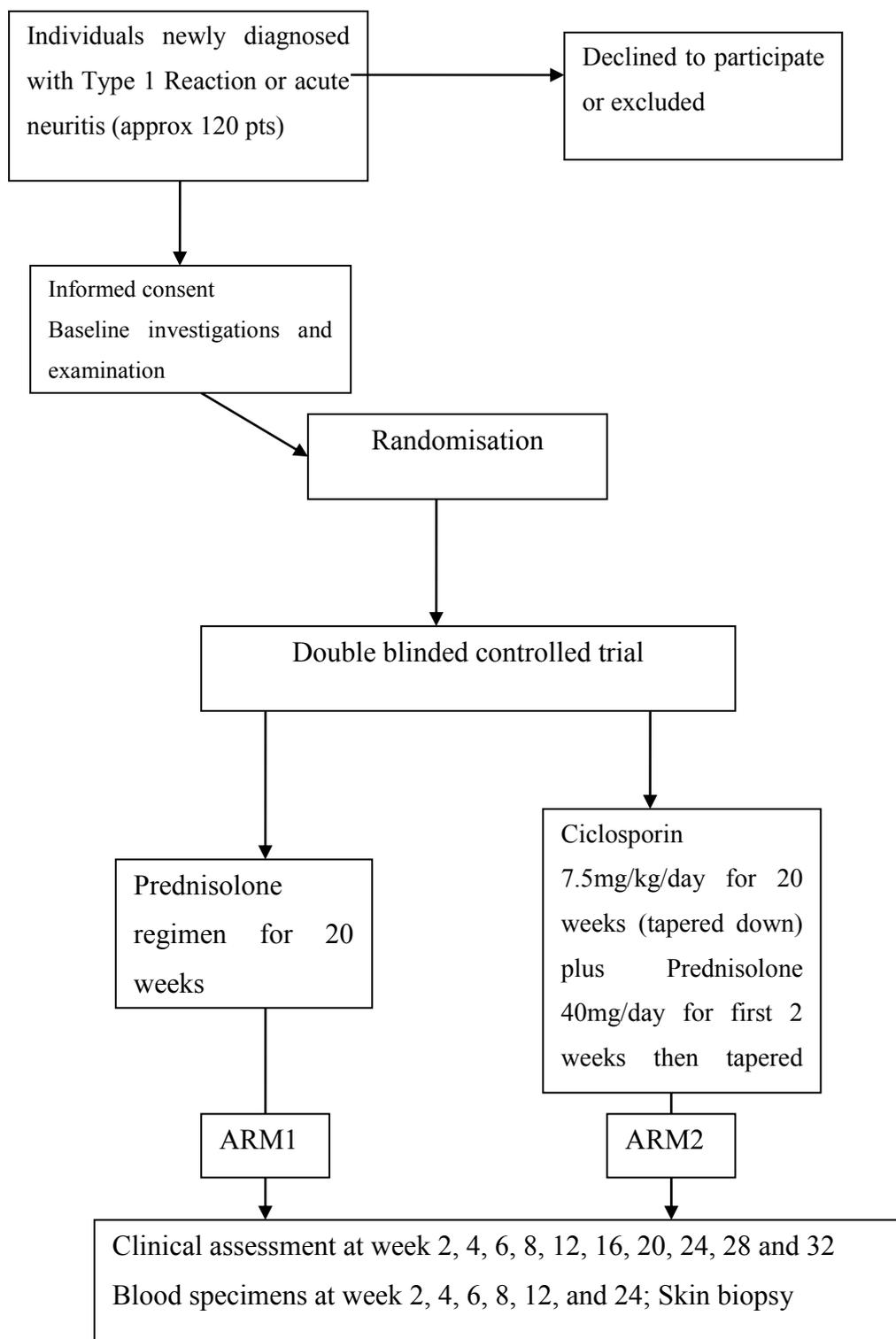
- Ciclosporin side effects
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- Drug interactions
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- Managing clinical symptoms
- Serious adverse events
- Hospitalization criteria

- Un-blinding procedure
- Late clinic attendance
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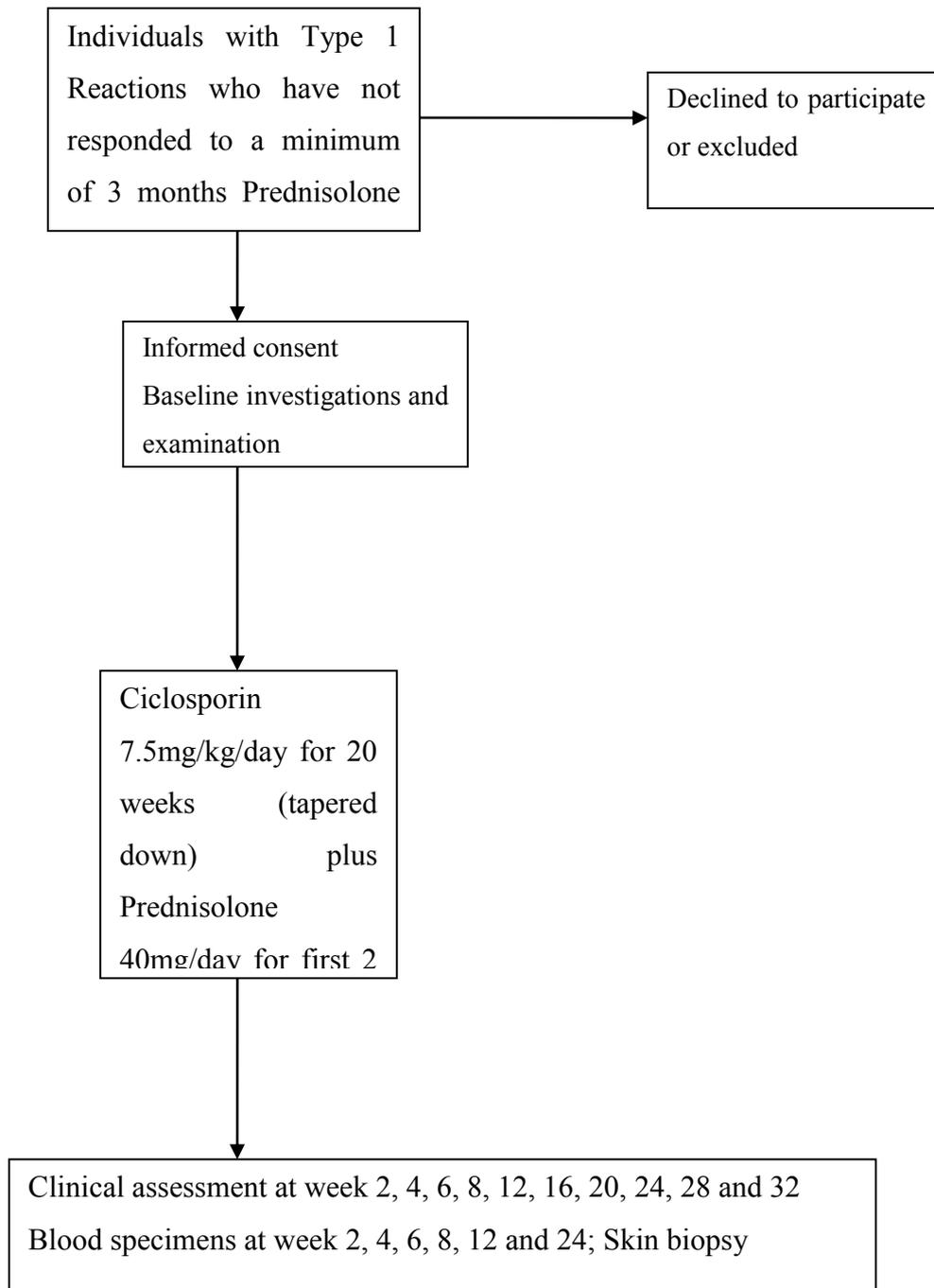
### DATA MANAGEMENT

