

*WORKSHOP REPORT*

**Erythema Nodosum Leprosum International Study  
Group: 3rd ENLIST Meeting Report, Mumbai,  
7th-9th April 2015**

Dr STEVE WALKER & Prof DIANA LOCKWOOD,  
LSHTM

**Introduction**

The third ENLIST meeting was hosted by Dr Vivek V. Pai and the Bombay Leprosy Project at the Hotel Plaza, Chembur, Mumbai. The organisations with which the participants are affiliated kindly allowed them to travel and participate at the meeting. The participants themselves generously gave of their time in order to collaborate and improve our understanding of ENL and our ability to treat it.

**The ENLIST Group**

The ENLIST Group was formed in 2012 following a meeting of physicians and scientists working in leprosy.<sup>1</sup> The meeting was organised by Dr Stephen Walker and Professor Diana Lockwood of the Leprosy Group of the London School of Hygiene and Tropical Medicine. Professor Lockwood's group is the leading research group in the field of reactions. It was recognised that a group such as ENLIST was vital to improve the understanding and treatment of ENL because each centre alone does not have enough patients to conduct clinical trials of the necessary size. The study of a complex disorder such as ENL requires a wide variety of skills from different disciplines.

**Who Are We?**

We are clinicians and laboratory scientists with extensive experience in the treatment and investigation of the causes of ENL. We are based at institutions in eight countries on four continents. The group is coordinated from London and includes four centres in the two countries with highest rates of leprosy: India and Brazil. In addition to India and Brazil, ENLIST members are also based in Bangladesh, Ethiopia, Indonesia, Nepal and the Philippines.

## **Aims of ENLIST**

1. To improve the understanding of the mechanisms which cause ENL
2. To improve the evidence to guide treatment decisions
3. To improve access to effective treatments

## **Objectives of the Meeting**

### DAY 1

- Share results of ENLIST 1 analysis
- Agree additional analysis needs
- Discuss lessons learnt from ENLIST 1
- Understand the process of scale development
- Agree usefulness of currently available ENL scales
- Develop consensus of ENL scale items for testing

### DAY 2

- Share results of ENLIST 2 Quality of Life (QoL) data
- Develop a consensus on standardisation of data presentation
- Agree publication submission details

### DAY 3

- Agree provisional ENL severity scale
- Agree provisional ENL severity scale validation methodology
- Identify complementary laboratory studies
- Agree next Leprosy Research Initiative ENLIST application
- Discuss the timing of the 4th ENLIST meeting

## **The Meeting**

### DAY 1

- (a) The inauguration of the meeting took place with a welcome from our host Dr Vivek Pai of the Bombay Leprosy Project, lighting of the lamp by Baban Kadu a person affected with leprosy and rehabilitated by Bombay Leprosy Project and a vote of thanks by Mr Subhash Hoval, Manager of Bombay Leprosy Project.
- (b) ENLIST 1 – Dr Walker presented the results of the analysis of the data collected at the centres that participated in the ENLIST 1 study. This study is the first of its kind to prospectively study the clinical features of ENL. The study provides prospective data collected on 292 individuals with ENL and is the largest study of its kind. The presentation was followed by a discussion of the results and their implications for the future work proposed by the group.

A draft manuscript for submission to a peer-reviewed journal was also circulated so that participants could provide feedback before submission. The paper is entitled:

“ENLIST 1- An international multi-centre prospective cross-sectional study of the clinical features of erythema nodosum leprosum”. The key points of the paper are:

- i. The clinical features of ENL are uniform around the world
  - ii. Severe pain is a significant feature of ENL
  - iii. Patients with chronic ENL were significantly more likely to be classed as severe
  - iv. The duration of ENL is associated with nerve function impairment
  - v. Fever is an important symptom but only demonstrated in 20% of cases
  - vi. Over 25% of patients receiving thalidomide require an additional agent
- (c) Scale development – The ENLIST Group has secured funding from the Leprosy Research Initiative (LRI) for one year to develop and validate an ENL severity scale. Dr Walker gave a presentation on the rationale for a clinical severity scale for ENL, the techniques employed and the requirements for participating centres. A detailed discussion about the processes for conducting a scale validation study took place. It was agreed to “test the ENL scale on people with an established diagnosis of ENL (ie had skin signs originally, not more than 3 months ago) even if now no active signs of ENL”.
- (d) The participants formed three groups to critique three ENL severity scales<sup>2-4</sup> that had been circulated prior to the meeting and used in clinical settings. A discussion of the good and bad points of each scale took place and a presentation of how the scales had performed in the clinical settings. Detailed contemporaneous notes were taken during this discussion to facilitate the development of a new ENL scale. The results of a preliminary regression analysis of the clinical data and severity assessments from the ENLIST 1 study was presented to support the discussion. Dr Walker undertook to incorporate the points made by the group into a draft scale to be circulated to the whole group on day 2.
- (e) Professor Lockwood gave a presentation on the assessment of pain in leprosy and the importance of recognising the different types of pain that occur. A discussion about the different tools that could be employed to assess pain took place.

