NEUROPATHIC PAIN IN LEPROSY: DEEP PROFILING AND STRATIFICATION OF PATIENT GROUPS

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Declaration

I, Omer Haroun, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Leprosy is a chronic granulomatous infectious disease, affecting the skin and nerves. Neuropathic pain (NP), which is defined as pain caused by a lesion or disease of the somatosensory nervous system, is now being recognized as an important complication of leprosy. It occurs in 10-20% of patients as a result of persisting nerve damage. Patient with NP is associated with significant suffering, morbidity and limitation of quality of life. Thus, the accurate identification of NP in patients with pain is required. The clinical aspects of NP in leprosy patients in India were investigated using highly specialised assessment tool; quantitative sensory testing (QST). A case control study was conducted in 90 patients with and without pain. Two validation studies were conducted among healthy volunteers in London (18 participants) and Mumbai (52 participants).

Somatosensory profiles were compared in leprosy patients to healthy control subjects. The pattern revealed a novel profile of loss of cool and warm detection thresholds and also mechanical detection but with preservation of vibration detection. This is different to profiles seen in other NP conditions. The QST parameters were effective in detecting neuropathy, but were not able to distinguish between patients with and without NP. Patients with leprosy NP had a high rate of abnormal findings in almost all QST parameters in the maximum pain area over the ulnar nerve. Their sensory profiles were categorised into two subgroups. The majority of patients have spontaneous pain with evidence of sensory loss, but no signs of sensory gain. The second subgroup had profoundly impaired pain and temperature sensation, but light mechanical stimuli often produce pain. Patients with NP had a poor quality of life and psychological well-being compared to pain-free neuropathy.

For all leprosy patients who are suffering pain worldwide.

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List of Abbreviations

AFB	Acid-fast bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALERT	All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre
AMFES	ALERT MDT Field Evaluation Study
ANOVA	Analysis of Variance
APC	Antigen-presenting cell
BAND	Bangladesh Acute Nerve Damage Study
BB	Borderline borderline
BCG	Bacille Calmette-Guerin
BI	Bacterial index
BL	Borderline lepromatous
BLP	Bombay Leprosy Project
BPI	Brief Pain Inventory
BT	Borderline tuberculoid
CDT	Cold Detection Threshold
CPT	Cold Pain Threshold
CI	Confidence Interval
CMI	Cell mediated immunity
DFNS	German Research Network on Neuropathic Pain
DM	Diabetes Mellitus
DMA	Dynamic Mechanical Allodynia
DN4	Douleur Neuropathique en 4 Questions
DNA	Deoxyribonucleic acid
ENL	Erythema Nodosum Leprosum

FDA	Food and Drug Administration
FMOH	Federal Ministry of Health
FMR	Foundation for Medical Research
g, mg, ng, kg	Gram, milligram, nanogram, kilogram
GCP	Good Clinical Practice
GHQ	General Health Questionnaire
GHQ-12	General Health Questionnaire-12
HC	Healthy Control
HHSG	The Hospital and Homes of St. Giles
HIV	Human Immunodeficiency Virus
HRQOL	Health Related Quality of Life
HPT	Heat Pain Threshold
HV	Healthy Volunteer
IASP	International Association for the Study of Pain
IENFD	Intra-Epidermal Nerve Fibre Density
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICL	Imperial College London
IFNγ	Interferon-gamma
IL	Interleukin
ILEP	International Federation of Anti-Leprosy Associations
INFIR	ILEP Nerve Function Impairment and Reaction
IQR	Inter-quartile range
kPa	Kilopascal
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LL	Lepromatous leprosy
LSHTM	London School of Hygiene and Tropical Medicine

MB	Multibacillary
MDT	Multi-drug therapy
MDT	Mechanical Detection Threshold
MF	Monofilament
MHC	Major histocompatibility complex
mN	Millinewton
MPS	Mechanical Pain Sensitivity
MPT	Mechanical Pain Threshold
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NCS	Nerve Conduction Study
NeuPSIG	Neuropathic Pain Special Interesting Group
NFI	Nerve function impairment
NP	Neuropathic Pain
NRS	Numeric Rating Scale
OR	Odds Ratio
PB	Paucibacillary
PCR	Polymerase chain reaction
PD-Q	PainDETECT Questionnaire
PHN	Post Herpetic Neuralgia
PHS	Paradoxical Heat Sensation
PI	Principal investigator
PN	Peripheral Neuropathy
PNL	Pure neuritic leprosy
PPT	Pressure Pain Threshold
PYAR	Person-years at risk

QOL	Quality of Life
QST	Quantitative Sensory Test
RCTs	Randomised Controlled Trials
RFT	Release from treatment
R-J	Ridley Jopling
RR	Reversal Reaction
SD	Standard deviation
SF-36	Short Form-36 Health Questionnaire
SW	Semmes-Weinstein
SWM	Semmes-Weinstein monofilaments
T1R	Type 1 reaction
TB	Tuberculosis
TCAs	Tricyclic Antidepressants
TENLEP	Treatment of Early Neuropathy in LEProsy
TNF-α	Tumour necrosis factor alpha
TRIPOD	Trial in Prevention of Disability study
TSA	Thermal Sensory Analyzer
TSL	Thermal Sensory Limen
TT	Tuberculoid
VAS	Visual Analogue Scale
VDT	Vibration Detection Threshold
VMT	Voluntary muscle test
WDT	Warm Detection Threshold
WHO	World Health Organization
WUR	Wind Up Ratio

Chapter 1 Introduction

1.1 PhD approach

This PhD work was a collaborative study between the leprosy group at the London School of Hygiene and Tropical Medicine (LSHTM) and the pain group at Imperial College London (ICL). Our international collaborators are from the London Pain Consortium (LPC) and the German Research Network on Neuropathic Pain (DFNS), and our local collaborators from India are: the Foundation for Medical Research (FMR) and Bombay Leprosy Project (BLP).

I came to LSHTM to study for an MSc in Tropical Medicine and International Health (TMIH) in 2007. I was supervised by Professor Lockwood and Professor Rice for my dissertation, which was on leprosy and neuropathic pain (NP). Since that time I have been interested in leprosy and research.

After I completed my MSc, and throughout my work as researcher at ALERT (The Leprosy Centre in Ethiopia), and at the Neglected Tropical Diseases at Federal Ministry of Health, Sudan, I noticed that although neglected tropical diseases are essentially preventable, little is done to control important endemic diseases such as Leishmaniasis, HIV/AIDS and Leprosy. The morbidity and mortality from infectious diseases are alarming. Since that time I have felt one of my responsibilities is to work for improvements in this situation.

Leprosy is still an endemic disease in developing countries. Management of leprosy (diagnosis and treatment) is still challenging. Antimicrobial therapy kills *M. leprae*, but immune mediated peripheral nerve damage can continue long after effective drug treatment. Consequently, as a result of persistent damage, patients who have been successfully treated with multi-drug therapy (MDT), suffer from NP and associated co-morbidity long after the infection has been cured. NP is now being recognized as an important long-term complication in a proportion of people previously treated for leprosy. Considering the high prevalence and morbidity of NP in treated leprosy patients, there is a pressing need for clinical trial evidence to assess the efficacy of pain therapies in the management of leprosy-associated NP.

This PhD work was conducted in Mumbai, India. The rationale for the study emerged in recognition of the growing challenges of NP, as well as a gap in the knowledge regarding identification and treatment of leprosy patients with NP, particularly in resource-limited settings. Preliminary discussion with leprosy and pain experts revealed that no single drug for the treatment approach stood out as a potential intervention study on NP in leprosy. Instead, key experts highlighted the need to accurately characterise the somatosensory profiles of leprosy patients with NP, in order to develop appropriate tools for the investigation and design of suitable treatment interventions. Preliminary work was then carried out to define the scope and design of the main PhD study of profiling leprosy NP patients. This information helped formulate the objective of the PhD work as conducting a case-control study using highly specialised tools to investigate the clinical characteristics of leprosy patients with NP and to inform development tools in the furure. As part of this PhD study, two validation studies were conducted in London and Mumbai. Validating the Mumbai site for study protocols in Hindi and Marathi, and establishing leprosy profiles in resource-limited setting were important preliminary steps to develop an optimal trial design to use for future studies.

1.2 PhD thesis timeline

I started my PhD work in October 2010. Recruitment for the validation study in London began in April 2011 and was completed in July 2011. During this time I trained and qualified in the use of the German Research Network on Neuropathic Pain DFNS-QST protocol (Appendix 40). I successfully upgraded from MPhil to PhD in November 2011. Recruitment for the local healthy volunteers study and the PhD main study took place between October 2012 and June 2013. Data recording, management, and writing up began in July 2013 and the thesis was submitted for examination in August 2014. The detailed timeline of my PhD thesis is shown in (Appendix 54).

1.3 Overview of my role in this PhD research

My roles in this study included writing the grant proposal, and designing the studies. I was responsible for the design and writing of study forms including consent forms and information sheets for both healthy volunteers and patients. I developed the study protocols with advice from Professor Lockwood, Professor Rice, Dr Nichols, Professor Maier, Professor Treede R-D, Dr Bennett, Dr Pfau, Dr Pai, Dr Shetty, Dr Walker and Dr Tudor. I was responsible for obtaining various ethical approvals. In addition, all

study work including patient recruitment, screening and enrolment procedures, clinical examination, administration of testing protocols, data recording and management presented in this thesis were performed by me, unless otherwise indicated. In particular, I conducted interviews in the local language through an interpreter. The study on the use of Semmes-Weinstein monofilaments to simplify the DFNS-QST protocol was conducted in collaboration with the DFNS group; I conducted the study and Dr Pfau completed the analysis and wrote up the findings. For the PhD main study, I conducted the data analysis with advice from Dr Nichols and Dr Tudor.

1.4 Structure of the PhD thesis

This thesis is organised into ten chapters:

Chapter one presents introductory and background information regarding NP in leprosy. It describes how the thesis is set-up, and introduces the reader to the burden of NP in leprosy patients. It then outlines the reasons for carrying out this research as well as the objectives of this study. Chapter two, the literature review, presents the current literature on leprosy, its complications and management; and looking particular at the central role of nerve damage in leprosy. Chapter three, the identification of neuropathic pain, gives a general introduction on the NP theme and, in particular, NP in leprosy. In chapter four the instruments for assessing sensory abnormalities, pain disorders and techniques for assessing the psychological impact of NP are assessed. Chapter five describes the clinical difficulties in identifying NP in diseases such as leprosy, with some current thoughts on NP pain assessment and the need to develop tools for the assessment of NP in leprosy. The background information from the above mentioned chapters aims to place the rationale of the PhD work in the context of current knowledge and identify a gap in existing research, thus providing a framework for this study.

Chapter six describes the study designed methods and chapter seven describes the validation studies. These include the validation of the investigator, the centre and study protocol. The aim of the first validation study was to validate the investigator in the London centre and the aim of the second was to validate the DFNS-QST protocol in the local Indian population and the site centre. The third validation study explored the utility of Brazilian Semmes-Weinstein monofilaments and aimed to simplify the DFNS-QST protocol. For these studies only healthy controls were recruited. This information

provided the basis of validating the investigator and the centre site in Mumbai for the use of DFNS-QST protocol.

Chapters eight and nine describe and discuss various aspects of the results. These include the baseline findings on the leprosy patients; the difference between healthy controls and the patient group; the assessment using pain questionnaires, clinical examination, quantitative sensory testing and psychological assessment techniques; and the role of somatosensory profiling in the assessment of leprosy-related NP.

Finally, based on the findings from this PhD work, the main summary of the findings and recommendations for future studies are presented in the last chapter, chapter ten.

1.5 Rationale of the PhD thesis

NP is a severe form of chronic pain caused by a lesion or disease of the somatosensory system and is associated with many diseases (Jensen et al., 2011). Leprosy, the most common cause of treatable neuropathy worldwide (Scollard et al., 2006), is now being recognised as one such disease. The Lancet Neurology highlighted the importance of leprosy as a neurological disease in an editorial in 2009 (Lancet, 2009), and we have recently shown in India and Ethiopia that 17-20% of treated leprosy patients cured of their infection but left with peripheral nerve damage, have significant NP, which is associated with reduced quality of life (Lasry-Levy et al., 2011, Haroun et al., 2012). Previous work has shown that patients with NP have significant levels of depression (Jensen et al., 2007, Doth et al., 2010). This makes NP one of the most prevalent disabilities among leprosy patients and thus a significant health problem worldwide. Thus, the accurate identification of NP in patients with chronic pain is crucial for targeting appropriate treatment as NP conditions require a different therapeutic approach from other pain types.

The German Research Network on Neuropathic Pain (DFNS) has developed a standardised QST battery that consists of 7 tests measuring 13 parameters (Rolke et al., 2006a, Rolke et al., 2006b), which may identify changes in sensory parameters related to chronic NP. This protocol has been used successfully to establish the somatosensory profile of patients with HIV-associated sensory neuropathy (Phillips et al., 2014). It has been also used in patients with different NP conditions such as post-herpetic neuralgia and diabetic mellitus, where a subgroup of patients with different somatosensory

profiles have been identified (Maier et al., 2010). Although NP occurs in approximately one-fifth of leprosy affected patients, little attention has been paid to assessing patients and treatment regimens have not been defined. No study to date has established the complete QST somatosensory profile of leprosy patients with NP. To better characterise this somatosensory profile, comparison was made to local Indian healthy control subjects, DFNS reference data, and to patients with and without neuropathy and pain. The ability to accurately identify sensory, psychological, and metabolic dysfunction profiles in leprosy patients with NP is essential for better understanding of the patho-physiological mechanisms as well as informing mechanism-based prescribing and thus has the ability to dramatically improve clinical trial design and NP treatment defined by drug response.

1.6 Aims of the PhD thesis

The overall aim of the study was to characterise the somatosensory profiles of leprosy patients with NP.

1.7 Objectives of the PhD thesis

1. To measure the somatosensory responses of leprosy patients including thermal detection and pain thresholds, paradoxical heat sensations, mechanical detection thresholds to von Frey filaments, vibration detection threshold, mechanical pain thresholds to pinprick stimuli and blunt pressure, stimulus/response-functions for pinprick and dynamic mechanical allodynia, and pain summation (wind-up ratio) and to compare these measures between leprosy patients with painful neuropathy; non-painful neuropathy, leprosy patients without pain and age and sex matched healthy controls.
2. To elucidate the impact of leprosy NP on quality of life and psychological well-being in patients with painful neuropathy compared with patients with non-painful neuropathy.
3. To stratify leprosy patients by symptoms, sensory profile and psychological state

1.8 Hypotheses of the PhD thesis

NP in leprosy patients could be caused by immune neuronal interaction which can be due to destruction or impaired functions of cells as a result of chronic inflammatory

processes, or it could be caused by sensitisation and spontaneous activity in sensory neurons which can be due to the effect of *M. leprae*. As a functional compensation pain thresholds are lower, leading to increased pain sensation even though the stimulus is minor. I hypothesise that:

- The thermal and mechanical detection threshold, pain threshold (CPT and WPT), pressure pain threshold (PPT), and vibration detection threshold (VDT) are lower in leprosy patients with painful neuropathy than patients with non-painful neuropathy
- There is significant impact of neuropathic pain on quality of life and psychological well-being in leprosy patients with painful neuropathy compared to patients with non-painful neuropathy.

Chapter 2 Review of Literature

2.1 Literature review of leprosy

2.1.1 Definition of leprosy

Leprosy is a chronic granulomatous infectious disease, affecting the skin and peripheral nerves (Britton and Lockwood, 2004). It is one of the most common causes of peripheral neuropathies worldwide. The disease is caused by *Mycobacterium leprae* (*M. leprae*) (Job, 1989), which is a unique intracellular organism discovered by Armauer Hansen in 1873. The organism is the only bacterium that invades and multiplies inside Schwann cells, which this is the hallmark of the disease (Job, 1989). *M. leprae* cannot be cultured in routine laboratory media, but will multiply slowly in certain animal species, such as the nine-banded armadillo, which is a natural reservoir of the organism (Truman et al., 2011).

2.1.2 Leprosy transmission

Leprosy is thought to be spread through aerosol transmission of nasal secretions of untreated lepromatous leprosy patients, but the precise mechanism, the route of entry, and the role of skin contact are still debated (Pfaltzgraff R. E and G, 1994). It is widely believed that *M. leprae* probably enters the body via the nasal mucosa with subsequent haematogenous spread to the skin and peripheral nerves (Scollard et al., 1999).

2.1.3 Epidemiology of leprosy

2.1.3.1 Global Leprosy Prevalence

Globally the prevalence of leprosy has declined over the last 25 years (WHO, 2013b). At the beginning of 2013, the WHO reported a global prevalence of leprosy of less than one per 10 000 population, with 189 018 registered cases compared to 1.2 million cases in 1995 (WHO, 2013b) (Figure 2.1). The global case-detection rate remains high, with about 230 000 new cases being detected worldwide and reported to the WHO during the year 2012. The global rate of new cases with grade two disabilities per 100 000 population was 0.25, with 14 409 registered cases during the year 2012 (WHO, 2013b). However, due to recent major operational changes relating to the diagnosis and

registration of cases in many countries, these leprosy statistics are probably under-estimates (Fine, 2008).

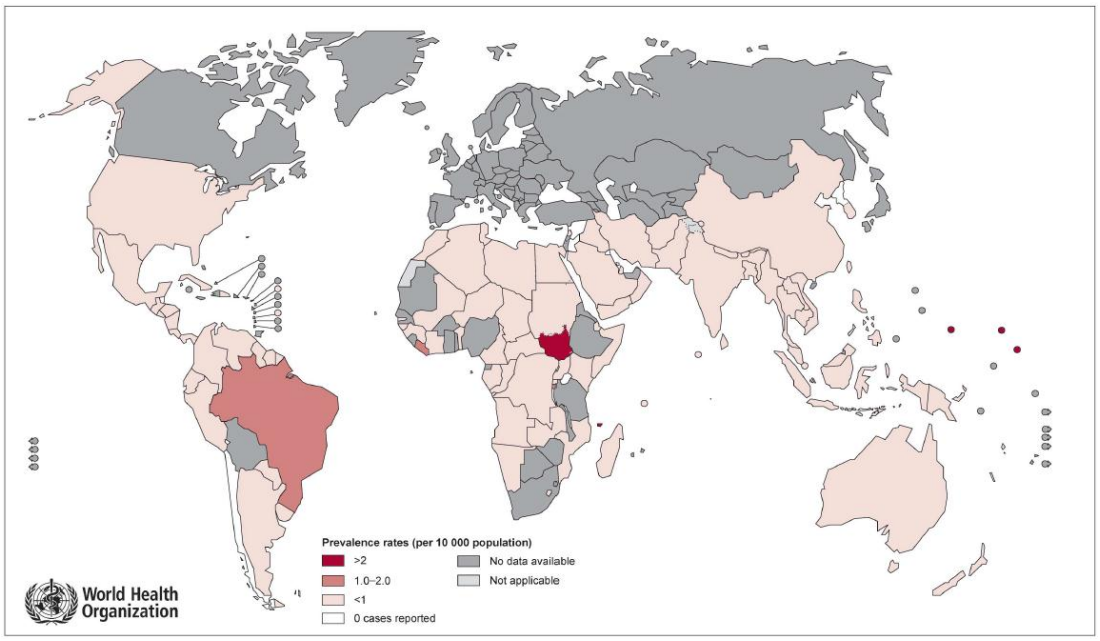

Figure 2.1. Global leprosy prevalence 2012

2.1.3.2 Regional Leprosy Prevalence

Leprosy patients are found mainly in the tropical and warm temperate regions of the world, but cases have been also reported elsewhere, as patients may present with the disease long after leaving an endemic region. Currently 95% of new leprosy cases are concentrated in three geographical regions, namely, South Asia (India: 91 743, Nepal: 3 118 and Bangladesh: 3 848); Latin America (mainly Brazil: 34 894); and sub-Saharan Africa (Angola: 1 076, the Democratic Republic of Congo: 5 049, Mozambique: 1 207, and the United Republic of Tanzania: 2 349). South Asia, Latin America, and sub-Saharan Africa still have a prevalence of more than 1 case per 10 000, with 60% of all leprosy cases worldwide being concentrated in Brazil and India (WHO, 2013b).

Leprosy in India

India is the largest country in South Asia with a population of more than one billion (WHO, 2013a). It is the biggest contributor to the global burden of leprosy with 134 752 new cases were detected during the year 2012 (WHO, 2013b).

The prevalence of leprosy has declined over the last decade in India according to government records. The total number of leprosy cases in India fell strikingly from 265 781 in 2004 to 91 743 in 2013 (WHO, 2013b). This changing picture is attributed to introduction of multi-drug therapy (MDT) and the duration of treatment being reduced from 24 months to 12 months. Another contributing factor to the decreased prevalence observed in India is operational activities, such as level of case finding activity and integration of leprosy services into primary health care services.

In recent years, heavy migration into cities such as Mumbai from under developed or poorly surrounded region such as Uttar Pradesh and Bihar may have contributed to an increase in leprosy cases in urban areas. In the Bombay Leprosy Project clinic, 80% of the newly diagnosed leprosy patients from January to November 2013 were reported from urban slums and outside Mumbai.

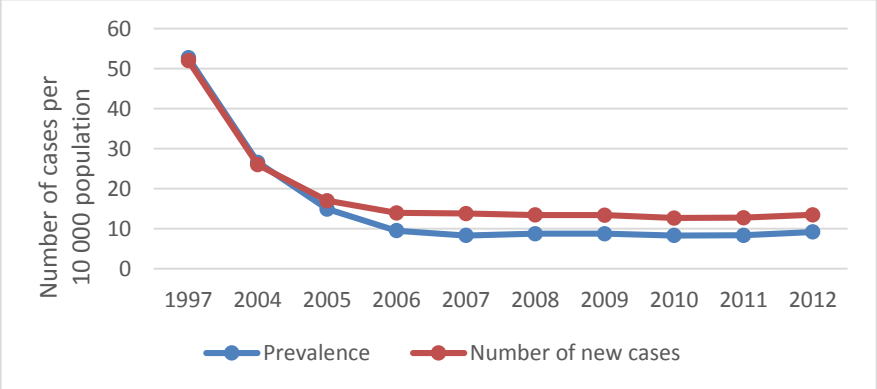

Figure 2.2. Prevalence and incidence of leprosy in India

Data for leprosy prevalence and number of new cases in India are shown in Figure 2.2. These data clarify the importance of using the number of new cases as a marker of transmission of leprosy. High numbers of new cases continue to be reported. For instance, 91 743 new cases were reported in 2012 compared to 83 187 cases in 2011. A cross-sectional study from Maharashtra, showed rates of three-to-nine cases per 10 000 population, of which 30% of these newly diagnosed patients were children. Furthermore, the WHO global leprosy update reported that 9.9% of new leprosy cases in India in 2012 were among children. Multibacillary (MB) cases were the most frequent type of leprosy among the total number of new leprosy cases detected during the reporting year in India (Kumar, 2010). In 2012, 30% of the newly diagnosed MB cases had neuropathy and nerve damage. These data indicate ongoing transmission of leprosy in India.

2.1.4 Leprosy Classification

The clinical features of leprosy are determined by the host's immune response. Therefore, there are two main systems used to classify leprosy patients. In 1966, Doctors Ridley and Jopling proposed a system of leprosy classification known as Ridley-Jopling classification. They described a spectrum of leprosy from tuberculoid (TT) to lepromatous leprosy (LL) based on their clinical, bacteriological, immunological and histopathological features (Figure 2.3). Between these two poles there are three borderlines: borderline tuberculoid (BT), mid-borderline (BB), and borderline lepromatous (BL). Borderline patients can remain in positions or more towards either end of spectrum. This classification is mainly used in referral centres. It helps to predict patients at risk of reaction and their prognosis, in addition to their appropriate treatment (Ridley and Jopling, 1966). The other classification scheme was recommended by WHO, which suggests that for the purpose of treatment it is adequate to classify patients on the basis of clinical features. Patients are classified as paucibacillary (PB) and multibacillary (MB) by the number of skin lesions they have: PB (one-to-five skin patches); and MB (more than five skin lesions). This operational classification was introduced to simplify disease recognition and to ensure that patients were appropriately treated with MDT.

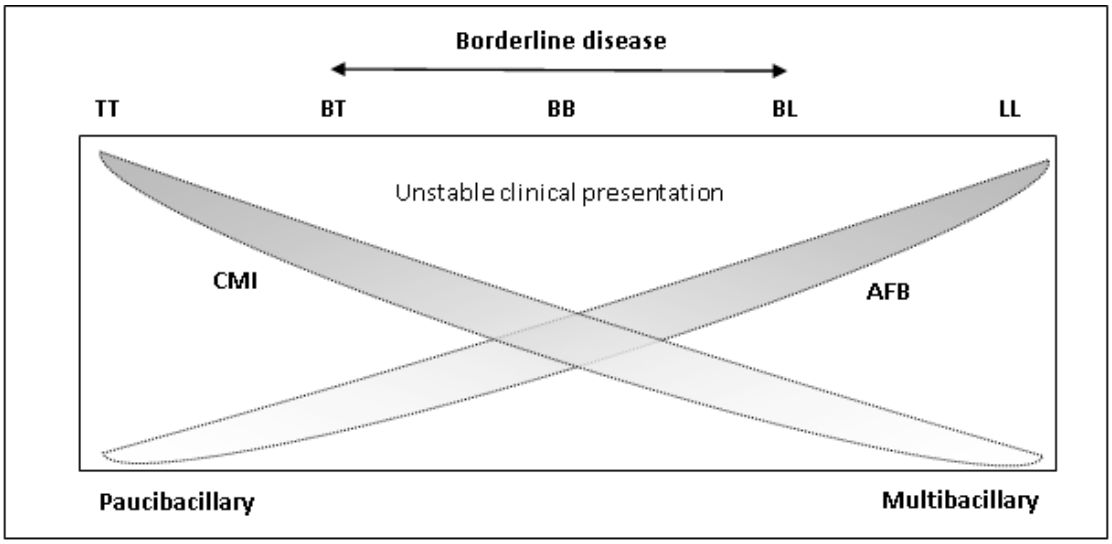

Figure 2.3. R-J scale and the relation with bacterial and immune response

The five forms of leprosy based on the Ridley-Jopling Scale are tuberculoid (TT), borderline tuberculoid (BT), midborderline (BB), borderline lepromatous (BL), and lepromatous (LL). CMI = cell-mediated immunity; AFB = acid-fast bacilli. Picture modified from (Walker and Lockwood, 2006)

2.1.5 Clinical Features of Leprosy

Patients with leprosy can present with prodromal symptoms and skin and nerve-related symptoms or complications of the disease. The prodromal symptoms, which is rare now and may occur only in LL such as nasal stuffiness, precede the typical skin and nerve features. The main presenting features are related to skin, nerve or reactions (Britton and Lockwood, 2004). A patient may present with a range of skin lesions such as macular hypo-pigmintation. Patients with affected nerves may present with new evidence of neuropathy such as, weakness and loss of function, or secondary to neuropathy e.g. ulcer. Patients with leprosy reaction can present with skin changes or neuritis. These features are diagnostic. The common presenting complications of leprosy are reactions. Patients may present with skin lesions that are erythematous, tender, and swollen due to type 1 leprosy reactions. Others may present with systemic manifestations, such as fever and malaise due to erythema nodusoum leprosum. Five-to-ten percent of leprosy patients may present with acute neuritic features, spontaneous nerve pain, new sensory or motor impairment of recent onset, or mixed-sign neuritis (Mahajan et al., 1996, Van Brakel et al., 1992).

Cardinal signs

There are three cardinal signs (WHO, 2012):

1. Definite loss of sensation in a pale (hypo-pigmented) or reddish skin lesion
2. Thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve
3. Presence of acid fast-bacilli in a slit-skin smear.

The clinical diagnosis is confirmed when a patient has at least one of the cardinal signs (Britton and Lockwood, 2004).

2.1.6 Diagnosis of Leprosy

The diagnosis of leprosy is important for the individual and the community. For the individual with leprosy, accurate diagnosis is essential for providing appropriate management and to reduce stigma associated with the disease. Early identification of suspected cases, will reduce the incidence of impairments and their effects. Also, it reduces the spread of leprosy to other individuals in the community.

The diagnosis of leprosy is made clinically based on clinical history and a full clinical examination of the skin and peripheral nerves (WHO, 2012). Bacteriological and histological investigations also aid in the diagnosis.

In the presence of clinical symptoms, the first step towards diagnosing leprosy is to think of the possibility of leprosy among those who are at risk of exposure to infection which includes residence in an endemic country and being a household contact.

2.1.6.1 History and clinical examination

For every potential leprosy patient seen, a detailed clinical history must include: any changes in skin colour and texture; area of sensory loss; weakness of the hands, feet, and eyes; and any signs of reactions. The clinical history is followed by examination of the skin and peripheral nerves. When looking for signs of leprosy the procedure should be carried out in good light and the patients should be examined while maintaining and respecting privacy. *M. leprae* multiplies at relatively low temperature; therefore, areas such as the ears, face, lateral aspects of the limbs, the back, and the buttocks are to be examined. These areas of skin have relatively low temperatures compared to other less affected regions such as the axillae, groin, perineum, and hairy scalp. The body map is used to record the results of the examinations of skin lesions, nerve thickening, and any tissue damage. For each patient, the following information is required; number and type of skin lesions; loss of sensory and motor functions; bacterial index if skin smear is taken; eye assessment; and treatment regimen.

2.1.6.2 Bacteriological examination

M. leprae can be demonstrated in slit skin smear and/or tissue biopsies. In suspected case, slit skin smears are taken to look for acid-fast bacilli. This test is one of the essential component of definitive leprosy diagnosis by demonstrating acid-fast bacilli on microscopy. Patients with pure neuritic leprosy, in which no visible skin lesions are found, may require a nerve biopsy for accurate diagnosis of leprosy.

Histopathological evaluation is essential for accurate classification of skin lesions across the spectrum. The diagnosis is made by the presence of granulomata and lymphocytic infiltration of dermal nerves in anaesthetic skin lesions. These criteria help to confirm and exclude the diagnosis of leprosy.

2.1.6.3 Diagnostic immunology in leprosy

There is currently no established role for an immunodiagnostic test (serology, skin test, or polymerase chain reaction) of leprosy. There is no good serological test with adequate sensitivity and specificity for leprosy. For instance, the serological tests for phenolic glycolipid have a good but insufficient specificity for the diagnosis of leprosy patients and their sensitivity is generally high for the MB patients (>90%), but low for the PB patients (50-60%). It has also been detected positive (15-20%) in household contacts (Chanteau et al., 1992). Polymerase chain reaction methods for detection of *M. leprae* DNA have been developed and are potentially highly specific and sensitive, detecting *M. leprae* DNA in >95% of MB and 55% of PB cases, but they cannot be used routinely due to reliance on skilled technicians and expensive equipment (Oskam et al., 2003, Parkash, 2011).

The diagnosis of leprosy is typically clinical but sometimes slit skin smears are needed to confirm the *M. leprae*. In each patient, the definite diagnosis of leprosy includes: the spectrum of disease, type of reactions, and nerve function impairments.

2.1.7 Treatment of Leprosy

A comprehensive approach to treating leprosy patients may be used, including chemotherapy, treating reactions and complications of nerve damage, prevention of neuropathic damage, education, psychological support, and stigma reduction.

Curing the active mycobacterium infection through chemotherapy is essential in the treatment of leprosy patients. In 1982, WHO introduced and recommends MDT regimens for all leprosy patients. The regimens are combinations of rifampicine, clofazimine and dapsone. There are two types of WHO-MDT regimens used: the PB-MDT (given for six months: 600mg rifampicin once a month, 100mg dapsone daily), and MB-MDT (given for 12 months: 600mg rifampicin once a month, 100mg dapsonedaily, and 300mg clofazimine once a month and 50mg daily) (Table 2.1). A regimen for children is also available in reduced doses of the drug format. Within this combination, rifampicin has the highest bactericidal activity compared to other two drugs. There are several second line of treatments to MDT. These antibiotics such as minocycline, ofloxacin, clarithromycin and moxifloxacin required a shorter duration of therapy (Britton and Lockwood, 2004). A single dose of monthly for six months MDT

known as ROM (rifampicin, ofloxacin and minocycline) in combination is now available for PB disease (Setia et al., 2011).

The WHO-MDT regimen is highly effective and has been used successfully in treating leprosy patients with a high cure rate, few side effects, and low relapse rates; globally, more than 14.5 million patients have been treated with good clinical response (Lockwood, 2002). Moreover, it is safe in pregnancy and in breastfeeding mothers. WHO technical advisory group in leprosy chemotherapy noted low relapse rates (0.79% for MB patients compared to 1.09% for PB patients). These relapse rates were obtained from 20 141 MB patients and 51 553 PB patients, where 67 and 306 patients respectively were reported to have relapsed over a nine year period of follow up in 1994 (WHO, 1994). Relapse in MB patients, which is defined as the multiplication of *M. leprae*, is associated with clinical deterioration in skin and nerve function impairments and marked increase in bacteriological index. In contrast, relapse in PB patients is difficult to recognise as it is hard to distinguish from type 1 leprosy reaction. The committee also noted no evidence of *M. leprae* having resistance to the WHO-MDT regimen (WHO, 2012).

Additional benefits of WHO-MDT regimens include the prevention of drug resistance and better patient compliance due to a fixed duration of treatment. Another advantage is that supervised drug administration and health education provided by field workers review patients in each visit where leprosy complications such as reactions and nerve function impairments can be early detected and treated.

There are some reports on the adverse effects of WHO-MDT regimens. For instance, clofazamine is documented to cause troublesome skin pigmentations in many leprosy patients in particular among females (Maia et al., 2013). Other adverse effects associated with individual MDT drugs are listed below. After giving WHO-MDT treatment few patients develop an immune upgrading response and get reactions, and some of them may develop pain (Haroun et al., 2012). This indicates that neuritis may be worsened by WHO-MDT treatment and then cause pain. However, there is no association of neuropathic pain with starting WHO-MDT treatment. Although minocycline is effective in preventing neuropathic pain in animal models, it has not yet been demonstrated to be effective in clinical trials (Rojewska et al., 2014, Martinez et al., 2013). It has not been shown to have a role in leprosy neuropathic pain. Minocycline is only used as second line drug in the treatment of leprosy.

2.1.7.1 Rifampicin

Rifampicin is a potent bactericide for *M. leprae*. Previous studies in untreated MB patients have shown that rifampicin administered in single doses of 600mg killed more than 99% of viable *M. leprae* within three or four days (Levy et al., 1976). Its mode of action is via inhibition of DNA-dependent RNA polymerase, and it needs to be combined with other anti-leprosy drugs to minimize the risk of developing drug resistance. In untreated MB patients, a single monthly dose of rifampicin (1200mg) plus daily dapsone was as effective as daily rifampicin (450mg) plus dapsone (Yawalkar et al., 1982). A single monthly dose has been the current dose used in WHO-MDT regimen with few serious side effects. This drug dose produce red-brown discoloration of bodily secretions such as urine and faeces, so patients should be warned.

2.1.7.2 Clofazimine

Clofazimine is a drug with dual activity in leprosy: anti-bacterial and anti-inflammatory. It has weak bactericidal action for *M. leprae*, the mechanism of which is unknown. After a few weeks of commencing 300mg of clofazimine once a month and 50mg daily, active skin lesions start to improve. The most common adverse effects of clofazimine are in the skin (lesions and normal skin), and include troublesome pigmentation and dryness. These pigmentations occur in almost all patients in the first few days to weeks as the drug becomes clinically effective, but are not severe enough to warrant discontinuation, since most symptoms resolve spontaneously (Maia et al., 2013). Discoloration may also occur in hair, the eyes, and in body excretions, such as urine and faeces. Other reported side effects of clofazimine are gastrointestinal-related, such as nausea, vomiting, and diarrhoea.

2.1.7.3 Dapsone

Dapsone is both bacteriostatic and weakly bactericidal against *M. leprae*. Its mode of action is predominantly via inhibition of the synthesis of dihydrofolic acid. Dapsone can cause a few side effects, including haemolytic anaemia and skin reactions. These effects are rare, occurring within the first few months of treatment.

Table 2.1. WHO-recommended MDT doses and regimes for adult with leprosy

Type of leprosy	Drug treatment		Duration of treatment
	Monthly, supervised	Daily, self-administered	
PB	Rifampicin 600mg; Dapsone 100mg	Dapsone 100mg	6 months
MB	Rifampicin 600mg; Clofazimine 300mg; Dapsone 100mg	Clofazimine 50mg; Dapsone 100mg	12 months

2.1.8 Immunological complications of leprosy

The role of immune system as causing leprosy complications is well documented (Walker and Lockwood, 2006). *M. leprae* invades and multiplies in Schwann cells and cutaneous macrophages (Britton and Lockwood, 2004). Such neuronal attack not only resulted in impairments of the sensory functions, but is also associated with a robust inflammatory immune response. As the damaged axons undergo Wallerian degeneration, non-myelinated Schwan cells proliferate and release chemokines, which recruit immune cells such as macrophages. Other resident cells such as mast cells and neutrophils provide the majority of the early immune cell attack, i.e. innate immune response. This process is followed by the accumulation of inflammatory mediators, which enhance the recruitment of immune cells such as CD4 and CD8, i.e. adaptive immune response. As a result, the transduction and transmission of signals are changed and cause ectopic activity and pain in affected nerve. The percentage of leprosy patients with nerve inflammation and pain is around 9% and 5% of patients with MB and PB respectively (van Brakel et al., 2005b, Richardus et al., 2004).

In neuropathic pain inflammatory models, activation of the Schwann cells, leukocytes, Toll-like receptors, inflammatory mediators and cytokines contributes to generation of pain and the severity of this responses is related to the degree of neuropathic pain (Gaudet et al., 2011, Lindenlaub and Sommer, 2003, Calvo et al., 2012). These mediators are important for the recruitment of immune cells such as neutrophils, macrophages, dendritic cells, and B and T lymphocytes to the site of nerve injury. The recruitment of inflammatory cells and cytokine expression such as TNF and IL-6 is also increased in nerve biopsies with inflammation in leprosy patients with neuropathic pain (Haanpaa et

al., 2004). This suggests that the immune cells is the main player in the generation of leprosy nerve damage and thus neuropathic pain. The nerve, M. leprae and host immune response interactions are discussed in detail under the central role of nerve damage in leprosy.

2.1.9 Leprosy Reactions

Leprosy reactions are an immunological complication of the disease, which are associated with inflammation and acute peripheral nerve damage. Forty percent of MB leprosy patients experience significant appearance of symptoms and signs of acute inflammation in skin lesions and nerves at some stage in their disease course (Pocaterra et al., 2006, Walker et al., 2008). These reactions could occur before, during, and after successful completion of leprosy MDT and are serious because they cause an acute inflammatory immune response. Such acute onset of inflammation may rapidly and extensively damage a peripheral nerve already affected by the disease.

The two main types of reactions are Type 1 (reversal reaction) and Type 2 reactions, also known as Erythema nodosum leprosum (ENL). Neuritis, which is known as nerve inflammation without a Type 1 or 2 reaction, is the third form of leprosy reaction.

2.1.9.1 Type 1 Reactions

Background

Type 1 (reversal) reactions are acute inflammatory episodes, which may occur as a result of increased cell mediated immunity towards *M. leprae* antigen (Lockwood et al., 2002). Up to 30% of individuals with leprosy will be affected, but the prevalence shows large variations in a retrospective study with 386 leprosy patients in Nepal, one third of patients had a type 1 reactions at recruitment (Van Brakel et al., 1994a). In similar study in Ethiopia, type 1 reactions was reported in 16.5% of 594 patients followed for 10 years (Saunderson et al., 2000b). Patients with the borderline leprosy (BT, BB, and BL), whose immunological status is unstable, are at greater risk (Walker et al., 2008, Ranque et al., 2007). Another group of patients who are also at high risk for type 1 reactions is women after child birth (Lockwood & Sinha 1999). The onset of T1R is in the first six months of anti-leprosy treatment, but may occur rarely many years after completion of MDT (Croft 2000).

Immune responses occurring in type 1 reactions

Type 1 reactions are the result of delayed type hypersensitivity reactions to *M. leprae* antigens (Lockwood et al., 2002). They are characterised by T cell activation resulting in inflammation in the affected skin and nerve (Lockwood et al., 2002, Schenk et al., 2012). The increase in cell mediated immunity could lead to immunological upgrading of the patients towards the tuberculoid pole of the clinical spectrum of leprosy. In the affected sites, the CD4+ T cells increase in number and secrete Th1- type pro-inflammatory cytokines, such as IL-1, IL-2, IL-12, and IFN-γ1, which may shift the immune response towards Th1 immunity. Th1-type cytokines could be responsible for the local tissue damage occurring in T1Rs, including: the swelling and painful inflammation in skin lesions and nerves. In addition, the increase in TNF-α is responsible for these local and systemic inflammatory symptoms that may occur in type 1 reactions (Khanolkar-Young et al., 1995, Little et al., 2001).

Clinical features of type 1 reactions

Patients with type 1 reactions presented with features localised to the skin lesions and peripheral nerves. Skin lesions develop swelling, redness and tenderness, with some emergence of new lesions. Erythema is often followed by desquamation and ulceration. Affected nerves will become rapidly swollen, extremely painful and tender. This is commonly followed by paraesthesia or pain in nerves distribution, accompanied very often by loss of sensory function. Loss of motor nerve functions also develops rapidly. If not treated, patients with type 1 reactions may end up with irreversible nerve damage.

Treatment of type 1 reactions

Type 1 reactions are usually treated with oral corticosteroids (40 mg/day of prednisolone reducing to 5 mg/day every month over six months) with monitoring of skin lesions and nerve function. However, a recent Cochrane systematic review, which looked at the frequency and features of nerve function impairment (NFI), noted that oral corticosteroids are accepted as treatment, but there is no consensus about the dose or duration of treatment, hence further randomised controlled trials (RCTs) are needed to identify the best treatment regimens (Walker and Lockwood, 2008).