- Storage of PRF
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- Data entry

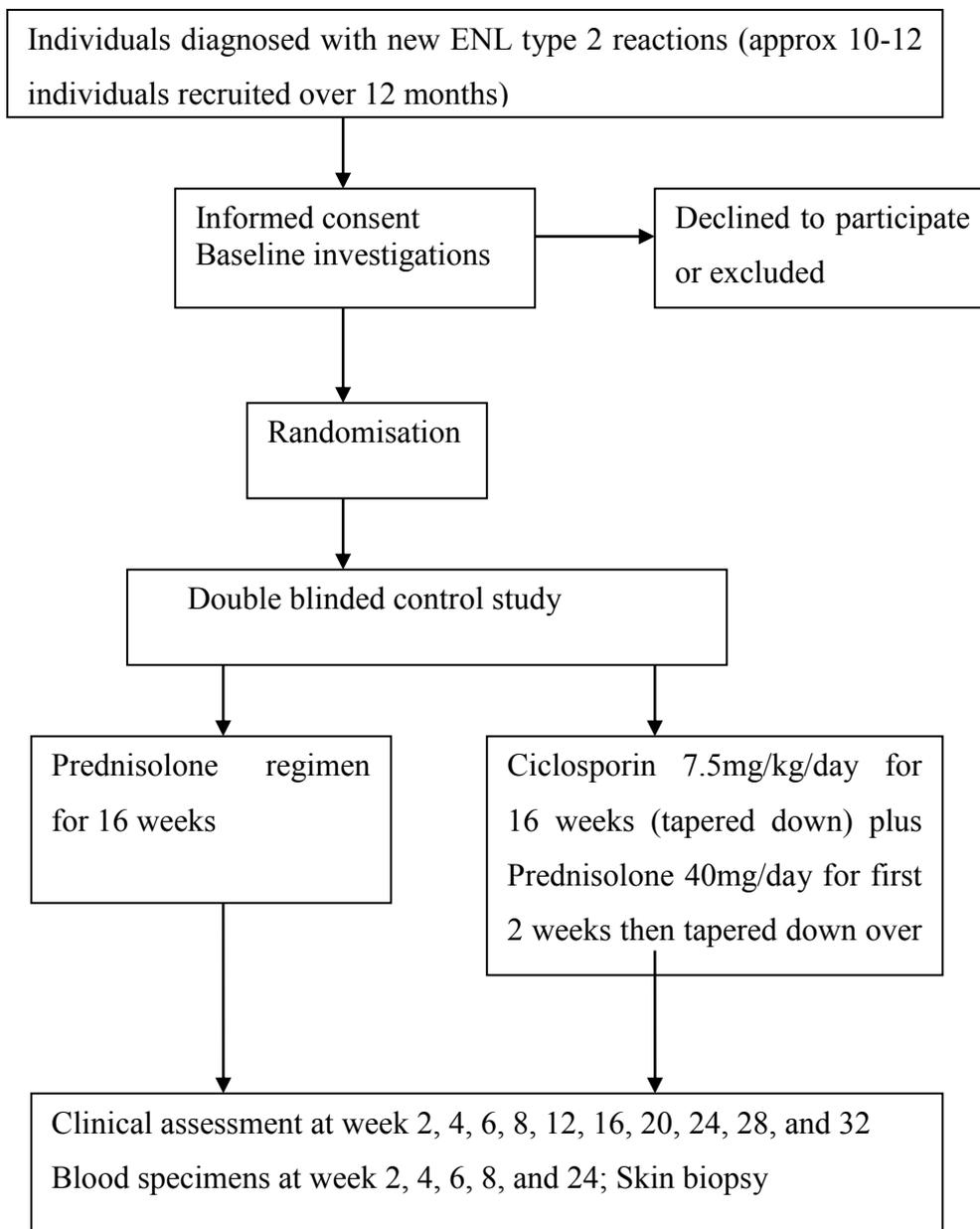
Profile of Study T1RA: A randomised controlled trial comparing the treatment of Type 1 reactions with Ciclosporin or Prednisolone.



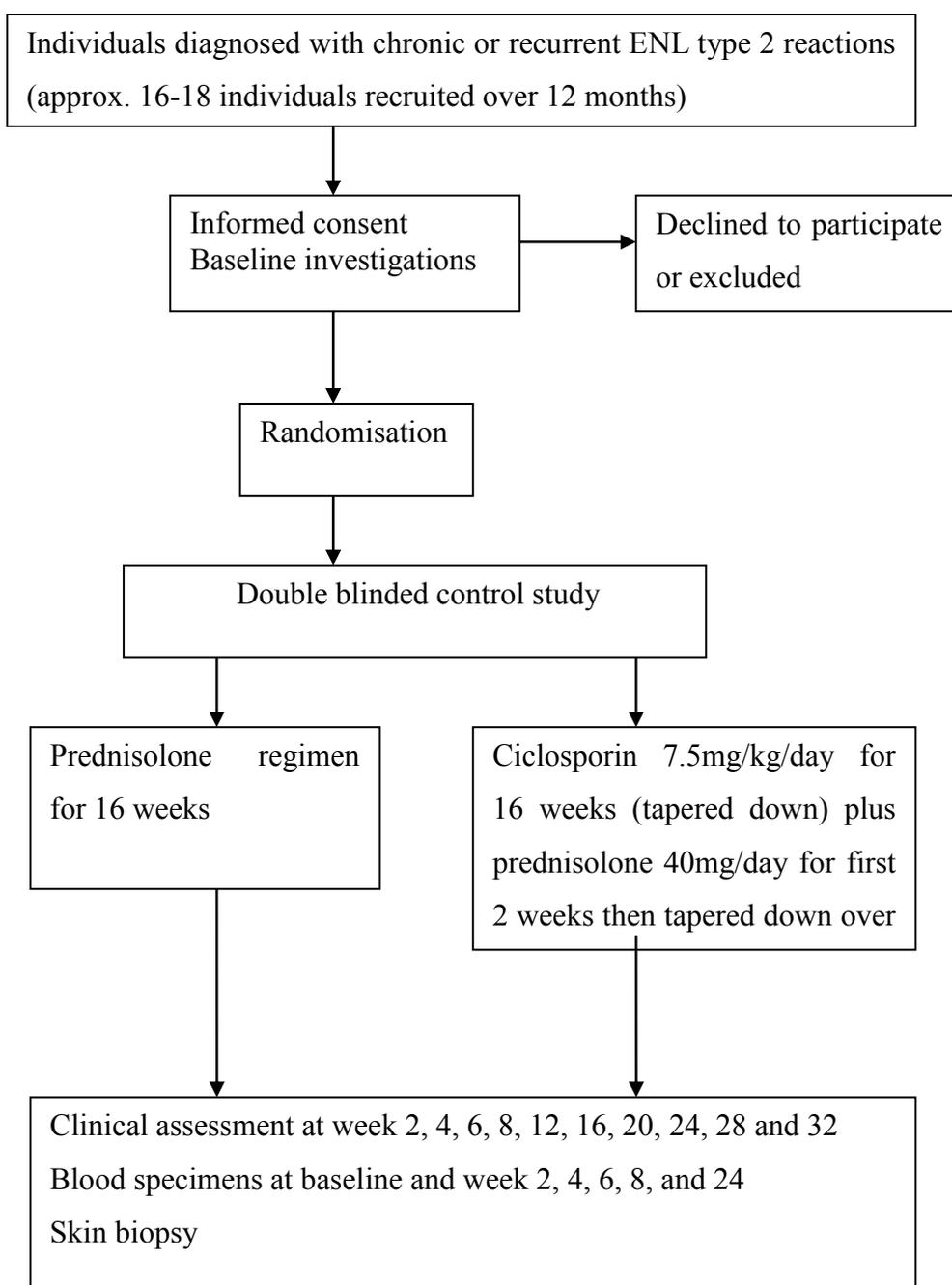
Profile of Study T1RB: A pilot study assessing the efficacy of Ciclosporin in steroid resistant Type 1 reactions.