## DAY 2

- (a) We welcomed participants from the Novartis Foundation – Dr Edith Roset Bahmanyar and Mr Martin Szczerbiak.
- (b) Dr Walker gave a presentation outlining the importance of ENL, the difficulties faced in managing the condition and the role of ENLIST. A draft ENL severity scale was circulated to the group.
- (c) Participants from each centre presented a preliminary analysis of the quality of life (QoL) data obtained.
- i. FIOCRUZ, Rio de Janeiro, Brazil – Dr Anna Sales
  - ii. TLM Purulia, India – Mr Pitchaimani
  - iii. ALERT Center, Addis Ababa, Ethiopia – Dr Saba Lambert
  - iv. General Soetomo Hospital, Surabaya, Indonesia – Dr Yulianto Listiawan
  - v. Anandaban Hospital, Kathmandu, Nepal – Dr Mahesh Shah
  - vi. Leonard Wood Memorial, Cebu, Philippines – Dr Armi Maghanoy
  - vii. Bombay Leprosy Project, Mumbai, India – Dr Vivek V. Pai
  - viii. TLM Bangladesh, Bangladesh – Dr Ruth Butlin

- (d) Dr Saba Lambert gave a presentation on the analysis and presentation of QoL data using her experience of QoL scale validation in Ethiopia and a recent publication of QoL data with respect to the neglected tropical disease podoconiosis.<sup>5</sup>

A discussion of the preliminary results, the further work required and final presentation of the data took place. It was agreed that the individual studies would be prepared to an agreed format and submitted together for publication along with a commentary piece written by Dr Lambert and Dr Walker. A template for manuscripts was produced and circulated.

The ENLIST meeting meal took place at the nearby Hotel Grand Central in the rooftop restaurant with musicians singing gazals. This provided the group with an opportunity for everyone to exchange ideas, get to know one another better and continue informal discussions. An extremely pleasant evening was had by all.

#### DAY 3

- (a) The morning session was used to discuss and improve the draft ENL severity scale that had been circulated on Day 2. The 14 items in the scale were increased to 16. Robust definitions were developed as well as notes for the use of the scale.
- (b) Dr Anastasia Polycarpou gave an overview of our understanding of the pathophysiology of ENL and the limitations of the evidence upon which this is based.
- (c) Dr Deanna Hagge gave a presentation outlining the types of laboratory based projects that could be performed within the network of ENLIST collaborating centres. To further this she had developed a detailed survey to ascertain what facilities (and expertise) are available at each centre for sample collection, storage and processing and for performing experiments.
- (d) Dr Walker outlined the opportunity for complementary work during the severity scale validation study. This would be a collaboration between ENLIST and the group of Professor Martin Hibberd at the London School of Hygiene and Tropical Medicine to perform genomic studies. It was agreed in principle if funding permitted to collect DNA specimens from study participants who provided written informed consent.
- (e) The methodology for the validation of the ENL severity scale was discussed in detail. Dr Pai has agreed to pilot the scale at the Bombay Leprosy Project while the necessary formalities for the study are completed. It was also agreed that each centre would also pilot two items in the scale to ensure that they were easy to apply in each ENLIST setting.
- (f) It was agreed by the group that the application to the Leprosy Research Initiative (LRI) for funding for a randomised controlled trial of methotrexate in ENL should be supported. The LRI have invited a resubmission of the application from 2014. Important issues concerning the design of the future trial were discussed and will be incorporated into the application.
- (g) Dr Joydeeba Darlong gave a presentation on the monitoring and assessment of adverse events in clinical trials using her experience of the AZALEP study.
- (h) It was agreed that a further ENLIST meeting would be essential and that this would be best held in March 2016.
- (i) The meeting was brought to a close by Dr Walker and Professor Lockwood who expressed their thanks to the participants for supporting the meeting and especially to

Dr Vivek V. Pai and the staff of the Bombay Leprosy Project for all their hard work on behalf of ENLIST.

### **Outcomes of the 3RD ENLIST Meeting**

1. ENLIST 1 data analysed and draft manuscript circulated
2. ENLIST ENL Severity Scale developed
3. ENLIST ENL Severity Scale pilot phase agreed
4. ENLIST ENL Severity Scale validation methodology agreed
5. Complementary genomic study sample collection agreed
6. ENLIST QoL studies format and deadlines agreed
7. Leprosy Research Initiative application developed
8. ENLIST Collaborator Survey: Field Lab Sampling, Analysis, Import and Export Capacities circulated

### **Conclusions**

The third ENLIST meeting was a remarkable success. The participants have laid the foundations for at least four major pieces of work on ENL which should greatly enhance our understanding of the condition. The continued commitment of all those involved will hopefully lead to improved strategies for managing this serious, life altering complication of leprosy.

### **Acknowledgements**

The ENLIST Group would like to thank the sponsors of the meeting, the Novartis Foundation and Cipla. We greatly appreciate the hard work and effort of Dr Pai and his team at the Bombay Leprosy Project which helped to make the meeting an outstanding success. Detailed note taking by Dr Butlin and Dr Darlong ensured that the scale development exercise and compiling this report were possible.

### **References**

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