2.1.9.2 Type 2 Reactions

Background

Type 2 reactions or (ENL) occurs as a result of antigen-antibody reactions with the formation of immune complexes that leads to systematic inflammation (Pfaltzgraff R. E and G, 1994). Type 2 reaction occurs in up to 50% of LL patients, and in 5-15% of patients with BL disease. The main risk factor for ENL is a high bacteriological index (Voorend and Post, 2013). The prevalence of ENL has decreased after the introduction of MDT, but there is still wide geographical variation. In an Indian retrospective study with 481 leprosy patients the prevalence of ENL was 49.4% in those with LL and 9% in BL cases (Pocaterra et al., 2006). In contrast, the prevalence in Ethiopia is low, where the AMFES study of MB patients found that 5.3% of individuals experienced ENL (Saunderson et al., 2000a). The onset of ENL often starts during the first year of MDT and can relapse intermittently over several years (Balagon et al., 2010).

Immune response occurring in type 2 reactions

Patients with type 2 reactions have high quantities of antibodies and *M. leprae* antigens. The relative increase in the antigen concentrations and precipitating antibodies could lead to formation of immune complexes, which are then precipitated out of the blood and can deposit in the tissues. This deposition can lead to vasculitis with immunoglobulin and complement activations in the vessel wall. During the ENL episodes, the immune complexes may lead to activation of neutrophils seen in vasculitis. Further, the episodes are associated with antigen-specific T cell activation. The mononuclear cell increase in number and release cytokines such as TNF-α (Oliveira et al., 1999). The over-production of TNF-α could be responsible for the tissue damage and systemic toxicity occurring during ENL reactions.

Clinical features of type 2 reactions

Clinical features of ENL reactions are usually systematic. Patients may present with painful, tender, erythematous skin nodules appearing in crops. Subsequently, they develop a generalized illness with high fever; malaise; and oedema of the hands, feet, and face. Other systemic involvement includes iritis, conjunctivitis, arthritis, arthralgia, dactylitis, lymphadenopathy, orchaitis, and renal disease. Peripheral nerves are also

affected in ENL, as the recurrent episodes can repeatedly affect them, and may result in damage.

Treatment of type 2 reactions

The aim of type 2 reaction management is to control pain and inflammation, acute neuritis, and eye damage. For mild cases, aspirin may be used, but many cases require treatment with steroids and an increased dose of clofazimine (up to 300mg) (Britton and Lockwood, 2004) or thalidomide. The anti-inflammatory effect of clofazimine has reduced the incidence of ENL reactions (Lockwood, 1996). Thalidomide is the treatment of choice for severe ENL but its availability and teratogenicity limits its use (Walker et al., 2007). It is given in a dose of 400 mg daily until the reaction is controlled, and then reduced gradually to 50mg daily. Thalidomide treatment has been shown in other conditions to cause peripheral neuropathy, but not seen clinically in leprosy.

2.1.9.3 Neuritis

Neuritis is an important aspect of leprosy reactions, because it is difficult to classify, difficult to treat and is associated with disability. Patients with leprosy may experience neuritis at different times during the disease. Two types of patients can be distinguished: those with neuritis associated with both type of reactions (reversal and ENL) and those with pure neuritis pain. The latter may be defined as inflammation of the peripheral nerve trunk without features of the above mentioned reactions (Mahajan et al., 1996). 5-10% of leprosy patients may present with pure neuritis. Those patients may present with spontaneous nerve pain, new sensory or motor impairment of recent onset, or mixed signs neuritis (Mahajan et al., 1996, Van Brakel et al., 1992). The absence of skin lesions and negative skin smear in those patients contribute to the delay of diagnosis (Mishra et al., 1995). Acute loss of function is a hallmark of neuritis in leprosy, which, if not treated rapidly and adequately becomes permanent. Neuritis may occur in the absence of pain and may go unnoticed by the patient 'silent neuropathy'. Patient with neuritis is treated with standard dose of prednisolone starting at 40–60 mg daily, decreasing by 5 mg every 2–4 weeks after evidence of nerve functions recovery (Britton, 1998, Kamath et al., 2014). Neuritis is reviewed under the nerve in leprosy too.

2.2 The central role of nerve damage in leprosy

2.2.1 Introduction and definitions

Nerve damage is a central aspect of leprosy, affecting autonomic, sensory, and motor functions. It is the major cause of morbidity in leprosy. A landmark pioneering publication in early 1950s by Fite stated that there is no leprosy without nerve damage (Fite, 1951). Since then the disease is best described as a neurological condition rather than a simple skin problem. *M. leprae* has a predilection for nerve tissue and the associated perineural inflammation is a characteristic and hallmark of early leprosy. Further complications arise from the host's immune-mediated events that occur during disease progression. Pain due to peripheral nerve damage and/or treated skin lesions is now being recognised as a late complication of leprosy among treated patients. The consequences of nerve damage, such as hands and feet deformities are also responsible for the associated social stigma and disability.

For the purpose of the current study, the term "nerve" refers to the small dermal nerves and peripheral nerve trunk. The general term "neuropathy" is a clinical term used here to mean any detectable abnormality in a particular peripheral nerve. It includes: peripheral nerve damage; nerve function impairment (NFI), such as a motor or sensory deficit; and pain and tenderness.

2.2.1.1 Epidemiology

The epidemiology of nerve damage, in particular, its incidence and natural history of neuropathy in patients with leprosy is well documented. There have been major studies in large groups of patients in geographically diverse settings that have been very useful. Longitudinal data from the Bangladesh Acute Nerve Damage (BAND) cohort support the contention that most patients with leprosy have some demonstrable nerve damage (Richardus et al., 2004). The authors found that the level of nerve damage in 2664 newly diagnosed leprosy patients was high, with up to 60% of MB patients having clinically apparent nerve damage at the time of diagnosis. Presentation of nerve damage at diagnosis is also described in the ILEP Nerve Function Impairment and Reaction ('INFIR') study. Van Brakel et al. studied a cohort of 303 newly diagnosed MB leprosy patients for two years in India and found that 38% of patients had nerve damage at the time of intake into the study (van Brakel et al., 2005b). This high level of nerve damage at diagnosis reflects the delay of leprosy diagnosis, which often takes years and allows

the development of neuropathy (Van Veen et al., 2006). Damage during treatment is noted by Schreuder et al., who investigated 640 newly diagnosed leprosy patients from Thailand. The authors found that the presence of nerve impairment at time of leprosy diagnosis is a key risk factor for new nerve functional impairment (Schreuder, 1998). The study showed that the incidence of NFI among patients without any abnormalities at first examination while on treatment was 1.7 and 12 per 100 person-years at risk (PYAR) for the PB and MB patients, respectively. In addition, 2% of the PB and 11% of the MB patients who already had impairments at first examination developed new NFI while on treatment. Damage after treatment is illustrated by Saunderson et al. who examined 594 new leprosy cases in study known as ALERT MDT Field Evaluation Study (AMFES) in Ethiopia and found that 12% developed new NFI after starting MDT (Saunderson et al., 2000c). Nerve damage in leprosy is common; 60% of MB patients have nerve damage at the time of diagnosis, 30% of patients may develop further nerve damage during MDT treatment and 10% may develop new nerve damage after drug treatment.

2.2.1.2 Risk factors

The major risk factors for nerve damage, especially clinical rather than genetic or immunological, can be grouped into personal factors, visible signs, advanced stage of nerve involvement, and others. The personal factors are: age; sex; pregnancy; and lactation. The criteria for advanced stage of nerve involvement are the WHO disability grades and other factors are the clinical and physical state of the patient. In the INFIR study (van Brakel et al., 2005b), which was designed to assess measures that may predict NFI in a cohort of 303 previously untreated newly diagnosed MB patients, found that age, pre-existing sensory loss, count of enlarged nerves, and WHO grade two were the main predictors of NFI. A further independent risk factor for neuropathy in leprosy is the presence of skin lesions overlying nerve trunks (van Brakel et al., 2005b). Croft and colleagues (Croft et al., 2000) described a simple method, based on disease classification and the presence of loss of nerve function at registration, to identify patients at risk of developing NFI in Bangladesh. Patients who had PB leprosy with no clinical evidence of NFI had a low risk (about 1%) of developing further NFI with treatment. Patients with PB leprosy and clinically detectable nerve function loss who received standard treatment over two two-year observation periods had a risk of around 15% for developing further impairment. The highest risk (around 65%) of further NFI was seen

in patient with MB leprosy and clinical NFI. Additional risk factors identified in the INFIR cohort study were deterioration in: ulnar above-elbow motor nerve conduction amplitude or latency; ulnar, median, radial or sural sensory nerve conduction amplitude or latency; and posterior tibial or sural cold or warm sensation (Smith et al., 2009).

2.2.1.3 Previous studies on leprosy neuropathy

While data from previous studies on leprosy neuropathy have contributed to the understanding of many aspects of neuropathy, research relying on leprosy neuropathy has important limitations:

- Limited opportunities to study persons early in process of neuropathy. Patients at diagnosis of leprosy may have already had neuropathy for some time.
- Limited generalisability to all leprosy patients with neuropathy, because patients in leprosy clinics often have severe or complicated cases of neuropathy; only few studies are based on patients in the field. Thus, by studying clinic-based patients, one cannot postulate the variability in and natural course of neuropathy.
- Limited opportunities to make a definitive diagnosis of neuropathy; various methods of nerve function assessment are used. The same case definition of leprosy neuropathy is not being applied by the different protocols. Thus, by using different protocols, one cannot identify the case definition of leprosy neuropathy.
- Limited generalisability to all leprosy patients with neuropathy, because the treatment may vary (steroids, thalidomide and MDT).

These limitations within leprosy neuropathy research suggest that the development of new tools may yield new insight into the course of neuropathy and its associated pain dysfunction.

2.2.2 The nerve in Leprosy

2.2.2.1 The nerve, M. leprae and host immune response interactions

The nerve damage in leprosy is characterised by the unique interaction of the *M. leprae*, the Schwann cell, and the host immune response; the mechanism underlying this process is still very poorly understood (Scollard, 2008).

Following entry into the human, *M. leprae* grows preferentially in the coolest and most superficial nerve branches, affecting the Schwann cells of the unmyelinated small sensory fibres. It has been suggested that in the skin, *M. leprae* first binds to exposed Schwann cells and then moves proximally within the nerve (Khanolkar, 1964). However, a more recent study from animal models indicated that *M. leprae* infects nerves via lymphatics and blood vessels. The authors postulated that *M. leprae* first aggregates in epineurial lymphatics and blood vessels and then enters the endoneurial compartment through its blood supply (Scollard, 2000, Scollard et al., 1999). At this stage, *M. leprae* targets the Schwann cell where several potential mechanisms of binding have been suggested (Ng et al., 2000, Rambukkana et al., 1997, Suneetha et al., 2001). The phenolic glycolipid-1 (PGL-1) of *M. leprae* binds specifically to the native laminin-2 in the basal lamina of Schwann cell axon units (Ng et al., 2000). Rambukkana has demonstrated that *M. leprae* specifically binds to α-dystroglycan in the presence of the G domain of the α2 chain on laminin-2 (Rambukkana et al., 1997). Other studies have also demonstrated the ability of myelin P0 to bind *M. leprae* (Suneetha et al., 2001). Once invaded, the Schwann cell provides a suitable environment for *M. leprae*. The blood-nerve barrier in the peripheral nervous system protects *M. leprae* from host immune attack (Job, 1989). At this stage, *M. leprae* appears to persist and grows slowly within Schwann cells.

There are arguments about the *M. leprae* Schwann cell interactions. Proponents of interactions between *M. leprae* and Schwann cells claim that the benign characteristic of *M. leprae* may contribute to this favourable environment. For instance, *M. leprae* is non-toxic and therefore, it does not harm the Schwann cell. They also maintain that the presence of *M. leprae* in the nerve may enhance Schwann cell survival in order to maintain the affected cell in an active stage (Lahiri et al., 2010, Tapinos et al., 2006, Hagge et al., 2002, Rambukkana et al., 2002). However, such an argument discounts the fact that *M. leprae* constantly interacts with host cells in the nerves and skin. It should be evident that the argument against the *M. leprae* Schwann cell interaction is not valid. On the contrary, studies have shown that human Schwann cells express toll-like receptor 2 (TLR2), and that the activation of TLR2 by *M. leprae* can lead to apoptosis (Oliveira et al., 2003). Furthermore, it has been shown that even in the absence of immune cells, *M. leprae* induced ErbB2 activation mediates demyelination (Rambukkana et al., 2002, Rambukkana, 2004). More recently, Masaki et al. (Masaki et al., 2013), investigated the interactions between *M. leprae* and Schwann cells and suggested a novel model to explain the spread of the infection. This study suggested that *M. leprae* bacillus not only interact

with Schwann cells, but also change its fate to become progenitor/stem cells with mesenchymal characteristics that promote bacterial dissemination (Masaki et al., 2013). However, these models have not been supported by human studies or even armadillo studies. In summary, the interaction between Schwann cells, *M. leprae*, and host immune responses yields nerve damage in leprosy.

2.2.2.2 Nerve damage mechanisms across the leprosy spectrum

The process of nerve damage in leprosy occurs gradually through the course of the disease and its presentation differs at different stages of the disease. Following entry into the human, *M. leprae* affects the Schwann cells of the unmyelinated small sensory fibres. In addition, the immune response to *M. leprae* may aggravate nerve damage, either by inflammatory and immune-mediated processes, or oedema induced mechanical processes (Haanpaa et al., 2004).

Several factors contribute to the development of nerve damage in leprosy. The direct presence of *M. leprae* within Schwann cells results in immunological stimulation. This interaction is mediated by toll-like receptors (TLRs), which kills Schwann cells and causes nerve damage (Krutzik et al., 2003, Oliveira et al., 2003). The presence of *M. leprae* enhances HLA-II expression on Schwann cells; mycobacterial peptides are presented to HLA-II-restricted CD4+ T cells, which can attack and damage Schwann cells. Additionally, activated natural killer cells may participate in these Schwann cell damaging processes. Another possible contributing factor for nerve damage is the ability of T cells to recognise the presence of mycobacterial antigens within the nerve, which contributes to chronic ongoing neural inflammation. Swelling within the perineurium leads to ischaemia, fibrosis, axonal death, and nerve damage. Furthermore, the presence of pro-inflammatory cytokines such as TNF-α in the affected nerve may also contribute to nerve damage. The direct effect of *M. leprae* on the nerve's protein also promote nerve damage (Save et al., 2004).

The unique pathology of nerve damage in leprosy is probably determined by the host's immune response, which differs across the leprosy spectrum. Additionally, the different clinical outcomes within leprosy sub-types may also contribute to the process of the nerve damage.

The two main processes of nerve damage are wallerian degeneration and demyelination. In tuberculoid disease (TT), the predominant process is wallerian degeneration. Patients

in this group have vigorous cell-mediated immune responses to *M. leprae* that lead to granuloma formation with gross destruction of the nerve fibres. The epithelioid cell response to bacilli within the nerve is a characteristic of this type of leprosy. It forms cuffs of epithelioid cells that enclose the nerve as a whole (Fite, 1951). Histologically, the bacilli are found in fair numbers within the nerve itself, but rarely in the granuloma. Clinically, the nerve damage occurs early, and may be severe, but is not widespread in the body (Britton and Lockwood, 2004).

In contrast, the predominant process in the other group, lepromatous leprosy (LL), is demyelination. Patients with a lepromatous-type disease show very poor cell-mediated immune responses, but vigorous humoral responses. The bacilli are seen in every part of the nerve fibre, intensifying around Schwann cells. There is therefore demyelination and damage of the nerve fibres. The nerve fibres are less severely damaged compared to tuberculoid leprosy (Britton and Lockwood, 2004).

In the borderline (BB, BT and BL) groups, the nerve damage is obvious. It is explained by the instabilities between the cell-mediated and humoral immune responses. The nerve damage process may be cell-mediated and/or humoral to varying degrees. Patients in this group may have a mix of direct effects of the *M. leprae* and inflammatory immune-mediated pathology (Haanpaa et al., 2004).

2.2.3 Clinical presentations

The clinical presentation of leprosy patients with nerve damage depends on two features: damage of small dermal nerves and/or the peripheral nerve trunks. Although symptoms related to cutaneous loss of sensation occurs early in leprosy, the majority of patients present with symptoms of skin lesions or reactions (enlarged, painful and tender nerve). Besides this, a considerable proportion of patients present with a weakness in their hands, feet or face caused by motor involvement. The high number of patients presenting with clinically apparent nerve damage reflects the delay between the appearance of early leprosy skin lesions and diagnosis.

Loss of sensation (cutaneous anaesthesia)

The loss of sensation and autonomic nerve fibre functions in affected skin lesions is an early manifestation of the disease. Patients may have impaired thermal perception (to temperature), nociception and touch sensation. The skin may be dry due to autonomic

fibre damage. Damage to the peripheral nerve trunks leads to regional sensory loss. These sensory abnormalities may be confined to the innervated territory of the affected peripheral nerves or it may show a glove and stocking distribution when it is severe and widespread.

Nerve thickness, tenderness and pain:

Patients with affected peripheral nerve trunks have thickened peripheral nerves, with or without tenderness and standard regional patterns of sensory and motor loss corresponding to the nerve affected. A thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve is one of the cardinal signs for a leprosy diagnosis (WHO, 2012). The nerve can be enlarged palpably in 40-55% of patients and it may be noticed by the patient, especially if it is painful or tender. In leprosy, certain nerves at certain sites are often more involved than others. This difference may be explained by the characteristics of *M. leprae*, which multiplies at relatively low temperatures and has an affinity for Schwan cells. The nerves most likely to be involved are therefore the peripheral nerve trunks in the upper and lower extremity, including: the ulnar nerve at the ulnar grove; the median nerve at the wrist; the cutaneous branch of the radial nerve at the lateral border of the radius; and the lateral popliteal nerve around the neck of the fibula. Figure 2.4 shows the most commonly enlarged nerves and the sites of enlargement in leprosy-affected patients.

Studies have shown that the ulnar nerve is the nerve most commonly affected by leprosy. Haroun et al. (2012) found that in a cohort of 80 leprosy patients who had completed MDT within 18 months, the ulnar nerve was the nerve most frequently affected (78%) (Haroun et al., 2012). Nerve enlargement can be identified by clinical examinations although this is not always reproducible. However, the degree of enlargement has little bearing on the severity of neuropathy. Nerve pain and tenderness is known as neuritis, which may be defined as inflammation of the peripheral nerve trunk without features of reactions (Mahajan et al., 1996). Patients with neuritis may present with spontaneous nerve pain or recent onset of new sensory or motor impairment (Mahajan et al., 1996). The nerve pain/tenderness may be so severe that even gentle palpation produces an electric shock-like sensation. A detailed description of the peripheral sensory fibres and function is discussed in Chapter 4.

Weakness:

Depending on the sites of the enlargement of the peripheral nerve trunk, the number of affected nerves and disease sub-type, the standard regional pattern of motor loss may include: claw hand; foot drop; and/or facial muscle weakness. The ulnar innervated muscles of the hand and forearm, the median innervated muscles in the hand, the tibial innervated muscles in the foot, the peroneal innervated muscles in the foot and the leg, and the facial innervated muscles are most commonly affected by the disease.

2.2.3.1 Clinical presentation of nerve damage across the leprosy spectrum

As described above, the involvement of peripheral nerves in patients with leprosy is clinically different across the disease spectrum as follows:

Neuropathy in tuberculoid leprosy:

The clinical neuropathy of tuberculoid leprosy is characterised by asymmetrical enlargement of a single nerve. Damage to the small dermal sensory and autonomic nerves produces hypoesthesia and anhidrosis (Bryceson and Pfaltzgraff, 1990). Marked nerve damage can occur in nerves underlying or surrounding skin lesions, which may result in wrist drop, clawing of the hand, and/or foot drop.

Neuropathy in lepromatous leprosy:

Nerve damage in lepromatous leprosy is slow and progressive. It characterised by bilateral symmetrical distal polyneuropathy. The damage to the small dermal sensory and autonomic nerves produces glove and stocking sensory loss. Damage to the nerve trunk produces bilateral and symmetrical thickening and tenderness, which may result in distal weakness of the intrinsic muscles of hands and feet.

Neuropathy in borderline leprosy:

In contrast to that seen in tuberculoid and lepromatous leprosy, nerve damage in borderline leprosy has a relatively rapid onset and acute progress. It is characterised by irregular and asymmetrical neuropathy. Damage to the small dermal sensory and autonomic nerves produces hypoesthesia and anhidrosis (Bryceson and Pfaltzgraff, 1990). Multiple affected nerves produces deformities in the hands and feet.

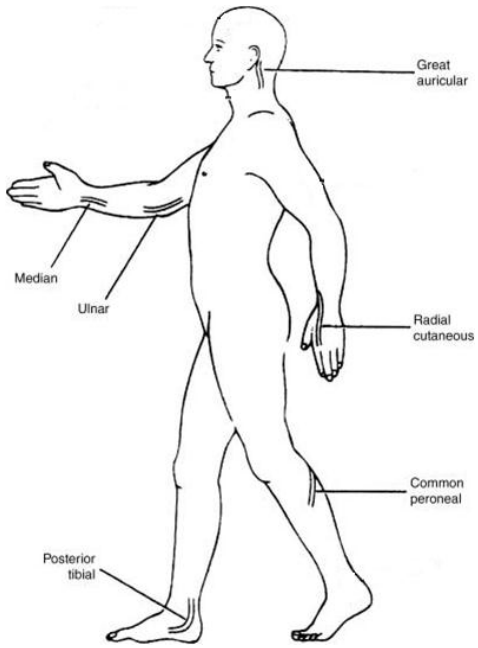

Figure 2.4. Commonly affected peripheral nerve in leprosy

Picture modified from Khambati and colleagues (Khambati et al., 2009)

2.2.4 Nerve function assessment

It is important to carry out a full/routine clinical assessment of nerve function in leprosy, as early detection of neuropathy will reduce the incidence of impairment and its effects. A comprehensive overview of the detailed methods for the assessment and detection of neuropathy will be explored further in Chapter 4, including the instruments for assessing of sensory abnormalities and pain-related phenomena.

2.2.4.1 Assessment of neuropathy:

History and clinical examination

The clinical history (described in section 2.1.6.1) is followed by palpation of the involved nerves to assess for nerve size, and tenderness.

Nerve assessment includes motor, sensory and autonomic functions. Table 2.2 shows different modalities of nerve fibre functions. A detailed description of the peripheral sensory fibres and function is discussed in Chapter 4. Aα/β fibres are large in diameter, myelinated and have fast conduction velocity (Barrett et al., 2010). They are normally activated by non-noxious mechanical stimuli such as touch. In contrast, Aδ fibres are medium in diameter, myelinated and have intermediate conduction velocity (Barrett et

al., 2010). They are normally activated by noxious stimuli and transmit sharp pain. C fibres are small in diameter, unmyelinated and have slow conduction velocity (Barrett et al., 2010). They are normally activated by noxious stimuli responsible for secondary pain, like burning and aching pain. These modalities can be assessed using electrophysiological methods such as nerve conduction study, cold and warm temperature sensation assessment or monofilaments.

Table 2.2. Physiological function of the motor, sensory and autonomic nerve fibres

Motor	**Sensory**			**Autonomic**
	Myelinated	Thinly myelinated	Un-myelinated	
Muscle control	Touch, vibration, position perception	Cold perception, pain	Warm perception, pain	Sweating

The choice of the test for the nerve function assessment depends on the availability of the tool and availability of qualified trained staff. For leprosy, nerve functions have been assessed using different methods such as cotton-wool, monofilaments, voluntary muscle testing, nerve conduction study and biopsies.

Assessment of autonomic nerve fibre function: The assessment of autonomic components of the nerve includes testing for sweating of the hands and feet.

Assessment of sensory function: Ideally testing should be for light touch, light pressure, pain and temperature, but it is rarely done in the field. The performance of the test depends on the availability of the tools and qualified trained staff. Light touch is the most frequent sensory modality assessed using different methods such as cotton wool, a ball point pen, and Semmes-Weinstein Monofilaments (MFs) in resource-limited settings (Brandsma et al., 2014).

Assessment of motor function: The assessment of motor components of the nerve is done by voluntary muscle testing in the face, hands and feet. Voluntary muscle testing assesses innervated facial muscles, ulnar and median nerves of the hand and common peroneal nerves of the feet using a modified Medical Research Council (MRC) scale

(Brandsma, 2000). MRC is a modified grading system to assess muscle weakness due to peripheral nerve involvement. It asses voluntary movement against resistance.

Voluntary muscle assessment is suitable for measuring NFI in a resource- limited setting. In a cohort study of 303 untreated MB patients from India, assessing the sensitivity and specificity of MFs and VMT using nerve conduction study as the gold standard for detecting NFI (Van Brakel et al., 2005a). The authors found that the concordance between VMT results and motor nerve conduction was good for the ulnar nerve, but very few median and peroneal nerves with abnormal conduction had an abnormal VMT. The authors also noted that both methods have good inter-tester reliability and reproducibility and good specificity of more than 80% for most nerves. A similar study on different tests of nerve function by Khambati and colleagues supports the conclusion that MFs and VMT have good specificity, but moderate-to-low sensitivity of less than 40% in detecting nerve involvement using NCS as a gold standard (Khambati et al., 2009).

2.2.4.2 Disability grading

The physical impairment associated with nerve damage in leprosy occurs mainly in the hands, feet and eyes. It can be assessed using WHO disability criteria, which defines grade zero as no loss of sensation or visible deformity, grade one as a loss of sensation without visible deformity, and grade two as the presence of visible deformity (WHO, 1988).

Physical disability from nerve damage in leprosy can occur before, during and after MDT. A recent survey of 1358 leprosy patients who had been released from MDT up to 5 years earlier in Indonesia found that 77% of the patients had a physical impairment (van Brakel et al., 2012). In the INFIR Cohort Study in India, 40.9% of the newly diagnosed Indian patients had a WHO disability grade of one and 9.6% had a disability grade of two at enrolment (van Brakel et al. 2005). The BANDS cohort had a prevalence of disability grades one and two of 9.6% and 6.0%, respectively (PB and MB patients) at enrolment. Among MB patients, the prevalence of disability grades one and two was 28.5% 18.2% respectively (Croft et al. 1999).

WHO's current 'Enhanced global strategy to further reduce the disease burden due to leprosy' aims to reduce the rate of new cases diagnosed with disability grade two (WHO, 2009a). The reduction of grade two disability is one of the new indices for successful

leprosy burden reduction as well as a marker for early detection of nerve damage. In 2011, a WHO report showed the proportion of grade two disability in newly diagnosed leprosy cases varied between India at 3% and China at 27% (WHO 2012a).

2.2.5 The differential diagnosis of neurological lesions of leprosy

The neurological disorders that share the similar features to leprosy are many, but most do not have sensory loss. In a patient from an endemic area and with enlarged nerves, Amyloidosis, Neurofibromatosis, Sarcoidosis, and Vasculitis may need exclusion. For peripheral neuropathy with generalized neuropathy rather than attributed to a specific nerve innervation, conditions such as Guillain-Barré syndrome, Vitamin B12 deficiency, HIV/AIDS, Alcoholism, Hypothyroidism, Hereditary disorders, and heavy metal poisoning will require consideration and appropriate investigation. If motor involvement is prominent, the possibility of trauma, Dupuytren's contraction, Cervical rib, and Scleroderma will arise. Leprosy ulcer has to be distinguish from tropical ulcer and other trophic ulcers. Tropical ulcer is the commonest cause of ulceration in the poorer leprosy-endemic countries. Ulceration in the presence of sensory loss can be seen also in Diabetic Mellitus, the most common cause of sensory neuropathy.

2.2.6 Nerve damage consequences in leprosy

Nerve damage is incapacitating for many people in countries where leprosy is endemic. Patients may develop dryness of the skin, impairment of various sensory modalities, and motor impairment causing muscle weakness. But with time and without appropriate care, these impairments may lead to skin cracks, wounds, clawing of digits, contractures and shortening of limbs, and blindness (Bryceson and Pfaltzgraff, 1990). Impairments may interfere with quality of life and activities of daily living. Therefore, patients continue to be stigmatised and suffer from associated co-morbidities.

Paradoxically, although leprosy is classically associated with sensory loss affecting the hands and feet, pain due to peripheral nerve damage and/or skin lesion may become a problem for some patients. Those patients who do experience pain may develop an additional quality of life burden over that of leprosy itself or leprosy with painless nerve damage. It is not known why some leprosy patients develop painful neuropathy while others are pain-free throughout the course of the disease.

Chapter 3 Identification of neuropathic pain

3.1 Literature review of pain

3.1.1 Definition of pain

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey and Bogduk, 1994). The unpleasant is perceived in the brain in the response of afferent activity in nociceptive sensory neurons. However, pain is more than a sensation, or the physical awareness of pain; it also involves affective aspects. This gives further information on the pain's nature, intensity and location. Other factors such as social, psychological and behavioural aspects of pain are also not considered in this definition. These factors need to be taken into consideration in any interaction with the patient (McMahon SB et al., 2013). The inclusion of the various cultural and behavioural aspects to pain would add further definition to the overall concept of pain.

3.1.2 Classification of pain

Pain can be classified into "nociceptive" or "neuropathic" types, Table 3.1.

3.1.2.1 Nociceptive pain

Nociceptive pain occurs as a result of tissue damage in response to a noxious stimulus, such as impending tissue injury, ongoing tissue destruction, or inflammation, in the presence of intact sensory nerve system e.g. osteoarthritis.

3.1.2.2 Neuropathic Pain

Neuropathic Pain is defined by the IASP as "pain caused by a lesion or disease of the somatosensory system" (Jensen et al., 2011).

Table 3.1. Nociceptive pain vs. Neuropathic pain

	Nociceptive Pain	**Neuropathic Pin**
Definition	Pain caused by physiological activation of pain receptors	Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system
Symptoms	Local +/- referred pain	At the neuro-anatomical lesion
Quality of symptoms	Easy to describe by patients (Good clinical descriptors)	Difficult to describe by patients (Poor verbal descriptors)
Treatment	Good response	Poor to moderate response

3.2 Literature review of Neuropathic pain

3.2.1 The concept of neuropathic pain

Neuropathy is defined as the disturbance of function or pathological change in a nerve (Merskey and Bogduk, 1994); therefore, NP is pain arises from this process. NP can occur as a result of a lesion or disease of the somatosensory system at the brain and spinal cord (central pain); or posterior roots and peripheral nerves (peripheral neuropathic pain). The definition of NP has been changed over the time due to a change in the use of terms referring to pain caused by sensory abnormalities, and uncertainties about the pathophysiology of chronic pain states. Originally NP term referred to pain due to peripheral neuropathies, but this brought out some difficulties such as the ability to distinguish neuropathic dysfunction from psychological interference. For instance, in patients with leprosy, chronic ulcer, arthralgia, skeletal deformities and depression may all significantly contribute to symptomatology of pain. Later in 1994, this definition was broadened to include the term "dysfunction", where the IASP defined NP, as "a pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system" (IASP, 1994). Recently, this has been also revised by a group of pain experts on the basis of how it could be distinguished from nociceptive pain (Treede et al., 2008) . In the new definition the word "dysfunction" has been removed and the phrase "a lesion or disease affecting the nervous system" has been specified to be "a lesion or disease of the somatosensory system".

3.2.2 Epidemiology

The prevalence of NP among the general population is variable and influenced by the rates of aetiology of the underlying disease and the method of assessment (Smith and Torrance, 2012). Torrance et al. (2006), who surveyed 3 002 people from the general population in the UK through a postal survey using the Leeds Assessment of Neuropathic Symptoms and Signs score (S-LANSS), noted that 8.2% had pain of predominately neuropathic origin (Torrance et al., 2006). Bouhassira et al. (2008), who investigated the epidemiology of NP among 23 712 participants using "Douleur Neuropathique en 4 questions" (DN4) sent to 30 155 randomly selected adults in the "Acess Sante" data base, found that 6.9% of them had chronic pain with neuropathic characteristics (Bouhassira et al., 2008). NP affects as much as 8% of general population and in 5% of these cases, it may be severe (Torrance et al., 2006, Bouhassira et al., 2008). These prevalences are related to wealthy western societies and may not necessarily reflect the occurrence of NP in developing countries. Table 3.2 shows the prevalence of peripheral NP in different conditions estimated from single studies.

Table 3.2. The prevalence of NP in different conditions

Condition	Neuropathic pain prevalence
Diabetic Mellitus	Prevalence 8% (Wu et al., 2007) and 20% (Davies et al., 2006)
Post herpetic neuralgia (PHN)	Prevalence ranging from 2.6 to 7.2% (Choo et al., 1997, Helgason et al., 2000, Scott et al., 2003)
HIV sensory neuropathy	42% (Smyth et al., 2007)

3.2.3 Neuropathic pain classification and aetiology

Neuropathic pain may result from disorders of both the peripheral and central nervous system. This classification is based on the anatomical site of the lesion, even though traditionally NP has been classified according to the aetiological diagnosis. The underling nerve damage may occur due to metabolic, ischemic, hereditary, traumatic, toxic, infectious or immune-related cause. Of those, the major causes of NP include: peripheral nerve trauma, spinal cord injuries, diabetes mellitus, multiple sclerosis, herpes zoster, and HIV infection (Merskey and Bogduk, 1994, Attal et al., 2008).

3.2.4 Development of neuropathic pain

The development of NP arises from pathological responses in somatosensory systems in response to nerve damage. NP and associated sensory aberrances probably represent disordered repair process in response to damage. It is important to note that NP is not an inevitable consequence of nerve damage; the minority of patients develop NP after somatosensory insult. Pathophysiological underlying mechanisms, either in the peripheral or the central nervous system, may lead to symptoms such as spontaneous pain or stimulus-evoked pain, as well as other associated sensory disturbances such as sensory loss (anaesthesia dolorosa), hyperalgesia, allodynia and hyperpathia. These collections of symptoms and signs are known as NP syndrome. The exact constellation of NP characteristic, and associated sensory aberrations, which are manifested in an individual patient are variable and complex and often only fully revealed by the use of sophisticated investigation techniques (Jensen and Baron, 2003, Baron et al., 2009). These patterns do not necessarily reflect the condition from which the nerve damage arose, but importantly may well reflect pain generating mechanisms and therefore give a clue to mechanisms and thus likely drug responses on an individual patient level. Thus, it is vital to accurately phenotype the sensory abnormalities in each patients.

3.2.5 Neuropathic pain underling mechanisms

Animal research and the use of human investigative techniques such as microneurography, functional brain imaging, quantitative sensory testing, skin punch biopsies and experimental human pain models have furthered human pain research. The rationale for the mechanism-based approached is to stratify patients according to mechanism and therefore have mechanism-based prescribing of appropriate drugs at the individual patient level. However, the mechanisms of NP have not yet been fully established and research has yielded an array of potential pain generating mechanisms any of which may be operating in an individual patient. This further emphasises the necessity of properly phenotyping patients as discussed in the preceding section. The broad domains of possible underlying patho-physiological pain related phenomena which might contribute to NP development (Baron, 2006, Bridges et al., 2001, Baron, 2009, Baron et al., 2010a, Costigan et al., 2009), are described in Table 3.3. However none of them are unifying hypotheses for the NP mechanism (Bridges et al., 2001).

Table 3.3. Possible neuropathic pain mechanisms

Neuropathic pain underling mechanisms *	
Peripheral mechanisms	**Central mechanisms**
Sensitisation and spontaneous activity in sensory neurons	Sensitisation in the spinal cord
Inflammation induced ectopic activities	Central sensitisation (changes in the brain)
Loss of trophic support for neurons	Loss of inhibitory controls and increased facilitation of pain signalling
Alteration in ion channel	
Immune-neuronal interaction	Neuronal immune and glial cell interactions

* Cited in Ralf Baron (Baron, 2006), Wallace VCJ and Rice ASC (Wallace and Rice, 2008), Costigan and colleagues (Costigan et al., 2009), and Scholz J, Woolf CJ (Scholz and Woolf, 2007)

3.2.6 Clinical features of neuropathic pain

3.2.6.1 Symptoms

Patients with NP commonly present features of spontaneous pain and/or stimulus evoked pain. The onset of these symptoms usually occurs soon after nerve damage. The overall intensity of pain rated symptoms in patients with NP is higher compared to nociceptive pain, possibly due to paroxysmal episodes (Wilkie et al., 2001). A brief description of these different types of pain is given below.

Spontaneous pain

Spontaneous pain, which is described as pain arise without stimulus, can be continuous or paroxysmal (McMahon SB et al., 2013). Continuous pain is described in terms of dysaesthesia: burning, pricking, tingling, cutting, and stabbing; or deep pain which described as aching, cramping, throbbing, and crushing. A recent definition of spontaneous pain as pain due to neuropathic spontaneous discharge in somatosensory neurons that is caused by changes that are intrinsic to the neuron was introduced (Bennett 2012). This definition was introduced by Bennett due to uncertainty about the concept of spontaneous pain making no sense when the pain is the result of an ongoing inflammatory reaction. Although spontaneous pain can be hardly distinguished from

ongoing pain, which is defined as pain due to inflammatory ongoing discharge caused by the ongoing presence of the products of inflammation, it might lead to ongoing pain. Spontaneous pain commonly occurs in neuropathic pain patients. For example, 100% of 1 236 patients with NP reported spontaneous pain, usually shooting, burning, or electric-shock like sensation (Maier et al., 2010).

Stimulus-evoked pain

Stimulus-evoked pain, which is described as abnormal responses to stimuli, is often referred to hyperalgesic and allodynic. It is characterised by hypersensitivity of the nervous system.

Hyperalgesia (increased sensation of pain in response to normally painful stimuli), allodynia (pain in response to normally non-painful stimuli) and hyperpathia (explosive pain response when stimulus intensity exceeds sensory threshold) are features of sensory gain (Baumgartner et al., 2002) (Cavenagh et al., 2006).

3.2.6.2 Signs

The demonstration of nerve damage dysfunction is essential evidence in the diagnosis of neuropathic pain. Damage can be due to motor, sensory or autonomic dysfunction attributable to a lesion of the afferent transmission system. A loss of sensation/ "negative" signs may result due to complete or partial loss of input to the nervous system and a corresponding sensory loss. A reduction of afferent input caused by a nerve lesion may contribute to regeneration and loss of inhibitory output with development of hypersensitivity resulting in gain of sensation/ "positive" signs (Jensen and Baron, 2003). These loss and gain signs can be demonstrated by clinical examinations and laboratory testing such as quantitative sensory testing.

Negative signs:

Negative signs refer to loss of sensory and/or motor function due to nerve damage. Loss of sensory function is usually to thermal and noxious stimuli, indicating damage to small-diameter afferent fibres or to the spino-thalamic tract. Sensory loss manifestations can result in loss of thermal sensations, light touch, pinprick, and vibration.

Loss of motor functions result in muscle wasting with motor weakness.

Positive signs:

Positive signs in patients with NP usually result from stimulus evoked pain. It can be exaggerated responses to stimuli with either reduced pain threshold (allodynia), normal pain threshold (hyperalgesia) or increased pain threshold (hyperpathia). Allodynia is defined as pain due to a stimulus that does not normally provoke pain (Merskey and Bogduk, 1994). Different types of allodynia are associated with different stimuli: mechanical, thermal and dynamic. Hyperalgesia is defined as increased pain from a stimulus that normally provokes pain (Merskey and Bogduk, 1994). Hyperpathia is a painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold (Merskey and Bogduk, 1994).

3.2.7 Diagnosis and assessment of neuropathic pain

Clinical evaluation is the common method for diagnosing neuropathic pain. It involves a series of systematic steps which include past and present history, a detailed description of pain distribution, quality and intensity of pain and a neurological examination with the emphasis on sensory testing (Jensen et al., 2001, Hansson, 2002). There are two definitive steps in the process: firstly to confirm that some form of damage to the somatosensory system has occurred, without this the diagnosis is impossible. Secondly, to determine that any pain is indeed neuropathic, this because the occurrence of nerve damage does not necessarily follow that any pain is neuropathic in origin, therefore screening tools such as DN4 may help in identifying symptoms and signs suggestive of NP. The sensory findings should be neuroanatomically logical and compatible with a definitive lesion site (Treede et al., 2008).

Patients may be classified as having NP according to the grading system for NP diagnosis, Table 3.4. The grading system considers pain to be definitive NP if all criteria are present, probable NP if criteria "1" and "2" are present, plus either "3" or "4," and possible NP if criteria "1" and "2" are present, without confirmatory evidence from "3" or "4" (Treede et al., 2008).

Table 3.4. Grading system for neuropathic pain

Criteria to be evaluated for each patient	
1.	Pain with a distinct neuroanatomically plausible distribution
2.	A history suggestive of a relevant lesion or disease affecting the PNS or CNS
3.	Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test
4.	Demonstration of the relevant lesion or disease by at least one confirmatory test

Recently, a comprehensive guideline on neuropathic pain assessment has been developed by the assessment committee of the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) (Haanpaa et al., 2011a). The guideline identifies five areas for the assessment as follows: investigation of underlying disease, evidence of somatosensory system dysfunction, confirmation pain is neuropathic pain, severity of pain, and the impact of the pain.

The diagnosis and assessment of neuropathic pain is discussed in detail in Chapter 4.

3.2.8 Psychological co-morbidity, quality of life and neuropathic pain

Neuropathic pain is associated with psychological problems which impact upon quality of life. It interferes with physical and psychological functioning and causes disability (Fishbain et al., 1997). The International Classification of Functioning, Disability and Health describes functioning as "the complex interplay of body functions, body structures, activities and participation, environmental and personal factors" (WHO, 2009b). Disability is defined as "a physical or mental condition that limits a person's movements, sense or activities" (Oxford, 2009).