Profile of Study ENLA: A pilot study randomizing patients with new acute ENL to treatment either with Ciclosporin or Prednisolone.



Profile of Study ENLB: A pilot study randomizing patients with recurrent or chronic ENL, already on Prednisolone treatment with Ciclosporin or additional Prednisolone.



Patient Work Flow on recruitment

1. Patient identified at Red Medical Clinic and registered
2. Patient informed about study, and recruited with consent
3. Patient sent for outstanding Laboratory investigations and skin biopsy
4. Patient sent to Physiotherapy for ST/VMT
5. All results gathered
6. Full history and examination by study physician
7. Patient referred to Pharmacist for treatment allocation and treatment distribution
8. Patient given review date

## RECRUITMENT PROCESS AT RMC

### Summary of studies:

There are four studies in this project:

Study T1RA and T1RB are for Type 1 reactions.

Study ENLA and ENLB are for ENL reactions.

Study T1RA: A randomised controlled trial comparing the treatment of Type 1 reactions with Ciclosporin or Prednisolone.

Study T1RB: A pilot study assessing the efficacy of Ciclosporin in steroid resistant Type 1 reactions

Study ENLA: A pilot study randomizing patients with new acute ENL to treatment either with Ciclosporin or Prednisolone.

Study 2B: A pilot study randomizing patients with recurrent or chronic ENL, already on Prednisolone treatment with Ciclosporin or additional Prednisolone.

### Study codes and patient numbers:

	New	Recurrent
Type 1 reaction	CnT1RA n=120	CnT1RB n=20
ENL	CnENLA n=12	CnENLB n=20

**Eligibility**

### Study (Fill in Recruitment Form)

#### Entry criteria

All Patients must be:

Aged 16-65

Weigh more than 30Kg

HIV negative

With either a Type 1 Reaction or ENL

#### Exclusion criteria

Anyone unwilling or unable to give consent.

Individuals with severe active infection such as tuberculosis or HIV/ AIDS.

Individuals with severe inter-current disease (cardiac, hepatic or renal disorder)

Pregnant women and women of child bearing capacity not accepting to use contraception for the duration of the study.

Individuals who have taken thalidomide within 3 months.

Anyone unwilling to return for follow-up.

IF ALL OF THE ABOVE ARE MET, LOOK AT THE NEXT SECTION TO ASSESS

ELIGIBILITY FOR SPECIFIC STUDY

### SPECIFIC ENTRY CRITERIA FOR EACH STUDY

Patients with Type 1 reaction

STUDY T1RA: New T1R

Individuals with clinical evidence of T1R with new nerve function impairment (NFI). A T1R is clinically defined by the acute development of erythema and oedema of skin lesions, often accompanied by neuritis and oedema of the hands, feet and face. New NFI is defined as less than 6 months duration of reduction in sensory, motor or autonomic function on history or examination.

OR

Individuals with new nerve function impairment without inflammation of skin lesions (if skin lesions are present)

STUDY T1RB: Recurrent T1R

Individuals with Type 1 Reactions who have not responded to at least 3 months of Prednisolone Treatment

#### Patients with ENL reaction

STUDY ENLA: New ENL

Individuals with clinical evidence of new ENL. New ENL is defined as the appearance of 6 or more tender, erythematous skin nodules for the first time in a patient with lepromatous or borderline lepromatous leprosy. In addition one or more of the following signs and symptoms may be present: fever (temperature  $>38^{\circ}\text{C}$ ), neuritis, joint pain, bone tenderness, oedema, malaise, anorexia and lymphadenitis.

STUDY ENLB: Recurrent ENL

Individuals with clinical evidence of chronic ENL. Recurrent or chronic ENL is defined by the presence of specific ENL symptoms in a patient with lepromatous or borderline lepromatous leprosy, who has had had ENL previously treated with prednisolone and has had a relapse or is still on prednisolone treatment but has poorly controlled ENL. The defining symptoms of ENL are 6 or more tender, erythematous skin nodules in conjunction with any of the following signs and symptoms: fever (temperature  $>38^{\circ}\text{C}$ ), neuritis, joint pain, bone tenderness, oedema, malaise, anorexia and lymphadenitis.

### **1. Informed consent**

- Trial carefully explained by investigator or nurse.
- Patient given a choice whether or not to take part in trial.
- Written explanatory note available in Amharic and English (APPENDIX 1 and 2). Please give this to patient
- Individual's signature or mark obtained on consent form and PRF as proof of consent to take part in the trial.
- Signature of enrolling researcher.
- Keep a record of reasons why patients NOT recruited into study in the screening log book.
- Any patients refusing consent will be treated according to the standard protocol of the centre.
- Patients will not be offered incentive to consent to study

### **1. Registration**

ONCE RECRUITED PATIENT WILL BE KNOWN ON ALL DOCUMENTATION BY A STUDY NUMBER.

The study number for each individual patient is made up of 10 letters or numbers.

To issue a study number:

1. Take STUDY CODE (4 letters: T1RA , T1RB, ENLA or ENLB) – describes which study the patient is in
2. NUMBER (3 digits) – patient recruitment sequence number in appropriate log book – there is a sequence for each study
3. PATIENTS INITIALS (3 letters: first name, second name, father’s surname)

Study number: |\_|\_|\_|\_|\_| |\_|\_|\_|\_|\_| |\_|\_|\_|\_|\_|

- RECORD DATE, NAME , CONTACT DETAILS, ALERT CLINIC NUMBER, STUDY NUMBER IN STUDY LOG BOOK – THERE IS A SEPARATE SECTION FOR EACH STUDY
- Write the study code of the study into which the patient has been recruited on the front of the patient’s ALERT clinic notes.
- Provide patient with Study card with his own study number recorded on it.
- Ensure all the results are back, fill in a SF-36 QOL form
- Obtain a blank Patient Record Form and refer the patient to the physician with all the documentation.

## **LABORATORY INVESTIGATIONS**

Study patient may have had most investigations prior to recruitment. Nurse to review all results and arrange any missing investigations. Please follow the following separate SOPs for:

- Specimen collection and transportation.
- Biopsy referral
- Biopsy procedure
- Laboratory
- Bacterial Index result second check

### Laboratory tests

Full blood count (Hb and WBC total and differential)

Renal function (Serum creatinine, urea and electrolytes)

Liver Function Test

Random blood sugar - random blood sugar over 11mmol/l should be followed by a fasting glucose to rule out Diabetes Mellitus

Stool specimen will be examined for ova, cysts and parasites – if positive for strongyloidiasis or ameobiasis treatment will be started immediately, and a repeat stool examination will be performed after 2 and 4 weeks. This does not exclude patient.

Urinalysis – dipstick urine to rule out glucose and protein.

Pregnancy test for women of child-bearing age done on urine sample. The women will need counselling on the importance of contraception during the study period and referred to Family Planning Clinic.

### HIV screening

All patients will be offered VCT by trained counsellor. The result will be discussed with patient with appropriate advice given. Record result.

HIV positive patients will be excluded from the Ciclosporin studies and will be referred to the ALERT HIV/ART department for further management.

### TB screening

## *Ciclosporin studies Protocol/ SOP*

Consider TB screening (if long term cough, night sweats, weight loss- refer for Chest Radiograph and sputum AAFBs)

### Skin Smear

- Skin smears from four sites including both ear lobes and two active skin lesions (the elbow or thigh should be used if there is only one skin lesion and both should be used if there are none). Smears are unnecessary if they have been done within 3 months of enrolment into the trial.
- All skin smear are stored in the lab for a period of one year minimum. When patients are recruited, please inform Lab Technician Tiruwork in order that she can review slides and confirm results

### **Biopsy**

Skin Biopsies are taken by Sister Genet or Nurse Jemal in the biopsy room at AHRI.

Please refer patient with the appropriate pathology forms (3)

Punch biopsy of skin is taken for Ridley-Jopling classification and histopathology

6mm punch biopsy of skin at baseline. The site of biopsy should be clearly documented to enable subsequent biopsies to be taken from an adjacent site. Ulcerated lesions should be avoided if possible. USE PLAIN 1 OR 2% LIGNOCAINE DO NOT USE LIGNOCAINE WITH ADRENALINE.

Skin biopsy to be analysed by Dr Jemal Hussein of ALERT/ AHRI histology department.

### **Arrangements for sample referral**

In case the ALERT Laboratory is unable to process certain samples (Potassium levels) arrangements have been made for referral to ICL (International Clinical Laboratories)

**Please see SOP – ALERT LAB**

## **Physiotherapy assessment**

The study physiotherapists have been trained to do an accurate VMT /ST assessment. The results are recorded on a form designed specifically for the study. The form for the initial and final visit is slightly different as it contains a disability scoring section.

The physio assessment sheets will be stored serially with the PRF in order for the physician to assess nerve function progress. The investigators will then use the physio assessment sheet as the source document to fill in the clinical severity scale in the CRF.

Additional nerve tested for sensation but not included in the Clinical Severity Scale are (marked on diagram with □):

1. Radio-cutaneous nerve – sensation at thumb web on dorsal surface
2. Sural nerve – lateral border of the foot on dorsal surface
3. Common peroneal – big toe web on dorsal surface

## **Physiotherapy SOP**

- 1. Patient brought by runner for Physiotherapy VMT/ ST**
- 2. Study Physiotherapist to use study form for VMT/ ST assessment**
- 3. Voluntary motor testing (VMT)**

Facial, ulnar, radial, median and lateral popliteal nerves on each side are assessed and scored using the modified MRC grading for muscle power.

Facial nerve - Forced eye closure (orbicularis oculi)

Median nerve - Thumb abduction (abductor pollicis brevis)

Ulnar nerve - Little finger abduction (abductor digiti minimi)

Radial nerve - Wrist extension (extensor muscles)

Lateral popliteal nerve- Foot dorsiflexion (tibialis anterior, peroneus longus and brevis)

Posterior tibial nerve – Great toe grip (intrinsic muscles of foot). This is an additional test not included in severity score.

## **Testing procedure for each movement** -The patient should be seated comfortably.

Facial nerve - Forced eye closure

- The patient is asked to close the eyes as tight as (s) he can.
- The tester tries to pull down the lower lid on both sides using his/her thumbs

Median nerve -Thumb abduction

- The wrist is held in extension and the patient is asked to lift his thumb up.
- Pressure is applied over the lateral side of the base of the proximal phalanx.

Ulnar nerve - Little finger abduction

- Ask the patient to abduct the little finger with MCP in slight flexion.
- Pressure is applied over the base of the proximal phalanx.

Radial nerve - Wrist extension

- Ask the patient to make a fist and lift the wrist up.
- Pressure is applied over the dorsum of hand.

Lateral popliteal nerve - Foot dorsiflexion

- Ask the patient to lift the foot up.
- Pressure is applied over the dorsum of foot.

Posterior tibial nerve – Great toe grip (intrinsic muscles of foot)

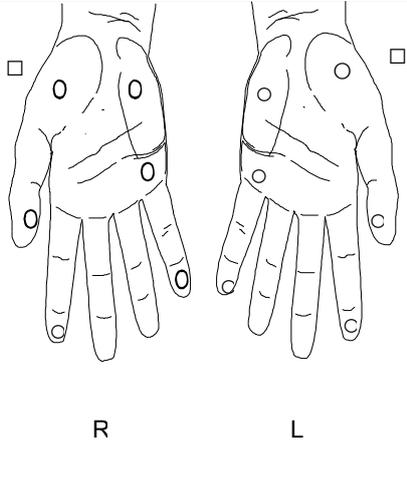
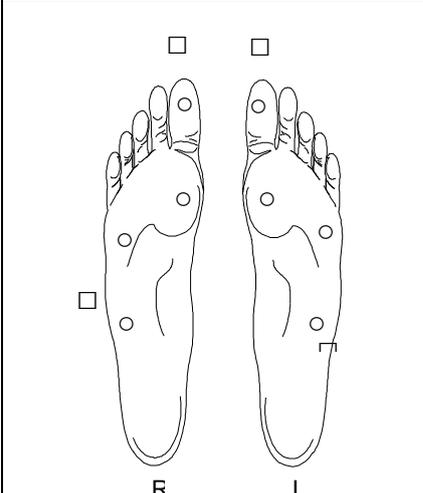
- Ask the patient to open up the space between the great toe and second toe.
- Pressure is applied the bases of the two toes

Score is derived for each nerve.

MRC modified grading of muscle power	
Score	Muscle response
5	Full range of movement (FROM)
4	FROM but less than normal resistance
3	FROM but no resistance
2	Partial range of movement with no resistance
1	Perceptible contraction of the muscle not resulting in joint movement
0	Complete paralysis

#### 4. Sensory Testing

- Trigeminal\*, ulnar, median and posterior tibial nerves on each side are tested with 5 filaments and recorded as follows

 <p>R L</p>	 <p>R L</p>	Perform the evaluation in the sequence listed below and document the first nylon with a positive response		
		Nylon colour	Approx force	
		Blue	0.2gm	5
		Purple	2 gm	4
		Dark Red	4 gm	3
		Orange	10 gm	2
		Thick red	300 gm	1
		No response		0
		Unable to test	Mark 'U'	U
		Missing	Mark 'A'	A
Mark the symbols clearly on the diagram above with appropriate filament number. Begin with 0.2gm filament ○ Palmar aspect    □ Dorsal aspect	Mark the symbols clearly on the diagram above with appropriate filament number. Begin with 2gm ○ Plantar aspect    □ Dorsal aspect			

#### 5. WHO disability grade done on the initial and final visits

WHO Grade	0	1	2
Eyes	Normal	-	Reduced vision (unable to count fingers at 6 metres). Lagophthalmos.
Hands	Normal	Loss of feeling in the palm of the hand	Visible damage to the hands, such as wounds, claw hands or loss of tissue.
Feet	Normal	Loss of feeling in the sole of the foot	Visible damage to the foot, such as wounds, loss of tissue or foot drop.

6. During follow visits the physiotherapist will record any history of nerve function loss
7. Physiotherapist to sign and date the assessment sheet.
8. Send patient back to clinic with the assessment sheet

### CLINICAL SEVERITY SCALE for TYPE 1 REACTION

This will be recorded by the investigators in the Case Record Form by selecting the required information from the physiotherapy assessment sheets

Score A is related to skin lesion assessment done by the physician see physician examination section.