There is good evidence that depression is a consequence of chronic pain in other conditions (Fishbain et al., 1997). Williams et al. found a high prevalence of depression (33%) in 483 patients with neurological problems followed for 12 months; pain was more likely to persist in those with depression and depression was more likely to persist in those with coexistent pain (Williams et al., 2004). This was supported by independent effect of antidepressant drugs on pain and depression. A study carried out by Meyer-

Rosberg et al. in 2001 assessed 126 patients suffering from NP due to a peripheral nerve lesion, recruited from two multidisciplinary pain clinics in Sweden (Meyer-Rosberg et al., 2001). The study identified depression, anxiety, altered sleep patterns, social isolation and reduced employment status as important co-morbidities (Meyer-Rosberg et al., 2001). Figure 3.1 shows co-morbidity associated with NP.

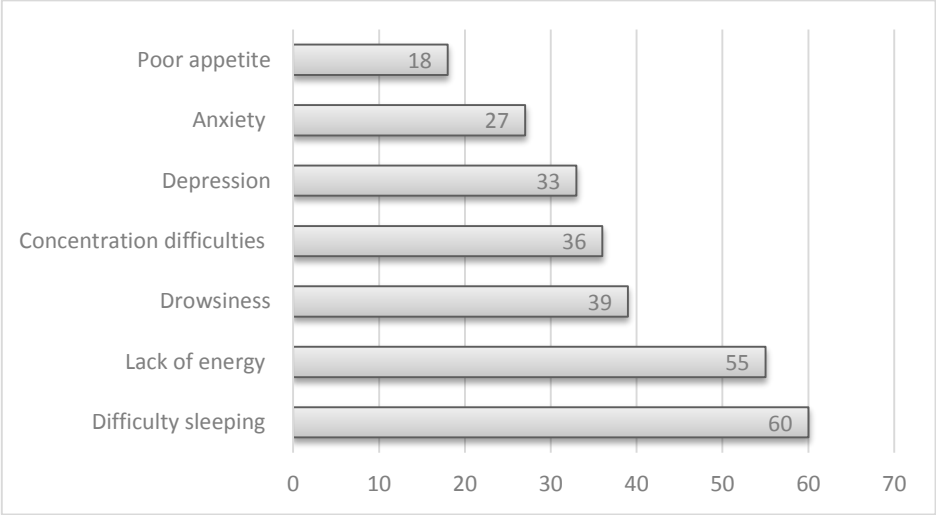

Figure 3.1. Co-morbidity associated with neuropathic pain

Patients with moderate to severe discomfort due to neuropathic pain symptoms (n=126), taken from study by Meyer-Rosberg (Meyer-Rosberg et al., 2001)

Daniel et al., 2008, who compared NP condition in 46 patients with post-herpetic neuralgia with a persistent pain of nociceptive origin in 55 patients with low back pain from pain management clinics in Scotland and England to determine the differences in physical and psychological function; factors that increase difficulties; responses to pain; beliefs about pain and problems experienced (Daniel et al., 2008). The authors noted that the differences between the two groups were not on the major variables of pain, mood, cognition and physical function. The main differences were in factors that increase pain, people's responses to pain, their beliefs about diagnosis and the cause of pain and the problems they reported as a result of experiencing pain.

3.2.9 Treatment of neuropathic pain

The management of patients with chronic NP is multifactorial. It may involve primary therapy for underlying neuropathy and disease, drug therapy for alleviation of pain and treatment of co-morbidity associated with pain.

3.2.9.1 Primary therapy for underlying neuropathy and disease

Early detection and treatment of the underlying cause may reduce the risk of nerve function impairment; controlling hyperglycaemia may attenuate diabetic neuropathy. However, permanent nerve damage that leads to chronic pain does not respond consistently to such treatment and other therapeutic agents may be needed.

3.2.9.2 Drug therapy for alleviation of chronic neuropathic pain

Both oral and topical drug therapies are used to treat NP. The main classes of oral therapy are tricyclic antidepressants, anticonvulsants, tramadol, and opioids. Topical therapies include capsaicin and local anaesthetic.

According to the European Federation of Neurological Societies (EFNS) guidelines on pharmacological treatment of NP, the first two classes of medication (tricyclic antidepressants and anticonvulsant) are recommended (Finnerup et al., 2010, Dworkin et al., 2007).

Other therapies such as opioids, topical local anaesthetics, topical capsaicin (0.075% and 8%) may be used, but the first two drugs still represent the main options for treating the condition and both of them are appropriate for use in developing countries (Finnerup et al., 2010).

Antidepressants

Tricyclic antidepressants have analgesic properties in addition to their antidepressant effect. This effectiveness has been shown in different clinical trials (Finnerup et al., 2005). Therefore, they are commonly used for pain relief in patients with NP (McCleane, 2003, Sindrup et al., 2005). The analgesic effects of antidepressants are not fully understood and their mode of action could be predominantly via inhibition of reuptake of serotonin and/or norepinephrine; blocking of sodium channels; or anticholinergic. The most common antidepressants used are imipramine, clomipramine, amitriptyline, desipramine, nortriptyline, venlafaxine, and duloxetine. A combination of drugs is often used. For instance, duloxetine and venlafaxine which are selective serotonin norepinephrine reuptake inhibitors were effective in patients with painful diabetic neuropathy (Baron, 2011).

Anticonvulsants

Anticonvulsants drugs such as oxcarbazepine, topiramate, lamotrigine, gabapentin, and pregabalin have an analgesic effect in chronic NP (McCleane, 2003). Anticonvulsants with Na+ channel actions such as carbamazepine are effective in trigeminal neuralgia (Baron et al., 2010a). Those acting on alpha2-delta-1 subunit of neuronal Ca++ channels, such as gabapentin and pregabalin, show efficacy in postherpetic neuralgia, diabetic painful neuropathy, central pain states and other NP conditions (Finnerup et al., 2005, Field et al., 2006).

Opioids

Opioid analgesics, such as morphine, codeine, methadone, and oxycodone, are used for the treatment of NP. Their mode of action could be predominantly via agonists at presynaptic and postsynaptic opioids receptors. Tramadol, which acts via inhibition of norepinephrine and serotonin reuptake, also has a role in the treatment of NP. Opioids have an analgesic efficacy the same as antidepressants; however, their use is limited, due to long term side effects and a lack of data supporting long term efficacy (Raja et al., 2002).

Capsaicin

Capsaicin is the active component of chilli pepper, produces burning and heat sensation in contact to skin. Interestingly, topical application of capsaicin was found to be useful in relieving chronic pain caused by nerve damage. Its mode of action was thought to occur at C-nociceptive fibres resulted in depletion of substance P and the nociceptor fibres (Attal, 2000). It is available in two forms: capsaicin cream (0.025-0.075%), and patch (8%). The former has had varying results in patients with painful diabetic neuropathy, and postherpetic neuralgia, whereas the topical high-dose capsaicin patch was found to be effective in patients with postherpetic neuralgia and HIV neuropathy (Backonja et al., 2008, Simpson et al., 2008). Use of capsaicin is limited due to its short-lived effect and burning sensation. It is predominately used as adjuvant therapy.

3.2.9.3 Treatment of co-morbidity

Depending on pain intensity and psychological assessment, patients with chronic NP may need further clinical, psychological and psychiatric treatment.

3.3 Pain in leprosy

3.3.1 Types of pain in leprosy

Patients with leprosy may experience skin and nerve pain at different times during the disease. Two types of patients can be distinguished: those with pain associated with tissue inflammation occurring during episodes of immune mediated reactions and those with leprosy affecting the somatosensory system.

3.3.1.1 Nociceptive pain

Leprosy nociceptive pain may occur due to activation of the nociceptive system either by tissue injury; ongoing tissue destruction such as pain around infected ulcer or swollen joint; or inflammation. Inflammatory pain is caused primarily by immune-mediated responses and can continue after completion of leprosy MDT.

3.3.1.2 Neuropathic pain

Leprosy neuropathic pain occurs due to damage to the somatosensory system. It may occurs in the skin lesions and/or nerves, even years after successful completion of the MDT.

3.3.1.3 Mixed pain

Leprosy mixed pain can occurs as a combination of both neuropathic and nociceptive pain; i.e., both components were present in different parts of the body.

3.3.2 Literature review of neuropathic pain in leprosy

3.3.2.1 Epidemiology

Recent studies show that NP is not uncommon among leprosy patients (Haanpaa et al., 2004). Table 3.5 shows NP studies that have been done in leprosy endemic settings over the last decade (Hietaharju et al., 2000, Haanpaa et al., 2004, Croft, 2004, Stump et al., 2004, Malaviya, 2005, Lund et al., 2007, Saunderson et al., 2008). The prevalence of NP range from 17.5% to 56.1%, however, these studies have been cross-sectional and hospital-based, which might over-estimate the prevalence of pain. In a cross-sectional study from Ethiopia with 96 patients who had been treated for leprosy more than 10 years prior to assessment, NP was found in 28 (29%) (Saunderson et al., 2008). Another

cross-sectional study on 358 leprosy patients from a referral centre in Brazil in 2004, reported 201 (56.1 %) of the patients had past or current moderate to severe NP that interfered with daily life activities (Stump et al., 2004).

Table 3.5. Overview of studies carried out on neuropathic pain in leprosy

Authors, year	Country	Type of study	Number enrolled	outcome
Hietaharju (Hietaharju et al., 2000)	Bangladesh	Cross-sectional	16	Majority of patients had a sensory changes suggestive of NP
Stump (Stump et al., 2004)	Brazil	Cross-sectional	358	56.1% of patients with treated leprosy had NP that interfered with daily life activities
Lund (Lund et al., 2007)	India	Cross-sectional	17	81.3% had neuropathy. All nerve biopsies showed intraneural inflammation
Saunderson (Saunderson et al., 2008)	Ethiopia	Cross-sectional	96	29% of patients treated for MB leprosy more than ten years previously had NP
Lasry-Levy (Lasry-Levy et al., 2011)	India	Cross-sectional	101	21% of patients had NP
Haroun (Haroun et al., 2012)	Ethiopia	Cross-sectional	80	17.5% of patients had NP
Reis (Reis et al., 2013)	Brazil	Cross-sectional	33	66.3% of patients had NP
Ramos (Ramos et al., 2014)	Ethiopia	Cross-sectional	74	70.3% of patients had NP

3.3.2.2 Psychological co-morbidity, quality of life and leprosy neuropathic pain

Patients with leprosy have a higher prevalence of psychiatric problems, probably because of the chronicity of the disease, disability caused by neuropathy and stigma. Although several studies have confirmed that depression was the most common psychiatric problem, affecting between 10% and 52.4% of patients, there is little published literature exploring the interactions between pain, psychological status and quality of life among leprosy patients (Fishbain et al., 1997, Williams et al., 2004, Meyer-Rosberg et al., 2001). A study from India in 2009, evaluated the association of chronic NP with psychological morbidity in 101 leprosy patients, the DN4 and GHQ-12 were used to identify NP and psychological morbidity, showed that 21.8% of the leprosy patients in the study had NP and that psychological morbidity was detected in 41% of patients with NP (Lasry-Levy et al., 2011). Another study, which included 80 patients from a leprosy centre in Ethiopia, noted that 68 (85%) of the patients had depression (Leekassa et al., 2004).

3.3.2.3 Mechanisms of NP in leprosy patients

In leprosy, there is increasing evidence that the development of neuropathic pain is probably immunologically mediated (Lund et al., 2007). Reactions, neuritis and inflammation, which are common among leprosy patients who develop NP, are a risk factor. The immune response in the peripheral nerves may recur and if they repeatedly affect the peripheral nerves, chronic-post inflammatory pain may result. Lockwood et al. (2002) have shown that *M. leprae* protein and lipid antigens are present in skin and nerves at the time of acute reversal reactions (Lockwood et al., 2002). A recent study, which examined 27 ulnar nerves of leprosy patients using nerve conduction studies in Brazil, showed the association between NP patients with reactions (Garbino et al., 2011). In addition, small fibre neuropathy (SFN), which is the most common neurological complication of leprosy, may have a significant contribution to the occurrence of NP in leprosy (Hietaharju et al., 2000). Table 3.6 shows the most typical symptoms of NP and possible related mechanisms that may occur due to nerve damage in leprosy.

Table 3.6. NP symptoms and related mechanisms in leprosy patients*

Symptoms	Possible related mechanism
Dysaesthesia	Ectopic discharges in Aβ fibres
Spontaneous paroxysmal shooting or lancinating pain	Ectopic discharges in C fibres, Inflammation induced ectopic activities or Immune-neuronal interaction
Continuous spontaneous evoked pain	Peripheral nociceptor sensitisation, loss of inhibitory control or ectopic discharges in C fibres

* Table adapted from Woolf and Mannion. Lancet 1999; 353: 1959-1964

3.3.2.4 Clinical presentation of leprosy patients with pain

Patients with leprosy NP commonly present with continuous burning pain, dysesthesia, paraesthesia and/or paroxysmal pain attacks (Hietaharju et al., 2000). Dysaesthesia and paraesthesia may occur as a result of increased expression of Na+ channels in injured nerve fibre which may leads to ectopic discharges in Aβ fibres (Woolf and Mannion, 1999). Ectopic discharges in C fibres may contribute to the occurrence of paroxysmal shooting or lancinating pain. Continuous burning pain may occur due to peripheral nociceptor sensitisation, loss of inhibitory control or ectopic discharges in C fibres in affected nerves (Woolf and Mannion, 1999).

A frequent finding in leprosy patients with NP is loss of pin-prick and temperature sensation (cold and warm). Other stimulus-dependent signs such as allodynia and hyperalgesia may not usually occur in leprosy patients (Hietaharju et al., 2000), but may occur in leprosy patients with chronic neuritis (Hietaharju et al., 2000). Allodynia, which is defined as pain due to a stimulus that does not normally provoke pain, and hyperalgesia, which is defined as an increased response to a stimulus that is normally painful, are typical in states with well preserved and irritated peripheral sensory fibre which are overactive and cause central sensitisation (Bridges et al., 2001, Baumgartner et al., 2002), but in leprosy there is silent inflammation and slow but complete destruction of the nerve (Job, 1989). Inflammatory pain is usually considered to be of nociceptive character, because it partly results from hyperexcitability of intact nociceptive dorsal root ganglion neurons innervating inflamed tissue. However, chronic inflammatory pain is often characterized by positive signs such as hyperalgesia and allodynia, suggesting

possible neuropathic component. Recent studies have shown that inflammation-induced nociceptor hyperexcitability is sustained by C-nociceptors, which may contribute to inflammatory hyperalgesia. This may also explain why in some inflammatory conditions both nociceptive and NP may overlap.

Hietaharju et al. reported detailed characteristics of chronic NP in 16 patients with treated multibacillary leprosy in Bangladesh (Hietaharju et al., 2000). 10 patients (62.5%) the pain had a glove and stocking like distribution, which suggests a distal symmetrical polyneuropathy, rather than mononeuropathy, in these cases. The quality of pain was burning in 9 (56.3%), and the occurrence of pain was continuous in 8 (50%) patients. A study from Brazil with 358 leprosy patients, showed that a glove (22.4%), and stocking (24.9%) like distribution of pain was common (Stump et al., 2004). In an Indian study with 17 leprosy patients with chronic NP who had completed MDT, the pain was burning in all patients (Lund et al., 2007). In leprosy, the presentation of painful neuropathy is heterogeneous, some patients have symptoms of polyneuropathy others may have mononeuropathy. Both neuropathies potentially may present in the same patients.

3.3.2.5 Diagnosis and assessment

Clinical evaluation is the common method for diagnosing NP in leprosy patients. It involves a series of systematic steps which include past and present history, a detailed description of pain distribution, quality and intensity of pain and a neurological examination with the emphasis on sensory testing (Jensen et al., 2001, Hansson, 2002). The diagnosis and assessment of NP in leprosy is discussed in detail in Chapter 5.

3.3.2.6 Treatment of neuropathic pain in leprosy

Amitriptyline for the treatment of neuropathic pain in leprosy

Overview of amitriptyline

Amitriptyline HCl is a tricyclic antidepressant drug, which possesses marked neurotrophic activity (Association, 2011). It was approved for depression by the Food and Drug Administration (FDA) in May 1983. Since then the drug has been widely and successfully used as a treatment for several conditions such as depression, nocturnal enuresis, migraine prophylaxis, and NP (Jang et al., 2009).

Amitriptyline has a well-documented efficacy on different types of NP. The drug dose is started at 10-25mg in the evening, and the dose is increased to adequate level of pain relief, with a maximum tolerated dose up to 150 mg per day. In addition, it is a known antidepressant drug and its effect on mood can be attained at lower doses. The amitriptyline dose for depression is started initially at 75mg daily in divided doses or as a single dose at bedtime escalated gradually as necessary to 200mg. The improvement in NP outcomes is independent of the effect of amitriptyline on mood (Max et al., 1987).

The anti-cholinergic adverse effects of amitriptyline include dry mouth, constipation, nausea, difficulty with micturition, sweating and cardiovascular effects (Association, 2011). These side effects are common in all tricyclic antidepressants drugs and can be reduced by starting with low dosages administered at bedtime.

Amitriptyline studies for the treatment of neuropathic pain

Previous studies on amitriptyline for the treatment of chronic NP have shown that a dose of 50-150mg is beneficial when used for treatment of painful neuropathy in a chronic disease (Max, 1987, Graff-Radford et al., 2000). These conditions include diabetic mellitus and post herpetic neuralgia. However, two studies found this drug to have no effect on HIV neuropathy compared with a placebo (Kieburtz et al., 1998, Shlay et al., 1998). Also, a similar study failed to find any effect of amitriptyline on chemotherapy induced neuropathic symptoms (Kautio et al., 2008). Appendix 53 shows various amitriptyline studies for the treatment of NP.

The results of the above studies were encouraging as it has been shown that amitriptyline was efficacious, and superior to placebo treatment, in treating NP caused by diabetes and post herpes infection. The median effective dose of amitriptyline in these studies was 75mg. Amitriptyline was not more effective than placebo in relieving pain in malignancy or chemotherapy induced neuropathy probably explained by low dose of 50 mg. In HIV neuropathy the results of amitriptyline have shown no significant pain relief. It is unknown whether this is explained by the underlying mechanism, because it also showed no effect in animal models (Phillips et al., 2010).

Although there are reports on the use of amitriptyline for the treatment of chronic pain in leprosy and clinicians often prescribe this drug and other antidepressants in treating NP, there are no data from controlled studies in well-defined groups of leprosy patients

that demonstrate efficacy and guide their use. A single unpublished abstract work evaluating the treatment of 49 patients with leprosy and paraesthesia in a randomised non-blinded comparative 8-week trial at an Indian hospital was conducted in 2006. The author found that both amitriptyline and gabapentin produce modest improvements of the condition (Bhat and Khanna, 2006).

3.3.3 Summary

- Neuropathic pain is being increasingly recognised among leprosy patients
- No standard methods for assessing chronic neuropathic pain in leprosy
- Patients with leprosy may have a higher prevalence of psychiatric problems, probably because of the chronicity of the disease, disability and stigma caused by neuropathy
- High prevalence and morbidity of neuropathic pain in treated leprosy patients warrant clinical trials to assess the efficacy of pain therapies for leprosy-associated neuropathic pain.

Chapter 4 Instruments for assessing sensory abnormalities, pain disorders and techniques for assessing the psychological impact of neuropathic pain

4.1 Introduction

This chapter provides an overview of the somatosensory system and the main instruments for assessing sensory abnormalities used in the study, namely; instruments for symptoms: pain questionnaires (DN4 and PainDETECT), and quality of life and psychological factors (BPI and GHQ-12 questionnaires); and instruments for clinical signs: quantitative sensory testing (QST).

4.2 Overview of the structure and function of the somatosensory system

4.2.1 Introduction

The nervous system is divided into the central nervous system (CNS) and the peripheral nervous system (PNS) (Figure 4.1). It integrates sensory information and controls motor and cognitive function. This section will focus on the somatosensory components, which are responsible for the sensations of light touch, vibration, temperature and pain.

Nerve fibres in the skin are initiated in the spinal cord and traverse through the dorsal root ganglia which host the cell bodies, into peripheral nerves (Figure 4.1). After entering the skin, the nerve fibres pass in nerve bundles to the superficial dermis. These are small sensory fibres that provide protective sensibility. It includes small myelinated fibres (Aδ) and unmyleinated axons. The latter, arranged in Remak bundles, is defined as a non-myelin forming Schwann cell and the unmyelinated C-fibre axons that it ensheathes. At the dermal-epidermal junction the smaller unmyelinated fibres penetrate into the epidermis, where individual epidermal nerve fibres emerge from the bundles and shed their collagen collar and Schwann cell sheath as they pierce the dermal-epidermal basement membrane. They penetrate through the epidermis to the stratum corneum, usually vertically, establishing free nerve endings (Griffin et al., 2001). In contrast the myelinated fibres tend to penetrate only into the dermis. Changes to these intra-epidermal nerve fibre densities (IENFD) are valuable in quantifying small fibre neuropathy.

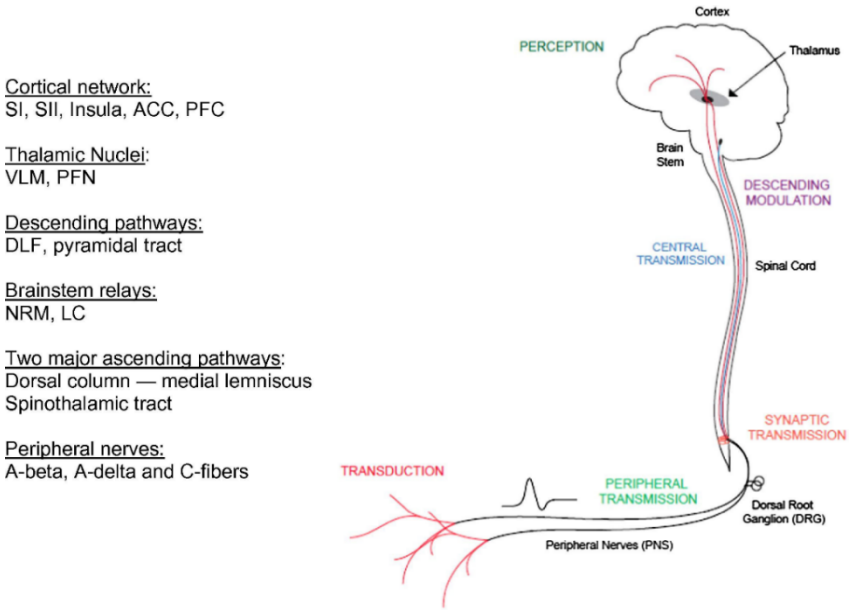

Figure 4.1. The somatosensory system

Picture modified from Backonja and colleagues (Backonja et al., 2013)

4.2.2 Types and functions of the peripheral nerve fibre

Two different methods are used to classify types of peripheral nerve fibres: letter and numerical classification (McMahon SB et al., 2013). The ABC classification is based on function, size and myelination of the fibres. Using size classification, the largest diameter fibres are classified as A. This group is further sub-divided into four groups; α, β, δ and γ. The number classification is based on conduction velocity I-IV in descending order of velocity. Table 4.1 shows the different types of peripheral nerve fibre and their classification. The table also shows the different modalities of somatosensory nerve fibre functions. The primary afferent fibres Aδ, Aβ and C, which transmit the initial stimulus from the periphery, are located in the skin. Aδ and C fibres are the main pain-mediating nerve fibre systems. Aα/β fibres are large diameter, myelinated and have fast conduction velocity (Barrett et al., 2010). They are normally activated by non-noxious mechanical stimuli such as touch, vibration and pressure. Following injury they have been shown to respond to mechanical stimuli and contribute to mechanical allodynia (Treede and Cole, 1993). Aδ fibres are medium diameter, myelinated fibres of intermediate conduction velocity (Barrett et al., 2010). They are normally activated by noxious stimuli and transmit the rapid phase of pain, which is sharp in nature. In contrast, C fibres are of small diameter, unmyelinated and have slow conduction

velocity (Barrett et al., 2010). They are normally activated by noxious stimuli responsible for secondary pain; burning, dull and aching pain (Craig, 2003). Different receptors related to C fibres have been described, including thermoreceptors which respond to warming and cooling, chemo specific nociceptors and low threshold mechanoreceptors which respond to pressure (Meyer et al., 2006). In addition to thermorreceptors, some C fibres respond to mechanical, heat, irritant chemical stimuli and itch also have been described (Meyer et al., 2006, Lynn et al., 1996). Some groups of Aδ and C fibres, known as 'silent nociceptors' may be insensitive to chemical or mechanical stimuli, but some sensitised following inflammation and then can be activated by mechanical stimuli. This may be the underlying mechanism for hyperalgesia (Xu et al., 2000). These fibres are thought to be important in inflammatory pain conditions and central sensitisation (Weidner et al., 1999). Damage to these fibres may also leads an ongoing pain and if this associated with sensory abnormalities the pain is defined as neuropathic pain (Jensen et al., 2011).

4.2.3 Somatosensory receptors

All the peripheral terminal branches of a primary axon form only one type of somatosensory receptor. Based on function, these sensory receptors can be divided into three groups: mechanoreceptors, thermoreceptors and nociceptors. The former contains ion channels that respond to stretching or changing in tension of the surrounding membrane. They mediate the sensations of light touch, pressure, vibration, flutter, limb position and movement. The second group has receptors for warm or cold stimuli. The third one is selective for different types of noxious stimuli such as thermal, mechanical, and chemical. These stimuli are those that can cause tissue damage.

Signals from these receptors are transmitted to the central nervous system (Table 4.1). Each sensory neurone in the peripheral has a cell body in the dorsal root ganglia of the spinal cord. These bipolar neurones have a long peripheral axon branch and a central axonal projection.

Following damage to somatosensory system, there may be a partial or complete loss of sensory functions, and the development of symptoms such as pain. This indicates that pain is a protective response preventing further damage to an affected area. For instance, injury to the sole of the foot leading to pain would cause the bearer to avoid putting further weight on the affected area until it was healed. Damage to this system

may also leads an ongoing pain and if this associated with sensory abnormalities the pain is defined as neuropathic pain (Jensen et al., 2011). This type of pain does not require any receptor stimulation and can be severe, chronic and intractable.

Table 4.1. Peripheral nerve fibre types and classification

Type of fibre	Diameter (micro-metres)	Conduction speed (m/s)	I-IV Class	Modality	Method of Assessment
A-α	8 – 13	44 -78	n/a	Efferent, motorneurone to muscle	n/a
A-δ	3 – 8	18 – 48	n/a	Efferent, motorneurone to muscle spindle	n/a
A-α	12 – 20	75 – 120	I	Afferent, limb, position and motion	-
A-β	6 – 12	30 – 75	II	Afferent, touch, pressure, vibration proprioception	MFs, JPS, brush, allodynia
A-δ	1 – 6	5 – 30	III	Afferent, fast pain, cold, crude touch	
B	1 – 3	3 – 15	n/a	Autonomic pre-ganglionic neurones	-
C	<1.5	0.5 – 2	IV	Afferent, slow pain, warm	Pinprick, hyperalgesia warm sensation, heat and cold pain

4.3 Instruments for assessing sensory and pain-related phenomena

A number of assessments tools are available for the identification of symptoms and clinical signs of pain-related sensory abnormalities. Symptoms including pain and psychological factors are assessed with a validated questionnaire. This is a list of purposely designed questions that captures the quality and intensity of pain-related sensory symptoms perceived by patients, i.e. patient-reported outcomes. Clinical examination, supplemented by additional diagnostic methods, is commonly used to

ascertain the clinical signs of the various sensory perturbations associated with nerve damage. These include quantitative sensory tests (QST), neurophysiological methods, microneurography and skin biopsy (Haanpaa et al., 2011b). QST is a psychophysical method that provides a comprehensive measure of the somatosensory functions. The perception thresholds to various thermal and mechanical sensory stimuli are accurately measured using the QST battery, but the outcome relies on the patient's subjective response. Neurophysiological methods, which include nerve conduction studies, somatosensory evoked potentials and laser-evoked potentials, are objective tests that assess function of large and small afferent fibres (Cruccu and Truini, 2009). Skin biopsy enables quantification of the number of intra-epidermal nerve fibres, which provides a measure of small fibre density (Griffin et al., 2001). Composite tools of symptoms screening questionnaires and diagnostic procedures are often used.

Neuropathic pain, which is defined as pain caused by a lesion or a disease of the somatosensory system, may be manifest in a variety of ways, depending on the location, severity and the underlying cause (Jensen et al., 2011).

The symptoms manifest in association with heterogeneous sensory disturbance range from sensory gain to sensory loss. For example, many patients with NP due to HIV neuropathy have loss of mechanical and vibration detection thresholds. Other "sensory gain" symptoms such as allodynia and hyperalgesia may have a variety of causes such as complex regional pain syndrome (CRPS), Trigeminal Neuralgia (TN) and Postherptic Neuralgia (PHN)(Maier et al., 2010). Analysis of somatosensory profile graphs may help in identifying the presence of sensory gain or sensory loss. However, this profiling and grouping of patients with sensory disturbance cannot be determined by clinical examination alone.

The ability to stratify patients by symptom, clinical signs and psychological state has greatly influenced the identification of NP. A mechanism based approach to NP treatment, guided by symptoms and sensory profiles, has been significantly enhanced by the use of different methods of assessing the pain-related sensory abnormalities. In the following sections, an overview is given of the standard tools that are currently available in existing NP clinical practice to determine whether these are valid for the purpose.

4.3.1 Pain scales and questionnaires for symptoms

Clinical investigators have long recognised the variety of pain experienced by patients, such as shooting, fearful descriptors of neurologic pain to the burning pain after peripheral nerve damage.

These symptoms, along with clinical examination, provide the key to diagnosis and may even suggest the course of treatment. In assessing such patients, it is important that the measure is: valid, reliable, reproducible and useful. I will now describe some instruments that have been validated and are reliable in assessing pain symptom.

4.3.1.1 Pain scores and scales

Pain intensity can be measured on Likert scales, Visual analogue scales (VAS), Verbal rating scales (VRS), or a combination of verbal and numerical rating (Gracely Pain Scale) (Haanpaa et al., 2011a). Verbal rating scales typically consist of a series of verbal pain descriptors ordered from least to most intense (no pain, mild, moderate, severe). The patient reads the list and chooses the one word that best describes the intensity of pain at that moment. A score of zero is assigned to the descriptor with the lowest rank; a score of 1 is assigned to the next lowest rank (McMahon SB et al., 2013).

The Likert numerical rating scale is the most frequently used scale for pain intensity (Farrar et al., 2001). It is recommended by the IASP for assessing pain intensity (Haanpaa et al., 2011a). Likert is an 11- point numerical scale ranging from "0" (no pain) to "10" (worst possible pain) (Farrar et al., 2001). The scale is validated and may be easier to use than the VAS (Dworkin et al., 2005). It is commonly used to assess treatment effect in chronic pain (Dworkin et al., 2005). Using this scale, patients are asked to describe the average intensity of pain by choosing the appropriate number between 0 and 10 in response to the question "tell me what number best represents the greatest pain you have had in the last week".

The other options for recording pain - the NRS and the VAS - are represented by a 10cm line, with one end representing no pain and the other representing worst pain; the patient is asked to mark a point on this line that represents their pain level, and this line is then measured to arrive at a numerical measurement (McMahon SB et al., 2013).

4.3.1.2 Pain questionnaires

To identify patients with sensory abnormalities and possible NP, no single symptom is found, but a combination of symptoms and signs. Several available screening tools are used, such as the PainDETECT Questionnaire (PD-Q), the Leeds assessment of neuropathic symptoms and signs (LANSS), the neuropathic pain questionnaire (NPQ), the McGill Pain Questionnaire (MPQ) and the Douleur Neuropathique en 4 Questions (DN4). These questionnaires are particularly recommended for non-specialists (Haanpaa et al., 2011a).

Pain Detect Questionnaire (PD-Q)

The PD-Q questionnaire is one of the most widely used questionnaires for recording somatosensory systems of NP. It was designed by Thomas R. Tolle in 2006 based on the German Research Network on Neuropathic Pain data base, and takes into account a large number of descriptors of pain (Freynhagen et al., 2006a). The PD-Q comprises nine questions regarding the severity, course, quality and nature of the patient's pain and the specific NP symptoms. Please see the Methods section for an illustration of the PD-Q score described here.

Leeds assessment of neuropathic symptoms and signs (LANSS)

The Leeds assessment of neuropathic symptoms and signs questionnaire was designed as a scale measure for identifying patients whose pain is dominated by neuropathic mechanisms. It was developed and validated in two different populations of chronic pain patients by Michael Bennett in 1999 (Bennett, 2001). The scale consists of seven items measuring five symptoms and two aspects of sensory dysfunction. Each item requires yes or no responses and the scores is compared with the cut-off values; a score of 12 or more suggests pain of predominately neuropathic origin (Bennett et al., 2005).

Neuropathic Symptom Inventory (NPSI)

Neuropathic Symptom Inventory (NPSI) is a validated questionnaire designed to evaluate the different symptoms of NP (Bouhassira et al., 2004, Crawford et al., 2008). It was validated in 176 consecutive patients with NP in France and Belgium (Bouhassira et al., 2004). It includes 10 items (plus two temporal items), quantified on a (0–10) numerical scale, that allow discrimination and quantification of five distinct clinical

relevant dimensions of NP syndromes and that are sensitive to treatment (Bouhassira et al., 2004, Crawford et al., 2008).

McGill Pain Questionnaire (MPQ)

The McGill pain questionnaire consists of three major classes of word descriptors (sensory, affective and evaluative) that are used by patients to specify subjective pain experience. It was designed by Roland Melzak in 1975, but later he recognised that the instrument was too long for use in clinical trials and introduced a short-form McGill pain questionnaire (SF-MPQ) (Melzack, 1975, Melzack, 1987). The SF-MPQ consists of 15 descriptors (11 sensory and 4 affective), along with a visual analogue scale for pain intensity. The sensory and affective descriptors are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. A maximum score of 55 indicate severe symptoms (Melzack, 1987).

Douleur Neuropathique en 4 Questionnaire (DN4)

The DN4 questionnaire is a widely used questionnaire in NP clinical practice. It was developed in France in 160 patients with either NP or nociceptive pain. It has been translated into several languages (Bouhassira et al., 2005). Please see the use of DN4 and the Methods section for an illustration of the score described here.

4.3.2 Clinical signs assessment

The assessment of clinical signs in patients with sensory abnormalities and pain is essential, because it helps the diagnosis and classification of patients. A range of methods from simple bedside examination to more sophisticated neurological techniques such as nerve conduction study and QST, are used to assess sensory abnormalities (Haanpaa et al., 2011a).

There are two definitive steps the clinician can use when examining patients for the diagnosis of the pain-related sensory abnormalities. Firstly to confirm that some form of damage to the somatosensory system has occurred, without this the diagnosis is impossible. The sensory findings should be neuroanatomically logical and compatible with a definitive lesion site (Treede et al., 2008). Secondly, to determine that any pain is indeed neuropathic, this because the occurrence of nerve damage does not necessarily follow that any pain is neuropathic in origin.

For the purposes of this study, an ideal test for an individual patient should:

i. provide specific information about pathophysiological nature of the mechanisms of disease when disease processes are taking place
ii. have sensitivity and specificity and positive predictive accuracy
iii. be interpretable within the context of clinical practice
iv. provide information about where the pathophysiology of pain takes place, i.e., the location of a lesion for neuropathic pain.

4.3.2.1 Clinical examination

Clinical examination is of paramount importance in assessing neurological disorder. It involves sensory, motor and autonomic signs (Hansson et al., 2001). The examination involves a series of systematic steps, including past and present history, a detailed description of pain distribution, quality and intensity of pain and a neurological examination with the emphasis on sensory testing (Jensen et al., 2001, Hansson, 2002).

Standard bedside neurological sensory testing

Neurological examination involves assessment of muscle tone and power, tendon reflexes and sensory examination. Sensory examination is critical in providing evidence necessary for the diagnosis of NP (Haanpaa et al., 2011b). Sensory abnormalities are mapped out using cotton wool for tactile sensation (Aβ fibres), pin-prick sensation with a small pin or cocktail-stick (Aδ fibres), gross temperature sensation with warm or cool objects (warm – C-fibres, cool – Aδ fibres) and vibration sense with a tuning fork (128Hz) (Aβ fibres) (Cruccu et al., 2004). This examination is performed to determine the presence of suspected sensory loss or gain of function that are associated with NP and at the same time to document the presence of allodynia, hyperalgesia and hyperpathia as hallmarks of NP.

However, clinical examination of a patient with pain which aims to assess the somatosensory system and may provide supporting evidence for altered function of the nervous system, can never prove any pain to be of neuropathic origin. In patients with a possible NP condition, the sensory dysfunction is coordinated by somatosensory abnormalities (Treede et al., 2008), and cannot be determined by clinical examination alone. For instance, if afferent fibres from the skin are affected, sensory abnormalities can be detected using simple bedside tools for supra threshold stimulation (Haanpaa et

al., 2011a). The light touch of cotton wool and the vibration stimulus of the tuning fork, which activate large A-beta fibres, as well as the dorsal columns and their thalamo-cortical extension, are used to assess the sensitivity to touch and vibration, respectively. Other test stimuli, such as cold and warm metallic rollers and pins could be used to assess thermal and pain sensation and hence activate different types of A-delta and C-fibres and spino-thalamo-cortical system. But, despite its clinical significance and identification of the neuroanatomical distribution of symptoms, pain in an area with sensory dysfunction is not to be associated with NP since other types of pain may be expressed in such an area (Hansson, P. and Lindblom 1993). A study by Freynhagen et al, reported that 5 out of 12 patients classified with painful radiculopathy had normal sensory function on bedside examination (Freynhagen et al., 2008). The diagnostic prerequisite in NP conditions, i.e. sensory abnormalities in the distribution of the affected nervous structure, is not identified by bedside examination. Given that sensory abnormalities are not confined only to NP states, the outcome of sensibility examinations, especially by clinicians lacking experience in detailed sensory examination, could be a source of confusion and possible diagnostic errors. Another drawback of these tests is that they are often not sensitive enough to show longitudinal change. Therefore, the characteristics of the pain need further assessment to allow for its classification. Quantitative Sensory Testing of perception thresholds in the above mentioned somatosensory channels could be used to complement the assessment of somatosensory abnormalities at bedside examination (Leffler and Hansson, 2008a).

4.3.2.2 Conventional electrophysiological studies

Nerve conduction studies

Nerve conduction study is considered as an extension of the patient history and clinical examination. It comprises an electophysiological test that assesses the motor and sensory function of the nerve. These are obtained by stimulating the nerve and a response is recorded directly from the nerve or from a muscle innervated by the tested nerve. In this way, NCS are able to detect and differentiate general from focal nerve abnormalities, type of neuropathy (demyelinating, axonal and conduction block), type of involved axons (motor, sensory and autonomic) and localisation (distal, proximal and entrapment site).

While NCS is a relatively non-invasive method, its main limitation is that it cannot be used to assess small fibre neuropathy or the function of nociceptive pathways (Cruccu et al., 2004). In such conditions, special methods are used such as testing thermal thresholds and quantitative mechanical testing. Quantitative sensory testing, in general, quantifies the functional status of the peripheral nervous system by nerve fibres of various sizes and by central pathways. The QST is most useful in the diagnosis of small fibre neuropathy.

4.3.2.3 Quantitative measurements

"Quantitative measurement" describes tests where the intensity and characteristics of the test stimulus are well controlled and reproducible, and the detection threshold is determined in parametric units that can be compared to established normal values. Stimuli are usually delivered in accordance with specific testing algorithms, and the subject's response is predefined according to standardised instructions. A number of instruments and validated tools for quantitative assessment of neuropathy have been established, ranging from simple instruments such as monofilaments to more sophisticated computer-aided systems such as quantitative sensory testing (Valk et al., 1997, Rolke et al., 2006a).

Semmes-Weinstein Monofilaments (MFs)

Monofilaments, which were originally made from horsehair, have been developed over time from simple, natural materials to synthetic devices. In the late 19th century, the horsehair was used as a method to quantify pain induced by punctate stimulation (Weinstein, 1968). Von Frey used various thicknesses of horsehair to determine the thresholds of touch recognition. Later this technique was refined and amended by others, such as Semmes and Weinstein in the 1960s. They developed a standard set of nylon monofilaments that exert predefined forces onto the skin (Semmes et al., 1960). Now, however, a more field friendly method has been introduced; Von Frey hairs made from optical glass. A testing kit comprises a standard set of glass filaments which are widely used in clinical practice by neurologists for assessing sensory abnormalities.

Semmes-Weinstein Monofilaments are a standard set of six coloured monofilaments ranging from 5mg, 200mg, 2g, 4g, 10g and 300g (Bell-Krotoski, 1990). When used for the hand specifically the stimulus was found to have a cut off 200mg, but for the foot the cut off was found to be 2g. Semmes-Weinstein Monofilaments were developed to

detect sensory loss in leprosy programmes but have been widely used by other programmes as a diagnostic technique for routine clinical and research purposes (Jamison, 1969). Their use has led to a significant improvement in screening diabetic patients; for example inability to feel a 10gm monofilament is recognised as a risk factor for ulcer (Birke and Sims, 1986).

Both MFs and VMT using a modified MRC scale are suitable and reliable tools for measuring nerve function impairment in a resource-limited setting (Brandsma et al., 2014). In a cohort study of 357 untreated multibacillary patients from India between 2001 and 2005, which assessed the sensitivity and specificity of MFs and VMT using nerve conduction study as gold standard for detecting nerve function impairment, the authors noted that both methods have good inter-tester reliability and reducibility and good specificity of more than 80%. The sensitivity of both tests in detecting nerve involvement was low, less than 40% (Khambati et al., 2009).