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

#### Score B: Sensory testing (ST)

- Trigeminal\*, ulnar, median and posterior tibial nerves on each side. The Purple 2g and Orange 10g Semmes-Weinstein monofilaments are used at 3 sites for each nerve on the hand (median and ulnar). The Orange 10g and Pink 300g monofilament at 3 sites for the posterior tibial nerves. (\* cotton wool is used)
- Record on the diagram of the hands and feet the result of the monofilament testing at each test site using the following symbols

Purple 2g felt - ▲

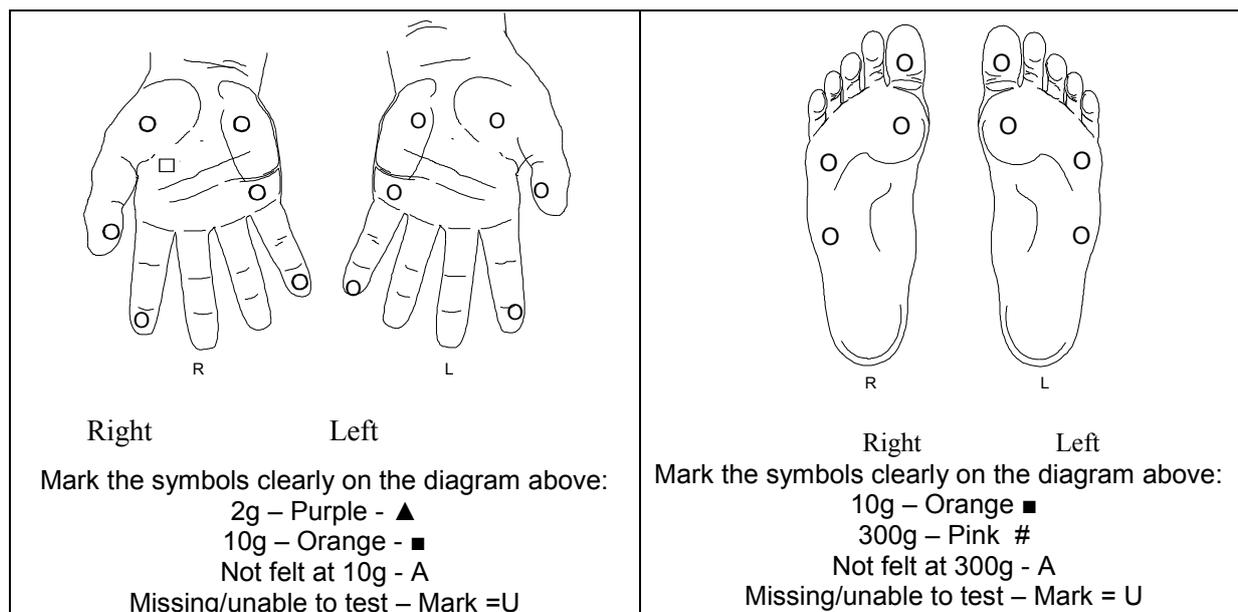
Orange 10g felt - ■

Pink 300g felt - #

Neither monofilament felt – A

(Orange not felt on hands, Pink not felt on feet then mark an A at the site in question).

### Sensory Assessment by Monofilament



	HANDS	Purple 2g Monofilament scores				Orange 10g Monofilament scores			Score	
	Nerves	0	0.5	1	1.5	2	2.5	3		
B1	RIGHT Trigeminal	Felt							Not felt	
B2	LEFT Trigeminal	Felt							Not felt	
B3	RIGHT ulnar	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
B4	LEFT ulnar	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
B5	RIGHT median	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
B6	LEFT median	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
	FEET	Orange 10g Monofilament scores				Pink 300g Monofilament scores			Score	
	Nerves	0	0.5	1	1.5	2	2.5	3		
B7	RIGHT posterior tibial	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
B8	LEFT posterior tibial	All sites felt	1 site not felt	2 sites not felt	3 sites not felt	1 site not felt	2 sites not felt	3 sites not felt		
B SCORE										

**Score C: Voluntary motor testing (VMT)**

i. Score is derived for each nerve.

MRC = 5 scores 0

MRC = 4 scores 1

MRC = 3 scores 2

MRC < 3 scores 3

If there is evidence of NFI for a given nerve then confirmation of the duration of the NFI should be sought from the affected individual to determine whether or not this is new.

Physiotherapist scores will be transferred into the severity scoring system.

	Nerve	0	1	2	3	Score
C1	RIGHT Facial	MRC	MRC=	MRC=3	MRC<3	
C2	LEFT Facial	MRC	MRC=	MRC=3	MRC<3	
C3	RIGHT Ulnar	MRC =5	MRC= 4	MRC=3	MRC<3	
C4	LEFT Ulnar	MRC	MRC=	MRC=3	MRC<3	
C5	RIGHT Median	MRC	MRC=	MRC=3	MRC<3	
C6	LEFT Median	MRC	MRC=	MRC=3	MRC<3	
C7	RIGHT Radial	MRC	MRC=	MRC=3	MRC<3	
C8	LEFT Radial	MRC	MRC=	MRC=3	MRC<3	
C9	RIGHT Lateral	MRC	MRC=	MRC=3	MRC<3	
C1	LEFT Lateral Popliteal	MRC	MRC=	MRC=3	MRC<3	
TOTAL C SCORE						

MRC modified grading of muscle power		Severity Scale Score
Score	Muscle response	
5	Full range of movement (FROM)	0
4	FROM but less than normal resistance	1
3	FROM but no resistance	2
2	Partial range of movement with no resistance	3
1	Perceptible contraction of the muscle not resulting in joint movement	3
0	Complete paralysis	3

Total score will be worked out as follows:

Total score	Scores of A+B+C	
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**PHYSICIAN ASSESSMENT:**

## HISTORY AT REGISTRATION

The physician will fill the patient's medical history as per Patient Record Form.

- Patient details
- Leprosy classification and date of diagnosis
- Leprosy treatment (type, starting and completion dates(RFT))
- Time since completion of leprosy treatment
- Type of reaction
- Date of onset of reaction
- Symptoms of reaction (with particular attention to date of onset)
- Previous history of reactions and treatment received

Please use the following table to assist with Ridley Jopling classification:

Classification		Bacterial index	Skin lesions	Nerve involvement	Systemic features
Ridley- Jopling	WHO				
Indeterminate	PB	0	Solitary hypo-pigmented 2-5cm lesion. May become TT-like.	None clinically detectable.	Nil
Tuberculoid (TT)	PB/MB	0-1	Few, often one macule or plaque with well-defined border and sensory loss. The patch is dry (loss of sweating) and hairless.	May have one peripheral nerve enlarged. Occasionally presents as a mono-neuropathy.	Nil
Borderline tuberculoid (BT)	MB	0-2	Several larger irregular plaques with partially raised edges. Satellite lesions at the edges.	Asymmetrical multiple nerve involvement	Nil
Borderline (BB)	MB	2-3	Many macular lesions and infiltrated lesions with punched out centres.	Asymmetrical multiple nerve involvement	
Borderline lepromatous (BL)	MB	1-4	Many small macular lesions and multiple nodules and papules	Widespread nerve thickening. Sensory and motor loss.	
Lepromatous (LL)	MB	4-6	Numerous nodular skin lesions in a symmetrical distribution, not dry or anaesthetic. May present as many confluent macular lesions. There are often thickened shiny earlobes, loss of eyebrows and diffuse skin thickening.	Widespread nerve enlargement. Glove and stocking anaesthesia occurs late in disease.	Nasal stuffiness, epistaxis. Testicular atrophy. Ocular involvement. Bones and internal organs can be affected.

Record carefully every section of the medical history including the specific nerve function history.

## EXAMINATION AT REGISTRATION

The physician will fill the patient's examination section as per Patient Record Form.

Clinical Examination includes:

- Full general clinical examination including T°, blood pressure and weight
- Leprosy clinical examination
  - i. Nerves - signs and symptoms of neuritis (pain, tenderness, enlargement)
  - ii. Skin - location of lesions (body chart)
    - type of lesions (patches, plaques, papules, nodules)
    - signs of inflammation in lesions
    - oedema of the hands and/or feet

Score A: Skin lesions and oedema

	Criteria	0	1	2	3	Score
A1	Degree of inflammation of skin lesions	None	Erythema	Erythema and raised	Ulceration	
A2	Number of raised and/or inflamed lesions	0	1-5	6-10	>10	
A3	Peripheral oedema due to reaction	None	Minimal	Visible, but not affecting function	Oedema affecting function	
A SCORE						

A record is kept on the body chart of any skin lesions and oedema

The Physiotherapist VMT/ST result should be assessed at this point.

**ENL severity will be recorded in the following form:**

ENL Severity data collecting form

*Ciclosporin studies Protocol/ SOP*

Symptoms of ENL

How many days have you been feeling unwell for (this episode of ENL): \_\_\_\_ days



How unwell do you feel now (tick one face)?

Have you noticed....	NO	YES
Any new lumps on your skin?		
Any new sensory loss?		
Any new weakness in your muscles?		
Any new tingling?		
Any new pain in your joints?		
Any new pain in your bones?		
Any new pain in your testicles?		
Painful eyes?		
Any visual disturbance?		

Examination

Number of ENL lesions (circle): 0 1-5 6-20 >20

Inflammation in the ENL lesions (circle):  
None  
Erythema and pain – function not affected  
Erythema and pain – function affected  
Erythema and pain – function affected plus ulceration

*(If patient has previous records use comparison to previous VMT/ST testing):*

VMT: MRC=5 MRC=4 MRC=3 MRC<3  
ST decreased in: None One nerve Two nerve ≥ three nerves  
Nerve tenderness: None Tender on palpation Withdraws

Bone tenderness (shin): None Tender on palpation Withdraws  
Oedema (ankle, face, hands): None Present Gross  
Joint swelling: None Present Affects function  
Which: \_\_\_\_\_

Lymph nodes: Normal Enlarged and tender  
Testicles: Normal Tender (? Size)  
Temperature: ≤37.5°C >37.5°C level: \_\_\_\_\_  
Proteinuria (by dipstick): Negative Positive level: \_\_\_\_\_  
Red eyes: Yes No Ophthalmology  
Diagnosis: \_\_\_\_\_

The second study physician will assess the patient's reaction severity and review the patient's VMT/ ST results before making a comment here on page 10 of the PRF:

Second Physician comment:

PATIENT HAS:

TYPE 1 REACTION   
ENL





- Then the pharmacist will provide the patient with right amount of the drugs along with the right advice and carefully instruction.
- The pharmacist will record the patient’s next review date in the patient treatment sheet as well as in the pharmacist diary or calendar in order to plan for follow up patient flow. The patient will be advised to return to the study physician after receipt of medication with the patient card.
- The study team will then record any changes in review date in the log book.

**Patient card and Transport compensation.**

Once the patient returns to the clinic, any new information will be recorded in the study log book. The patient will be provided with his own personal study card on which all the necessary information is recorded as well the phone number of his physician and the next appointment date.

Ciclosporin Study Patient card :

Name: \_\_\_\_\_

ALERT Hospital File number: \_\_\_\_\_

Study number: [ ] [ ] [ ] [ ] : [ ] [ ] [ ] [ ] : [ ] [ ] [ ] [ ]

Present this card on arrival at RMC so your file can be prepared and you are seen by the correct physician

If you are unwell and attend the doctor outside ALERT Hospital, tell them you are on special treatment (immunosuppressive) and that they should contact the ALERT physician.

Physician’s name: \_\_\_\_\_

Tel n°: \_\_\_\_\_

The patient’s transport costs will be compensated following the instruction on the patient travel SOP.

**Quality of Life Questionnaire:**

During the process of recruitment a Quality of

Life Questionnaire: The SF-36 translated into Amharic will be complete with the help of a study nurse.

	Appointment date dd/mm/yyyy	Date seen dd/mm/yyyy	Extra notes
First visit			
Week 2			
Week 4			
Week 6			
Week 8			
Week 12			
Week 16			
Week 20			
Week 24			
Week 28			
Week 32			

**CHECKLIST AND PATIENT FLOW ON RECRUITMENT**

Patient screened: Leprosy AND Reaction CONFIRMED. No exclusion criteria.  
Patient informed re study, consent obtained

Study number issued: Enter patient in study log book and issue correct study number

Patient investigation: Nerve function: Physiotherapy worksheet

Laboratory: VCT for HIV

## *Ciclosporin studies Protocol/ SOP*

Bloods: FBC, Electrolytes, Creatinine, random glucose, LFT, ESR  
Skin smear  
Skin biopsy  
Stool: Microscopy  
Urine: dipstick and microscopy  
Urine: pregnancy test if woman in childbearing age  
Chest X-ray/ sputum if TB suspected

Quality of Life Questionnaire: to be done by study nurse

Patient review by physician with results:

Fill in physician worksheet, ensuring all results available

Patient care: Exclude if HIV positive – refer to ART clinic for standard ALERT management

Exclude if suspected with TB

If newly diagnosed leprosy patient: ensure registered in National register and started on MDT (WHO), refer to patient education, eye check and shoe room

If woman of child bearing age: discuss contraception and refer to Health Centre or ALERT Gynaecology team

If stool positive treat for ova and parasite, treat appropriately

If urine positive for infection treat with antibiotics

Study action steps: Refer patient to pharmacy with a study card

Patient will be allocated into treatment arm

Patient will receive treatment from pharmacist

Patient returns to Physician with study card

Transport money: Provide patient with review date and transport money

### **STORING SOURCE DOCUMENTS AND PRF**

All the following source documents must be gathered and handed to the Study co-ordinator or PI:

Recruitment form

Consent Form

VMT/ST form

Laboratory results:

Bloods

Stool

Urine

BI

Biopsy number

Pregnancy test result

Any extra investigations dozen (eg Xray....)

Quality of Life Questionnaire

Patient to Pharmacy card

Completed PRF

All documentation will be reviewed by Study co-ordinator or by PI and stored in the metal cabinet in RMC under lock.

### **FOLLOW UP SCHEDULE**

Patients will be reviewed according to a pre-specified schedule.

TABLE SUMMARISING TESTS DONE ON PATIENTS

	<u>Base-</u> <u>line</u>	<u>Wk</u> <u>2</u>	<u>Wk</u> <u>4</u>	<u>Wk</u> <u>6</u>	<u>Wk</u> <u>8</u>	<u>Wk</u> <u>12</u>	<u>Wk</u> <u>16</u>	<u>Wk</u> <u>20</u>	<u>Wk</u> <u>24</u>	<u>Wk</u> <u>28</u>	<u>Wk</u> <u>32</u>	<u>Tot</u>
<u>Clinical</u> <u>assessment</u>	X	X	X	X	X	X	X	X	X	X	X	12
<u>Renal</u> <u>function</u>	X	X	X	X	X	X			X			7
<u>FBC, LFT</u>	X			X					X			3
<u>Glucose</u> <u>(glucometer)</u>	X	X	X	X	X	X	X	X	X	X		10
<u>Stool (OCP) -</u> <u>PRN</u>	X											1
<u>Urinalysis -</u> <u>PRN</u>	X											
<u>HIV</u>	X					X			X			2
<u>Pregnancy</u> <u>test</u>	X		X		X	X	X	X	X			7
<u>TB screen</u>	X											
<u>Skin Biopsy</u>	X						X					2

Clinical assessment will consist of:

- focussed questions to assess skin and nerve function and to detect adverse drug effects
- a general physical examination
- charting of skin lesions and nerve condition
- VMT ST assessment by physio
- weight
- Blood glucose and dipstick urinalysis for glucose and protein

Skin biopsy will be done at baseline for morphology and cytokines studies at baseline, week 16 and possibly at the end of the study.

HIV test will be repeated during the study period if clinically indicated by symptoms or worsening health status. It will be done also at the end of the study.