Quantitative Sensory Testing (QST)

Quantitative sensory testing is defined by the Peripheral Neuropathy Association as the technique(s) used to measure the intensity of stimuli needed to produce specific sensory perceptions (PNA., 1993). For more details on QST please, see section 4.6.

4.3.3 Skin biopsy

Intra Epidermal Nerve Fibre Density (IENFD)

Intra-epidermal nerve fibre density is a technique for measuring the endings of small peripheral nerve fibres in the epidermis (Lauria et al., 2005). It has been used for identifying the presence of nerve damage (Lauria et al., 2005). Both myelinated (Aβ and Aδ) and unmyelinated (C) nerve fibres can be assessed (Devigili et al., 2008). These nerve fibres along with sweat glands, blood vessel, epidermis cells and superficial dermis are investigated using skin biopsy. Skin biopsy is a safe and reliable technique used to investigate IENF (Lauria et al., 2005). Nerve fibres are immunostained by antibodies against PGP 9.5 using either immunohistochemistry or immunofluorescence, and fixed by 2% paraformaldehyde-lysine-periodate (2% PLP) or Zamboni's solution. Fibres crossing the dermal epidermal junction are counted and quantified to confirm the clinical diagnosis of neuropathy (Lauria et al., 2005). The density is calculated in at least three sections as the number of IENF per length of the section (IENF/mm) (Lauria et

al., 2005). Devigili et al. who screened 486 Italian patients and collected 124 patients with neuropathy found 67 patients had small fibre neuropathy using skin biopsy (Devigili et al., 2008). The author noted that quantification of IENF density in skin biopsy for diagnosis of neuropathy showed a diagnostic efficiency of 88.4% (Devigili et al., 2008).

European Federation of Neurological Societies (EFNS) has recommended the use of skin biopsy with linear quantification of IENF density as a reliable and efficient technique to confirm the clinical diagnosis of small fibre neuropathy (Lauria et al., 2010).

Previous studies on IENF, pain and QST parameters

As peripheral neuropathic pain abnormal sensations may be related to dysfunction of Aβ, Aδ or C- fibres, IENFD may be correlated with pain. Studies have identified IENFD, pain and QST parameters correlation in post herpetic neuralgia, Diabetics and HIV pain neuropathy (Zhou et al., 2007, Sorensen et al., 2006, Devigili et al., 2008, Loseth et al., 2008, Vlckova-Moravcova et al., 2008a).

In patients with post herpetic neuralgia, the number of intra-epidermal fibres is lower in the biopsies taken from pain area compared to the control site. (Oaklander, 2001) Sorensen et al. 2006, who studied the correlation between IENF density and pain in 38 patients with diabetes using skin punch biopsy, noted that IENF density was significantly lower in the biopsies taken from those with pain compared with those without pain (Sorensen et al., 2006). A similar conclusion, greater fibre loss correlated with more severe pain, was obtained also by Zhou et al. 2007, who studied the relationship between IENF density and pain in 101 patients with HIV neuropathy (Zhou et al., 2007).

Other studies have shown the correlation between IENFD and QST parameters. Studies carried by Devigili et al. 2008, Loseth et al. 2008 and Moravcova et al. 2008, who assessed patients with sensory neuropathy to demonstrate the relationship between the IENF density and QST, have shown an inverse correlation between IENFD and thermal threshold, a significant correlation between IENFD and QST parameters and IENFD correlated with warm detection threshold on QST, respectively (Devigili et al., 2008, Loseth et al., 2008, Vlckova-Moravcova et al., 2008a).

4.4 Techniques for assessing psychological impact of neuropathic pain

4.4.1 Introduction:

Measurement of subjective experience, such as pain, inevitably relies heavily on self-report, which is valuable but its impact is difficult to determine. The complexity of pain phenomena in an area of sensory loss, also known as NP, is a factor that hinders its management and control. For instance, pain intensity and interference with function can have a marked impact upon daily routine, affective and motivational states, social relationships, sleep and economic factors. This indicates the importance of evaluating the relationship between the intensity of pain, disability and depression with the quality of life of individuals with chronic pain. Instruments, such as quality of life questionnaires are used to deepen knowledge of the perceived pain and thus enable an evaluation of effectiveness of the treatment used. I will now describe the instruments that have been validated and are reliable in assessing psychological impact of NP.

4.4.2 Quality of life and psychological state questionnaires literature review

Health is defined by the World Health Organization (WHO) as a state of complete physical, mental and social well-being and not merely the absence of diseases and infirmity (WHO, 1946).

4.4.2.1 General Health Questionnaires (GHQs)

The GHQs is the most widely used standardised self-completion measure of psychological well-being globally. It was developed by Godberg in the 1970s for use in primary practice settings (Goldberg, 1972). Its main focus is to assess psychological components of ill health, in particular screening for common psychiatric disorders such as anxiety and depression.

Content: the initial version of the GHQ contains 60-items which measure common mental health problems/domains of depression, anxiety, somatic symptoms and social withdrawal dimensions. Shorter versions of 30, 28, 20 and 12-items have also been developed. The 12-items version, is in fact, as efficient as the 30-items version as a case detector (Bowling, 2005). The questions assess psychological well-being state over the past few weeks, including:

Have you recently:

- Been able to concentrate on whatever you are doing
- Lost much sleep over worry
- Felt that you are playing a useful part in things
- Felt capable of making decisions about things
- Felt constantly under strain
- Felt you couldn't overcome your difficulties
- Been able to enjoy your normal day to day activities
- Been able to face up to your problems
- Been feeling unhappy and depressed
- Been losing confidence in yourself
- Been thinking of yourself as a worthless person
- Been feeling reasonably happy, all things considered

Scoring: Detailed instructions on the rating, coding and scoring procedures are described in Chapter 6.

The GHQ-12 is one of the most commonly used screening tool for mental health assessment in community settings (Furukawa and Goldberg, 1999), and has been validated in other mental disorders around the world (Goldberg and Williams, 1988, Goldberg et al., 1997). Particularly relevant to this study is its validation both in India and leprosy (Gautam et al., 1987, Verma and Gautam, 1994, Senturk et al., 2007, Jindal et al., 2013, Bandyopadhyay et al., 1988, Sriram et al., 1989). Further, The GHQ-12 has been demonstrated to be a valid screening in patients with leprosy NP (Lasry-Levy et al., 2011, Haroun et al., 2012)

4.4.2.2 Brief Pain Inventory (BPI)

The short form of the BPI is constructed of nine self-report items and measures two main domains: the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension). It is probably the most widely used measurement scale for clinical pain (Cleeland and Ryan, 1994), and its validity comes from several studies of cancer pain and pain of other diseases. It also demonstrates good test-retest item correlations over short time intervals (Daut et al., 1983). Patients rate their pain on a 11 – point numerical scale for the average, worst and current pain in the preceding 24 hours. The second part of the questionnaire ask patients to indicate the extent to which

pain interferes, on a scale of 0 ('pain has not interfered') to 10 ('pain completely interfered'), with the daily activities addressed by the subscales (e.g. general activity, mood, mobility, normal work, relations with others, sleep, enjoyment of life, self-care, recreational activities and social activities).

4.5 The use of DN4 and PD-Q questionnaires for assessing NP

This section describes the items and structure of the main questionnaires, namely; DN4 and PD-Q, used for the screening and measurement of NP in this study, as well as their potential value and limitations.

4.5.1 Overview:

DN4 consists of 10 items: seven interview items and three clinical signs. The interview items are related to the quality of pain (burning, painful cold, electric shocks) and its association to abnormal sensation (tingling, pins and needles, numbness, itching). The clinical signs are related to sensory examination in the most affected area (touch hypoesthesia, pinprick hypoesthesia, tactile allodynia) (Bouhassira et al., 2005). Items are grouped in four sections; each one requires yes or no responses to questions on the quality of pain or clinical signs. The DN4 rating and scoring is simple; a score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of the 10 items and the cut-off value for the diagnosis neuropathic pain is a total score of 4 out of 10 (Bouhassira et al., 2005).

DN4 is often compared to other screening tools for neuropathic pain (LANSS, NPQ, PD-Q); however some differences should be recognised. In particular, these tools require no clinical examination. In contrast, the full versions of DN4 and LANSS are clinician-administered questionnaires. In these screening tools the clinical signs are tested by the examiner. Short versions of DN4 (DN4-Interview) and LANSS (S-LANSS), which omit the items related to sensory examination, have been developed for use as self-administered questionnaires (Bouhassira et al., 2008, Bennett et al., 2005). Another relevant difference from screening tools is the method of validation. The DN4 validation study included patients with either peripheral or central NP, whereas other studies included only patients with peripheral NP. In addition, the DN4 validation study included only patients with pure NP, while other studies included patients with mixed pain (PD-Q) or complex regional syndrome type 1 (LANSS). The number of items,

their phrasing and the scoring methods also differ between DN4 and the other screening tools.

Despite the methodological differences between DN4 and other questionnaires mentioned above, it appears that most of the DN4 items are also present in the final versions of these questionnaires. For instance, the DN4 pain descriptors "hot or burning," "shooting or electric shock," "numbness," "tingling," pins and needles" and items related to abnormal clinical signs "allodynia" are used in all the other questionnaires. This may suggest that DN4 has the main common symptoms of NP conditions.

4.5.2 Limitations of the DN4 and PD-Q questionnaires

As will be discussed in Chapter 5, DN4 has become one of the most common screening questionnaires for NP; in particular for the identification of possible NP among leprosy patients. As discussed earlier, no single symptom is diagnostic of NP, but combinations of certain symptoms, pain descriptors and clinical findings increase the possibility of a NP condition. Both DN4 and PD-Q attempt to provide an accurate selection of patients with symptoms and signs suggestive of NP. However, as in other questionnaires, the following issues have been identified as drawbacks:

First, DN4 has limited diagnostic value in patients with widespread pain. It has been validated in patients with pain at a single body location. Their ability to distinguish between pain and pain-free neuropathy is reliable only when applied to a limited painful area. A study carried by Attal and colleagues, which investigated the neuropathic components of chronic low back pain in 132 patients with and without lower limb pain using the DN4 questionnaire, showed that DN4 can be used to assess patients with up to three pain locations (Attal et al., 2011b). Hence, DN4 is less practical in patients with multiple pain locations, i.e. more than three. Secondly, DN4 is increasingly used for NP epidemiological studies in different settings, but validation studies for this purpose are necessary. Furthermore, NP screening questionnaires fail to identify 10 to 20% of patients with clinician diagnosed NP (Haanpaa et al., 2011a). This implies that screening questionnaires cannot replace clinical judgment, but may play role in guidance for further diagnostic evaluation and pain management. Another limitation of the DN4 questionnaire is that it provides no information about the relationship between symptoms and lesions or disease mechanism. This is illustrated by Rasmussen et.al, in a

study that compared verbal pain description and detailed sensory testing using the short form of McGill pain questionnaire (Rasmussen et al., 2004). The authors examined 214 patients with suspected chronic NP of moderate to severe intensity. They proposed clinical criteria for NP based on pain aetiology and presence of pain sensory loss, and labelled patients as having "unlikely", "possible" and "definite" NP. The authors found no differences in verbal descriptions across the groups. The identification of NP conditions may require a further clinical examination, together with imaging, laboratory, or electrophysiological tests in some cases (Baron et al., 2010a, Haanpaa et al., 2011a, Haanpaa et al., 2009). Finally, PD-Q has limited applicability for assessment of the effects of treatment.

4.6 The use of QST methods for assessing sensory abnormalities and NP

4.6.1 Introduction

This section explores the background information behind quantitative sensory testing measurement of sensory function, the basic principles of QST, the type of information obtained and their potential clinical utility as an aid to the diagnosis of NP. There are several protocols for QST and this will be discussed further in section 5.2.2 under available protocols for QST. A comprehensive overview of the detailed parameters and methods of DFNS-QST protocol will be provided in Chapter 6.

4.6.2 History and background

Quantitative sensory testing (QST) in medicine has roots in quantification and non-invasive testing and the first descriptions of the potential of QST as a standard evaluation procedures took place in the 1970s. A landmark pioneering publication by Fruhstorfer (Fruhstorfer et al., 1976) described the use of QST for thermal thresholds that may detect preclinical diabetic neuropathy. Fruhstorfer's group went on to develop a quantitative technique for the examination of thermal sensibility and, in parallel with other researchers across the world, developed a method for quantitative thermal thresholds in the late 1970s. At this early stage, the main advantage of the quantification technique was that its ease of use enabled it to be employed routinely and repeatedly in patients with symptoms of, or the potential, for neurologic damage or disease. Since then, there has been increasing interest in using QST to give insights into the underlying pathophysiological mechanisms of pain. The next break through was the development

of various quantitative methods for assessing sensory abnormalities, such as Von Frey hairs for touch, which enable the clinician to assess other modalities of sensory abnormalities, rather than just using a selected thermal test. A major improvement in quantitative sensory testing quality arrived with the development of electronic devices in the late 1980s and early 1990s. Table 4.2 shows the devices cleared by the Food and Drug Administration (FDA) in the 1980s and 2000s. Despite the advantages of being non-invasive, non-interventional techniques to complement standard neurological bedside examination, in order to help detect and quantify positive and negative sensory phenomena, there was no standardised QST testing procedure. For instance, there was no consensus regarding which specific QST device or algorithm should be used preferentially. This showed the growing need to develop standardised QST protocols. In recent years, the German Research Network on Neuropathic Pain-DFNS has developed a standardised and comprehensive QST protocol (Rolke et al., 2006a).

The emergence of DFNS-QST as a new and comprehensive protocol for quantifying somatosensory changes in human skin and even pain-related phenomena has made it the technique of choice for assessing diseases of the central and peripheral nervous system. The DFNS-QST battery consists of seven tests measuring 13 parameters, including various types of mechanical and thermal detection and pain thresholds for the hand, foot and face. The QST protocol was implemented in 180 healthy volunteers, thus providing a complete profile of sensory function (gender, age and location matched) and normative data that can be used as reference values for statistical analysis in studies on patients with NP (Rolke et al., 2006a). By affording such accurate measurement of sensory loss and gain, as well as psychophysical responses, DFNS-QST offers a high degree of detailed and precise information in the clinical diagnosis domain.

Table 4.2. Devices cleared for marketing by the FDA (1980-2003)

Year	Product	Comments
1987	Thermal Threshold Tester (TTT)	Teca, Inc.
1992	CASE IV Computer Aided Sensory Evaluator	Vibration & thermal threshold testing
1993	Thermal Sensory Analyzer (TSA)	Medoc Corporation
1994	Nk Pressure-Specified Sensory Device	NK Biotechnical Corporation

1994	Neurometer	Current Perception Threshold
1994	Pressure-Specified Sensory Device	Sensory Management Services LLC
1997	Medi-Dx 7000	Neuro Diagnostic Associates
2003	Vibration Perception Threshold (VPT) meter	Xilas Medical

4.6.3 Literature review of QST

In this section, I describe the basic principles and information behind QST. I review the different methods of stimulation that are currently available and provide an overview of the methods used by the DFNS. For the purpose of the current study, the DFNS-QST protocol will be the main protocol for QST.

4.6.4 Overview of the QST principle

QST is a non-invasive, sophisticated clinical examination of the sensory nervous system, whereby the perception thresholds to various thermal and mechanical sensory stimuli are accurately measured using the QST battery. The thermal testing modality assesses small myelinated (A-δ fibre) and unmyelinated (C-fibre) sensory nerve function, whereas the mechanical testing (light touch and vibration) evaluates the large myelinated A-α and A-β sensory fibres (Vinik et al., 1995). The pain modality, heat-pain and cold-pain threshold tests have been found to document increased pain sensitivity (hyperalgesia, allodynia and hyperpathia) (Verdugo and Ochoa, 1992). Others, such as mechanical pain and pressure pain have been used to document hyperalgesia (dynamic and static) and pain sensitivity (cutaneous and deep), respectively (Ochoa and Yarnitsky, 1993, Treede et al., 2002). Therefore, QST and in particular DFNS-QST, can study large myelinated, small myelinated and unmyelinated fibres in addition to documenting sensory gain and loss (hyperalgesia and hypoesthesia).

4.6.5 QST algorithms

A number of algorithms of testing and finding thresholds are used to quantify the sensory thresholds and pain-related phenomena in clinical practice. The test should yeilded accurate and reproducible results within a reasonable amount of time. Tests for pain sensation have the additional requirement of minimizing the number of stimuli that

are unpleasant to the patient. In QST, the method of limits and the method of levels are the most common algorithms used. This makes QST reasonably reproducible over the course of several days to a week (Heldestad et al., 2010). However, describing an algorithm in these terms does not in itself ensure that a particular standard or adequate algorithm is being used. A number of issues should be taken into consideration for any QST algorithm.

Factors influencing QST algorithm:

- Type of instrument
- Room temperature and humidity
- Site of stimulus
- Patient related factors: age, gender, cooperation and motivation
- Availability of standardised protocol.

The method of limits and the method of levels – the two common algorithms for pain threshold - are described in more detail. Others, such as tolerance, magnitude estimation of supra-threshold pain intensity and summation are excluded from the present review.

Method of limits: is one of the most commonly used algorithms for quantitative sensory testing (Figure 4.2). The threshold is determined with ramped stimuli that are stopped immediately when the subject presses a button. Two types of ramp stimuli are used: the ascending ramp and the descending ramp. In the former, the intensity of the stimulus is gradually increased until the subject perceives the stimulus as painful; the so-called appearance threshold. Another, less common, approach is the determination of a disappearance threshold, by decreasing the stimulus intensity until it is no longer detected. Thermal and vibratory thresholds are frequently assessed with this method (Verdugo and Ochoa, 1992, Chong and Cros, 2004). The advantage of this algorithm is that pain threshold can be determined very quickly (Dotson, 1997). Thus the chance that fatigue, loss of motivation, inattention and malingering will occur is minimal.

The feedback mechanism, however, is the main disadvantage of the method of limits. The subject's reaction time is the period between processing the information and the subject's indication of a response. For example, a subject needs to perceive the stimulus, process the information and generate an action to indicate a response. This may lead to an overestimation of the pain threshold. The extent of overestimation of the threshold

depends on the rate of stimulus change, i.e., the slope of the ramp (Dyck et al., 1990, Shy et al., 2003, Chong and Cros, 2004, Hansson et al., 2007).

Method of levels: is an algorithm method that obtains results by applying a series of predefined stimuli to the skin in ascending or descending order (Figure 4.2). The stimulus has a defined intensity and duration and the subject has to choose whether or not the stimulus is felt after each trial. Hence, it is also referred to as "forced choice" algorithm (Shy et al., 2003).

While the method of levels does not depend on reaction time, its main limitation is that it cannot be used frequently. The method of levels is generally more time-consuming and may subsequently lead to boredom and inattention (Hansson et al., 2007).

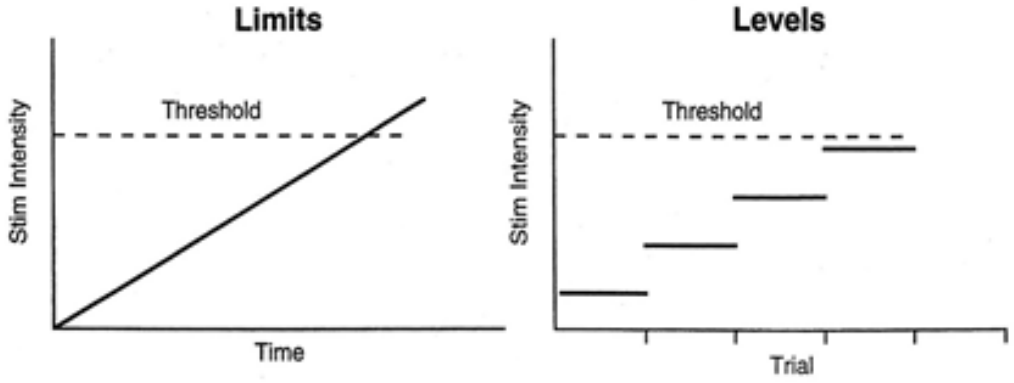

Figure 4.2. Summary of the methods used for QST

4.6.6 QST instruments

Detailed descriptions of the thermal and mechanical instruments are described in Chapter 6.

4.6.7 QST and standard bedside neurologic sensory testing compared

While the focus of this study is the profiling and stratification of leprosy patients, it is useful to make a comparison, in this preliminary chapter, of the known advantages and disadvantages of the validated techniques. I have summarised the practicalities of the QST compared to other methods in Table 4.3 and Table 4.4.

Table 4.3. QST and standard bedside neurologic sensory testing

	Quantitative Sensory Testing	**Standard bedside sensory testing**
Advantages	○ Stimuli delivered in accordance with specific testing algorithms ○ Greater precision ○ Potential possibility of diagnosis of sensory neuropathy (Shy et al., 2003, Chong and Cros, 2004) ○ Possible to follow up	○ Highly reproducible (Bouhassira et al., 2005) ○ Generates and ranks other types of pain as matter of differential diagnosis ○ Answers the question where on the somatosensory system is the pathology that generates neuropathic pain ○ Can distinguish between pain and pain-free condition (Rasmussen et al., 2004) ○ More sensitive than QST
Disadvantages	○ Time-consuming ○ Lack standardization ○ Subjective	○ Stimuli are not calibrated ○ Not able to prove any pain to be neuropathic origin

Table 4.4. QST and conventional electrophysiological techniques

	Quantitative Sensory Testing (QST) (Cruccu et al., 2004)	**Conventional electrophysiological techniques (NCS)**
Advantages	○ Psycho-physical	○ Does not require responses from the subject ○ No active cooperation required ○ Useful to localise the nerve lesion, its severity and to suggest prognosis ○ Training required for investigators but not for subjects ○ Published normative data and available data from most electro-physiological laboratories ○ Objective
Disadvantages	○ Requires a response from the subject, so is subjective and not objective ○ Standardisation ○ Time-consuming ○ High cost ○ Lacks reproducibility (Bird et al., 2006)	○ Tests only large fibres

*cited in (Backonja et al., 2013)

4.7 Previous studies on painful and painless neuropathy using QST

Several studies have considered neuropathy and pain using QST, (Table 4.5). The main findings of these studies were encouraging as it appeared that QST parameters may

show distinct changes in patients with painful neuropathy compared to patients with pain-free neuropathy.

Vrethem et al. measured the different responses to the panel of stimuli used in the QST in 55 diabetic patients, with neuropathy, in Sweden. The study showed that touch was more affected in patients with painful neuropathy compared with patients with painless neuropathy; otherwise, there were no differences between the patient groups (Vrethem et al., 2002). In HIV-related neuropathy, Martin et al. 2003 examined 36 HIV infected patients with painful (20 patients) and non-painful (16 patients) sensory neuropathy assessed by clinical, quantitative thermal testing and nerve conduction examination. Control reference data were obtained from 49 healthy participants with a corresponding age and sex match. The authors showed that patients with painful neuropathy had a significantly lower cold pain threshold than healthy controls which demonstrates impairment of C-fibres function (Martin et al., 2003). A similar conclusion, low cold detection threshold associated with HIV neuropathy compared to healthy controls, was also obtained by Simpson et al. 2002, who studied a cohort of 270 HIV patients from the United States (Simpson et al., 2002). In contrast, Ulf et al. 2002, who assessed the patterns of sensory changes caused by different conditions using the QST parameters in 30 patients with dysaesthesia and 15 controls in Germany, noted no association of any parameter obtained by QST with a particular disease (Baumgartner et al., 2002). In a QST profile study of 66 HIV infected participants, Phillips and colleagues (Phillips et al., 2014), reported no differences in regard to thermal and mechanical perception thresholds between painful and non-painful sides of denervated skin.

Despite the differences in assessing sensory changes caused by different conditions in these studies, QST may help to identify the sensory modalities mediated by different nerve fibres. In diseases such as PHN and traumatic lesions QST parameters were found to differentiate between patients with and without pain, whereas in DM and HIV neuropathy the finding were not generalised. Overall, the findings emphasise the importance of sensory profiles of patients who presented with neuropathy and pain, which might help in grouping patients according to the changes of the sensory patterns identified by QST.

Table 4.5. QST studies on painful neuropathy and painless neuropathy

Authors, year, country	Purpose of the study	Study population, N	Controls	Intervention / test	Main findings
Vrethem et al. (Vrethem et al., 2002) Sweden	To study pain characteristics in diabetic patients	55 patients: painful neuropathy 37, painless neuropathy 18	Healthy controls: 14 and non-DM neuropathy: 18	Clinical, neurophysiology and QST	there were no differences between the patient groups, except for touch ($p = 0.02$)
Martin et al. (Martin et al., 2003) Sweden	To investigate sensory profile in HIV patients	36 AIDS patients: 20 painful, 16 non painful	Healthy controls: 49 participants	Clinical, QST and NCS	Warm Hypothaethesia ($p =0.06$) and CPT ($p =0.03$) gain greater in painful group
Simpson et al. (Simpson et al., 2002) United States	To investigate HIV associated neuropathy	236 patients with HIV neuropathy nested from a cohort of 270	No controls	QST	CDT associated with pain in HIV neuropathy
Fitzek et al. (Fitzek et al., 2001) Germany	To identify clinical predictors in patients with pain	12 patients with dorso lateral medullary infarction	No controls	Thermal testing and MRI	Facial pain predicted by loss of pinprick heat/cold pain, TSL
Finnerup et al. (Finnerup et al., 2003) Denmark	To investigate NP mechanism	40 patients with SCI: painful 20, pain free 20	Healthy controls: 20 participants	Clinical, QST and somatosensory evoke potentials	At lesion level hyperalgesia differs ($p =0.03$)
Ulf et al. (Baumgartner et al., 2002) Germany	To assess underlying mechanism of NP	Patients with dysaesthesia: 30	Healthy controls: 15 participants	MDT, S/R (stimulus/response) functions	No association of QST parameters in a particular disease
Phillip (Phillips et al., 2014), UK	To assess sensory profile in HIV patients	HIV-SN: 38 HIV-no SN 28 patients	Healthy controls: 66 participants	Clinical, QST, NCS, IENFD	No single QST parameters were different between the groups

4.8 Chapter summary

This chapter summarised neuropathic pain and the methods, particularly profiling methods, used to aid in its diagnosis and impact. Only two of the profiling methods discussed have the capacity of adding somatosensory profiling measurements: QST and skin biopsy. While QST techniques are well established in term of quantification of sensory profile, they are often limited by its applicability in limited resource setting. QST techniques have the advantage of being able to test the entire sensory axis from receptors to brain. However, as will be outlined in Chapter 5, the use of QST techniques to quantify the peripheral sensory system has not yet been fully investigated in leprosy.

Chapter 5 The clinical problem and aims of the thesis

5.1 The clinical difficulties in NP in diseases such as leprosy

5.1.1 Problems of defining neuropathic pain in leprosy

5.1.1.1 Case study: a problem of identifying a case of NP in leprosy

Case history 1:

A 49 year old female from Worli village, Mumbai sub-urban district. She is a service worker and the family's only earning member. She has received full treatment for multi-bacillary (MB) leprosy, completed in September 2002. She has no other medical comorbidities and notably has no clinical evidence of hypertension or diabetes mellitus on laboratory investigations.

Presenting complaint

Severe pain, tingling, numbness and burning sensations in both hands and feet bilaterally for the last 5 years

Origin, duration and progress of leprosy

In 2001, when the patient was 37 years of age and in the third trimester of her first (and last) pregnancy, she presented with painful nodules on her leg arms and back with associated fever and joint pain. She was admitted to hospital, diagnosed as having MB leprosy with erythema nodosum leprosum reaction (ENL), and commenced one year multi-drug treatment (MDT). She had a normal vaginal delivery, and gave birth to healthy baby with no medical problems.

Post-delivery she had repeated episodes of ENL reactions. During the first episode, in 2001, she received a six months course of prednisone. The second episode in June 2003 was managed with a further six months of prednisone. After the third recurrent episode of ENL reaction in 2004, she was diagnosed as chronic ENL and commenced and completed another 6 months treatment with prednisone.

After anti reaction treatment, she showed steady improvement. Her pain and skin lesions subsided, and she felt better. However, seven years later in 2008; she developed

burning sensations, tingling and numbness in both hands and feet. By late 2011, she was admitted to hospital with bilateral weakness, sensory loss and severe burning sensations in her hands and feet. Two weeks later, she complained of insomnia due to her pain. The pain in her hands and feet was described as sharp, stabbing, burning and "electric shock" like and the patient described it as "putting her hands and feet into a fire". No formal assessment of her pain symptoms was made by the attending physician. Neurological examination of her limbs was normal. She completed steroid treatment after consultation with a dermatologist to relieve pain, but her description of the pain remained as before. Treatment with MDT for the second time had been recommended by her doctor in a private clinic along with analgesics, but this did not improve her pain.

Radiological imaging (MRI of cervical spines) on 26/11/2012 was normal and included the basal ganglia. Nerve conduction studies (NCS) revealed predominately a severe sensory peripheral neuropathy in all four limbs, so a neuropathic mechanism was suspected as the dominant cause of her pain. The second course of MB-MDT was stopped after three months and her steroid dose was reduced. She commenced analgesic treatment with Amitriptyline 10 mg initially, increased to 75 mg which was effective in relieving her pain and then shifted to combination of Gabapentine 30 mg TDS and Duloxetine 20 mg BD. This produced substantially better pain relief without any disability for several weeks.

Assessment

Initially, her pain was considered to be nociceptive in type, i.e., pain caused by normal activation of peripheral nociceptors following tissue damage. It was managed by combination of MDT and increasing oral prednisolone up to 60 mg per 24 hours (median daily dose between 40 mg and 60 mg tapering over 6 months). Despite this she described only 50 % pain relief and showed symptoms and signs suggestive of psychological disturbance (GHQ score = 7). Over the last five years she had missed her work several times because of her pain.

Throughout her illness, this patient always described the pain as tingling, numbness, burning and "electric shock" like. Several pathological processes were suspected as aetiological factors such as, an immune mediated inflammatory process, leprosy relapse or reinfection. However, her clinicians were unable to elucidate the neuropathic

component of her pain until a late stage and therefore the period of ineffective pain management could lead to psychological disability.

Case history 2:

An 18-year-old boy from Dharavi, Mumbai' largest slum (Figure 5.1). He is a right handed student. He was newly diagnosed with PB leprosy on 30.03.2013 and he is on pain medication for the last week. He has no other medical comorbidities and notably has no clinical evidence of hypertension or diabetes mellitus on laboratory investigations.

Presenting complaint

Severe pain, burning, and tingling sensations in the right medial aspect of the forearm, and associated with right hand weakness for the last three days.

Origin, duration and progress of the condition

The condition started in early March 2013 (four weeks prior to the current visit), when the patient developed an acute onset of pain sensations in the medial aspect of the right hand. The pain was described as "insects crawling" in his hand and associated with burning and shooting pain along the medial side of his right forearm. The patient sought medical advice at a private clinic and received combiflam pain-killers (a combination of Paracetamol and Ibuprofen), one tablet four times a day. After pain killer treatment, he showed improvement. His pain subsided and he felt better. However, one week later; he developed sever pain around his right ulnar nerve associated with reduced function of the right hand. By late March 2013, he was referred to the BLP clinic by a leprosy affected member of the Dharavi slum community. At the BLP clinic he was diagnosed as having PB leprosy with neuritis, based on clinical examination: the presence of single skin lesions located on the face, and painful right ulnar nerve with reduced function. Further investigation such as skin smear was requested. The treatment plans was a high dose of prednisolone (60 mg), PB-MDT treatment for the next six months, and hand physiotherapy.

Assessment

This patients with leprosy presented with symptoms of acute pain while seeking treatment. Initially, the nature of the pain was nociceptive inflammatory pain, which is

usually amenable to treatment such as steroids, other anti-inflammatory medications, or immobilisation, but the nerve function impairment may continue even after starting MDT, which may serve as a source for the development of NP (Haanpaa et al., 2004, Haroun et al., 2012). This patients had right ulnar neuritis with sensory loss in the right ulnar nerve territories, hence the possibility of having acute NP cannot be ruled out.

Figure 5.1. Dharavi, Mumbai' largest slum

Source: this picture was taken in March 2013 in Mumbai

5.1.1.2 Summary of the case studies

From the above two different scenarios, leprosy patients with neuropathy and pain could benefit from a much clearer distinction between mono-neuropathies–the usual presentation of NP in leprosy–and distal symmetrical poly-neuropathies which are much more unusual.

5.1.2 Challenges in defining NP in leprosy patients

5.1.2.1 Introduction

NP, recognised to occur in approximately one-fifth of treated leprosy patients, is a major issue for patients and the health system care. Previous work has shown that patients with NP have significant levels of depression (Lasry-Levy et al., 2011, Haroun et al., 2012). For individuals, life with neuropathic pain can be disabling even after their disease has been "cured" adding a burden to the patient's suffering and health service cost. As diagnosis is challenging for clinicians, misdiagnosis often leads to further health and social consequences. Because of the resource poor setting we need better diagnostic

tests purely for identification as this the main barrier to effective treatment. This is caused by a number of obstacles which still exist in clinical practice.

The first difficulty is the variety of symptoms and signs of pain-related sensory abnormalities. The exact constellation of neuropathic pain characteristics, and associated sensory aberrations, which are manifested in an individual patient are variable and complex and often only fully revealed by the use of sophisticated investigation techniques (Jensen and Baron, 2003, Baron et al., 2009). This can result in common clinical features such as spontaneous pain or stimulus-evoked pain, as well as other associated sensory disturbances such as sensory loss (anaesthesia dolorosa).

It has been argued that rather than categorising neuropathic patients according to their aetiological diagnosis, the stratification of patients on the basis of individual symptom sensory profiles should be done to understand better the underlying processes (Baron et al., 2012). In a study from Germany, Baron and colleagues (Baron et al., 2009) examined symptom profiles in more than 2000 patients with diabetic neuropathy and post herpetic neuralgia using standard clinical examination and the PD symptom questionnaire. The authors found that patients with NP could be sub-grouped based on specific symptom profiles. The authors identified 5 subgroups where the symptom profiles were found to be different on the basis of the prominent features. For instance, subgroup 1 report spontaneous burning pain. Whereas, subgroup 2 demonstrates only severe pain attacks. In subgroup 3 the values of the sensory profile are mainly concentrated around the zero-line for all parameters. In contrast, subgroup 4 demonstrates considerable evoked pain symptoms and less burning sensations and paresthesia. Others such as subgroup 5 demonstrate considerable spontaneous symptoms without cutaneous allodynia or hyperalgesia. This indicates that the information obtained from pain questionnaires and clinical examination can be used to distinguish symptom profiles in patients with NP across different conditions. A similar grouping of NP patients based on sensory symptom profiles and co-morbidity, obtained in study of more than 2000 patients with painful radiculopathy (Mahn et al., 2011). These patterns do not necessarily reflect the condition from which the nerve damage arose, but importantly may well reflect pain generating mechanisms and therefore give a clue to mechanisms and thus likely drug responses on an individual patient level. Thus it is vital to accurately phenotype the sensory abnormalities in each patient with leprosy and NP.

Another major difficulty is the distinction between the different types of pain which are associated with leprosy. These are difficult to distinguish clinically, yet require different management strategies. Patients with leprosy may experience skin and nerve pain at different times during the disease. Skin lesions may affect sensory processing, but the pain mechanism differs from patients with nerve damage (i.e. not peripheral mechanism). Two main groups of leprosy patients experiencing pain can be distinguished: those with pain associated with reactions, and those with NP. However the two categories overlap (Haroun et al., 2012).

In addition to the difficulties of assessing the heterogeneous features following nerve damage and the distinction between the different types of pain, relationships between underlying pain and sensory deficit cannot be accurately determined. The process is based primarily on patients' descriptions supported by examination and investigation. Whilst any leprosy patients with neuropathy and pain is highly categorised as NP, the evidence of associations are required. This may not be a proven causation; neuropathy can be identified objectively, but it cannot be assumed that a causal relationship exists with the patient's pain. This scenario is further complicated, as illustrated in the preceding section, when mixed types of pain exist in the presence of a progressive immunological and pathological process or in the occurrence of pain in subclinical neuropathy. There are several advantages of accurately phenotyped abnormalities, if uncertainties regarding the relationships between different sources of underlying pain are to be avoided.

Finally, assessing an experience of pain itself is difficult. According to the IASP, irrespective of the underlying mechanism, pain is always subjective (IASP, 2009). Each individual feels and reports their pain experience differently, and the sensation of pain itself cannot be objectively measured. Even though certain behaviours have been identified as associated with pain, these are only corroborative. Also, although numerous psychophysical methods exist for the measurement of pain, these are entirely subjective (Chong and Cros, 2004).

The variability of nerve damage in leprosy, the existence of different types of pain, the uncertainty in the relationships between underlying pain mechanisms and the subjective experience of pain makes the identification of pain-related sensory abnormalities a continuing challenge. Therefore, a new classification of leprosy patients with NP could take into account subgroups of patients with different sensory profiles. This provides

information about the pathophysiological process that helps improve understanding of the various NP mechanisms operating in leprosy.

5.1.2.2 How to define neuropathic pain in leprosy

For this current study, a two-step case definition was used to define NP in leprosy:

1) Is there evidence of nerve damage?

In accordance with the above definition the demonstration of nerve damage is an essential pre-requisite to diagnosing the presence of neuropathic pain.

2) Is the pain neuropathic?

Although demonstration of nerve damage is an essential first step in this diagnostic triage, the mere presence of nerve damage does not necessarily indicate that any pain is neuropathic in origin. Therefore, an essential second step is to classify any pain as being likely neuropathic origin. For this two criteria are required:

i. Is the pain distributed in a "neuroanatomically plausible" location (e.g. a single peripheral nerve innervation)? A body chart where the pain location is drawn is used.
ii. Is the symptom profile/ pain descriptors characteristic of neuropathic pain? For example by a score of ≥ 4/10 using the DN4 questionnaire.

There are two definitive steps in the process: firstly to confirm that some form of damage to the somatosensory system has occurred, should be neuroanatomically logical and compatible with a definitive lesion site, without this the diagnosis is impossible (Treede et al., 2008). In leprosy, somatosensory system damage is a recognised complication. Body charts, which are routinely used in leprosy clinics to map skin lesions, can be used to identify distribution of pain by drawing pain location; in addition to patient's pain description (i.e. is the pain for example burning, stabbing or aching). The demonstration of pain distribution may determine whether pain lies within dermatomes or peripheral nerve distribution. Also, pain patterns such as glove and stocking distribution can be mapped on the body template. This may help in understanding the relationship between the location and quality of pain. Likert scales, Visual analog scales (VAS), Verbal rating scales (VRS), or a combination of verbal and

numerical rating (Gracely Pain Scale) can be used to determine the severity of pain. BPI can be used for assessing fluctuation of pain over time (Haanpaa et al., 2011a).

Secondly, to determine that any pain is indeed neuropathic, because nerve damage does not necessarily mean that pain is neuropathic in origin. To identify patients with possible NP, several screening tools are available such as the DN4, LANSS, NPQ and PD-Q. These screening tools are recommended particularly for non-specialists to consider the diagnosis of NP (Haanpaa et al., 2011a). It helps to determine the prevalence of NP in epidemiological studies, and it may also help to distinguish between inflammatory pain that is due to ongoing acute leprosy reactions and NP that is due to the effects of leprosy on sensory fibres. Nevertheless, these screening tools cannot replace clinical judgment in diagnosing NP in leprosy patients.

5.1.2.3 How to apply a case definition of NP in leprosy

Variation of defining NP in diseases such as leprosy

Different types of leprosy-related pain may occur during the course of the disease; inflammatory and NP (Haroun et al., 2012). Pain associated with neuritis reaction, which is defined by the development of inflammation of a nerve sheath without abnormal findings in sensory testing, is clinically defined as nociceptive pain (Bove and Light, 1997). Importantly this term has been noted not to be used unless inflammation is thought to be present (IASP, 2012). However, if an inflammatory neuritis causes nerve damage then the pain is by definition neuropathic. Another subtype of NP is neuralgia, which is defined as pain arising in the distribution of a nerve or nerves (IASP, 1994). Although neuralgia is the preferred term used generically to describe chronic pain following herpes zoster reactivation, it is used to describe NP arising from a lesion of specific nerves. NP in leprosy may occur even years after completion of the MDT. It usually occurs in distribution that is anatomically appropriate to the affected nerve(s) and in skin lesions.

5.1.3 The impact of diagnosis on treatment

Although there are no data from controlled studies in well-defined groups of leprosy patients that demonstrate the efficacy of the NP drugs, the treatment of the condition is less satisfactory. There are three principle reasons for this, the first being the difficulty in identifying and defining NP cases in leprosy. The second is the failure to identify the

presence of NP mechanisms. The third is the use of treatment that is based on one specific mechanism when each patient with NP is likely to have more underlying causes leading to pain. For instance, clinicians often prescribe a tricyclic antidepressant when treating chronic pain in leprosy based on reports on the use of these drugs with no clinical evidence. Thus for some patients, even optimal use of current treatments by experienced clinicians will not relieve their pain.

5.1.4 The need of profiling and stratification of leprosy patients group

Despite the problems outlined above regarding the identification, defining and treatment of neuropathic pain in leprosy, a majority of leprosy patients will benefit from the new profiling and stratification of neuropathic pain in order to:

i. improve clinical trial design
ii. identify neuropathic pain mechanisms
iii. shape the development of new drugs
iv. individualise treatment leading to improved pain control

Given that the neuropathic pain mechanism-based approach is guided by targeted treatment according to pain mechanisms, it seems unlikely that there is a way to measure the mechanisms routinely. Therefore, identification of neuropathic pain mechanisms from symptoms and sensory profiles stratification would appear to be a sensible approach to inferring mechanisms operating at the individual patient level. In fact, Baron described an ideal situation in which subgrouping of patients with different sensory profiles guides the clinician in matching a particular treatment to a particular patient with predictable responses especially in clinical trial setting (Baron et al., 2012).

The identification of sensory profiles can be best achieved with validated questionnaires such as the DN4 or BPI as regards symptoms, and with an extension of the clinical examination such as QST for sensory signs (Haanpaa et al., 2011a, Backonja et al., 2013). For the purpose of this study the different approaches related to mechanisms and patients subgrouping are explained as follows: the mechanism-based is approach adopted by NP expert to target treatment with mechanisms; Patient profile (phenotype) is grouping of patients according to their symptoms and signs. Any profiling approach should stratify patients by symptom, sensory and psychological state. This has the potential to improve clinical trial design and might be adopted into routine practice.

5.2 The role of instruments for assessing sensory abnormality and psychological impact of NP in leprosy

This section describes the role of different instruments for assessing pain-related sensory abnormalities, their availability and justification for use in leprosy.

5.2.1 The role of pain questionnaires

5.2.1.1 Background

Pain questionnaires are tools that can accurately identify patients with symptoms and signs suggestive of neuropathic pain (Haanpaa et al., 2011a).

5.2.1.2 Available instruments

There are several validated questionnaires designed to identify neuropathic pain characteristic. These instruments can be classified into two groups: diagnostic screening and symptom profiling questionnaires. The former include LANSS, NPQ, DN4, PD-Q, StEP and ID-pain questionnaires, which have sensitivities ranging from 66% to 94% and specificities in the range 69% to 97% (Üçeyler and Sommer, 2011). Whereas, the symptom profiling questionnaires include NPS, NPSI, PQAS and SF-MPQ. For leprosy work the linguistic and cultural (context) validation are required in local languages and the DN4, LANSS and the NPSI have been used (Saunderson et al., 2008, Lasry-Levy et al., 2011, Haroun et al., 2012). I will present here the screening tools used in leprosy neuropathic pain, others are explained in detail in Chapter 3.

Pain screening questionnaires and leprosy

In recent years, more attention has been given to screening tools in identifying neuropathic pain among leprosy patients. The preference is given to a tool validated in the language in which it will be applied. Stump (Stump et al., 2004) described the use of McGill pain questionnaire which identified 53 (15%) patients with pain in sample of 358 Brazilian leprosy patients, but there was no information regarding the validation. In contrast, DN4 has been used for studies in India and Ethiopia (Lasry-Levy et al., 2011, Haroun et al., 2012). The different screening tools are summarised in Table 5.1. I elected to use the DN4 questionnaire.

Table 5.1. Overview of screening tools in studies carried out on leprosy NP

Authors, year	Country	Study population	Tools
Hietaharju (Hietaharju et al., 2000)	Bangladesh	16 leprosy patients with chronic pain	Clinical assessment
Stump (Stump et al., 2004)	Brazil	358 leprosy patients from a referral centre	McGill Pain Questionnaires
Lund (Lund et al., 2007)	India	17 leprosy patients who had completed MDT	Clinical assessment
Saunderson (Saunderson et al., 2008)	Ethiopia	96 leprosy patients who had completed MDT more than 10 years	NPSI
Lasry-Levy (Lasry-Levy et al., 2011)	India	101 leprosy patients who had completed MDT	DN4 and LANSS
Haroun (Haroun et al., 2012)	Ethiopia	80 leprosy patients who had completed MDT within 18 months	DN4 and LANSS
Chen (Chen et al., 2012)	China	275 leprosy patients	NPSI
Felipe Reis (Reis et al., 2013)	Brazil	33 leprosy patients with pain	DN4
Raicher (Raicher et al., 2013)	Brazil	90 leprosy patients with pain	DN4 and NPSI
Gosling (Gosling et al., 2013)	Brazil	114 leprosy patients with pain	DN4 and McGill Pain

5.2.1.3 Justification for using DN4 in identifying NP among leprosy patients

In the current study, leprosy patients have been assessed for NP using highly specialised assessments tools. Of these validated tools, the DN4 was selected, which may help in identifying NP characteristics.

First, DN4 is a simple, short and validated questionnaire to identify patients with NP. It uses both interview questions and brief bedside examinations, so it helps in assessing symptoms as well as clinical signs of NP. Whereas, other questionnaires are more complex, lengthy and have limited clinical examinations.

Secondly, DN4 has a good diagnostic yield. Previous studies evaluating diagnostic characteristics of DN4 for neuropathic pain of different aetiology have found values of sensitivity and specificity for neuropathic pain from 82% to 95% and from 78% to 97%, respectively (Bouhassira et al., 2005, Perez et al., 2007, Unal-Cevik et al., 2010).

Furthermore, in leprosy, DN4 is commonly used to identify patients with NP. It has a higher sensitivity as screening tool for NP in leprosy. In the 18th International Leprosy Congress, Raicher (Raicher et al., 2013), who investigated the prevalence of NP among 90 leprosy patients with pain using DN4 in Brazil, reported sensitivity and specificity of 96% and 58%, respectively. Similarly, in the 14th World Congress on Pain, Stump (Stump et al., 2012) reported high sensitivity of DN4 as a screening tool for NP in leprosy (>90%) in a study with 358 patients. In an study performed by our group in 2009; 80 leprosy patients, who had completed MDT within 18 months in Ethiopia, were assessed using DN4 and LANSS (Haroun et al., 2012). In this study we asked patients to evaluate the screening questionnaires. The study found that the DN4 was easier to administer than other tools in assessing NP. This finding was proved by patients' choices. Although the sensitivity of DN4 was found to be excellent (100%), its specificity was far lower than in the validation studies (45%). This could be because of the high numbers of patients with inflammatory pain that were recruited. This should not have affected the results concerning DN4 diagnostic accuracy; rather, it indicates that patients studied were similar to those usually encountered in regular clinical practice. Another study performed by our group in India, has come to a similar conclusion; DN4 is easier to apply in identifying NP among leprosy patients (Lasry-Levy et al., 2011).

5.2.2 The role of Quantitative Sensory Testing

5.2.2.1 Background

Quantitative Sensory Testing (QST) is a diagnostic method for accurately assessing somatosensory changes in human skin caused by nerve damage (Maier et al., 2010). It has been also recommended by NeuPSIG as a useful diagnostic instrument in the assessment of NP (Haanpaa et al., 2011a). It is a non-invasive procedure which is a sophisticated clinical examination of the sensory nervous system, whereby the perception thresholds to various mechanical and thermal sensory stimuli are accurately measured. Although it's utility in routine clinical NP assessment may have limitations such as difficulty in standardising and being time consuming (Cruccu et al., 2004), there is increasing interest in using QST to give insights into the underlying patho-physiological mechanisms of chronic pain.

5.2.2.2 Available instruments

DFNS-QST protocol

The German Research Network on Neuropathic pain (DFNS) has developed the DFNS-QST protocol in 2006 (Rolke et al., 2006a). It is a comprehensive and validated tests including all somatosensory modalities mediated by different nerve fibres (Aβ, Aδ and C), that measures: cold and warm detection thresholds, number of paradoxical heat sensations during the thermal sensory limen procedure, cold and pain thresholds, mechanical detection threshold and mechanical pain sensitivity, dynamic mechanical allodynia, temporal pain summation and pressure pain threshold (Rolke et al., 2006b). This offers a high degree of detailed and precise information in the clinical diagnosis of leprosy related NP. The protocol is a well-established instrument for the assessment of NP and data has been collected internationally in over 3,000 neuropathic pain patients. In a study of 43 German patients who had neuropathy and dysesthesia in 2008, the QST parameters showed a high specificity (80%) but low sensitivity (37%) in the prediction of a reduced intraepidermal nerve fibre density as correlate for neuropathy (Scherens et al., 2009).

Quantitative sensory testing and leprosy

Although QST is widely used as an assessment tool for small fibre function and sensory profiles in neuropathies associated with pain (Maier et al., 2010, Rolke et al., 2006b), it

has not been used much leprosy patients and certain individual components have been measured (e.g. thermal and vibration thresholds) as opposed to the full battery of tests required to give the complete sensory assessment, Table 5.2.

Villarrole et al. in 2007 measured the different responses to the panel of stimuli used in a thermal testing analyser and monofilaments in 108 leprosy patients with skin lesions. They found that all patients had impaired warm and cold perception (Villarroel et al., 2007b). This study found that the cut-off points for warm and cold perception threshold determined from thermal sensory analysis were 35.1ºC and 28.95ºC, respectively (Villarroel et al., 2007a). Facer et al. 1998, who measured the responses to the thermal sensory analyser applied in the skin lesions in 28 leprosy patients, has also concluded that thermal threshold for cold and warm were significantly different (Facer et al., 1998). However, these studies have assessed the skin lesions in leprosy patients with no evidence of nerve function involvement and measured only thermal testing. A similar result, showing that warm and cold detection threshold were commonly affected, was obtained by van Brakel et al. 2008, who measured the different responses to the panel of QST thermal stimuli in a cohort of 303 Indian leprosy patients (van Brakel et al., 2008b).

Lund et al. 2007 measured the different responses to the panel of stimuli used in the QST in 17 leprosy patients with chronic pain in India and found 65% of the patients had sensory loss for all tested modalities (Lund et al., 2007). The study found that patients with chronic pain had lower IENF density and QST parameters (Lund et al., 2007), however this study has contained relatively small numbers of subjects.

Table 5.2. Quantitative Sensory Testing studies in leprosy neuropathy

Author, year, country	Main purpose of the study	Study population, N	Intervention / test	Main findings
Villarroel et al. (Villarroel et al., 2007b) **Brazil**	To assess leprosy skin lesion sensory impairment	Leprosy patients: 108	Thermal Sensory Analyser and Monofilaments	All patients had impaired warm and cold perception
Villarroel et al. (Villarroel et al., 2007a) **Brazil**	To determine the frequency of thermal sensation	Leprosy patients: 108	Thermal Sensory Analyser (TSA-2001)	Warm perception threshold: 35.1 o C and CPT: 28.95 o C
Abbot et al. (Abbot et al., 1996) **Iran**	To assess un-myelinated fibre impairment	Leprosy patients: 39	Laser Doppler flowmetry, electo-pysiology and QST	Significant relationship between fibres and sensory impairment
Facer et al. (Facer et al., 2000) **India**	To explain early loss of cutaneous pain sensation	Leprosy patients: 28	Thermal test, light touch, Laser Dopler and skin biopsy	Sensory loss in affected skin
Brakel et al. (van Brakel et al., 2008a) **India**	To compare diagnostic test for neuropathy	Leprosy patients: 303 INFIR study	NCS, Quantitative thermal sensory test, MFs and VMT	WDT more frequently affected (29%), CDT (13%)
Lund et al. (Lund et al., 2007) **India**	To demonstrate the possible factors for NP	Leprosy pts completed treatment 17	QST and skin biopsy	65% had total sensory loss for all modalities

5.2.2.3 Justification for using DFNS-QST protocol in leprosy

This is the first study to document pain sensation using DFNS-QST in leprosy patients. These reasons for using the DFNS protocol include the standardisation, the highly precise detection of the sensory loss and gain, the validity of the DFNS-QST protocol, and its ability to assess the individual's sensory profile. This protocol is commonly used in other conditions such as peripheral nerve injury, postherpatic neuralgia and trigeminal neuralgia related neuropathic pain (Maier et al., 2010). The assessment of the exact sensory phenotype by QST is also a crucial part of this research project and this comprehensive technique is not yet used in leprosy.

The DFNS-QST protocol is a reliable and well-validated protocol. In recent years, several studies indicate a high diagnostic value of its results in both healthy subjects and in patients with NP. Maier (Maier et al., 2010) explored the spectrum of sensory abnormalities in 1236 patients with neuropathic pain due to different underlying diseases. In this large cohort of patients, DFNS-QST was found to be reliable; 92% of all patients with proved neuropathy had at least one sensory abnormality compared with the contralateral unaffected body area or with the reference data obtained from healthy controls. This indicates a good validity of the QST-DFNS protocol as a tool for quantifying somatosensory changes and even pain-related phenomena.

The DFNS-QST protocol is sufficiently sensitive to document the results related to the loss of function, i.e. sensory deficit and to abnormal pain-related phenomena, which clinically present as various manifestations of pain. This may help to assess the patient's sensory profile and subgrouping of the patients, and thus can be valuable to evaluate the underlying NP mechanisms in leprosy.

This protocol has been recommended by the IASP for the assessment of patients with NP, and leprosy patients will benefit from such tool (Haanpaa et al., 2011a, Backonja et al., 2013).

5.2.3 The role of skin biopsy and IENFD

5.2.3.1 Background

Skin biopsy provides insight into disease pathophysiology, which may lead to improve diagnosis and treatment of chronic pain condition. Its diagnostic yield has already been established in many peripheral neuropathies and especially useful when small fibre

neuropathy is being considered (Lauria et al., 2009). For instance, skin biopsy is used to aid in the diagnosis of Parkinson's disease specifically to evaluate the potential role of alpha-synuclein as a biomarker for this disease (Nolano et al., 2008). Moreover, skin biopsies have demonstrated involvement of epidermal small sensory fibres in patients with Amyotrophic Lateral Sclerosis (ALS) (Weis et al., 2011). Furthermore, skin biopsies have demonstrated involvement of cutaneous innervation in patients with Spinobulbar Muscular Atrophy (Kennedy's disease) (Manganelli et al., 2007). These utilities help to evaluate and better understand of somatosensory dysfunction.

The principal role of skin biopsy in the diagnosis of NP is to determine intra-epidermal nerve fibre density (Lauria et al., 2010). Unmylinated C-fibre, which is the only fibre that penetrates into the epidermis, is frequently involved in patients with NP. This can be assessed by quantifying IENF density in the affected area (Lauria et al., 2010).

Several studies in clinical settings have examined the correlation between IENF density and pain (Devigili et al., 2008, Sorensen et al., 2006, Vlckova-Moravcova et al., 2008b, Quattrini et al., 2007, Polydefkis et al., 2002, Zhou et al., 2007). Sorensen (Sorensen et al., 2006) investigated 25 diabetic patients with NP and 13 patients without pain using skin biopsy obtained from distal leg. The authors found IENF density was lower in patients with NP compared to those without. In HIV-related sensory neuropathy, 101 patients underwent standardised NP assessment, IENF density was found inversely correlated with pain severity assessed with both VAS and the Gracely Pain Score (Zhou et al., 2007). Devigili and colleagues (Devigili et al., 2008) investigated 67 patients with pure small fibre neuropathy (diagnosed by the presence of at least two abnormal results on clinical examinations, QST, and skin biopsy) selected from a cohort of 124 patients with sensory neuropathy. The authors noted that Lower IENF density may be associated with the presence of NP, but it does not correlate with the intensity of pain.

5.2.3.2 Available instruments

Two main methods; punch biopsy and blister techniques are often used to obtain skin biopsy samples for assessing small fibre neuropathy. The former one is the most commonly performed using 3-mm disposable punch. It is standardised procedure that provides information on epidermal nerve fibres, sweat gland, hair follicles, and artero-venous anastomosis. The technique is validated, safe and minimally invasive (Lauria et al., 2010). Whereas, the latter is less invasive and has not been systematically used to

investigate patients with small fibre neuropathy. In addition, it does not provide information on dermal and sweat gland. In this study I use the 3mm disposable punch biopsy technique.

5.2.3.3 Intra-epidermal nerve fibre density (IENFD) and leprosy

In leprosy, skin biopsy is often used to define disease classification, but there have been only two studies on IENF density measurement and its correlation. The first study is performed by Facer in India, investigated 28 leprosy patients and found an inverse correlation between nerve fibres in the sub epidermis and thermal threshold (Facer et al., 1998). The second one is performed by Lund examined 17 leprosy patients with chronic pain (Lund et al., 2007). The authors found IENF density was significantly lower compared to the control skin biopsies.

Studies have revealed a significant correlation between IENFD, pain and QST parameters in post herpetic neuralgia, diabetics and HIV neuropathy (Zhou et al., 2007, Sorensen et al., 2006, Devigili et al., 2008, Loseth et al., 2008, Vlckova-Moravcova et al., 2008a). It is uncertain whether intra-epidermal nerve fibre density is correlated with pain and quantitative sensory testing parameters in leprosy, although studies confirm leprosy-related peripheral sensory neuropathy is a small fibre neuropathy. Previous study in leprosy has also suggest that a significant correlation between IENFD and QST parameters in patients with chronic pain (Lund et al., 2007), however this study has contained relatively small numbers of subjects.

5.2.3.4 Justification for using skin biopsy and IENF density in leprosy

In this current study, leprosy patients and controls have been assessed for NP using standardised clinical assessments and a skin biopsy taken from a pain affected area. A crucial part of the pain evaluation is the determination of the density of intra-epidermal nerve fibres in the affected areas.

The 3-mm punch biopsy with linear quantification of IENF density is a reliable and efficient technique to confirm the clinical diagnosis of small fibre neuropathy. The technique is ethically approved and widely used in other conditions. No side effects have been reported in published studies. Recently, it has been recommended by the European Federation of Neurological Societies/Peripheral Nerve Societies (EFNS/PNS).

5.2.4 The role of Psychological co-morbidity and HRQoL instruments

5.2.4.1 Background

NP is often associated with psychological conditions such as depression and anxiety, which may affects daily activities and overall quality of life (Meyer-Rosberg et al., 2001). This section describes the role of psychological co-morbidity and HRQoL questionnaires in the assessment of the impact of leprosy NP.

According to the World Health Organization health is defined as "a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity" (WHO, 1948). Quality of life questionnaires are important measures of the general aspects of an individual's life, whereas HRQoL questionnaires more specifically measure the impact of disease on the patient's physical, psychological and social functioning.

NP is often associated with a reduced quality of life (Meyer-Rosberg et al., 2001, Haanpaa et al., 2011a). A systematic review of the association between NP and health related quality of life (Jensen et al., 2007) revealed strong evidence that the presence and severity of NP are associated with greater impairments in a number of important HRQoL domains. For example, pain intensity and pain interference with function can have a marked impact on daily functioning activities, affective and motivational states, social relationships, sleep hygiene and economic factors. This impact varies as a function of the HLQoL domain being considered and that different measures of HRQoL are differentially sensitive to the effect of NP. The principle role of HRQoL questionnaires in patients with NP is to provide information about the impact on quality of life, particularly when associated with chronic severe pain and suffering (Guyatt et al., 1993, Nelson and Berwick, 1989).

5.2.4.2 Available instruments

Depending on the outcome measures, the HRQoL instruments can be grouped into generic, condition-specific and preference-based measures (Vetter, 2007). The generic HRQoL instruments, such as SF-36 and WHOQOL questionnaires, are more general and comprehensive. These are often used for evaluating the impact of pain on the common elements of health, well-being and functionality. Whereas, the condition-specific instruments are more suitable for detecting changes due to disease progression

or remission. They are also used to detect treatment response (Patrick and Deyo, 1989). For instance, NePiQoL and Neuroqol are specifically designed for neuropathy and pain. Another important condition-specific instrument is the Brief Pain Inventory (BPI), which assesses the impact of NP on the patient (Coplan et al., 2004). BPI has been validated in patients with non-cancer pain (Keller et al., 2004). On the other hand, the preference-based instruments such as SF-6D and EQ-5D are designed to incorporate patients' opinions of the utility value of a particular health state rather than simply describe the condition. They are suitable for cost-effectiveness analysis and can be used for a comparison across diseases (Vetter, 2007).

5.2.4.3 Justification for using GHQ-12 and BPI questionnaires in leprosy

For this current study, I have looked at the HRQoL questionnaires and found that it is more general and not relevant to our patient group, category of measurement, primary purpose or setting. For instance, the WHOQOL social relationship questions are not relevant to our ultimate objective. Moreover, while WHOQOL includes overall pain as one domain, a condition-specific measure can evaluate in depth the impact of NP on quality of life. For example, the WHOQOL's specific pain focused questions, such as "Do you worry about your pain or discomfort?" may not detect a clinically significant change in leprosy related sensory abnormalities. Furthermore, even if pain is assessed as a separate dimension on WHOQOL, the effects of pain severity on health-related quality of life is not considered. Hence, I decided to use condition-specific tools for NP such as BPI, which are designed to assess specific diagnostic groups particularly with the aim of determination of the impact of NP.

Another important reason is the validity and availability of BPI. Although, no recommendations exist on the use of specific HRQoL questionnaires for the assessment of quality of life (Haanpaa et al., 2011a), BPI is preferred to be used in cases of severe neurological conditions or in short-lived NP conditions (Coplan et al., 2004, Zelman et al., 2005). In painful diabetes neuropathy and herpes zoster studies, the usefulness of BPI measures of functionality and quality of live have been demonstrated. In an early study performed by our group in 2009; 80 leprosy patients, who had completed MDT within the previous 18 months in Ethiopia, were assessed using BPI (Haroun et al., 2012). In this study the intensity of patient's pain on health related quality of life, such as physical functioning, sleep and mood were assessed. The short version of BPI and validated tools are freely available.

5.3 Aims and objectives of the thesis

5.3.1 Aims of study

The overall aim of the study is to characterise the somatosensory phenotype of leprosy patients with chronic neuropathic pain.

5.3.2 Statement of the hypothesis

I hypothesised that;

- The thermal and mechanical detection threshold, pain threshold (CPT and WPT), pressure pain threshold (PPT), and vibration detection threshold (VDT) are lower in leprosy patients with painful neuropathy than patients with non-painful neuropathy
- There is significant impact of neuropathic pain on quality of life and psychological well-being in leprosy patients with painful neuropathy compared to patients with non-painful neuropathy.

Specific objectives

i. To measure the somatosensory responses of leprosy patients including thermal detection and pain thresholds, paradoxical heat sensations, mechanical detection thresholds to von Frey filaments, vibration detection threshold, mechanical pain thresholds to pinprick stimuli and blunt pressure, stimulus/response-functions for pinprick and dynamic mechanical allodynia, and pain summation (wind-up ratio) and to compare these measures between leprosy patients with painful neuropathy; non-painful neuropathy, leprosy patients without pain and age and sex matched healthy controls.

ii. To elucidate the impact of leprosy NP on quality of life and psychological well-being in patients with painful neuropathy compared with patients with non-painful neuropathy.

iii. To stratify leprosy patients by symptoms, sensory profile and psychological state

Chapter 6 Materials and Methods

6.1 Overview

This chapter presents the search strategy and definitions of terms used in the study, and an overview of the study design including the description of a case-control study as a research design and its applicability to this study. The methods of clinical and laboratory assessments, including the DFNS-QST protocol are then defined. Finally, an account of the data recording and management approaches are provided, including strategies of analysis that were used in this study.

6.2 The search strategy and search criteria

Literature published up to August 2014 related to leprosy and NP was searched. The literature review of leprosy and neuropathic pain was performed using search terms listed in Table 6.1. The search was limited to articles published in English. Various combinations of the terms were employed (leprosy and neuropathic pain). The main research resources used were search engines and bibliographic data-bases. These included: PubMed (chosen as it provides a wide coverage of health topics), EMBASE (chosen as it provides access to articles with a focus on general medicine), MEDLINE (chosen to complement the EMBASE search), and the Cochrane library (chosen to ensure capture of articles with clinical interventions). Reference lists in the articles found were also searched for relevant articles and the function "related articles" in PubMed was used. WHO documents on leprosy were checked on the WHO website. DFNS publications on QST were also checked on the DFNS website. Additional references were gathered from conference lists and Google internet searches. PhD theses available on EThoS (UK theses) and through the LSHTM, and ICL libraries were also checked for relevant information.

Table 6.1 Search terms used in the study

Leprosy	**Reactions**	**Neuropathy**	**Pain**	**QST**
Hansen's disease	type 1 reaction "T1R"	subclinical neuropathy	Pain	DFNS-QST
	reversal reaction	Nerve damage	Neuropathic pain	Quantitative sensory testing
	erythema nodosum leprosum "ENL"	peripheral nerve damage "PN"	non-neuropathic pain	DFNS
		nerve function impairment "NFI"	nociceptive pain	

6.3 Definitions of terms used in this thesis

6.3.1 Definitions

Motor test: test of the function of motor fibres of the nerves, normally performed by checking muscle power using voluntary muscle testing (Appendix 24).

Voluntary muscle test (VMT): test of the function of (voluntary) muscles innervated by a particular nerve trunk, normally performed by checking the ability of the patient to put a limb into a given position and to hold that position against resistance applied by the tester. For standardisation where possible a comparison is made to the unaffected side.

Motor impairment: motor neuropathy resulting in obvious weakness of the muscles innervated by a given nerve.

Sensory test: test of the function of sensory fibres of the nerves, normally performed by checking light touch sensation using application of monofilaments (Appendix 25).

Semmes-Weinstein monofilament test (MFs): a graded test of touch sensibility based on indenting the skin surface with a series of increasing thickness of standard nylon filaments. For each thickness it is recorded whether or not the patient feels the touch. Three or four sites per nerve may be tested, the severity of the sensation impairment

being measured by the thickness of filament just felt by the patient. A normal level of 0.2g for the hand and 2g for the foot (excluding the heel) is appropriate.

Sensory impairment: neuropathy of the sensory fibres resulting in obvious reduction in the sensory ability of the patient using Semmes-Weinstein monofilaments.

Clinical neuropathy: sensory, motor or autonomic neuropathy evidenced by clinically detectable obvious reduction in function in sensory and/or motor using Semmes-Weinstein monofilaments and/or VMT.

6.3.2 Case definitions

1. **Leprosy neuropathy**

   A leprosy neuropathy case was defined as a patient with a clinical evidence of sensory and/or motor impairment in an area innervated by one or more nerve using Semmes-Weinstein Monofilaments (MFs) and MRC scale.

   Sensory impairment was defined by a decrease in sensation as measured by Semmes Weinstein monofilament testing. In the hands, this was defined as not being able to perceive the 0.2gm monofilament at 2 points out of 3 in each nerve of the hand. In the feet, this was defined as not being able to perceive the 2gm monofilament at 3 out of 4 sites of the foot.

   Motor impairment was defined by a decrease in voluntary muscle testing (VMT) score, by 1 point or more from the normal score of 5, using the modified MRC scale.

2. **Sub-clinical neuropathy**

   Patients with no clinical evidence of neuropathy based on Semmes-Weinstein Monofilaments (MFs) and/ or MRC scale, but who showed abnormal NCS or thermal testing were allotted to "Subclinical neuropathy".

3. **No clinical evidence of neuropathy**

For the purpose of this study, no clinical evidence of neuropathy was clinically defined by the normal sensory and motor impairment result using Semmes-Weinstein Monofilaments (MFs) and MRC scale, respectively. Sensory neuropathy detectable by Semmes-Weinstein monofilaments, but not meeting the criteria of sensory impairment is clinically defined as no clinical evidence of neuropathy.

4. Neuropathic pain

A case of NP was clinically defined by the presence of negative or positive neurological signs concordant with the distribution of pain at the affected peripheral nerves based on a score of ≥ 4/10 using the DN4 questionnaire and clinical neurological examination. Duration of this pain for three months or more is defined as chronic NP.

5. Non-neuropathic pain (nociceptive pain)

For the purpose of the curent study, a case of non-neuropathic pain was clinically defined by the occurrence of sharp, dull, or aching pain score of < 4/10 using the DN4 questionnaire (Costigan et al., 2009). Pain associated with neuritis reaction, which defined by the development of inflammation of nerve sheath without abnormal findings in sensory testing, is clinically defined as nociceptive pain (being originated from nervi nervorum) (Bove and Light, 1997, Sauer et al., 1999). Also, pain associated with type 1 and type 2 reactions is clinically defined as non-neuropathic pain.

6. Type 1 reaction

A type 1 reaction was diagnosed when the patients had erythema and oedema of skin lesions. There may be accompanying neuritis and oedema of the hands, feet and face. The skin signs were obligatory; the nerve and general signs optional (Van Brakel et al., 2005a).

7. Type 2 reaction

A type 2 reaction was diagnosed when the patients had crops of tender subcutaneous skin lesions. There may be accompanying neuritis, iritis,

arthritis, orchitis, dactylitis, lymphadenopathy, oedema and fever. The skin signs were obligatory; the nerve and general signs optional (Van Brakel et al., 2005a).

8. **Neuritis**

   A case of neuritis is clinically defined if the patient has any of the following: Spontaneous nerve pain, paraesthesia or tenderness; new sensory, motor or autonomic impairment of recent onset; or mixed signed.

6.3.3 Pain terminology

The pain terminology, which was based on the updated IASP taxonomy (IASP, 1994), is given in (Appendix 50).

6.4 Study design

6.4.1 An overview of the study design and research procedures

A range of study designs could be used for this type of analysis. In cross-sectional studies, which is a "snapshot" of the population at a single point in time, the exposure and disease status are assessed simultaneously in each individual. It is good for measuring the scale of a problem e.g. prevalence of disease, but it cannot assess the sequence of events, so cannot show that exposure came before the outcome. In case control studies, people who have the disease in question (cases) and those who do not (controls) are compared with respect to the past exposure of potential causative factors. Sometimes case control studies referred to as retrospective studies, because they look backwards from the disease to potential causes. In cohort studies, a group of people with a particular risk factor is followed to determine whether they develop the disease of interest.

I adopted a case control study to assess the somatosensory parameters related to NP in leprosy patients using the QST in 90 leprosy patients. A defining feature of a case-control study is that the starting point is identification of people with the outcome in question. In relation to this study, I chose to identify NP cases among leprosy patients. The case definition of NP was clinically defined, and I included all prevalent cases of NP (i.e. all NP cases within leprosy population in the BLP catchment area at a specific

point in time). Our controls were drawn from the same population and were classified into different groups by their neuropathy status and the presence of pain (Table 6.2). Three control groups were randomly selected from the leprosy population presenting at the BLP and FMR clinics. One group of controls was selected from patients with no pain and no clinical evidence of neuropathy. The other two groups were patients with pain-free neuropathy and patients with pain and no clinical evidence of neuropathy. In addition, a group of healthy volunteers was recruited from the local Indian population. Although, this group was not part of the case control series, their data were used for comparison with patients along with the DFNS database reference. The reason I selected more than one group was due to the heterogeneity of leprosy neuropathy and pain. The aim of the study was to investigate the clinical aspect of NP in leprosy. If the study had used only healthy controls, the comparison would have been between patients who had developed NP and healthy, which might may have introduced inaccuracies in the profiling if the patients with leprosy who had pain reported similar profiles to healthy controls. In addition, we felt that profiling leprosy without pain might detect new neurological abnormalities that could be tested by comparing cases with the control group who had neuropathy and pain. Individual matching methods were applied in this study. For each individual case, a control was selected who was similar to that case with respect to the age and gender. Cases and controls were individually matched by age (within approximately 10 years) and sex. For example, if our case was a 34-year-old female, I selected a control who was a female aged 30 – 39.

Table 6.2. Design of study groups selection

		Neuropathy	
		Yes	***No***
Pain	***Yes***	? NP	? Non-NP
	No	Pain free neuropathy	No evidence of neuropathy

In relation to this study, the selection of controls was appropriate. The use of these methods helped the study as follows: firstly, the population-based controls minimised the systematic selection bias. Secondly, having three controls per case improved the statistical precision of the profiling estimate. However, increasing the number of controls was logistically difficult because of additional resources and time required to

interview a greater number of controls. Finally, the advantages of the age and gender-matched control techniques used for each patient in this study reduced potiential sources of confounding and increased the efficiency of the study. Matching our controls to cases by age ensured that the age distribution of cases and controls was the same. This meant that the effect of the matched age was removed from analysis (i.e. I controlled for any confounding effect of age). Another advantage of matching was examining fewer patients per group, because the cases and controls were more similar to each other than they would be if they were not matched. I tried to match the recruitment across the leprosy spectrum (TT, BT, BB, BL and LL), but it became difficult to find appropriately matched controls for each case, because the R.J classification was poorly documented. However, the matching method is prone to bias by making cases and controls more similar than they would otherwise be. Therefore, it is not possible to examine the effect of an exposure that has been matched.

In this study, I chose to characterise the somatosensory profile of leprosy patients with NP, and compared the profile among those with leprosy neuropathy and those without. However, the study did not consider the association between the leprosy neuropathy and NP, or the effect of leprosy or exposure to other variables, for these would fall outside the timeframe and objectives of the study. The study would only look at profiling characteristic of leprosy patients with NP at one point in time.

The benefit of a case-control study design is that it can be carried out rapidly and relatively cheaply compared to cohort studies. It is also useful for studying rare diseases such as leprosy that may take a long time to manifest. However, case-control studies are prone to selection bias, particularly in the selection of controls. The design is also prone to information bias, because exposure status is determined after the outcome has occurred. In addition, case-control studies may not provide information about the sequence of events leading up to an exposure or outcome. These studies are also not suitable for estimating disease incidence or prevalence. Therefore, in this this study, I was unable to estimate the occurrence of NP among leprosy patients. I was also unable to establish the causality of NP, and whether leprosy is a consequence or a cause. Information on cause-and-effect relationships can be collected by applying a longitudinal study design.

A cohort study, similar to a case-control study, is observational. Two types of cohort study are known: descriptive and analytic. In descriptive cohort studies, a group of

participants who have experienced an exposure of interest are selected and followed over a period of time to determine the incidence of one or more outcomes. In analytical cohort studies, the association between an exposure and an outcome are tested. Study participants are classified as exposed or unexposed to the risk factor of interest.

Cohort studies are particularly useful for rare exposures and in situations where more than one outcome is of interest. In cohort studies, the exposure is measured at the start of the study before the outcome occurs, and so measurement of the exposure is not biased by the presence or absence of the outcome. These studies can provide data on the time course of the development of the outcome(s), including late effects. Rare exposures can be investigated using appropriately selected populations.

Our study requires the description of the distribution of leprosy NP related to time, place, and person. Since the onset of leprosy is usually gradual, if we want to describe the onset and characteristics of NP, a cohort study would be the best study design. Leprosy is a rare disease, so such a study would require a large study population. In nested case-control studies, both cases and controls are derived from the same population, with controls being representative of a sample of non-cases. The benefit of such study over a case-control study one is that the risk of selection bias is reduced. It would thus seem that a cohort study would be the design of choice as it provides a wider scope, but due to its nature, some disadvantages are unavoidable. Prospective cohort studies are slow and potentially expensive if there is a long period between the exposure and the outcome. They are inefficient for rare diseases. Retrospective cohort studies depend on pre-existing records of exposure being available and being reliable. The exposure status may change during the study in which case exposure status may need to be determined again at intervals throughout the study. Furthermore, differential loss to follow-up may introduce bias, which is a particular problem when follow-up is of a long duration. In long-term cohort studies, it may be hard to ensure that diagnostic criteria remain consistent throughout the study, particularly if outcomes are ascertained from routine data sources. In nested case-control studies, a cohort study needs to be done first. The rarity of disease and long latency are not contra-indications for cohort studies, although their disadvantages need to be balanced against the superior quality of evidence cohort studies deliver compared with other study designs, such as case-control studies.

For this study, a single time case-control study was feasible in the time frame available. This design is quick by nature and it also solves some of the problems associated with the cohort study designs, and most importantly, it can provide information of interest as discussed above.

6.4.2 Study setting

6.4.2.1 Study sites

India

Each year India registers about 130 000 new leprosy patents so doing this study in India is important and will increase the impact of the study (Figure 6.1). For the current study, we collaborated with two Indian centres, The Foundation for Medical Research Indi (FMR) and the Bombay Leprosy Project (BLP), where our leprosy group have successfully recruited to other leprosy studies, 101 patients were recruited for a study on NP. In addition, an ongoing study (TENLEP) associated with Professor Lockwood is also based on these two sites. FMR was chosen for the laboratory work (QST testing), while BLP was acted as sources of patients into our study.

Figure 6.1. Study site – Mumbai

Foundation for Medical Research (FMR)

The Foundation for Medical Research was established in 1975 as a Public Trust and is recognised as a Scientific and Industrial Research by the Government of India. It is a continuation of the founder H. Antia interest in leprosy. Dr Antia is a pioneer plastic and reconstructive surgeon for leprosy and this continuation of his initial interest of leprosy is maintained and extended to involve research on drug-resistant TB and medical plants. The foundation has a well-established laboratory facilities (Figure 2.1).

The leprosy research at the Foundation for Medical Research focuses on neuropathy and leprosy treatment. Dr Shetty, who leading the leprosy group, has a pioneering and sustained research work on mechanisms of nerve damage which has implications for treatment and regeneration. The leprosy group has also been actively involved in assessment of drug regimens for treatment of leprosy and prevention of nerve damage. FMR is also a recognised centre for epidemiological study and its estimate of the current load of leprosy in rural and urban areas challenged the claim of elimination and provided the basis for further course of action by the national control programme.

Figure 6.2. Foundation for Medical Research – Mumbai

Bombay Leprosy Project (BLP)

The Bombay Leprosy Project, founded in 1976, is the largest referral centre for people affected with leprosy and other skin disease in Mumbai. It was established by Dr Ganapati with the objective of improving the quality of life of leprosy patients. The project covers 23 health posts in Mumbai covering a population of approximately 2

million. All consultations at BLP outpatient services and rehabilitation activities are provided free of charge for people affected with leprosy. The services are divided into satellite leprosy daily outpatient's clinic, general clinics for people affected with leprosy and their families, inpatient services in collaboration with Somayia Hospital and clinics for people with other skin diseases. The BLP in particular serves a wide population and receives referrals from all over the city as well as the Maharasha region and the whole country. Also, it has an intensive data on slum record in the city.

An average of 2 to 3 new leprosy cases were diagnosed weekly at BLP over the period from January to June 2013. In addition, an average of 30 to 35 patients were seen daily at the referral centre during the same period and these were mainly leprosy cases with complications, many of whom were referred from regions.

Over the last three decades of leprosy work BLP has reached 1.95 million people of which 60% are from slums of Dharavi and other similar slums in G and H wards of Mumbai (BLP annual report, 2013). 30,000 patients have been cured with MDT. Disabilities have been prevented in 2500 patients. 300 leprosy patients and general handicapped persons have been rehabilitated. In addition to the activity related to diagnosis and treatment of patients, the BLP has been carrying out operational and technical research in the field of leprosy and has published over 300 scientific papers in India and International journals. The efforts of BLP have been highly recognised for its excellence in leprosy research.

Figure 6.3. Bombay Leprosy Project – Mumbai

6.4.2.2 Study team

The study teams from the BLP and FMR clinics received regular training and updates throughout the study. The clinical psychologist had to undergo piloting study questionnaire exercises, and the research assistant had onsite training on diagnosing leprosy and NP. This step aimed to familiarise teams with the study materials and to ensure that they understood the procedures. This was done at the beginning of the study. A joint meeting with the director of the BLP (Dr Pai) and Dr Shetty, senior researcher at FMR (Figure 6.3), was held on a regular basis (every two weeks for the first three months, then monthly till the end of the study). This helped to recruit enough patients and to harmonise the work between the two centres.

6.4.2.3 Study population

Participants and recruitment

The following group of participants were recruited for this thesis:

i. Leprosy patients without pain and no clinical evidence of neuropathy
ii. Leprosy patients without pain and sub-clinical neuropathy
iii. Leprosy patients without pain and established clinical evidence of neuropathy
iv. Leprosy patients with established pain and clinical evidence of neuropathy
v. Healthy control participants, aged matched to the patients group in India
vi. Healthy control participants for QST investigator validation in UK
vii. Healthy control participants for monofilament comparison study in Germany.

Recruitment

Patient recruitment

Patient cohort were recruited from leprosy affected people attending two main centres: the BLP and FMR clinics in Mumbai during the period October 12th 2012 to June 30th 2013 (Appendix 11 and Appendix 12). I attempted to recruit patients across the leprosy spectrum (TT, BT, BB, BL and LL) in each cohort where applicable, but as most of participants were treated patients at the time of the recruitment it was very difficult to retrospectively identify the type of leprosy. All patients had to fulfil the diagnostic criteria for leprosy, which includes hypo-pigmented lesions with definite loss of sensation, thickened peripheral nerves, and acid fast-bacilli on skin smears (Britton and

Lockwood, 2004). All potential participants underwent an initial screening (Appendix 23). Prior to inclusion in the study, patients underwent a comprehensive assessment in order to further determine if they met the eligibility criteria for recruitment. A study team member interviewed each participant using a pre-tested questionnaire. The assessment of each patient took one hour on average. The clinical assessment was comprised of patient's history and pain drawings including the location, description, and intensity of pain. In addition, documentation of clinical evidence of neuropathy were collected and related neurological bedside examinations of sensory and motor function were conducted. Information from medical records and data relevant to peripheral neuropathy and results from any other medical investigations that were available were reviewed. All participants were asked to provide a urine sample for sugar testing and a blood sample for complete blood counts, blood glucose, thyroid function, vitamin B_{12} level, syphilis, HIV and pregnancy (for women).

The patient's records, including the findings of the clinical examination and the available investigations, were reviewed by the investigator. Individuals who were anaemic, diabetic, had hyperthyroidism or hypothyroidism, were B_{12} deficient, had positive serological test for syphilis and/or HIV or women who were pregnant were not eligible to enter the study. These patients were able to access routine services and were also referred to the nearest facility for special service according to their condition. Those who had satisfied the eligibility criteria were invited to take part in the study.

In particular, patients with symptoms and signs suggestive of NP were recruited through a two stage process (Figure 6.4). All patients were screened for neuropathy using MFs and the MRC scale after they signed the informed written consent sheet. Those who had neuropathy were further screened for pain. Of them, patients with pain were assessed for NP using the DN4 questionnaire. Patients who proved to have the two criteria for the case definition were considered as leprosy NP.