**Summary of treatment regimens**

Study 1: Cn and prednisolone in Type 1 Reactions

		ARM 1	ARM 2		
		PREDNISOLONE	CICLOSPORIN		PREDNISOLONE
		Prednisolone	Ciclosporin	AND	Predn
Clinical R.	Day 0				
	Week 1	40mg	7.5mg/kg		40mg
Clinical R.	Week 2	40mg	7.5mg/kg		40mg
	Week 3	35mg	7.5mg/kg		20mg
Clinical R.	Week 4	35mg	7.5mg/kg		10mg
	Week 5	30mg	7.5mg/kg		
Clinical R.	Week 6	30mg	7.5mg/kg		
	Week 7	25mg	7.5mg/kg		
Clinical R.	Week 8	25mg	7.5mg/kg		
	Week 9	20mg	7.5mg/kg		
	Week 10	20mg	7.5mg/kg		
	Week 11	20mg	7.5mg/kg		
Clinical R.	Week 12	20mg	7.5mg/kg		
	Week 13	15mg	6mg/kg		
	Week 14	15mg	6mg/kg		
	Week 15	15mg	6mg/kg		
Clinical R.	Week 16	15mg	6mg/kg		
	Week 17	10mg	4mg/kg		
	Week 18	10mg	4mg/kg		
	Week 19	5mg	2mg/kg		
Clinical R.	Week 20	5mg	2mg/kg		
	Week 21	n/a	n/a		
	Week 22	n/a	n/a		
	Week 23	n/a	n/a		
Clinical R.	Week 24	n/a	n/a		
Clinical R.	Week 28	n/a	n/a		
Clinical R.	Week 32	n/a	n/a		

Placebo not marked on above table for simplification

Study 2: Cn and Prednisolone in ENL Management

		ARM 1		ARM 2		
		PREDNISOLON E		CICLOSPORIN		PREDNISOLONE
		Prednisolone		Ciclosporin	AND	Predn
Clinical R.	Day 0					
	Week 1	60mg		7.5mg/kg		40mg
Clinical R.	Week 2	55mg		7.5mg/kg		40mg
	Week 3	50mg		7.5mg/kg		20mg
Clinical R.	Week 4	45mg		7.5mg/kg		10mg
	Week 5	40mg		7.5mg/kg		
Clinical R.	Week 6	35mg		7.5mg/kg		
	Week 7	30mg		7.5mg/kg		
Clinical R.	Week 8	25mg		7.5mg/kg		
	Week 9	20mg		7.5mg/kg		
	Week 10	20mg		7.5mg/kg		
	Week 11	15mg		7.5mg/kg		
Clinical R.	Week 12	15mg		7.5mg/kg		
Clinical R.	Week 13	10mg		6mg/kg		
	Week 14	10mg		6mg/kg		
Clinical R.	Week 15	5mg		4mg/kg		
	Week 16	5mg		2mg/kg		
	Week 17	n/a		n/a		
	Week 18	n/a		n/a		
	Week 19	n/a		n/a		
Clinical R.	Week 20	n/a		n/a		
Clinical R.	Week 24	n/a		n/a		
Clinical R.	Week 28	n/a		n/a		
Clinical R.	Week 32	n/a		n/a		

Placebo not marked on above table for simplification

## **FOLLOW UP ACTIVITIES**

### **1. Welcoming patient**

Study participants will all carry a card with name, study number and list of a review dates. This will be presented at the clinic on arrival so as to direct the patient correctly through the process of that review.

### **2. Checking register and marking visit**

Nurse or runner receiving patient will check in log file for the patient's details, confirm details with patient and obtain the PRF

### **3. Obtaining PRF and organising planned investigations**

All PRF are kept in the locked metal cupboard in Red Medical Clinic. Obtain the correct PRF, confirm the follow up week number and organise list of investigations for that specific week. Fill in request forms for the laboratory

### **4. Nurse's review: weight BP pulse**

The nurse will obtain the following vital statistics and attach to patient's record: Temperature, pulse, Blood pressure and weight

### **5. Laboratory sample collected**

Depending on the week number, the sample collecting and tracking forms are filled in and the corresponding specimens collected as per standard. Specimens are sent to lab as soon as possible (see Laboratory SOP)

### **6. Physiotherapy assessment**

The patient is then sent to Physiotherapy for VMT and ST assessment with the appropriate for, attention of study physiotherapists

### **7. Physician's history and examination**

Once results are collected, the nurse will check that all necessary documentation is attached to the PRF and refer the patient to the study physician. After the physician's assessment and management of any complications the patient is given a "Clinic to Pharmacy card" with today's weight and the next review appointment

### **8. Referral to Pharmacy**

The study pharmacist will receive the patient with the card above and proceed to identify the patient and obtain his treatment card.

Any weight adjustment will be taken note of. The patient will then be issued with the treatment drugs and instructions on how to take these. See Pharmacy SOP

**9. Appointment date registered**

The pharmacist will approve the review date and mark the number of days treatment was supplied for on the patient card, before referring patient back to clinic

**10. Transport allowance provided**

The patient's appointment date will be record in the clinic diary and he will be provide with the transport cost as per travel SOP.

**11. All results gathered and attached to PRF**

Physician will ensure that all source documents are attached to the PRF

**12. PRF storage**

Study Physician or co-ordinator will ensure that completed documents are stored in the locked metal cabinet

• **CHECKLIST ON REVIEW**

History

Physical examination

Nerve studies by physiotherapy department

Skin smears if not done in previous 3 months

Skin biopsy from the edge of an area of reactional (non-ulcerated) skin –only week 6, 16 and 32

Blood test: FBC, renal function, random glucose

Stool sample, Urine sample

Chest Xray and Sputum if suspicion of TB

Encourage appropriate contraception in females with childbearing capacity

Refer to pharmacy to collect further treatment

Review date arranged. Transport provided

**USING ADDITIONAL PREDNISOLONE**

When additional Prednisolone is required, the standard pink tablets will be prescribed.

- Criteria for using additional prednisolone
  - i. Sustained deterioration for a period of at least two weeks of:
    - a. Deterioration in nerve function
    - b. Nerve pain unresponsive to analgesics
    - c. Palpable swelling of skin patches
    - d. New erythematous and raised skin patches
  - ii. Deterioration in nerve function which the study doctors believe requires immediate additional Prednisolone
- The patient must be examined by at least two of the study doctors and they should be in agreement about giving the patient additional Prednisolone.

- The reasons for the additional Prednisolone and the date started should be recorded.

**Regimen for additional prednisolone**

- If there is recurrence of T1R with NFI (or nerve pain unresponsive to analgesics) on treatment then add extra Prednisolone to make up a total of 40mg when the present dose of Prednisolone is known, and then taper according to the original regimen.
- In cases belonging to Study 1A, where the study is blinded and the clinician is unable to know whether the patient is on Prednisolone or Ciclosporin, then add Prednisolone 20mg and taper down.
- If there is recurrence of T1R with skin signs but no NFI then:
  - i. If recurrence within the first ten weeks of treatment or there is facial involvement then add extra Prednisolone to make up a total of 40mg and then taper according to the original regimen.
  - ii. If recurrence after ten weeks of treatment then add extra Prednisolone to make up a total of 20mg and then taper according to the original regimen.

## Adverse events

### Managing Adverse Events

At each clinical review during the study period the patient will be closely monitored for any signs of adverse effects related to the study drugs, but also unrelated adverse events will be recorded as will the causality be assessed.

Adverse events will usually be picked up in the careful history taking and general examination, but specific known drug related adverse event are listed in Table below and the physician should enquire about each one specifically.