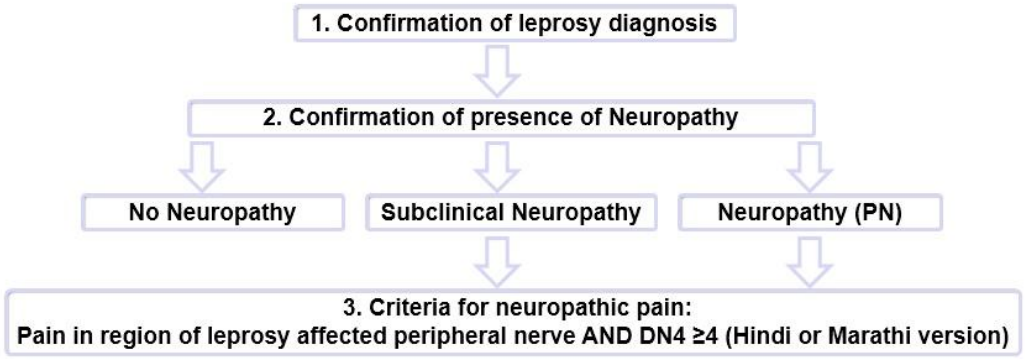

Figure 6.4. Assessment of neuropathy and NP case-definition

PN: Peripheral Neuropathy

Subclinical Neuropathy: Patients with no clinical evidence of neuropathy based on Semmes-Weinstein Monofilaments (MFs) and/ or MRC scale, but who showed abnormal NCS or thermal testing were allotted to "Subclinical neuropathy".

All participants had the following assessments:

- Demographic description and medical and drug history
- Completion of pain questionnaires
- Clinical assessment
- Quantitative sensory testing

Healthy volunteer recruitment

Healthy volunteer participants were recruited from the general population by personal invitation and word of mouth. For the study in India, participants were selected from the patient's relatives attending the leprosy clinic based at BLP and staffs from BLP and FMR. Potential participants were approached and invited to participate in the study (Appendix 5 and Appendix 6). Those who volunteered in response to the invitation were given brief feedback asking them to contact the research team should they wish to discuss the study or be sent further information. Potential participants were given a participant information sheet and then asked to sign a consent form. Eligible participants received a questionnaire about their general health status, the "Participant's State of Health Questionnaire" used in the DFNS guidelines. All participants were asked to provide a urine sample for sugar testing and a blood sample for complete blood counts, blood glucose, thyroid function, vitamin B_{12} level, syphilis, HIV and pregnancy

(for women). Then they underwent a comprehensive clinical examination using DFNS QST measurement parameters.

More details on the recruitment of healthy volunteers in Germany and UK are presented in Chapter 7.

Participants

Patients with leprosy

Eligibility

The study participant had to be a confirmed leprosy case irrespective of whether they were receiving, or had received multi-drug therapy or have symptoms of a peripheral neuropathy. Study specific entry criteria are described below:

Inclusion Criteria

- Able to give informed consent
- Age 18 to 65 years
- Able to comply with the protocol

Exclusion criteria

- A history of concomitant severe infection such as TB or any other serious underlying disease (cardiac, renal, or hepatic) that potentially might affect the evaluation of the patient's pain response.
- A history of other conditions associated with peripheral neuropathy such as Diabetes Mellitus (DM), HIV/AIDS, or nutritional deficiency (Thiamine, B_{12} deficiency)
- Other neurological or psychiatric disease
- A history of regular, excessive intake of alcohol (alcoholism)
- Evidence of Thalidomide treatment
- Evidence of pregnancy or lactating mother
- Insufficient level of communication (i.e., lack of fluency in any of the three languages of the study: English, Hindi, or Marathi).

Healthy controls

Inclusion Criteria

- Signed the written consent form themselves
- Age 18 to 65 years

Exclusion Criteria

- A history of pain and/or paraesthesia and/or nerve lesion in the extremities
- Evidence of pain treatment scheduled for the time of the study and intake of medication during the time of the study (antidepressant, analgesics, or hypnotics)
- A history of surgery that potentially might affect the sensations in the tested site
- Evidence of medical disease
- Other neurological or psychiatric disease
- Insufficient level of communication as described above

6.4.3 Sample sizes

A sample size of 15 participants in each patient group was estimated to be sufficient to adequately assess the sensory changes in leprosy patients with NP. The study was powered against sensory modalities data required to detect the prevalence of sensory changes associated with the risk of developing HIV neuropathy from the pain in the HIV-related neuropathy study (Phillips et al., 2014). The HIV study is one of a few studies using quantitative sensory testing to assess sensory parameters in NP caused by infectious diseases. I had to choose one of the 13 parameters of the DFNS profile on which to conduct our power calculation; since loss of mechanical sensation is one of the primary manifestations of leprosy we determined that this was the most useful parameter. In the previous HIV study, the mechanical detection threshold (MDT) showed a significant difference between the z-scores for QST parameters in multi-ethnic population (MDT mean Z-score difference was 1.4 with a standard deviation of 1.0). The sample size was calculated based on this result, using a standard deviation of 1.0, power of β=90% and significance of α=0.05%.

6.4.4 Ethics and consent practice

The study protocols and recruitment procedures were approved by the following ethics committees in London and Mumbai:

1. London School of Hygiene and Tropical Medicine Research Ethics Committee, ethical approval reference number: 6181 (Appendix 1).
2. Imperial College Research Ethics Committee (ICREC), ethical approval reference number: ICREC_11_2_3 (Appendix 2).
3. Foundation for Medical Research Ethics Committee, IEC No _ FMR/ IEC/ LEP/ 04/ 2012 (Appendix 3).

I undertook two courses in good clinical practice (GCP), one at the LSHTM prior to starting the study, followed by a refresher course (online) organised by Imperial College London. All studies were conducted in adherence to the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Subjects participated in the study after giving written informed consent. The process was conducted by a native Hindi/Marathi speaker after he had fully explained the study and answered any questions. The study information leaflets (Appendix 13, Appendix 14, and Appendix 15) and consent forms (Appendix 20, Appendix 21, and Appendix 22) were available in Hindi, Marathi and in English. Participants were informed that they had the right to refuse to participate without given reasons. They were also assured that they could withdraw at any time from the protocol without giving reasons and without prejudicing further treatment. The consent forms were signed by all participants prior to inclusion in each study (if they were unable to sign, a thumb print was used instead and witnessed by the person obtaining the consent).

6.5 Clinical and laboratory assessment

6.5.1 Patient interviews and examinations

6.5.1.1 Clinical history

The patient's demographic information was collected for age, sex, time since leprosy symptoms first developed, the clinical R-J classification of their disease, treatment with MDT, previous reactions, and past medical history (Appendix 23). A detailed history of

their skin and nerve symptoms was taken. The number and morphology of skin lesions, the presence of peripheral oedema, nerve tenderness, and paraesthesia or nerve pain was recorded. The location of pain was recorded by using a template body map (Appendix 26); the patient marked the distribution of any type of pain he had. Patients were asked about their type of pain, its duration, and the treatment used for it.

6.5.1.2 Measures

Translation

Using standard translation and back translation methods, the English version of all questionnaires including the DFNS-QST protocol were translated into local languages (Hindi/Marathi) by an independent translation centre in Mumbai (Appendix 52). The translated questionnaires were then reviewed by a panel of experts, using the repeated 'forward-backward' procedure. The experts were from BLP, FMR, and the Neurology department at JJ Hospital in Mumbai. They are fluent in both English and Hindi/Marathi as well as the terminology used in the leprosy and pain field. The translation procedure review was conducted several times until an agreement was reached for the final version. The translation procedure is further detailed in Chapter 7.

Patient groups

Patients who were positive on the screening test for pain then completed the DN4, PD-Q, and BPI questionnaires.

Pain intensity

A supervised assessment of patient pain intensity was adopted due to variable barriers of using a pain diary. The patient's weekly average pain intensity was determined using an intensity numeric rating scale which consists of an 11- point numerical scale ranging from "0" (no pain) to "10" (worst possible pain) (Farrar et al., 2001). Patients were requested to describe the weekly average intensity of pain by choosing the appropriate number between 0 and 10 in response to the question, "tell me what number best represents the greatest pain you have had in the last week" (Appendix 23).

The intensity of the various pain components was documented on verbal rating scale (mild, moderate, and severe) as part of PRF.

The worst and average pain intensity over the week preceding the testing session and pain intensity at the time of questionnaire completion were documented on a numeric rating scale as part of PD-Q (0 = no pain, 10 = maximum pain).

Screening questionnaire for NP

Two NP screening tools were used in this thesis to identify the likely presence of suggestive symptoms and signs of NP: the DN4 and the PD-Q. The former questionnaire was used for the case definition in this study. The local version of the DN4 questionnaire (Appendix 29 and Appendix 30) was obtained from our leprosy group study in Mumbai (Lasry-Levy et al., 2011). The PD-Q that was validated in Hindi and Marathi was obtained with permission from Pfizer Medical information, India (Appendix 32 and Appendix 33).

DN4 Questionnaire

The DN4 was applied in an interview format and contained seven sensory descriptor items and three clinical examination items. The latter test for allodynia using cotton gauze and altered sensation (hypoaesthesia) to touch or a pinprick in the painful area. The Hindi/Marathi version of DN4 questionnaire was applied by the local team member in the presence of the principle investigator. The first seven items were answered and the clinical assessment was done by the principle investigator. The scoring of the items ranged from 0 to 1. A score of 1 is given to each positive item and a score of 0 to each negative item. The total score was calculated as the sum of all 10 items, and the cut-off value for the diagnosis of NP was a total score of 4/10 (Bouhassira et al., 2005).

Pain detect questionnaire (PD-Q)

The PD-Q is comprised of nine questions regarding the severity, course, quality and nature of the patient's pain and the specific NP symptoms (Appendix 32 and Appendix 33). The scoring of the sensory descriptors ranged from "0" (indicating that the person does not experience the relevant sensation) to "5" (indicating that the person feels the sensation very strongly). Based on PD-Q results, patients were grouped as follows: unlikely NP (a score of 0-12, which indicates a negative result and a NP component is unlikely); probably NP (a score of 13-18, which indicates an unclear or ambiguous result

that does not preclude a NP component); and definitely NP (a score of ≥ 19, which indicates a positive result and NP is likely) (Freynhagen et al., 2006b).

Brief pain inventory (BPI)

Patients were asked to respond to the Hindi/Marathi version of the BPI (Appendix 35 and Appendix 36), rating their current pain intensity and also pain in the last 24 hours at its worst, least, and average by using a numeric 11-point scale ranging from 0 "no pain" to 10 "pain as bad as you can imagine".

Pain-related interference of activities of daily living was assessed using the pain interference scale of the BPI (Cleeland and Ryan, 1994). The scale assesses pain interference within seven domains: general activity, walking, work, relationships, mood, life enjoyment, and sleep. Patients were asked to rate the extent to which their pain interfered with these seven quality of life domains on an 11-point scale ranging from 0 "does not interfere" to 10 "completely interferes".

All patients

Psychological co-morbidity measures

Psychological factors were assessed with the GHQ-12 (Appendix 37), which is an established instrument used to screen for the presence of mental distress (Goldberg, 1972). In particular, the GHQ-12 asks questions about anxiety and depressive symptoms over the past four weeks (Goldberg and Williams, 1988). The GHQ-12 version, which was validated in Hindi (Gautam et al., 1987), was obtained with permission from Professor Shiv Gautam, former president of the Indian Psychiatric Society (Appendix 38 and Appendix 39). Before asking the GHQ-12 questions, patients were asked to refer to how they had felt during the past four weeks. If they had any unhappy feelings, they were asked what causes contributed to them and how much was due to their pain, leprosy itself, or general life. These responses were all recorded in the PRF. The GHQ-12 questions were administered by a native Hindi/Marathi speaker. The interview lasted 5 – 10 minutes. The patients' responses were scored on a four point scale "not at all", "same as usual", "more than usual" and "much more than usual" giving a score from 0 "no problem" to 12 "severe problem". Higher scores indicated greater psychological distress. For the coding and interpretation of the answers see data analysis section below.

6.5.1.3 Structured clinical examination

A comprehensive structured clinical examination was developed to detect clinical signs of peripheral neuropathy. The clinical examination was performed on each patient and included assessment of neurological examination with special attention to loss of sensation over skin lesions and nerves and disability (Appendix 23).

Neurological clinical assessment

The neurological examination was performed on each patient and included assessment of light touch using cotton gauze and a pinprick sensation using a disposable safety needle. Thermal and vibration perception were assessed as part of QST testing. Joint position sense of the index finger and big toe were assessed and graded as normal or absent. Deep-tendon reflexes (knee, ankle) were also assessed and graded as normal, decreased (if present with reinforcement), or absent. Muscle wasting and motor power were assessed using a modified MRC scale (described below). An abnormal result was taken as two or more symmetrical signs in the hands or feet consistent with peripheral neuropathy.

Skin assessment

The location and appearance of skin lesions and whether they were overlying the course of a peripheral nerve trunk or pain site was recorded on a body map (Appendix 26).

Nerve assessment

Nerve function impairment present for more than six months was recorded. The nerve involved and the functional modality affected (sensory or motor) was also documented.

Nerve thickening and tenderness

The main peripheral nerves, namely the greater auricular, ulnar, median, radial cutaneous, lateral popliteal, and posterior tibial nerve were assessed for enlargement and tenderness. A palpable nerve was assessed clinically by pressing the nerve against bone. The results of nerve palpation, along with the presence of a skin lesion and/or a positive skin smear were used to confirm the diagnosis of leprosy, but it was not considered in the diagnostic criteria for neuropathy in this study.

Nerve function assessments

Sensory nerve function was assessed using a standard set of coloured Semmes–Weinstein monofilaments. The monofilaments were designed to apply a graded test of touch sensibility based on indenting the skin surface with a series of increasing thickness of standard nylon filaments (0.2g, 2g, 4g, 10g and 300g). For each thickness it was recorded whether or not the patient felt the touch. Three sites per nerve in the upper limb and four in the lower limb were tested. The test sites in the upper and lower limbs are shown in Appendix 25. The severity of the sensation impairment was measured by the thickness of the filament felt by the patient. A result of monofilament of 0.2gm for the hand and 2gm for the foot was taken as a normal reference (van Brakel et al., 2005b). A patient was diagnosed as having sensory impairment when the monofilament threshold was increased from the normal reference. In the hands, this was defined as not being able to perceive the 0.2gm monofilament at two points out of three in each nerve of the hand. In the feet, this was defined as not being able to perceive the 2gm monofilament at three out of four sites of the foot.

Motor nerve functions were assessed by voluntary muscle testing (VMT) using the 0-5 modified Medical Research Council (MRC) scale (Appendix 24). An abnormal result in the hands or feet was taken as a decrease in VMT score by one or more points from the normal score of five using the modified MRC scale.

Disability assessment

Leprosy-related disability was assessed using the WHO disability criteria, which defines grade 0 as no loss of sensation or visible deformity, grade 1 as loss of sensation without visible deformity, and grade 2 as presence of visible deformity (WHO, 2006).

The patients' record forms, including the clinical examination, pain symptomatology, quality of life, and psychological co-morbidity measures were administered before the DFNS-QST testing was performed. Of these questionnaires, the sensory testing assessment of the DN4 questionnaire was performed at the area of maximum pain of the ulnar nerve territory (Dermatome C8) just prior to administration of the DFNS-QST testing protocol.

6.6 Quantitative Sensory Testing

6.6.1 Testing sites

Quantitative sensory testing (QST) was performed for all subjects in the ulnar side of the dorsum of the hand bilaterally (supply area of the ulnar nerve dermatome C8) or S1 dermatomes of the foot bilaterally. These sites were defined and documented on each patient's body map during the screening assessment based on the maximum pain in the most affected area as determined by the patients. In patients with bilateral pain, the most painful area was chosen as the test site, and the contralateral mirror site as a control. However, during the course of patient recruitment it became apparent that many patients experienced their maximum pain along the ulnar nerve territories proximal to the dermatome C8 or in other body regions. The pressure pain threshold (PPT) for dermatome C8 of the hand was assessed over the hypothenar eminence muscle. The PPT for the S1 of the foot was assessed over the medial aspect of the plantar. Vibration detection threshold (VDT) of the hand and foot was recorded over the bony prominence of the ulnar (ulnar styloid process) and medial malleolus, respectively (Rolke et al., 2006a, Rolke et al., 2006b). The dorsum of the hand (dermatome C8) was the main site for the QST measurements in this study (Figure 6.5). This site was selected because the ulnar nerve is the most common nerve affected in leprosy, and also to obtain a consistent QST measurement. The lower limb site was selected for patients with foot pain. The reason for recruiting four patients with foot pain was to assess the IENFD.

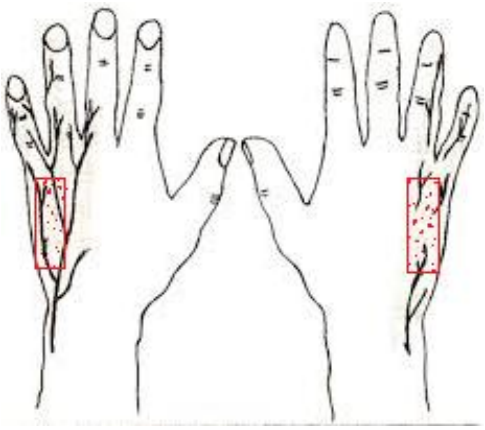

Figure 6.5. QST Testing sites

6.6.2 Testing protocol

QST measures were taken according to the standardised DFNS-QST protocol of the German Network on Neuropathic Pain, using the same equipment and standardised instructions. Applications of the procedure can be seen in the published guidelines by Rolke (Rolke et al., 2006a, Rolke et al., 2006b), and an updated version of the protocol in Hindi and Marathi can be seen in Appendix 41 and Appendix 42. The test was conducted at the FMR laboratory which was quiet, spacious and had a constant room temperature. All measures were performed on each subject by the same investigator, who was trained and qualified in using the DFNS-QST assessments and instructing subjects. Standardised verbal instructions were given to all subject by a native Hindi/Marathi speaker. The subject's positioning remained unchanged for each body site to be tested. All tests were first performed over a demonstration site that was not later tested during the session. This step aimed to familiarise subjects with the tests and to ensure that they understood the procedures. For all patients, testing was performed in a standardised order (i.e. control side was tested prior to affected side) (Rolke et al., 2006a, Rolke et al., 2006b), and for those who were bilaterally affected, the maximum pain site was selected as the test site. For healthy subjects, the control and test sites were determined randomly from the list. The time needed to complete testing of the full protocol per test site was approximately 30 minutes, with the total examination time taking 2–2.5 hours. All QST measures were recorded on a specific data collection sheet provided by the DFNS.

The DFNS-QST protocol comprises a set of psychophysical tests that assess the functional status of specific somatic sensory modalities in the following standardised order:

- Thermal detection and pain thresholds
  - Detection threshold for cold (CDT)
  - Detection threshold for warm (WDT)
  - Difference threshold for cold and heat (TSL)
  - Cold pain threshold (CPT)
  - Heat pain threshold (HPT)
  - Paradoxical heat sensations (PHS)
- Mechanical detection threshold (MDT)

- Mechanical pain threshold (MPT)
  - Detection threshold for pressure
  - Pressure pain threshold
- Stimulus-response functions
  - Mechanical pain sensitivity (MPS)
  - Dynamic Mechanical Allodynia (DMA)
- Wind-up ratio (WUR)
- Vibration detection threshold (VDT)
- Pressure pain threshold (PPT)

A description of the QST procedures and the needed equipment for each test follows:

Determination of thermal detection and thermal pain thresholds

Methods and background: The thermal QST tests were the first modality assessed and consisted of six different parameters. First, thermal detection thresholds for the perception of cold (CDT) and warm (WDT) were measured using the thermal machine, followed by thermal sensory limen (TSL: the different threshold for alternating cool and warm stimuli), to PHS. Then, the thermal testing battery was conducted by measuring cold and heat pain thresholds (CPT; HPT). The method of limits was used (Chong and Cros, 2004). For each threshold test, three repetitions were performed at each site. All thresholds were determined by continuous ramping of temperature by 1^0C/s, which were immediately stopped when the subject pressed a button. The subject was instructed to press the stop-button as soon as the slightest change of temperature (for detection threshold) or the first painful sensation (for pain threshold) was perceived (Appendix 40). The base line temperature to which the thermode returned before each test was 32^0C, and the cut-off temperatures were 10^0C and 50^0C. The contact surface area for the thermode was 2.5 cm x 5 cm. An average threshold was calculated from three measurements in each area.

Equipment: The MSA Thermal Sensory Analyzer (Somedic AB, Farsta, Sweden) was used to determined thermal detection and pain thresholds (Figure 6.6). It is widely used in routine clinical diagnosis to functionally diagnose pain and temperature-conducting nerve fibres (C and A-delta fibres).

Figure 6.6. MSA Thermal Sensory Analyzer – Somedic

Mechanical detection threshold (MDT)

Methods and background: The MDT was determined with a standardised set of modified von Frey hairs that exert forces between 0.25 and 512mN. The threshold was defined as the smallest force necessary for patient perception in response to one von Frey filament bending on the skin. This was determined by performing a modified "method of limits" manner using series of alternative ascending and descending stimulus intensity in five series. Subjects were asked to indicate when they felt the slightest touch of the filament (Appendix 40). The von Frey hairs eliciting 16mN force were applied first, followed by hairs of consecutively lower intensity until the patient could not detect the stimulus being applied. This respective force represents the first threshold value. The order in which the stimuli were applied was then reversed and stimuli of consecutively greater intensity were applied until sensation was detected (this intensity became the second value). Again, hairs with decreasing intensity were applied until in total five upper and lower values of detections were fulfilled from which the mechanical detection threshold was determined. If the first von Frey filament with an intensity of 16mN was not detected, the next highest intensity filament to be detected was used as a starting intensity, and the above procedure were applied. This procedure were repeated five times. The final threshold was the geometric mean of the five series of ascending and descending stimulus intensities (i.e. 10 determinations) (Rolke et al., 2006b).

Equipment: A set of standardised von Frey hairs (0.25 mN, 0.5 mN, 1 mN, 2 mN, 4 mN, 8 mN, 16 mN, 32 mN, 64 mN, 128 mN and 256 mN) (Optihair2-Set, Marstock Nervtest, Schreisheim, Germany). The contact area of the hairs with the skin is of uniform size (about 1 mm2) and texture (rounded contact area to avoid sharp edges, which could facilitate nociceptor stimulation).

Mechanical pain threshold (MPT)

Methods and background: The MPT was measured using a standardised set of pinprick punctuate probes that exert fixed stimulus intensities between 8 mN and 512 mN. The patient's skin response was sensed to the needle probe itself and not to the guided tube. The introduction and removal of the pinprick probes were carried out in smooth movements, allowing the probe to be in contact with the skin for two seconds. The threshold was defined as a geometric average of the MPT in the tested skin area, which was determined by performing a modified "method of limits" using a series of alternative ascending and descending pinprick stimulus intensities in five series. A pinprick probe with 8 mN was used as starting force. The tip of the needle was gently placed perpendicular to the skin's surface, then a weight was applied. Subjects were asked to indicate if the sensation was felt "sharp" or "blunt". Beginning with an applied force of 8 mN stimuli, intensity increased until the sensation induced was described as "sharp". The corresponding force used represented the first threshold value. To follow, the order in which the stimuli were applied was reversed by applying stimuli of consecutive lower intensities until the quality of the sensation was detected as not sharp (i.e. blunt). This force became the second value. The procedures were continued in this fashion until, in total, five first and second values of detection were completed from which the MPT was determined. The final threshold was the geometric mean of five series of ascending and descending stimulus intensities (Appendix 40).

Equipment: A set of seven metal probes with standardised stimulus intensities (8 mN, 16 mN, 32 mN, 64 mN, 128 mN, 256 mN and 512 mN) (MRC Systems GmbH, Germany) with uniform skin contact area (0.2 mm diameter). Penetration of the skin with these stimuli is not possible.

Stimulus-response functions: mechanical pain sensitivity (MPS) for pinprick stimuli and dynamic mechanical allodynia (DMA) for light touch

Methods and background: The MPS was assessed using the same weighted pinprick probe stimuli of different stimulus intensities as for MPT. These seven pinprick stimuli were applied in a balanced order; each stimulus was applied five times. Subjects were asked to give a pain rating for each stimulus on an NRS (range 0–100) where 0 means "no pain" but is not synonymous with "not felt/ detected" (Appendix 40). An undetected stimulus should be noted as Ø. The most intense pain imaginable is represented by 100. Pain in response to light touch (i.e. DMA) was tested using innocuous stimuli (Q-tip, cotton wisp, and soft brush) applied in between the pinprick stimuli in balance and standardised order, and subjects were asked to give a rating on the same scale as for pinprick stimuli. The tests for MPS and DMA were applied given in runs of 10 (five runs per test sites) and each run consisted of a different randomised sequence of seven pinprick stimuli and three tactile stimulus. MPS was calculated as the geometric mean of all numerical rating for pinprick stimuli and DMA as the geometric mean of all numerical rating across all three different types of light touch stimulators. Thus, a stimulus-response function aimed to explore whether a hyper- or hypoalgesia or mechanical allodynia was present.

Equipment: A set of seven metal probes with standardised stimulus intensities (8 mN, 16 mN, 32 mN, 64 mN, 128 mN, 256 mN and 512 mN) (MRC Systems GmbH, Germany) with uniform skin contact area (0.2 mm diameter). In addition, a set of three light intensity stimuli: a cotton wisp (3 mN), a cotton wool tip (Q-tip) fixed to an elastic strip (100 mN), and a paint brush with an applied force of between 200 mN and 400 mN was used.

Wind-up phenomenon (WUR)

Methods and background: WUR is the perceptual correlate of temporal pain summation for repetitive pinprick stimuli. In this test the perceived magnitude of a single pinprick stimulus (256 mN) was compared with that of a series of 10 pinprick stimuli of the same force repeated at a 1/s rate within an area of 1 cm^2. The time interval was standardised using a metronome timer (Korg MA-30, Japan). In general, immediately following the single stimulus and series of stimuli, an evaluation of the sensation was provided according to a verbal numerical scale (0–100: 0, "no pain"; 100, "most intense pain imaginable"). First, a single stimulus was applied and the subject was asked to give a pain rating for this stimulus. Then the repeated stimuli were applied and the subject was requested to give a pain rating representing the pain over that whole

series of the 10 stimuli. This procedure of single pinprick stimuli was alternated with the series of 10 stimuli until both were performed five times at five different skin sites within an area of 1 cm^2 of the same testing site. A geometric average of the "wind-up" was calculated from the five ratios (Appendix 40).

Equipment: A single pinprick stimulus with standardised intensity (256 mN) of the pinprick set applied in a flat contact area of 0.25 mm diameter.

Vibration detection threshold (VDT)

Methods and background: A standardized tuning fork (64 Hz) was used for the measurement of vibration detection threshold. The tuning fork had two arms, both of them with calibrated weights at their ends. A shape of an elongated triangle and a nine-point arbitrary scale from 0–8 beside the triangle were imprinted on each weight. Once the turning fork start to vibrate, the triangle on each arm appears as two virtual, intersecting triangles. The triangles moves exceptionally up the scale, as the arms' vibration decreased. Once the subject indicated that the vibration was no longer felt, the nearest value (to the closest half-point) to the point of intersection of the triangles was then recorded as the vibration threshold. The threshold was determined by performing three series of descending stimulus intensities decided from the "wandering" tip of a triangle moved by means of the vibration and indicated on the tuning fork that was placed over a bony prominence of the ulnar (ulnar styloid process) for upper extremities or medial malleolus for lower extremities (Rolke et al., 2006b). It was measured three times as the amplitude at which the vibration was no longer detected, which was indicated verbally (Appendix 40).

Equipment: A Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) (Martin, Tuttlingen, Germany) as used routinely in the clinic (Figure 6.7).

Figure 6.7. Tuning fork

Pressure pain threshold (PPT)

Methods and background: The deep PPT was measured above the hypothenar eminence muscle of the test and control sites. Pressure was increased continually using a pressure stimulus (with an application rate of approximately, 0.5 kg/s corresponding to 50 kPa/s) until pain was indicated verbally by the subject. The subjects were asked to say "now" as soon as the sensation changed from pressure alone to pressure and pain. An average of three measurements per site were taken and the mean value of these was used for analysis (Appendix 40).

Equipment: A blunt mechanical stimulus (contact area of the probe is 1 cm^2, applied force up to 20 Kg/2000 kPa/200 N), with an in-built pressure gauge (Pressure algesiometer Wagner Instrument – Somedic AB, Farsta, Sweden).

6.7 Data recording and management

6.7.1 Overview

All data were recorded during the interview assessment on standardised patient record forms (PRF) (Appendix 23). The study forms were kept in a separate set of case notes from the usual clinical records. All study records were kept in a locked area accessed only by two nominated study team members.

The EpiData 3.1 software, which has an adequate electronic data capture module especially for data validation, was chosen as a database for the study. The design and

development of the database was done by me. The EQUISTA database system (described below), which was developed and provided by the DFNS, was used for the QST data.

6.7.2 Data preparation

Various steps were taken to prepare the data for statistical analysis. The completed questionnaires from healthy participants and patients were checked for missed and/or unclear answers. Data from the PRF and questionnaires (GHQ-12, BPI) were coded to represent the category they belonged to, for example, female subjects were assigned the code 0, and males were assigned 1. The coding sheets were designed before starting data collection. The coding system was standardised to maintain consistency through all data sets. The data were then verified and entered from the PRF into the data base by myself. As there were validation checks in the EpiInfo, the single entry was considered viable to ensure that the recorded data on the PRF was transcribed into the database. In addition, double entry was done for five patients who were randomly selected for validating the quality of data entry process.

6.8 Statistical analysis

6.8.1 Strategy of analysis

Data analysis was conducted using Stata/IC version 13.1 (Stata Corp LP, College Station, Texas, USA). Further, QST data analysis was conducted using GraphPad Prism version 6.0 for Windows (GraphPad Software, San Diego California, USA). Patients with NP or who had a GHQ-12 of three or above (i.e. symptoms and signs suggestive of depression) were considered as cases and the outcome was coded as 0 or 1 for the purposes of logistic regression. The controls were selected from group 1, 2, and 3, and from healthy volunteers.

The statistical analysis was conducted in two steps: descriptive and analytical. The descriptive analysis was carried out for all patients and in groups; the participants were described in terms of demographic data and their responses to study questionnaires. The second step was the test for the association between exposures and outcome variables. Data is presented throughout as mean ± standard error mean unless stated otherwise. The QST measures were plotted as dot plots with overlaid box plots for mean/median, variance (box), and range (bars).

The statistical tests used were: paired and unpaired Student's t-tests; the Mann-Whitney U test (also called Wilcoxon rank-sum test); the Kruskal-Wallis test; Pearson's Chi-squared test; and Spearman's correlation coefficient. A statistical advisor supervised the statistical analysis of the data and verified the appropriateness of the tests. The flow chart of the appropriate statistical tests is shown in Figure 6.8.

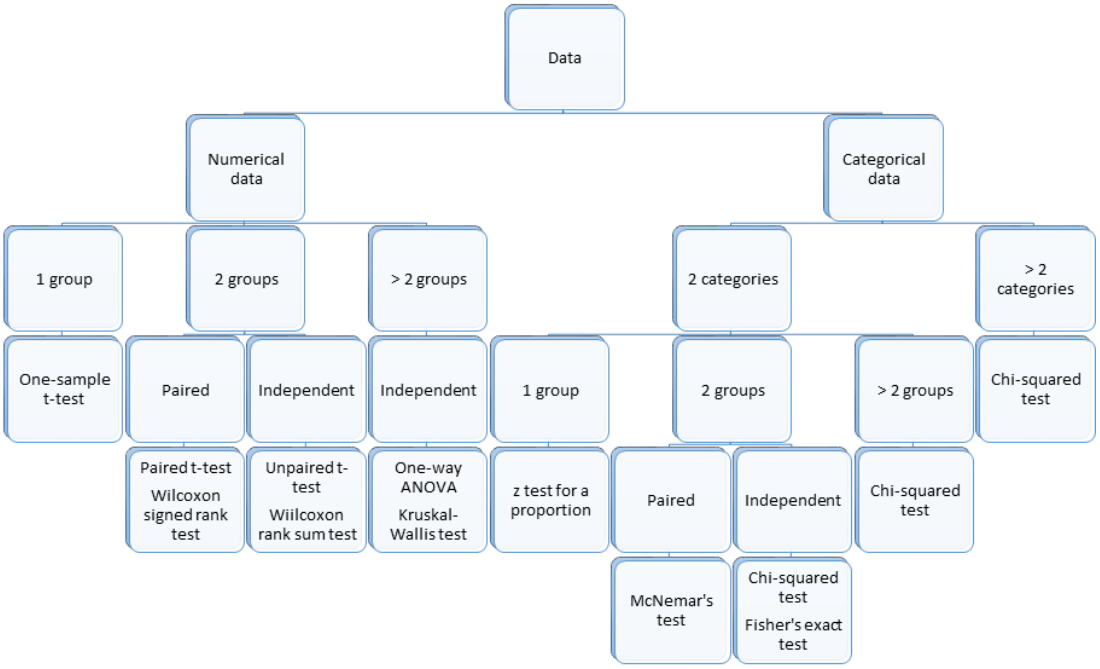

Figure 6.8. Flow charts indicating appropiate statistical test

The flow chart shows the appropriate techniques in different circumstances. Modified from basic statistics road map by Petrie (Petrie and Sabin, 2009)

The normality of the distribution of the continuous data was assessed by generating normal histograms for the variables of interest. Two steps were performed to check for the skewed or non-normal results: first the bell-shape was checked based on the eyeball test, then a confirmatory test was performed using the Shapiro-Wilk test. The null-hypothesis for this test is that the variable has a normal distribution - a non-significant result indicates normality. In case the assumption of normality could not be rejected then a parametric test was applied. If the assumption of normality was not reasonable and had to be rejected then the non-parametric Mann-Whitney U test was applied. The unpaired Student's t-tests were performed to assess for significant differences between

two independent samples testing one variable. One-way ANOVAs were used to assess for significant differences between two or more independent samples with one variable tested. The two-way ANOVAs were calculated to assess for significant differences between two or more independent samples with two variables tested. Non-parametric tests were used to assess statistical significance. The Mann-Whitney U test was used to assess non-parametric result. The Mann-Whitney U test was used for all statistical tests of continuous variables and Fisher's exact test was used to compare dichotomous variables. A significance level of at least p-value ≤0.05 was used to state whether a result was significant or not, unless stated otherwise. The number of data values that were included in the calculation was represented by "n".

6.8.1.1 Descriptive analysis

In this study the distributions of each of the variables were created to see the characteristics of the study population and the validity of the data. For quantitative data, the frequency of distribution, cumulative relative frequency, and percentage were calculated. For each grouping variable, such as age, the minimum and maximum values were obtained and the row data were checked for the accuracy of the limits. The variable age was divided into five age-group (18–19/20–29/30–39/40–49/50–59). However, the scarcity of events led to a new grouping for analysis purposes. Therefore, during multivariate analysis, age was categorized into two groups ≤30 years and >30 years. This cut off (30 years) was used as the median age skewed to the right on the age histogram. Similarly, the period of symptoms prior to diagnosis was grouped into the delay in presentation and divided into <six months, from six months to one year, and >one year. Other variables that were grouped were: thickened nerves, tender nerves, sensory impairment, motor impairment, and depression. These were grouped into present or absent. Mean, median, and mode were calculated as measures for data location. Range, percentile, and standard deviation (SD) were calculated as measures of data spread. The mean and its confidence interval (CI) were reported for continuous normally distributed variables, whereas the median and inter-quartile range (the difference between the 25th and 75th quartiles) were reported for non-normally distributed variables.

Data were also displayed in graphs. Bar and/or pie charts were used for graphing frequency distribution of categorical data, while for the quantitative continuous data the histogram was used. Bar charts were also used to represent qualitative data.

Brief pain inventory (BPI)

The descriptive statistics including mean, SD, median, and interquartile range were calculate for each patient. To further explore BPI, the worst pain score was taken as a reference point, and all patients with a baseline pain score of 0–3 were labelled as having mild pain, all patients with a baseline pain score of 4–7 were labelled as having moderate pain, and all patients with a baseline pain score of 8–10 were labelled as having severe pain. Pearson correlations were then performed to assess associations between all of the BPI pain scores in relations to the GHQ-12 scores within each group.

General health questionnaire (GHQ-12)

The scoring procedure and calculation methods were applied according to recommendations by the author of the GHQ (Goldberg and Williams, 1988). The binary scoring using the 0 0 1 1 method for questions on the GHQ, with 0 signifying absence of illness was used. The threshold value of three was made to maximise sensitivity. Previous studies on leprosy mental disorder used a threshold values range from two-to-four (Bhatia M.S et al., 2006, Senturk et al., 2007, Haroun et al., 2012, Jindal et al., 2013). The cut-off point of three was considered appropriate, as the utilisation of the GHQ-12 in my study was to identify the probable cases and not definite ones. In addition, the mean GHQ-12 score of three for the previous study on psychological disorders among treated leprosy patients with NP in Mumbai (Lasry-Levy et al., 2011), also provided a guide to the best cut-off points as suggested by Goldberg and colleagues (Goldberg and Williams, 1988).

Descriptive statistics including mean, standard deviation, median, and interquartile range were calculated for GHQ-12 items. I first graphically compared the distributions of the male and female scores for leprosy patients. I then compared the scores between patients with no neuropathy, neuropathy, and NP.

6.8.1.2 Analysis

Logistic regression was used for the analysis to produce odds ratios and 95% confidence intervals for the associations and p-values for any differences in proportions seen using the Pearson's Chi Squared Test, and Mantel Haenzel Odds Test. P-values ≤ 0.05 indicated significance. Analysis was done at two levels: first univariate analyses followed by multivariate analyses.

Univariate analysis

Initially univariate analysis was applied to assess any possible univariate association between all the potential variables and outcomes. It was used to look at the strength of associations of the NP (Appendix 46), depression outcomes (Appendix 48), and the differences between two groups.

Multivariate analysis

To investigate the association between these variables more closely, a logistic regression model was developed adjusting each variable for the other one. First multiple logistic regression was carried out to look at groups of variables together, followed by stepwise logistic regression, which identified an overall simplified model including only the important variables. Using this model, variables were added using step-wise methods. They were added in the order of effect estimated from the univariate analysis (Appendix 47 and Appendix 49).

6.8.2 QST data analysis

QST data were first entered into an Excel-based spreadsheet (Excel 2007, Microsoft USA) data analysis system provided by the DFNS (EQUISTA, Casquar GmbH Germany). EQUISTA was designed for data entry of patient demographic and QST raw data. The programme automatically performed z-score transformations of raw QST data values by comparing them against normative reference data published by the DFNS (Magerl et al., 2010); generated thresholds, average ratings, and numbers of observed paradoxical heat sensations. The obtained data were entered into Prism 6 (GraphPad Prism 6.02) to generate specific QST graphs.

QST data transformation

The mathematical transformation of QST data to z-scores has been described by Rolke and colleagues (Rolke et al., 2006b). QST data were log-transformed (log10 units) prior to statistical analysis except HPT and VDT which were normally distributed as raw data (Rolke et al., 2006a, Rolke et al., 2006b). To compare a patient's QST data profile with control data independent of the different units of measurement across QST parameters, the patient's data were z-transformed for each single parameter by using the following expression:

$$\text{Z-score} = (\text{X [single patient]} - \text{Mean [healthy controls]})/\text{SD [healthy controls]}$$

Z-score values were calculated based on the included healthy control group data. This approach allowed site-specific normalisation of QST data, where each individual parameter was related to its age, gender, and anatomical test site-specific reference range. This procedure resulted in a QST profile where all parameters were displayed as the number of standard deviations above or below the healthy controls. The algebraic sign of z-score values was adjusted for clarity of presentation for each parameter so that it reflects the patient's sensitivity for this parameter. Z-scores above 0 indicate a gain of function, where the patient is more sensitive to the tested stimuli compared with healthy controls (hyperalgesis, allodynia, hyperpathia), while z-scores below 0 indicate a loss of function, referring to lower sensitivity (hypoaesthesia, hypoalgesia) of the patient. Thus, elevations of threshold for any of the 13 parameters measured resulted in negative z-scores.

After this z-transformation it was straightforward to compare a single patient with the group mean of healthy controls, since the reference range of a standard normal distribution is defined as follows:

$$95\%\ \text{reference range} = \text{Mean [healthy controls]} \pm 1.96\ \text{SD [healthy controls]}$$

The QST scores for individual patients and groups were summarised and presented graphically. Significance was accepted at p-values <0.05 for all analyses. The correlation between leprosy pain symptomatology and physiological and psychological morbidity were assessed by fitting an analysis of rank correlation using Spearman's test.

The DFNS coding system published by Maier and colleagues (Maier et al., 2010) was used to examine combinations of somatosensory function in leprosy patients with neuropathy and pain. A value of 0 was designated for a QST parameter that was found within the normal DFNS reference range; the presence of loss of thermal modalities (i.e. a loss of WDT or CDT) was designated as L1, and the presence of loss of mechanical modalities (i.e. the loss of MDT or VDT) was designated L2. Gain of sensory function to thermal modalities was designated G1 and gain of sensory function to mechanical modalities as G2. When both thermal and mechanical abnormalities were present they were designated as L3 and G3 respectively.

Chapter 7 Validation studies

This chapter describes the pre-implementation work which was conducted prior to the introduction of the main QST profiling study. This stage aimed to validate the investigator, local centre, and population in India in using the DFNS-QST protocol. Further, the training courses on clinical assessment of NP are also discussed. Finally, the chapter presents reflective approaches to simplify the DFNS-QST protocol.

7.1 Background

Normally for the validation of a new investigator or centre for a certification protocol of QST laboratories, the DFNS requires 18 healthy controls in order to validate compatibility (Geber et al., 2009). This is for quality internal assay control purposes to ensure that the values obtained for this population are within the normative ranges held in the large German Research Network on Neuropathic Pain database (DFNS) and giving the guarantee to deliver highest possible objectivity within the range of psychophysical testing.

Two validation studies were conducted among healthy volunteers in London (18 participants) and Mumbai (52 participants). The first study was done in London with 18 healthy volunteer participants. However, in term of validating the site in India, I decided to increase this number to 30 in case there were environmental site differences and ethnic differences in the population studied, since the DFNS normative data were almost entirely collected in European centres with predominately Caucasian population. Should the normative data from this site have differed from those held in DFNS database, we would have been able to use this local population of 30 healthy controls for data analysis. An additional reason for selecting more local Indian healthy volunteers was the targeted number for skin biopsy. As obtaining a biopsy from this population was challenging, the recruitment was continued till I reached 30 participants with both QST and biopsy. The validation studies were important preliminary work in order to conduct a comprehensive somatosensory profile of leprosy patients with NP in a resource-limited setting.

7.2 Overview of my preparation in this PhD research

During my PhD research in Professor Lockwood and Professor Rice's laboratories, I sought to understand the clinical aspects of NP in leprosy. Throughout this time I was continually developing my experience by attending lectures, seminars, meetings, international conferences and training days, all of which employed various teaching and learning techniques. In particular, the training in clinical assessment of NP that I had was as follows:

- Professor Lockwood's clinic (Leprosy clinic at HTD)
- Professor Rice's clinic (Pain clinic at CWH)
- Professor Hadi Manji's clinic (Neurology clinic Queens Square)
- Neuropathic pain training course in Finland (Professor Aki Hietaharju)
- DFNS-QST Training course in Germany (Professors Maier and R-D Treede)
- Dr Bennett's lab (Skin biopsy techniques at KCL)

I developed a broad knowledge of leprosy and NP, and gained the technical skills necessary to clinically assess patients with NP. The knowledge and technical skills obtained have been critical during my PhD research.

7.3 Healthy volunteers study to validate investigator

7.3.1 Introduction

In order to obtain accurate data, high quality training and validation of QST investigators is essential. This training occurs in two phases: firstly the investigator visits a training centre in Germany to be trained in the technique (Geber et al., 2009). The QST-training includes information on the equipment, the investigation technique, recommended procedures for quality control and analysis and interpretation of results. Secondly, the investigator is validated by performing QST on a number of healthy volunteers; these data are then submitted to the central DFNS database in order to check their validity against a large normal dataset. I qualified in the use of DFNS-QST protocol after attending QST-training in Bochum, Germany, and completed the healthy volunteers study in London.

7.3.2 Participants and methods

I examined the QST sensory parameters in 18 healthy participants aged between 18 to 55 years (mean ages 32.2 years, SD 9.8). There was more female (n= 11; 61%) than male (n= 7; 39%) included in the study. Participants were recruited from the general population and/or staffs and students from the LSHTM and ICL by personal invitation and word of mouth (Appendix 4). Participants were screened for relevant medical history and were specifically questioned about migraine headaches and low back pain. Participants suffering from any acute or chronic pain condition were excluded. All participants were without any pain medication for at least 24 hours before the investigation (Appendix 43). The study was approved by the Imperial College Research Ethics Committee (ICREC_11_2_3) (Appendix 2). All subjects participated after giving written informed consent.

I assessed the sensory parameters in the dorsum of the hands: the ulnar side of the dorsum of the hand (supply area of the ulnar nerve territory, dermatome C8) and the radial side (supply area of the radial nerve, territory C6), using DFNS-QST protocol. Testing took 30 minutes per site. The study was conducted at Chelsea and Westminster Hospital. The detailed testing procedures of the DFNS-QST protocol are described in Chapter 6, in summary the following parameters (Figure 7.1) were assessed:

Thermal detection and pain thresholds and the number of paradoxical heat sensations: The thermal tests were performed using a MSA (SOMEDIC, Sweden, available in three centres). Cold and warm detection thresholds were measured first (CDT, WDT). In addition, subjects were asked about PHS during the thermal sensory limen (TSL) procedure of alternating warm and cold stimuli. Then cold pain and heat pain thresholds were determined (CPT, HPT). The mean threshold temperature of three consecutive measurements was calculated.

Mechanical detection threshold: MDT was measured with a standardised set of von Frey hairs that exerts forces upon bending between 0.25 mN and 512 mN. Using the methods of limits, five thresholds determination were made, each with a series of ascending and descending intensities. The final threshold was the geometric mean of these five series.

Mechanical pain threshold: MPT was measured using pinprick stimuli as a set of seven pinprick mechanical stimulators with fixed stimulus intensities that exerted forces of 8 mN, 16 mN, 32 mN, 64 mN, 128 mN, 256 mN, and 512 mN. The stimulators were applied at a rate of 2 second on, 2 second off in an ascending order until the first percept of sharpness was reached. The final threshold was the geometric mean of five series of ascending and descending stimuli.

Mechanical pain sensitivity: MPS was assessed using the same set of seven weighted pinprick stimuli to obtain a stimulus–response function for pinprick-evoked pain. Subjects were asked to give a pain rating for each stimulus on a '0–100' numerical rating scale ('0' indicating "no pain", and '100' indicating "most intense pain imaginable").

Dynamic mechanical allodynia: ALL was assessed as part of the test above, using a set of three light tactile stimulators as moving innocuous stimuli: Cotton wisp exerting a force of 3 mN, a cotton wool tip fixed to an elastic strip exerting a force of 100 mN, and a standardized brush exerting a force of 200–400 mN. The tactile stimuli were applied with a single stroke of approximately 2 cm in length over the skin.

Wind-up ratio: Participants were asked to give a pain rating intensity of a single pinprick stimulus (256 mN pinprick) this was compared with the estimated mean over the whole series of 10 repetitive pinprick stimuli of the same physical intensity (1/s applied within an area of 1 cm^2) using a '0–100' numerical rating scale. The whole procedure was repeated five times. WUR was calculated as the ratio: mean rating of the five series divided by the mean rating of the five single stimuli.

Vibration detection threshold: VDT was performed with tuning fork (64 Hz, 8/8 scale) that was placed over ulna styloid process and a head of the radius, and left there until the subject could not feel vibration any more. VDT was determined as a disappearance threshold with three stimulus repetitions.

Pressure pain threshold: PPT was performed over the thenar and hypothenar muscle with a pressure gage device with a probe area of 1 cm^2 that exerts forces up to 20 kg/cm^2 corresponding to 2000 kPa. The pressure pain threshold was determined with three series of ascending stimulus intensities, each applied as a slowly increasing ramp of 50 kPa/s (0.5 kg /cm^2 s).

Figure 7.1. Complete set of QST devices

Picture taken from Professor Rice's lab, 2012

7.3.3 Data evaluation and results

Data entry and transformation was carried out using the Equista database that developed by the DFNSp. The following analyses were carried out:

i. Comparison of the results to the 95% confidence interval of the DFNS reference data base.
ii. Number (percentage) of abnormal values
iii. Calculation of Z-values: data are presented as mean ± SD and based on the DFNS reference database, I calculated the z-score for each participant:

    Z-score = (value [single participant] - Mean [controls])/SD [controls]

iv. Statistical analysis of the z-values of right vs. left ulnar and right vs. left radial using t test for the differences between the parameters within each group.

The result was compared to the 95% confidence interval of the DFNS reference data base, DFNS. Of the total 18 subjects only one had 3 parameters; namely (CPT, HPT and VDT) for the test side, Figure 7.2, and (WDT, CPT and HPT) for the control side, Figure 7.3; which fell outside of the DFNS reference database. The percentage of abnormal values in this group is less than 5% and it is therefore acceptable for DFNS investigator validation.

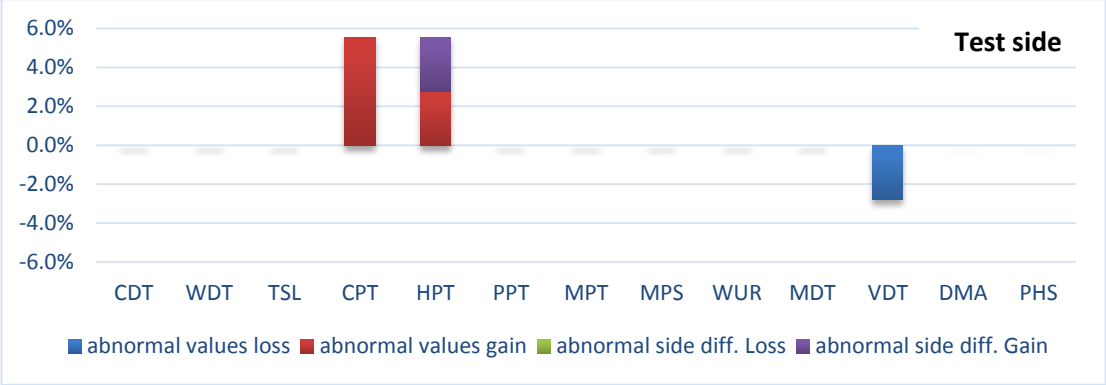

Figure 7.2. Abnormal parameters in test area compared to DFNS reference

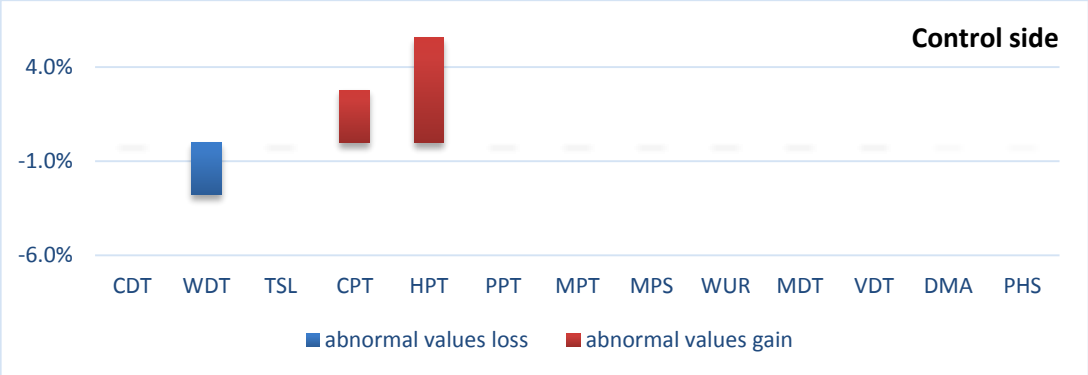

Figure 7.3. Abnormal parameters in control area compared to DFNS reference

Of the 13 parameters obtained for 2 body regions, dynamic mechanical allodynia did not occur among healthy subjects. No significant right-left differences for the ulnar nerve side were observed (p-values for each parameters where greater than 0.05 and range from 0.1 to 0.9) except for MPS (p-value < 0.05) (Figure 7.4 and Figure 7.5).

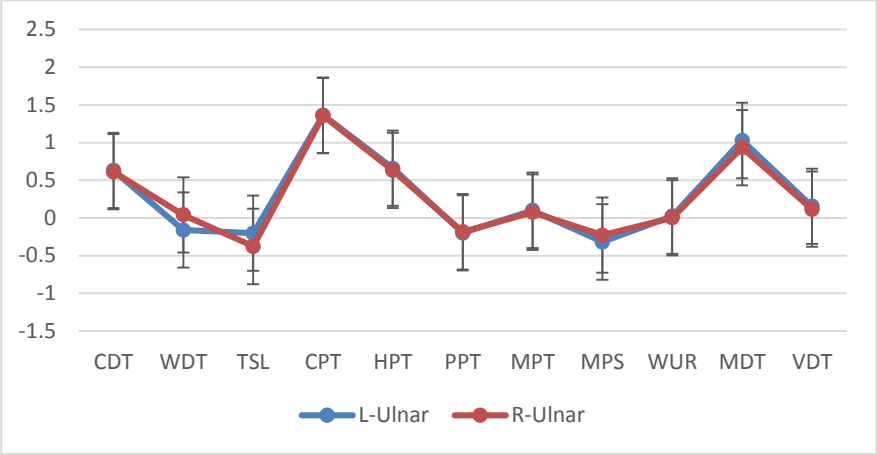

Figure 7.4. Z-score of Rt vs. Lt ulnar of the 18 subjects compared to DFNS

Graph shows the Ulnar nerve mean values and 95% confidence intervals of all QST parameters in 50 healthy volunteers. The upper confidence limits of all QST parameters were within the limits of the reference data. Rt: Right, Lt: Left

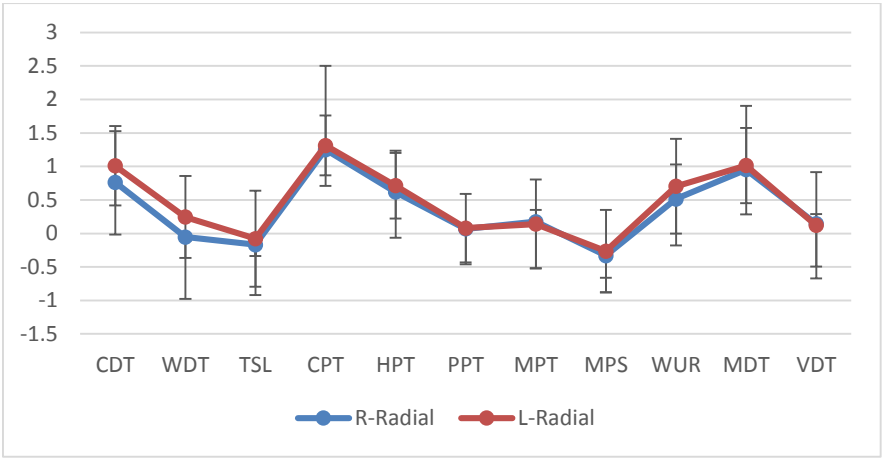

Figure 7.5. Z-score of Rt vs. Lt radial of the 18 subjects compared to DFNS

Graph shows the Radial nerve mean values and 95% confidence intervals of all QST parameters in 50 healthy volunteers. The upper confidence limits of all QST parameters were within the limits of the reference data. Rt: Right, Lt: Left

7.3.4 Discussion

Despite using crude thermal sensory testing for more than a century in the assessment of neuropathy in leprosy patients, its application in clinical and research practice has been limited (Backonja and Lauria, 2010). The DFNS-QST test is a standardised protocol, including standardised instructions for the investigator and subject. It is a non-invasive method used comprehensively to assess the function of both un-myelinated and thinly myelinated small fibres, as well as of the large fibres. Therefore, it has ability to characterise somatosensory functions across the full spectrum of nerve fibres (Krumova, 2010), (Table 7.1). In addition, because it tests the entire system from transduction to perception, the loss of function which manifested clinically as sensory deficit, and the abnormal facilitatory phenomena, which clinically present as various manifestations of pain, can be easily assessed (Walk et al., 2009). It also characterises the function of nociceptive system, which is not possible with standard methods of clinical electro-neurophysiology (Cruccu et al., 2004). These factors make it an appropriate tool for assessing sensory parameters related to pain in leprosy patients.

Table 7.1. Sensory functions represented by different QST parameters

Axon type	QST parameters
Aβ-fibre	Mechanical detection threshold for von Frey hairs and vibration tests
Aδ-fibre	Cold detection threshold and the mechanical pain threshold for pinprick stimuli
C-fibre	Warm detection threshold and heat pain threshold

Furthermore, recent guidelines on NP assessment recommend the importance of exploring QST for prospective therapeutic outcome prediction (Haanpaa et al., 2010). In a study by Dyveke and colleagues, the differentiation between the DFNS somatosensory profile of sensory loss and gain functions was found useful to predict the responses to treatment. This was a randomised, double-blind, placebo-controlled, and phenotype-stratified clinical trial in which 97 patients with peripheral NP due to polyneuropathy were treated with oxcarbazepine or placebo in two 6-week periods. The authors reported that oxcarbazepine is more efficacious for relief of NP in patients with a sensory gain profile than with a sensory loss profile (Demant et al., 2014).

7.4 Healthy volunteers study to validate local centre and population in India

7.4.1 Introduction

The aim of this study was to validate the QST parameters in the Indian population and the site centre. This was for the purposes of internal assay quality control to ensure that the values obtained for this population were within the normative ranges held in the large DFNS database, which is based on data from European centres and mainly Caucasian subjects.

7.4.2 Participants and methods

7.4.2.1 Study design

This study was initiated as a prospective study to investigate the DFNS-QST protocol in an Indian population. It was done at the FMR clinic, from October 2012 to June 2013.

The study was conducted according to the principles of research in humans specified in the Declaration of Helsinki. Ethical approval was obtained from the local Ethics committee of the Foundation for Medical Research, Mumbai, India (IEC No _ FMR/ IEC/ LEP/ 04/ 2012) (Appendix 3).

7.4.2.2 Participants

Fifty-two healthy Indian participants, 28 women and 24 men, mean age 30.75 years, range from 18 to 56 years, were recruited in the study (see section 6.4.2.3). All subjects participated voluntarily after giving written informed consent. Participants were excluded if they had been diagnosed with, or suspected to potentially have, any neurological disease including different forms of neuropathy, cutaneous lesions in the tested site, systematic disease, chronic pain, or were taking medication during the time of study (see Methods section 6.4.2.3). Of the 58 volunteers screened for the study, six subjects were excluded. Of these, four had a low Vitamin B_{12} level, one was anaemic and one was pregnant. Travel expenses were reimbursed for all volunteers including those who were excluded.

7.4.2.3 DFNS-QST protocol translation

A rigorous method for translating and checking DFNS-QST protocol was adopted. The forward-translation and back-translation methods were used. This process was only of

rigorous translation, but the protocol was not validated (Maki et al., 2014). The aim of the translation was to achieve an Indian version of the English DFNS-QST questionnaire that was cross-cultural and conceptually equivalent to the local Indian population (Maki et al., 2014, Maneesriwongul and Dixon, 2004). The validation process, which is the process of investigating the reliability, conceptual equivalence, and content validity of translations of questionnaires measures, is beyond the scope of this thesis to explain it in detail. The guidelines provided by WHO were considered during the translation process (WHO, 2014).

Forward translation was conducted first by an independent translation centre in Mumbai (Appendix 52). The local language versions were then reviewed by a member of our research team, Ms Maitreyi Nigwekar, who is a bilingual clinical psychologist. She is familiar with the psychophysical terminology of the DFNS-QST instrument and instructions, as well as being equipped with the interviewing skills required for the task. Also, she is fluent in written and spoken English and is a native speaker of Marathi Indian.

Using the same approach as that outlined in the forward translation, the protocol was then translated back into English by an independent translator (Appendix 52). Final consensus versions were conducted via an expert panel. The panel included the original translator, a clinical psychologist and Dr S. Khadilkar, a neurologist from the Neurology department at JJ Hospital. The panel also included Dr Pai from BLP, Dr Vanaja Shetty, Ms. Capadia and Dr Pandya from FMR. They are fluent in both English and Hindi/Marathi, and are familiar with the terminology used in the leprosy and pain fields. The local language versions were reviewed by the panel and any inadequate expressions/concepts in the translation were identified and discussed. In addition, any discrepancies between the forward translation and the existing or other comparable previous versions of the questions were discussed. Discrepancies were discussed until a satisfactory version was agreed. The translation procedure review was conducted several times until an agreement was reached for the final Hindi/Marathi version.

Following completion of the translation work, the final versions of the translated protocol were sent to the DFNS for approval. Pre-testing of the protocol on the target population was done before the final version was used for the study. The pilot was tested on a sample of five participants: two volunteers from FMR staff and three patients from the BLP clinic. The goal in this step was to test the DFNS-QST

instructions and the time taken to complete an interview. The main methodological change and modification as a consequence of the piloting was to test only one site. The decision to restrict the site of the test to the hand (dermatome C8 bilaterally) instead of the hand and feet was made in order to minimise the duration of the interview.

7.4.2.4 Recording techniques and testing protocol

The DFNS-QST protocol was tested bilaterally on a defined area on the dorsum of the hand (sensory region of the ulnar nerve, dermatome C8) or dorsum of the foot (dermatome S1). Participants were tested under identical conditions in a comfortable position. Testing was conducted in a quiet room with the ambient temperature controlled at 21^0C to 23^0C. All participants underwent a practice session in which the different parameters were applied to the forearm until they were familiarised with the measurement procedure and the equipment. Participants were unable to watch the computer screen at any times during the test procedures. They were also not given auditory or visual clues to indicate the start of individual stimuli. Testing of each site took ~30 minutes and a complete test at all two sites took ~60 minutes. All tests were carried out by the same investigator who was trained in the use of QST according to the DFNS protocol. All participants who underwent the protocol began with the determination of thermal thresholds followed by mechanical thresholds. The detailed testing procedures of the different parameters of the standardised QST battery according to DFNS protocol is described in chapter 6. These different parameters can be listed chronologically as follows:

- Thermal detection for cold and warm detection threshold (CDT, WDT);
- Number of paradoxical heat sensations (PHS) during thermal sensory limen procedure (TSL);
- Thermal pain threshold for cold and heat pain threshold (CPT, HPT);
- Mechanical detection and pain threshold (MDT, MPT);
- Mechanical pain sensitivity for pinprick stimuli (MPS);
- Dynamic mechanical allodynia (DMA) for stroking light touch;
- Wind-up ratio (WUR);
- Vibration detection threshold (VDT);
- Pressure pain threshold (PPT).

7.4.3 Data evaluation and results

Data entry and transformation was conducted according to the DFNS guidelines. Data were first entered into an Microsoft Excel-spread sheet (Equista database) provided by DFNS, which automatically generated thresholds and average ratings and number of observed paradoxical heat sensations. The obtained data were entered into a STATA data file and GraphPrism to generate analysis and graphs, respectively. The following analyses were carried out:

- Comparison of the results to the 95% confidence interval of the DFNS reference data.
- Number (percentage) of abnormal values
- Calculation of Z-values: data are presented as mean ± SD and based on the DFNS reference database, I calculated the z-score for each participant:

  Z-score = (value [single participant] - Mean [controls])/SD [controls]
- Statistical analysis of the Z-values of right ulnar vs. left ulnar and using t test for the differences between the parameters within each group.

Fifty-two volunteers participated in this study. All subjects completed all QST measurements and 30 subjects completed both QST and skin biopsy interventions; there were no drop-outs. None of the subjects reported any adverse effects. Forty-eight subjects completed all QST measures in their hands, two subjects on feet, and two subjects on both hands and feet. The data obtained from all QST measurements for the two test sites are presented as mean and SDs in Table 7.2, Figure 7.6, and Figure 7.7. QST in two different test sites yielded values that were within the published DFNS reference values; the number of values outside the 95% confidence interval (5.27%) was actually slightly higher than its expected published value (5%) (Rolke et al., 2006a, Maier et al., 2010). The result was validated by the German Neuropath Pain Group (DFNS).

7.4.4 Discussion

This is the first study to use the DFNS-QST protocol in a resource-limited setting outside of Europe and validates the Mumbai Centre for the use of the QST. Normative QST data are generated by evaluating somatosensory function in healthy volunteers, a process in which one body area is assessed using the QST measures according to the DFNS protocol.

The findings in our study revealed that one or more somatosensory abnormalities were present in healthy controls. The percentage of abnormal findings expected in healthy controls is 5%, with the exception of DMA, which is not present in healthy controls. In accordance with this exception, our data showed abnormal sensory function for 5.27%. Although our healthy volunteer data is in line with data published by the DFNS and others, the main abnormality occurred mostly in one parameter. For instance, of those volunteers who had abnormal findings at the test site "dorsum of the hand", the wind-up ratio represented one-third of these abnormalities. This could be explained by the complexity of the test and the interpretation by subjects.

The normative QST data generated from the dermatome C8 of a non-Caucasian population may help to increase the generalizability of the DFNS reference database. In addition, validating the Mumbai site for QST protocol in Hindi and Marathi may help to establish somatosensory profiles in other diseases such as diabetics and HIV/AIDS in India.

Table 7.2. QST results performed in hands (n=50) and feet (n=4)

QST parameter *		**Test sites**			
		Hand (n=50)		**Foot (n=4)**	
		Mean ± SD	Number of subjects outside the 95% CI	Mean ± SD	Number of subjects outside the 95% CI
Thermal thresholds					
Cold detection threshold (CDT)	Δ ˚C from baseline 32˚C	-0.29 ± 0.87	2	-0.23 ± 0.25	0
Warm detection threshold (WDT)	Δ ˚C from baseline 32˚C	-0.45 ± 0.87	3	-0.77 ± 0.57	0
Thermal sensory limen (TSL)	Δ ˚C	-0.78 ± 0.59	1	-1.04 ± 0.48	0
Paradoxical heat sensations (PHS)	x/3	0.00 ± 0.00	0	0.00 ± 0.00	0
Cold pain threshold (CPT)	˚C	1.20 ± 0.49	3	1.01 ± 0.79	0
Heat pain threshold (HPT)	˚C	0.40 ± 0.63	1	0.36 ± 0.29	0
Mechanical thresholds					
Mechanical detection threshold (MDT)	mN	0.97 ± 0.67	1	0.39 ± 0.38	0
Mechanical pain threshold (MPT)	mN	0.27 ± 0.41	0	0.42 ± 0.15	0
Mechanical pain sensitivity (MPS)	NRS	0.14 ± 0.66	4	0.43 ± 0.18	0
Dynamic mechanical allodynia (DMA)	NRS	0.00 ± 0.00	0	0.00 ± 0.00	0
Wind-up ratio (WUR)		1.15 ± 1.44	0	0.23 ± 1.00	0
Vibration detection threshold (VDT)	x/8	0.41 ± 0.42	0	0.41 ± 0.42	0
Pressure pain threshold (PPT)	kPa	-1.22 ± 0.86	4	-1.22 ± 0.86	0
			5.27%		0%

* Data are presented as log data (mean and SDs). In addition, number of values outside the 95% confidence interval of the published DFNS reference values for each parameter are given (in %) which are calculated as follows: 11 tests x 50 subjects = 550 divided by the number of values outside the 95% confidence interval.

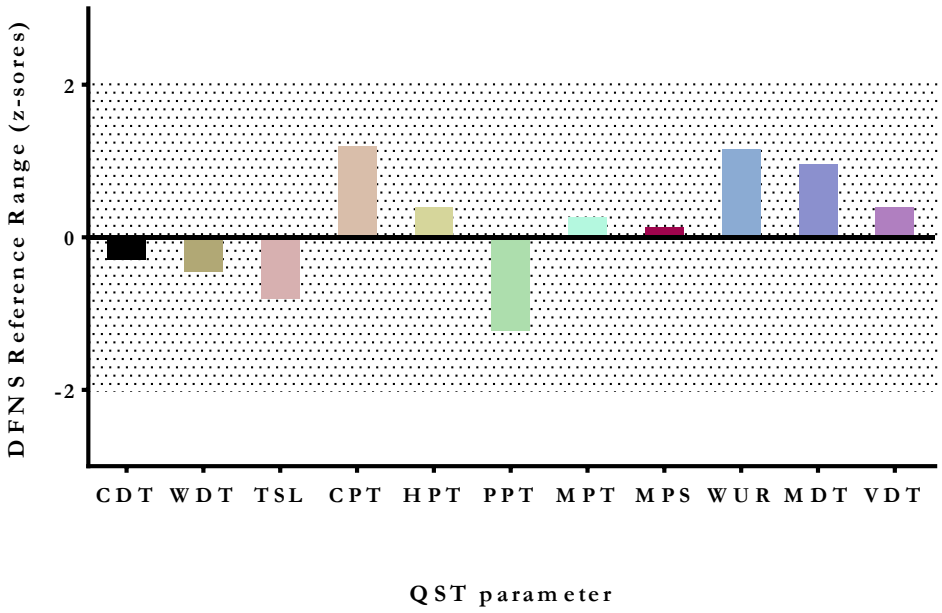

Figure 7.6. Thermal and Mechanical QST results in hands (n=50)

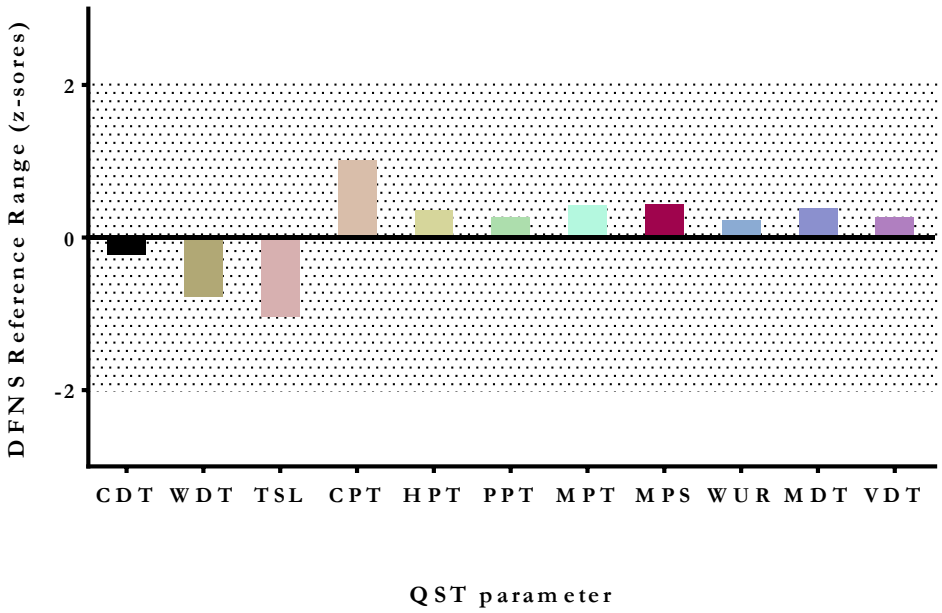

Figure 7.7. Thermal and Mechanical QST results in feet (n=4)

7.5 Comparability of mechanical detection and pain thresholds in QST using different devices

7.5.1 Introduction

The aim of this study was to investigate comparability between different devices namely: the Semmes-Weinstein monofilaments, von Frey filaments and "electronic von Frey" using the same psychophysical methods for mechanical detection threshold (MDT), mechanical pain threshold (MPT), and mechanical pain sensitivity (MPS) within the DFNS criteria. The study was designed jointly with Prof Rolf-Detlef Treede from the DFNS group. I conducted this study in Prof Treede's laboratory in Germany and Dr Doreen Pfau from the DFNS group completed the analysis and wrote up the findings.

7.5.2 Materials and Methods

7.5.2.1 Subjects and test areas

Thirteen healthy control subjects (7 female, 6 male; mean age 29 years) were investigated between March 1st and 25th 2011, after giving written informed consent for the QST procedures. Participants were invited and recruited from Mannheim Medical Centre, Mannheim. Ethical approval was obtained from the Ethics committee of University of Mannheim, Mannheim, Germany. Procedures were in accordance with the Declaration of Helsinki.

Tests were performed in the innervation territories of the right and left ulnar nerve on the hand dorsum and on the palmar fingertip (small finger). In the face, test area was within the innervation territory of V2 (maxillary nerve) bilaterally.

7.5.2.2 Equipment

Von Frey filaments

The set of von Frey filaments commonly used within the DFNS protocol for testing the mechanical detection threshold (MDT) (Marstock nervetest; Marburg, Germany) consists of glass fibre filaments with different length and strength. Those factors determine the intensity of the force applied to the skin. The tip of the filaments is rounded tip in order to avoid sharp edges and subsequently in order to avoid a possible nociceptor activation due to sharp edges (Greenspan and McGillis, 1991). Nominal

bending forces are logarithmically increasing forces of 0.25 mN, 0.5 mN, 1 mN, 2 mN, 4 mN, 8 mN, 16 mN, 32 mN, 64 mN, 128 mN, 256 mN and 512 mN.

Semmes Weinstein monofilaments

The Semmes Weinstein monofilament (Brazilian filaments; SORRI-Bauru; Brazil) consists of a plastic handle supporting a nylon filament. Applying forces of 0.05 g, 1 g, 2 g, 20 g, 40 g, and 300g (corresponding to 0.5 mN, 9.8 mN, 19.6 mN, 196.1 mN, 392.3 mN and 2942.0 mN) on the skin using different filaments with the same length but different strength. In contrast to the DFNS von Frey filaments, tips presented an edge leading to a sharp sensation in some subjects at higher stimulus intensities. For this reason, this set of filaments was also used to test the mechanical pain threshold (MPT). They are designed to be cheap robust and suitable for use in low/medium resources settings.

Devices for Mechanical pain threshold and Mechanical Pain Sensitivity

The set of weighted pinprick stimulators used within the DFNS protocol (The Pinprick, MRC systems, Heidelberg, Germany) consists of different steel tubes with a standardized diameter of about 1 cm. Inside the tubes, weights rest on a rim at the end of the tubes when held perpendicularly without touching the skin and end in blunt steel rod with a standardized tip diameter of 0.25mm. As soon as the tips touch the skin and the tubes are moved slightly towards the skin, forces delivered by the weights are completely carried on the skin by the small steel rods, resulting in healthy subjects in "blunt" sensation for lower and "sharp" sensations for higher forces. This set of stimulators covers intensities representing logarithmically increasing forces of 8 mN, 16 mN, 32 mN, 64 mN, 128 mN, 256 mN and 512 mN.

Electronic von Frey filament

The electronic von Frey filament (Somedic, Sweden) represents a device eligible for the testing of a mechanical pain threshold (MPT). The tip diameter is 0.25 mm and thus comparable with the set of DFNS pinprick stimulators. The replaceable and sterilisable tip tapers in a cylindric form to avoid skin penetration and is connected with a handpiece and a force sensor and was connected via a force transducer and a computer with the corresponding software. A visual feedback control of the applied ramp rate is possible due to flashing lights on the back of the handpiece. Subjects could indicate the

first sharp sensation (mechanical pain threshold; MPT) by a stop button or the pain intensity (mechanical pain sensitivity; MPS) by an electronic visual analogue scale (VAS).

Optical feedback control indicated by flashing lights on the holder was limited to a lowest ramp rate of 10g/s, corresponding to about 100 mN/s. As the lowest mechanical pain threshold within the normal range according to the DFNS protocol depending on age and gender of tested subjects (Magerl et al., 2010) is expected at about 40mN, threshold would be missed by applying a ramp rate of 100 mN/s. For this reason we added a testing trial with a ramp rate of 1g/s corresponding to ≈10mN/s. Instead of the optical feedback control directly on the handpiece, the control of ramp rates was possible by an optical feedback given by functions for pressure vs. time on the computer screen. Applied stimulus ramps were thus 10g/s and 1g/s, respectively, to test a possible influence of subject's reaction time or the influence of steeper increasing pressure ramps delivered by sharp stimuli per se (List et al., 1991).

Cut-off value for testing on the hand was 74 g, corresponding to 724mN as presenting the calculated cut-off value within the DFNS procedure using "The Pinprick" to avoid tissue damage. Those values are calculated when the 512mN pinprick stimulator is perceived as non-pricking, and a virtual value of 1024 is then defined as pricking stimulus intensity, resulting in a geometrical mean value of 724 mN for the mechanical pain threshold. Similarly, the cut-off value for testing in the face was 37g, corresponding to 362 mN. As the 512 mN Pinprick stimulus is recommended not to be used in the face to avoid any skin damage, 512 mN is defined as virtually pricking value if the 256 mN device is perceived as blunt sensation, resulting in a geometrical mean value of 362mN.

7.5.2.3 Procedures

Mechanical detection threshold (MDT)

Mechanical detection threshold was performed according to the DFNS protocol using a method of limits (Rolke et al., 2006b),

1) with the DFNS von Frey filament, starting with a probable suprathreshold filament of 16mN
2) with the Semmes Weinstein monofilaments, starting with a probable suprashreshold stimulus intensity of 2g, corresponding to 20mN

Five subthreshold and five suprasthreshold values were defined. Geometric mean values of sub- and suprashreshold stimuli then represent the mean tactile detection threshold.

Mechanical pain threshold (MPT)

Mechanical pain threshold was performed with different procedures as described below:

1. according to the DFNS protocol using the method of limits and asking the subject of differentiate between a sharp or blunt sensation evoked by
    i. a set of seven weighted pinprick stimuli (‚The Pinprick'), starting with a probable sub-threshold stimulus intensity of 8mN
    ii. Semmes Weinstein monofilaments with a probable sub-threshold stimulus intensity of 2 g, corresponding to ≈20mN; as filaments are more flexible, any pain sensation was expected for higher intensities compared to the blunt needle stimulator (The pinprick).

Then five sub-threshold and five supra-threshold values were defined. Geometric mean values of sub- and supra-threshold stimuli then represent the mean mechanical pain threshold.

2. using a three-time threshold determination of a continuously increasing ramp rate at both, 1g/s or 10g/s using the electronic von Frey Filament with a stop button. Subjects were asked to press the stop button as soon as they perceive any sharp sensation representing the activation threshold of nociceptors (cite).

Mechanical pain sensitivity

Using the weighted pinprick stimulators and the Semmes-Weinstein filaments, the procedure for testing the mechanical pain sensitivity (MPS) used within the QST protocol according to DFNS protocol was used. Mechanical pain sensitivity was tested with the same standardized punctate probes as used for testing of the mechanical pain threshold. Dynamic mechanical allodynia (DMA) was tested using standardized light touch stimuli: (1) a cotton wisp applying a force of about 3 mN, (2) a Q-tip, fixed in a flexible plastic mount, exerting a force of about 100 mN when slightly bent, and (3) a standardized brush applying forces of 200–400 mN (Senselab Brush-05, Somedic, Sweden). To evaluate the pain intensity of subjects, a numerical rating scale from 0 (no pain) to 100 (most intense pain imaginable) was used for all test stimuli. Subjects were

free to use integers as well as fractions ad libitum. They were instructed to distinguish pain from the perception of touch or pressure by the presence of a sharp or slightly pricking or burning sensation.

Using the electronic von Frey filament subjects rated the intensity of any pain-related sensation on an electronic VAS which was connected via the force transducer (SenseBox) with the computer, recording ratings and applied forces. Ramp rates were the same as for the testing of the mechanical pain threshold via the evF as are 1g/s and 10g/s. For data analysis, corresponding ratings to the forces within the DFNS protocol applied (8, 16, 32, 64, 128, 256 and over extra-trigeminal areas additionally 512 mN) were extracted. A small constant of 0.1 was added to each rating to avoid a loss of zero values during data analysis (Magerl et al., 2010).

Order of test procedures

Within the test protocol, test procedures were performed in the following order:

i. Mechanical detection threshold (MDT)
ii. Mechanical pain threshold (MPT)
iii. Mechanical pain sensitivity (MPS)

Order was balanced over test areas (face, fingertip, hand dorsum) and over the application order of used test devices.

7.5.3 Results

7.5.3.1 Mechanical detection threshold

Mean values for MDT tested by von Frey vs. Brazilian monofilaments did not differ over all test areas (Figure 7.8), (mean values over face: 0.46mN vs. 0.59mN (log-mean ± SEM: -0.338±0.098 vs. -0.229 ± 0.067); fingertip: 0.57mN vs. 0.62mN (-0.241 ± 0.103 vs. -0.208 ± 0.053); hand dorsum: 1.88mN vs. 1.83mN (0.273 ± 0.121 vs. 0.263 ± 0.129) and were highly correlated (r=0.71-0.81).

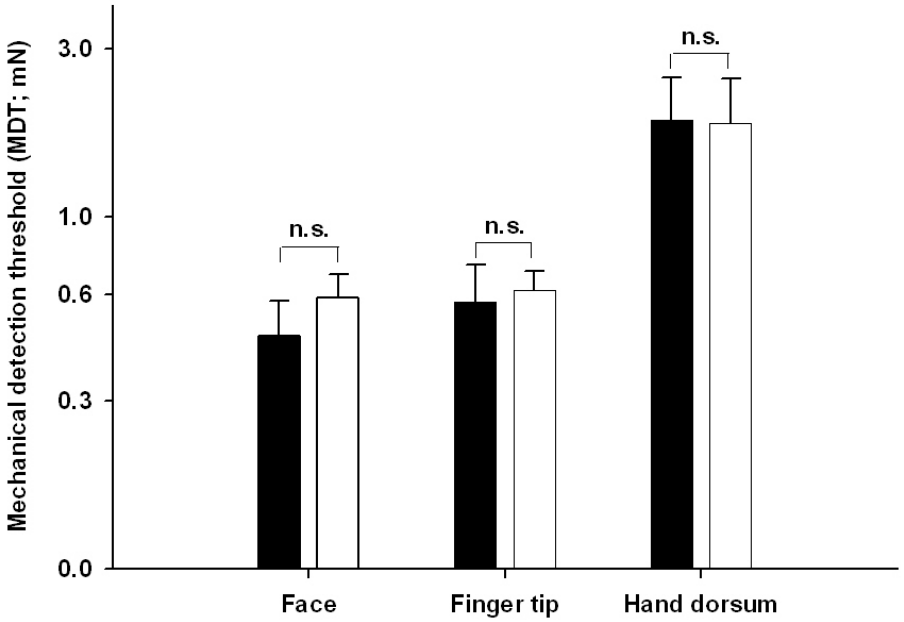

Figure 7.8. MDT results from the face, fingertip and hand

von Frey (dark bar column) and Brazilian monofilaments (white bar column)

7.5.3.2 Mechanical pain threshold

Mean values for MPT differed significantly for pinprick stimuli vs. Brazilian monofilaments by 24.9mN vs. 12.7mN over face (log-mean ± SEM: 1.396 ± 0.041 vs. 1.103 ± 0.094; p-value <0.01) but not for the fingertip: 55.1mN vs. 78.1mN (1.741 ± 0.074 vs. 1.893 ± 0.206) and the hand dorsum: 55.4mN vs. 69.8mN (1.744 ± 0.064 vs. 1.844 ± 0.182). Compared to values tested by pinprick stimuli, mean values tested by the evF differed significantly for both ramp rates in all test areas; in the face with 90.3mN (1.956 ± 0.054; 1g/s) and 176.0mN (2.245 ± 0.055; 10g/s), on the fingertip with 121.8 mN (2.085 ± 0.060; 1g/s) and 223.4mN (2.349 ± 0.034; 10g/s) and on the hand dorsum with 144.6mN (2.160 ± 0.061; 1g/s) and 239.6mN (2.379 ± 0.061; 10g/s) (Figure 7.9).