Symptoms or signs to monitor	
Moon face	<input type="checkbox"/>
Acne	<input type="checkbox"/>
Gum hyperplasia	<input type="checkbox"/>
Cutaneous (including nails) fungal infections	<input type="checkbox"/>
Gastric pain requiring antacid	<input type="checkbox"/>
Gastrointestinal bleeding	<input type="checkbox"/>
Nocturia, polyuria, polydipsia	<input type="checkbox"/>
Diabetes mellitus	<input type="checkbox"/>
Psychosis or other mental health problems	<input type="checkbox"/>
Weight loss >5kg	<input type="checkbox"/>
Weight gain	<input type="checkbox"/>
Glaucoma	<input type="checkbox"/>
Cataract	<input type="checkbox"/>
Hypertension BP > 160/90 on 2 separate readings at least 1/52 apart	<input type="checkbox"/>
Infections	<input type="checkbox"/>
Infected ulcers	<input type="checkbox"/>
Corneal ulcer	<input type="checkbox"/>
Tuberculosis	<input type="checkbox"/>
Night sweats	<input type="checkbox"/>
Convulsions	<input type="checkbox"/>
Vomiting	<input type="checkbox"/>
Diarrhoea	<input type="checkbox"/>
Breathing difficulties	<input type="checkbox"/>
Abnormal blood results (hyperkalaemia, abnormal LFT)	<input type="checkbox"/>
Pruritus	<input type="checkbox"/>

A list of common medication related side effects is attached here to help the physician identify the potential causal factor and plan appropriate management of the patient:

### **Prednisolone side effects:**

- Major adverse events
  - i. Gastrointestinal bleeding
  - ii. Nocturia, polyuria, polydipsia
  - iii. Diabetes mellitus
  - iv. Psychosis or other mental health problems

- v. Weight loss >5kg
- vi. Weight gain
- vii. Glaucoma
- viii. Cataract
- ix. Hypertension >160/90 on two separate readings at least one week apart
- x. Infections
- xi. Infected ulcers
- xii. Corneal ulcer
- xiii. Tuberculosis
- xiv. Night sweats
- Minor adverse events
  - i. Moon face
  - ii. Acne
  - iii. Cutaneous (including nails) fungal infections
  - iv. Gastric pain requiring antacids

**Ciclosporin side effects:**

- i. Hypertension
- ii. Nausea, vomiting, diarrhoea
- iii. Weakness, fatigue, weightloss, headache
- iv. Renal impairment
- v. Hypertrichosis
- vi. Gingival overgrowth

**Contra-indications to Ciclosporin:**

- i. Abnormal renal function
- ii. Uncontrolled hypertension
- iii. Breastfeeding (Ciclosporin passed into breast milk)
- iv. Acute severe infections (including active TB)

**Drug interactions with Ciclosporin:**

- i. Agents that increase Ciclosporin levels:

Erythromycin	Ketoconazole	Allopurinol
Doxycycline	Cimetidine	Oral contraceptives
Clarithromycin	Metoclopramide	Grapefruit juice
Norfloxacin	Verapamil	
Chloroquine	Diltiazem	

- ii. Agents that decrease Ciclosporin levels:

Rifampicin	Phenytoin	Carbamazepine
Trimethoprim (IV)	Phenobarbitone	

- iii. Agents that increase nephrotoxicity:

NSAIDS (care with high	Co-trimoxazole
------------------------	----------------

doses)	
Aminoglycosides	Trimethoprim

- iv. Ciclosporin increases the plasma concentration of prednisolone.

**Important laboratory monitoring:**

1. Serum Creatinine:  
If level increases more than 30% above baseline, on more than 1 measurement, then dose of ciclosporin should be reduced by 1mg/kg  
If level increases more than 50% above baseline, reduce dose of ciclosporin by 50%
2. Serum Potassium  
If serum Potassium ranges 5.0 – 6.4mmol/l, reduce ciclosporin dose by 1mg/kg. Repeat Potassium after 2 days. If still in this range then reduce dose by 1mg/kg and repeat blood test every 2 days until within normal level.  
If serum Potassium >6.4 mmol/l, STOP ciclosporin. Give 50ml of 50% IV dextrose plus 5 units of Actrapid over 20 minutes followed by 1 litre 10% dextrose IV given over 12 hours. Repeat serum Potassium the following day and every 2 days after until within the normal range.

**Managing clinical symptoms:**

<b>Clinical Parameter</b>	<b>Level</b>	<b>Action</b>
Blood Pressure	If BP> 100mg diastolic after maximal antihypertensive therapy	Stop Cn
	If BP moderately elevated	Reduce ciclosporin by 25% or introduce anti-hypertensive (avoid K+ sparing agent – may cause hyperkalaemia)
Gingival overgrowth	Severe	Reduce Cn by 1mg/kg
Hypertrichosis	Noticeable but not unacceptable to patient	Reassure and continue Cn
Hypertrichosis	Unacceptable to patient	Stop Cn
Nausea and vomiting	Mild, treatable	Anti-emetics
Nausea and vomiting	Severe	IV rehydration STOP Cn
Diarrhoea	Severe (every hour and leading to dehydration)	Stop Cn and restart dose reduced by 1mg/kg after dehydration resolved
Malaise		Measure Potassium
Gastric pain		Antacids/ Ranitidine

All adverse events will be recorded in the Patient Record Form and Case Record Form.

**Definitions**

**Adverse Event (AE)**

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. 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)**

All untoward and unintended responses to an IMP related to any dose administered. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to the IMP qualify as adverse reactions.

**Serious Adverse Event/ Reaction (SAE/SAR)**

Any adverse event or adverse reaction that at any dose:

- results in death
- is life-threatening
- requires hospitalisation, or prolongation of existing inpatients' hospitalisation.
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

### **Suspected Serious Adverse Reaction (SSAR)**

Any adverse reaction that is classed as serious and which is consistent with the information about the IMP listed in the Summary of Product Characteristics.

### **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

Any adverse reaction that is classed as serious and is suspected to be caused by the IMP that is not consistent with the information about the IMP in the Summary of Product Characteristics, i.e. it is suspected and unexpected.

Severity and causality will be commented upon by the study physician in the CRF.

### **Serious Adverse Events**

A reporting form has been prepared for Serious Adverse Events.

These will be immediately reported to the DSMB by the study physician and/or the PI.

### **Admission**

Patients may be admitted for the first day (Day0) to have all initial tests done and results back prior to starting study, if this is more convenient for patient.

Patients will generally be treated as out-patients, but may be offered admission at ALERT if unwell.

### **Criteria for hospitalization:**

1. Patient is too unwell to be at home
2. Patient develops severe infection
3. Patient develops severe nausea, vomiting and /or diarrhoea requiring i.v. re hydration
4. Patient has abnormal blood results with potassium > 6.4 mmol or serum creatinine increased by 30% above baseline
5. Patient is unable to travel between home and hospital, e.g. foot ulcer requiring bed rest; lives too far and is willing/ prefers admission.

### **Arrangements for breaking the code in the event of an agreed clinical emergency.**

- In the event of a major adverse event necessitating hospital admission then the code can be broken for that individual in order to aid management of the problem.
- Two study physicians will agree on the necessity to break the code.

- The pharmacist will be informed and provide details of treatment allocation.
- The patient will be withdrawn from the study.
- A Serious Adverse Event Form will be completed.
- The DSMB will be informed of this event.

### **Late Clinic Attendances**

If a trial subject does not attend a scheduled assessment then they will be contacted and asked to come as soon as possible for their assessment. It is essential that the date of the attendance is recorded. The number of the assessment should not be changed regardless of how late the assessment is carried out.

The next assessment after this should be scheduled as though the original assessment had been performed as planned. If the assessment is so late that the following assessment has also been missed then the next assessment should be scheduled for 28 days (four weeks) later.

If a participant has missed certain trial investigations then these should be performed when they next attend.

### **Unscheduled Clinic Attendances/examinations**

- All unscheduled examinations (if an inpatient) or clinic attendances should be recorded on Form 7: Unscheduled visit
- It should be documented if the clinician feels the attendance is related to prednisolone or ciclosporin therapy.

### **Data management**

- Each subject enrolled into the study will have two individual case booklets for recording of all clinical and laboratory data:
  1. Patient Record Form: all forms needed for patient management, including physician and physiotherapist worksheets and source documents (eg lab results...). This will be used in clinic to record all information during patient attendance.
  2. Case Record Form: this is the data record which is essential for study data. It will be filled in daily by the study physician following patient attendance. This will be stored separately in a secured place and only accessible to named study physicians.

- An anonymised Access database will be created for storage of trial data which will subsequently be analysed using standard statistical packages.
- Double entry of data into database will be done. One entry to be done by PI and second entry by data management staff at ALERT/AHRI. The two entries will be crossed checked for errors using EPI-INFO, and any differences verified by going back to original data on CRF.
- Data analysis will be done using SPSS.
- PRF and CRF will be stored at the end of the study in the secure archiving area at AHRI and remain the property of ALERT/AHRI.