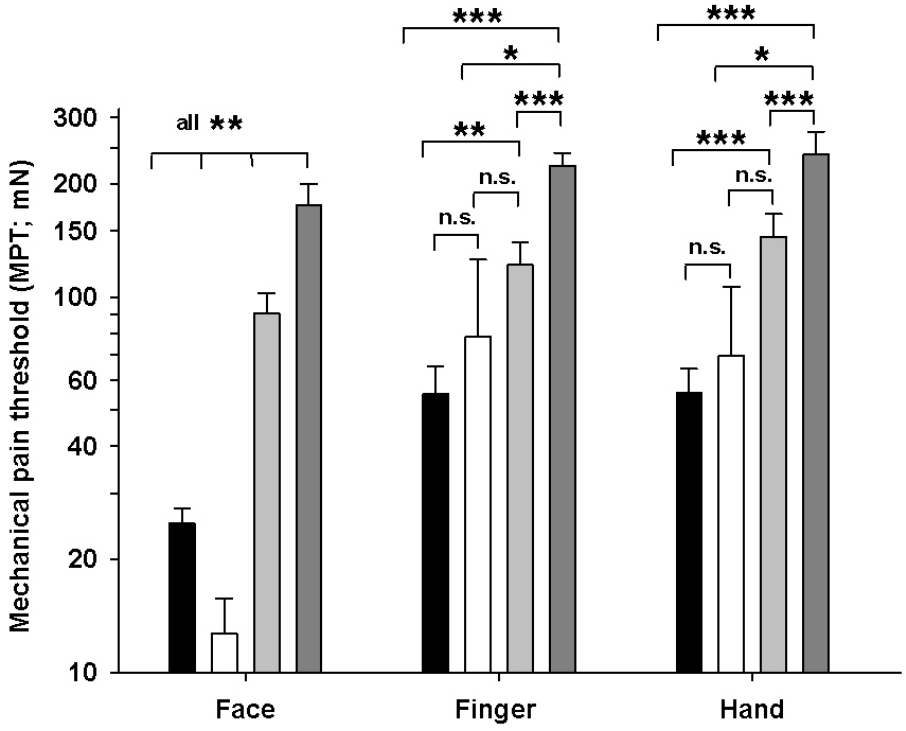

Figure 7.9. Comparison between Pinprik, MFs and evF

Comparison of the set of weighted Pinprick stimuli (black bars) with the Brazilian monofilaments (white bars) and an electronic von Frey filament with the ramp rates of 1 g/s and 10g/s (light/dark grey bars). n.s. = non-significant, *p-value <0.05; **p-value <0.01; ***p-value <0.001; paired t-test.

7.5.3.3 Mechanical pain sensitivity

Mean values for complete MPS-DFNS procedure were 1.09/100 in the face (0.039 ± 0.082), 0.92 on the fingertip (-0.037 ± 0.117), and 0.84 on the hand dorsum (-0.077 ± 0.083). The calculation of MPS with the evF was not possible as subjects did not rate pain below stimulus intensities of 128mN, and cut-off value for the face was set at 256mN. For this reason, we used a stimulus response function with only 2 stimulus intensities for comparison. Mean pain rating for 'short' MPS in the face was 7.75 (0.889±0.103) for Pinprick stimuli vs. evF 1g/s: 0.56 (-0,254 ± 0.138) and evF 10g/s: 0.25 (-0.601 ± 0.066). On the fingertip, rating was 3.56 (0.551 ± 0.178) for the Pinprick vs. evF 1g/s: 0.71 (-0.149 ± 0.153) and evF 10g/s: 0.24 (-0.621 ± 0.089). On the hand, rating was 3.59 (0.555 ± 0.134) vs. evF 1g/s: 0.6 (-0.210 ± 0.148) and evF 10g/s: 0.17 (-0.758 ± 0.041).

7.5.4 Discussion

The DFNS-QST protocol is a standardised method. It has been used globally to explore somatosensory profiles in patients with neuropathic pain. The high standardization of this QST protocol requires specific devices to be used within the protocol. This may represent one of the most important limitations of further expansions of the use of the protocol due to high costs and restricted practicability.

In this study the Semmes-Weinstein monofilaments yield similar results for the testing of MDT and MPT according to the DFNS protocol in healthy subjects. Due to larger increments of applied intensities compared to the DFNS von Frey filaments, neuropathies may be underestimated in more sensitive test areas (face, fingertip). Additional variance may arise from non-standardized tip surfaces of the Semmes-Weinstein monofilaments. The suitability of the use on the hand should be confirmed by testing of subjects with sensory loss and gain, i.e. under pathological condition. Semmes-Weinstein monofilaments are more robust than the von Frey filaments used within the DFNS and cost effective. Further, they are not usually affected with dust or required calibration. For these reasons their use would be favourable in resource-limited settings, and may also be used for the testing of MDT and replace a set of von Frey filaments stimuli used within the DFNS.

MPT and MPS tested with the electronic von Frey filament are not comparable with the responses measured by pinprick stimuli within the DFNS-QST protocol which may be caused by a different mode of application (static stimuli vs. dynamic stimuli). For the dynamic application, reaction time may play an important role, which is demonstrated by different MPT and MPS values for different ramp rates. This indicates that investigating comparability between inter-observer testing and test-retest in same subjects are needed.

7.5.5 Conclusions

The use of the Brazilian monofilaments yield similar results as the DFNS instruments for both, MDT and MPT on the hand dorsum but has a limited range of use in more sensitive areas due to a limited grading of intensities at lower forces. The electronic von Frey filament was frequently insufficient to reach the threshold for sharp sensation as used for the DFNS protocol and is not suitable for the use within that protocol.

Chapter 8 Results

8.1 Introduction

This chapter presents the results of the data analysis as follows: first, descriptive results are shown for all leprosy patients, and study groups; followed by results for pain description questionnaires; clinical examinations; and Quantitative Sensory Testing. The last result section describes the impact of neuropathic pain on quality of life.

8.2 Descriptive analysis

8.2.1 Baseline characteristics of study population

8.2.1.1 Participants

Ninety-nine leprosy patients with and without pain; and 52 healthy volunteers were enrolled into Leprosy Pain India study (LePaIn) between 10th October 2012 and 30th April 2013. Patients were allocated into four groups based on clinical evidence of neuropathy and presence of pain (Figure 8.1). Thirty-six patients had pain at interview. Of these, twenty-four participants were clinically identified as having neuropathic pain in the affected ulnar nerve based on a score of ≥ 4/10 of the DN4 questionnaire and clinical neurological examination.

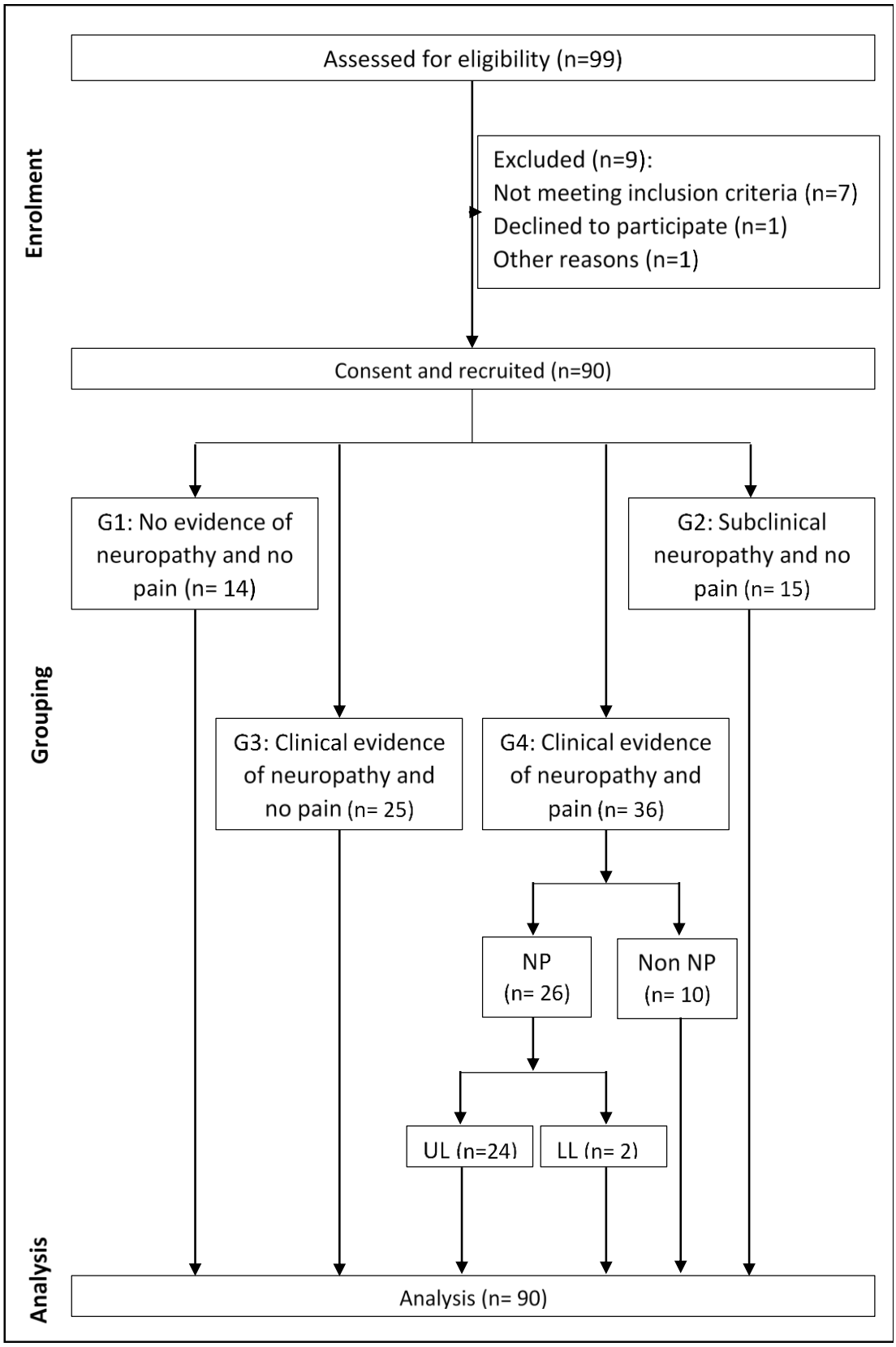

Figure 8.1. Flow diagram for LePaIn study

G1: Group 1; G2: Group 2; G3: Group 3; G4: Group 4; UL: Upper limbs; LL: Lower limbs

Demographic and clinical characteristics

Age and sex distribution

The mean age of included patients was 32.8 years (range 18-60 years). More than two third of patients were in the age groups 20-29 and 30-39 years. Approximately one fifth of the patients were female. The proportion of male and female patients was not evenly distributed across age groups. There were relatively few patients aged below 20s and above 50s age group (Table 8.1).

Table 8.1. Age distribution of the sample by sex

Age group (Years)	**Male N = 69 (77%)**	**Female N = 21 (23%)**	**Total N = 90 (100%)**
<20	5 (7.3%)	1 (4.8%)	6 (6.7%)
20-29	31 (44.9%)	6 (28.6%)	37 (41.1%)
30-39	21 (30.4%)	4 (19.1%)	25 (27.8%)
40-49	6 (8.7%)	6 (28.6%)	12 (13.3%)
50-60	6 (8.7%)	4 (19.1%)	10 (11.1%)

Geographical distribution

Ninety patients were seen during the period under study, of which 74 patients (82.2%) were recruited from the BLP clinic in Mumbai. Patients came from a wide range of leprosy endemic areas in India. Approximately 50% had migrated from outside BLP catch-up area of services; the remainder were within the state of Maharashtra. The largest single group of patients (42 patients (46.7%)) came from Maharashtra state, with 33.3% from Mumbai; followed by Uttar Pradesh (31 patients (34.4%); and Bihar (10 patients (11.1%)). One patient was from Nepal, and had acquired his leprosy in India, where he had been living since 1990. The majority of the study population (64 patients) had primary education (50 patients) or no formal education (14 patients). Figure 8.2 shows the geographic origin of 90 patients presenting with leprosy to the BLP and FMR.

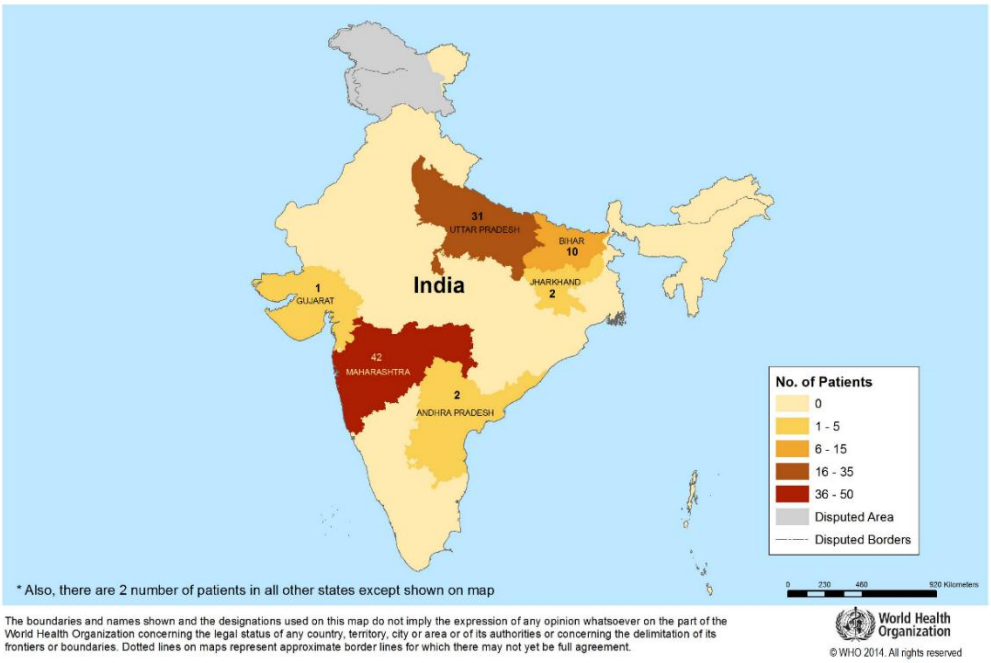

Figure 8.2. Geographical origin of 90 patients presenting with leprosy

This map is developed by the WHO office in Delhi for the purpose of the current study; with kind permission from GIS / SEARO.

Patients' clinical characteristics

The demographic and clinical details of the study population are shown in Table 8.2. In 65 (72.2%) patients, the diagnosis of leprosy was made after six months from the patients' first symptoms. There was a long lag time between the appearance of first symptoms and disease diagnosis, mean 2.1 years (range 0.3 – 22 years). In 14 (7BL, 7LL) patients, the latent time to diagnosis was 2.1 years (range 0.4 – 10 years). This subgroup were potentially infectious to others before diagnosis and treatment. The main reason for delay was misdiagnosis or an unusual presentation mimicking other common conditions, such as skin diseases. In 33 patients a misdiagnosis was made, all were dermatological related conditions such as psoriasis. Two patients had an unusual presentation described as neurological condition with no skin involvement. Patient factors can cause delay: 31 patient were unaware or neglected their symptoms.

Patients reported a variety of symptoms at the start of their problems, although none of them thought of the possibility of leprosy. In the vast majority (62 patients), these were the descriptions of typical leprosy skin lesions. 29 patients mentioned symptoms related

to nerve damage: eighteen had anaesthesia; two had loss of warm sensation; four had burning and tingling sensations; and five had loss of muscle strength, at their first consultation at the BLP clinic. Patients with leprosy frequently presented with complications such as reactions. Seven patients were in reaction at the time of presentation: three of these were Type I (reversal) reactions requiring treatment with oral prednisolone. Four had ENL. In these patients the signs and symptoms of the reaction were the stated reason to seek medical assistance. Over three quarters of the patients (69 (76.6%)) presented their problem to a private doctor. Only 11 (12.2%) of the patients presented directly to leprosy hospital or clinic. Traditional healers, alternative medical practitioners and pharmacists were first consulted in 5.7%, 3.3% and 2.2% of the patients, respectively.

Of the total sample, 18 (20.0%) patients were newly diagnosed and not started MDT at the time of interview; 26 (28.9%) patients had been diagnosed and received MDT within the first six month; 11 (12.2%) between six month and one year; and 35 (38.9%) more than one year after developing their first symptoms of leprosy (Table 8.2).

Patients were classified according to WHO field classification as follows: 57 (63.3%) patients had MB, and 33 (36.7%) had PB. Only 68 (75.6%) patients had been classified clinically using the RJ clinical classification, the remaining 22 (24.4%) was not classified. Of the 68 patients, four patients (5.9%) had TT leprosy, thirty (44.1%) had BT, two (2.9%) had BB, thirteen (19.1%) had BL, nine (13.2%) had LL, six (8.8%) had pure neuritic leprosy, and three (4.4%) had indeterminate leprosy. Of the 90 patients, 18 (20.0%) patients had not yet received leprosy MDT, 26 (28.9%) patients were already taking MDT, and 46 (51.1%) had been released from leprosy treatment (RFT). Of these RFT, the mean time since completed treatment was 3.5 years (range 0.04 – 30.9 years). Twenty five (27.9) patients had received at least two courses of leprosy treatment.

Table 8.3 documents the severity of nerve involvement at diagnosis, 36 (40.0%) patients had evidence of Grade 1 disability from nerve damage involving their hands or feet, with 10% having Grade 2 disability of hands or feet. Two (2.2%) patients had ocular disability due to leprosy, one of which had a Grade 2 disability.

Table 8.2. Demographic and characteristics of the study population (n=90)

Variable		Frequency	Percentage	Variable		Frequency	Percentage
Centre	BLP	74	82.2%	Dominant hand	Right	86	95.6%
	FMR	16	17.8%		Left	4	4.4%
Language	Hindi	56	62.2%	Education	Illiterate	14	15.6%
	Marathi	32	35.6%		Primary	50	55.6%
	English	2	2.2%		Secondary	11	12.2%
Religion	Hindu	63	70.0%		High school	3	3.3%
	Muslim	25	27.8%		Higher secondary	4	4.4%
	Christian	1	1.1%		College and above	8	8.9%
	Others	1	1.1%	Alcohol status	No	64	71.1%
Smoking status	Current smoker	9	10.0%		Yes	26	28.9%
	Former smoker	8	8.9%	Frequency of alcohol use	Daily	3	3.3%
	Occasionally	9	10.0%		Weekly	6	6.6%
	Never smoked	64	71.1%		Occasionally	17	18.9%

Variable		**Frequency**	**Percentage**	**Variable**		**Frequency**	**Percentage**
Occupation	None	3	3.3%	RJ classification	TT	4	4.4%
	Housewife	14	15.6%		BT	31	34.4%
	Labour	41	45.6%		BB	2	2.2%
	Farmer / skilled labour	9	10.0%		BL	13	14.4%
	Office worker / Business	3	3.3%		LL	9	10.0%
	Student	7	7.8		PN	6	6.7%
Delay in diagnosis	No	25	27.8%		Indeterminate	3	3.3%
	Yes	65	72.2%		Not known	22	24.4%
Delay in diagnosis	<6month	26	36.1%	WHO classification	PB	33	34.4%
	6months-12month	11	15.3%		MB	57	65.6%
	>12months	35	48.6%	Duration of disease	Newly diagnosed	18	20.0%
Main reasons for delay	Misdiagnosis	33	50.7%		<6months	26	28.9%
	Patients factors	31	47.7		6months up to 1yr	11	12.2%
	Admin factors	1	1.54		Longer than 1year	35	38.9%

Table 8.3. Disability grades present in patients at diagnosis (n=90)

	Grade 0	**Grade 1**	**Grade 2**
Hands and feet	54 (60.0%)	36 (40.0%)	9 (10%)
Eyes	89 (98.9%)	-	1 (1.1%)

8.2.1.2 Study Groups

Number of participants by group

Patients were divided into the following groups: leprosy patients with no clinical evidence of neuropathy and no pain (Group 1); leprosy patients with subclinical neuropathy and no pain (Group 2); leprosy patients with clinical evidence of neuropathy and no pain (Group 3); leprosy patients with clinical evidence of neuropathy and pain (Group 4). Healthy volunteers group (H.V) (Table 8.4). Group 4 is further divided to neuropathic pain subgroup (NP) and non-neuropathic pain subgroup (Non NP).

Patients with No pain (Group 1, 2 and 3)

Fifty four patients were recruited in three groups of patients with no pain. Of these, 29 patients had a diagnosis of leprosy and no clinical evidence of neuropathy: one group of 14 newly diagnosed leprosy patients had no evidence of neuropathy prior to the study (G1); and the other group consisted of 15 patients with leprosy and had subclinical neuropathy (G2). Another group consisted of 25 patients had leprosy and had clinical evidence of neuropathy (G3).

Patients with pain (Group 4)

In total, 36 patients were recruited with pain. There was poor recruitment in the leprosy patients with pain and no clinical evidence of neuropathy group mainly because patients having completed leprosy treatment with no neuropathic complication may not come to the leprosy clinic for their pain condition. Out of 36 patients with pain, 32 (88.9%) reported pain in their hand and 4 (11.1%) had lower limb pain.

Demographic and clinical characteristics of participants by group

The five groups were not significantly different with respect to age, weight, height, or metabolic factors: Thyroid hormone profiles, glucose, BMI and vitamin B_{12} level. Patient demographics and characteristics by groups are shown in Table 8.5.

Table 8.4. Number of participants and study groups (n=142)

Group	Number	Gender	Age (mean, range)
Healthy volunteers	52	24 male, 28 female	30.75 (18-55)
No evidence of neuropathy and no pain	14	13 male, 1 female	31.74 (20-51)
Subclinical neuropathy and no pain	15	10 male, 5 female	30.96 (18-56)
Clinical evidence of neuropathy / no pain	25	18 male, 7 female	30.39 (18-53)
Clinical evidence of neuropathy and pain	36	24 male, 12 female	35 (18-60)

Table 8.5. Demographic and clinical characteristics of participants by group (n=142)

Variable©		**Groups**				
		Healthy	Patients			
			Group 1	Group 2	Group 3	Group 4
Participant's §		52 (63.6)	14 (9.9)	15 (10.6)	25 (17.6)	36 (25.4)
	Male	24 (25.8)	13 (12.9)	10 (10.8)	18 (19.4)	28 (30.1)
	Female	28 (57.1)	1 (2.0)	5 (10.2)	7 (14.3)	8 (16.3)
Age (years) *		30.8±10.1	31.1±9.6	30.9±10.5	30.4±9.2	35.8±13.1
	Male	30.8±11.2	31.6±9.9	28.2±10.4	30.8±9.6	32.4±12.3
	Female	30.7±9.3	25.1	36.6±9.1	29.3±8.7	47.9±7.9
Weight *		59.9±13.6	60.1±9.8	54.6±11.3	58.4±12.8	62.3±10.1
	Male	65.1±14.0	61.9±7.5	56.6±9.7	61.7±13.5	62.7±10.9
	Female	55.0±11.4	37.0	50.6±14.3	49.9±5.4	61.3±7.3
Height †		159.4±8.4	163.4±9.5	157.7±11.0	159.2±7.8	161.0±8.4
	Male	163.0±8.1	164.8 ±8.2	163.9±6.7	162.7±5.5	164.4±6.7
	Female	156.1±7.4	145.0	145.2±5.9	150.3±5.3	150.5±5.2
BMI (kg/m2)		23.6±4.9	22.5±2.8	22.0±4.2	22.9±4.0	24.1±3.8
	Male	24.5±5.2	22.8±2.5	21.0±3.0	23.2±4.5	23.1±3.3
	Female	22.7±4.6	17.6	23.8±5.9	22.1±2.2	27.2±4.0
HbA1C *		5.7 (0.5)	4.9 (1.3)	4.9 (1.0)	4.8 (1.1)	6.9 (8.9)
	Male	5.8 (0.5)	4.9 (1.3)	5.0 (1.0)	4.7 (1.1)	7.5 (10.4)
	Female	5.4 (0.4)	1.0 (5.0)	4.6 (1.2)	4.9 (1.2)	5.3 (1.5)

T3 *		133 (27)	94 (52)	125 (17)	112 (22)	94 (20)
	Male	145 (29)	93 (59)	122 (24)	112 (22)	98 (19)
	Female	115 (8)	100	130	121 (34)	85 (26)
T4 *		8.6 (2.6)	6.6 (2.1)	8.4 (0.6)	9.0 (2.1)	17.8 (53.3)
	Male	10.0 (2.4)	7.0 (2.2)	8.0	7.5 (1.3)	6.5 (1.5)
	Female	15 (24.9)	5.0	9.0	11.0	50 (103)
TSH *		1.9 (0.9)	1.8 (0.4)	1.3 (0.6)	1.9 (1.3)	2.0 (2.0)
	Male	1.9 (1.0)	1.8 (0.5)	1.0 (0.0)	2.5 (1.3)	1.8 (1.5)
	Female	2.0 (0.5)	2.0	2.0	1.0 (1.0)	3.0 (3.1)
Vitamin B_{12} *		387 (168)	267 (173)	303 (106)	348 (167)	523 (410)
	Male	360 (118)	234 (180)	333 (131)	281 (114)	436 (207)
	Female	427 (248)	400	243.0	436 (207)	927 (595)

©Data are means (SD) (mean ± standard deviation) or numbers (%); HbA1C – Glycated Haemoglobin results are displayed as percentage, reference range (4 to 6%); T3 total are displayed as ng/dl, reference range (70 to 204ng/dl); T4 total are displayed as μg/dl, reference range (4.87 to 11.72 μg/dl); TSH are displayed as μIU/ml, reference range (0.45 to 4.5 μIU/ml); Vitamin B_{12} results are displayed as pg/ml, reference range (187 to 883). *Continuous data if normally distributed were analysed with one way anova test (ANOVA). Mean values and SDs shown; † Continuous data not normally distributed were analysed using Kruskal Wallis test. Mean values and SDs shown. § Categorical data were analysed using Chi squared test of association. Values and percentages shown. BMI Body Mass Index.

8.3 Clinical symptoms findings

8.3.1 Pain and sensory symptoms in leprosy patients with pain

8.3.1.1 Patient details

Twenty-six patients (72%) had symptoms and signs suggestive of NP identified by the DN4 questionnaire and 10 patients (28%) with predominately musculoskeletal/ nociceptive pain (non-NP) conditions.

8.3.1.2 Patient characteristics for pain group

General characteristics

The sample of 36 leprosy patients with pain represented a range of neuropathic and non-NPs. There were no significant differences between the two pain subgroups with respect to age, sex, average pain intensity and frequency in the last four weeks and pain intensity during interview. Table 8.6 shows the characteristics of patients with pain classified according to the case definition as having Non-NP or NP in both upper and lower limbs.

Site of pain

Although the most frequent sites of pain for all patients were upper extremities (88.9%), which reflects the study methodology, pain frequently occurred in skin lesions, peripheral nerves or generalized pain (Table 8.7). Of the 36 patients, 13 had skin lesion pain: in 5 patients pain was located in the active untreated skin lesions, and 8 in the treated skin lesions. A wide spectrum of pain site presentation was reported in peripheral nerves: 9 patients had hand and feet pain; 17 patients reported pain at the site of the nerve; and 18 patients had pain in the area of sensory loss over nerve distribution, the nerve most often affected by pain was the ulnar nerve in the upper limbs followed by the lateral common peroneal nerve in the lower limbs. 14 patients had joint pain, and 2 patients had foot neuropathic ulcer pain.

Table 8.6. Characteristics of patients (n=36) with pain

Variable	Non-NP pain group (n=10)	NP pain group (n=26)	P-value
Age (years) [a]	31.9 ± 11.8	37.3 ± 13.8	0.28 *
Sex (female/male)	3/7	5/21	0.49 §
Pain duration (weeks) [b]	4.5 (1; 10)	36 (4; 72)	<0.001†
NRS at interview (NRS 0-10) [b]	5.5 (5; 8)	6.5 (5; 9)	0.87 *
Maximum pain intensity during last 4 weeks [b]	9.5 (7; 10)	7.5 (6; 9)	0.10 †
Average pain intensity during last 4 weeks [b]	5 (4; 6)	5 (4; 7)	0.17 *
Current pain treatment [c]	8 (80.00%)	21 (80.77%)	0.96 §
Number on antidepressant/anticonvulsants [c]	0	5 (19.23%)	0.13 §
Number on analgesics (NSAIDs) [c]	4 (40.00%)	14 (53.84%)	0.71 §
Number on analgesics (steroid) [c]	4 (40.00%)	6 (23.08%)	0.41 §
Pain relief by medication [c]	7 (70.00%)	13 (50.00%)	0.28 §
NRS pain relief (NRS 0-10) [b]	1 (0; 7)	1 (0; 5)	0.09 †

[a] mean ± standard deviation; [b] median (25th percentile; 75th percentile); [c] number (%); *Continuous data if normally distributed were analysed with Student t test. Mean values and SDs shown; † Continuous data not normally distributed were analysed using Mann-Whitney Rank Sum test. Median and quintile (25th percentile; 75th percentile) shown in brackets. § Categorical data were analysed using Chi squared test of association. Values and percentages shown.

Table 8.7. Pain localisation in 36 patients with leprosy

Site		Frequency (%)
Skin lesions	Active untreated skin lesions	5 (13.9%)
	Treated skin lesions	8 (22.2%)
Peripheral nerves	Hands and feet	9 (25.0%)
	Nerve pain	17 (47.2%)
	Area of sensory loss over nerve distribution	18 (50.0%)
Others	Joint pain	14 (38.9%)
	Ulcer pain	2 (5.5%)

Duration and severity of pain

Patients with NP had longer pain duration than those with non-NP and less likely to have current pain due to reactions, Table 8.6. Pain had been present for one month or less in non-NP patients; whereas neuropathic patients reported pain for longer than nine months. The timing of the pain was reported as all the time by 27 (75.0%) patients, as less than two hours every day by 6 (16.7%) patients, as occasionally by 3 (8.3%) patients, and no patients reported as at least once a week (Figure 8.3).

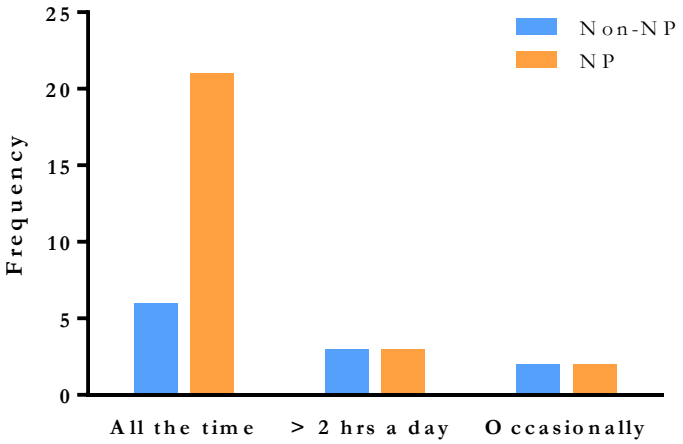

Figure 8.3. Pain frequency in 36 patients with leprosy

Patients with NP rated their present pain as more intense than those with non-NP (Table 8.6 and Figure 8.4). This finding was not significant and influenced by taking into account gender, or interview setting. Patients with NP were more likely to be taking analgesic treatments during the 24 hours prior to the interview than those with non-NP. A larger proportion of patients with NP subgroup were on pain medication compared to the subgroup with non-NP. Pain intensity at interview (interview NRS) was significantly correlated to pain intensity and frequency over the previous week (Spearman's correlation, P value<0.001). Patients more likely to have non-NP had higher maximal pain scores during the preceding weeks.

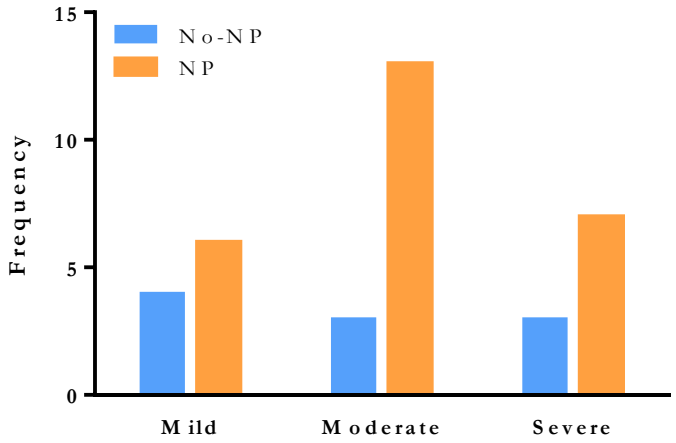

Figure 8.4. Pain grade in 36 patients with leprosy

Reaction and pain groups

Of the total sample, 26 patients had reactions at the time of interview; and 45 patients had never experienced reaction. Of these 26 patients, 9 (34.6%) had a T1Rs, 5 (19.2%) had ENL and 12 (46.1%) had neuritis (Table 8.8). 40 (56.3%) patients had a previous history of reaction either at diagnosis, during or after MDT treatment. Of these, neuritis was commonest (64.4%).

Non-NP (nociceptive/inflammatory pain) was found in 10 (11.1%) patients of the total sample. Of these 10 patients, 7 (70.0%) had a current reaction, 2 (20%) had ulcer in their hands or feet, and the remaining 1 (10.0%) had neither reaction nor ulcer.

Table 8.8. Association of pain with reactions at the time of examination (n=26)

Leprosy reaction	No pain	Pain		Total
		Non-neuropathic	Neuropathic	
T1R n (%)	2 (22.2%)	5 (55.6%)	2 (22.2%)	9 (100%)
ENL n (%)	1 (20.0%)	2 (40.0%)	2 (40.0%)	5 (100%)
Neuritis n (%)	2 (16.7%)	2 (16.7%)	8 (66.7%)	12 (100%)
Total	5 (19.2%)	8 (34.6%)	12 (46.2%)	26 (100%)

Disability assessment

Disability assessment results reflected high disability for patients with NP and mild disability for patients with non-NP, see clinical examination findings below.

8.3.1.3 Pain description questionnaires

Pain symptoms using DN4 and PD-Q

The Hind/Mahrati version of the DN4 was administered to 36 patients with leprosy and pain presenting at the clinic. Of the 36 patients who had pain, the description of numbness occurred mainly in NP subgroup. Itching, aching and dull type pain was most frequently reported in the non-NP subgroup (44.4% – 61.1%). Burning; tingling; sharp; pins and needles sensation; and the descriptor electric-shock like were reported in more than two thirds of NP patients compared to less than one fifth of non-neuropathic. Spontaneous pain was reported in 28 patients during the clinical examination and on PD-Q with increased frequency and increased likelihood of neuropathic pain (non-neuropathic, n=2; neuropathic pain, n=26). Figure 8.5 shows the frequency of reported pain descriptors from patients classified as having neuropathic pain, or non-neuropathic pain using the DN4 questionnaire.

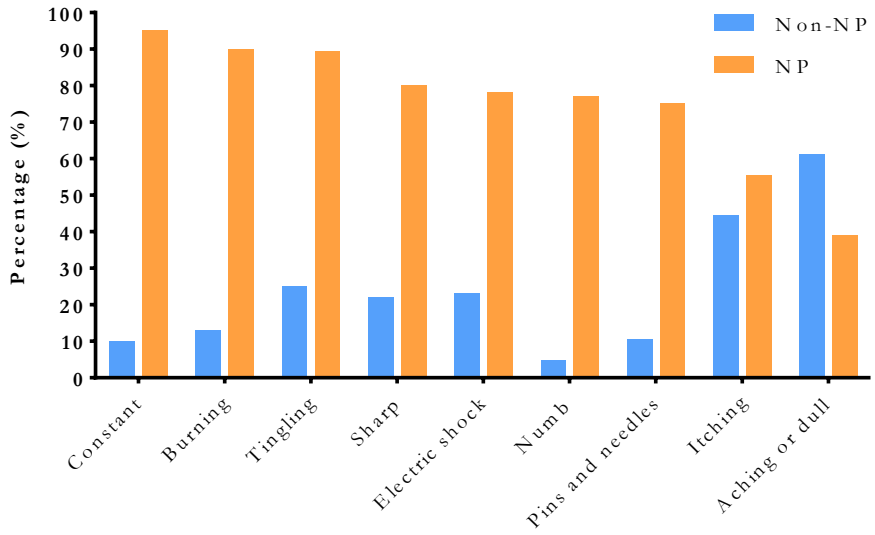

Figure 8.5. Frequency of pain descriptors

Frequency of pain symptoms (seven symptoms from DN4 questionnaires; others: constant and aching or dull are from patients history) reported by 36 patients with pain, classified as non-neuropathic pain and neuropathic pain.

DN4 questionnaire analysis

Of the 32 patients with pain concordant with the distribution of sensory loss at the affected ulnar nerve in the upper limb, the DN4 identified 24 patients with symptoms and signs suggestive of NP (of the 32 patients with upper limb pain, 24 patients had a score of 4 or more indicating the presence of NP), (median score 6, interquartile range (IQR) 2.0; mean score 5.6, standard deviation (SD) ± 1.4) and 8 patients without NP (median score 2.5, interquartile range (IQR) 1.0; mean score 2.5, standard deviation (SD) ± 0.5). Figure 8.6 shows the DN4 scores in patients with pain.

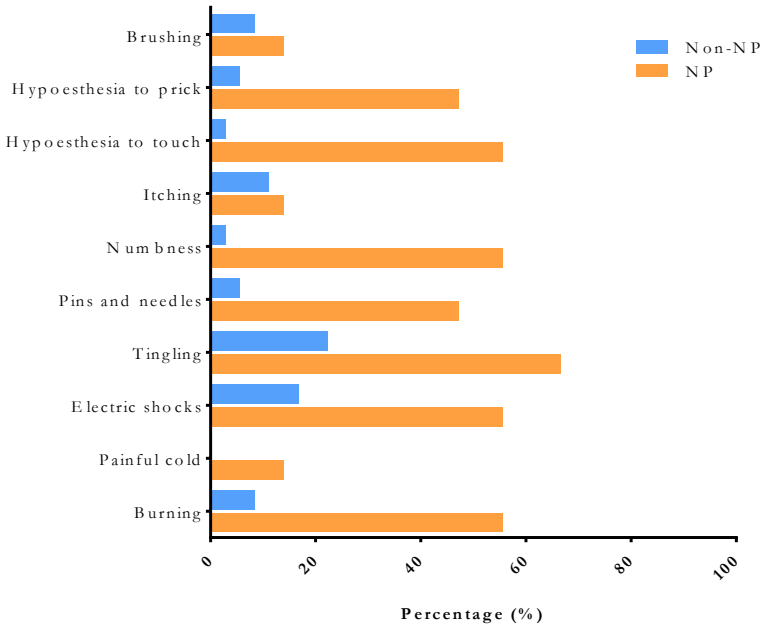

Figure 8.6. DN4 scores in 32 leprosy patients with upper limb pain

Frequency of the DN4 scores from 32 patients with upper limb pain, classified as non-neuropathic pain (8 patients) and neuropathic pain (24 patients).

Pain symptoms data obtained from patients, who were classified as having non-NP and NP using the DN4 and clinical examination of upper limbs, were analysed. A non-parametric analysis (Mann-Whitney two-sample statistic) between these two subgroups was performed. The result showed that questions 1 (burning sensations); question 5 (pins and needles); question 6 (numbness); question 8 (hypoesthesia to touch); and question 9 (hypoesthesia to pin-prick) were associated symptoms between non-NP and NP subgroup (p-value ≤ 0.05; more present in NP patients). When the DN4 score was considered in total points, there was also a difference between the two pain subgroups (p-value ≤ 0.001). When the analysis was repeated using binary coding for the DN4 questionnaire responses in the upper limbs instead of categorical coding, the findings were unchanged. Subsequent analyses were performed using binary codes for pain symptoms. Significantly, different symptoms were found for five pain symptoms between the two pain groups (Table 8.9).

Table 8.9. A comparison of symptoms detected by DN4 in pain groups (n=32)

Q1-10: Clinical relevant complaint §	**Frequency of patient's descriptor present**		
	Non-NP (n=10) (%)	NP (n=22) (%)	P- value
Q1, burning sensation	3 (30.0%)	16 (72.7%)	0.02*
Q2, painful cold	0	5 (22.7%)	0.10
Q3, electric shocks	6 (60.0%)	17 (77.3%)	0.31
Q4, tingling sensation	8 (80.0%)	20 (90.9%)	0.34
Q5, pins and needles	2 (20.0%)	14 (63.6%)	0.02*
Q6, numbness	1 (10.0%)	19 (86.4%)	0.001*
Q7, itching	4 (40.0%)	5 (22.7%)	0.31
Q8, hypoesthesia to touch	1 (10.0%)	17 (77.3%)	0.001*
Q9, hypoesthesia to pin-prick	2 (20.0%)	15 (68.2%)	0.01*
Q10, painful brush	3 (30%)	5 (22.7%)	0.66

† DN4 questions significant levels Cochran's nonparametric analysis (McNemar chi-squared test) for the upper limb pain (n=32). § Q1-10: Question 1 to 10 of DN4 questionnaire. *P-value ≤0.05

PD-Q questionnaire analysis

Of the 32 patients with pain concordant with the distribution of sensory loss at the affected ulnar nerve in the upper limb (Figure 8.7), the PD-Q identified 13 patients with a likely neuropathic pain component (median score 6, IQR 2.0; mean score 5.6, SD ± 1.4) and 19 patients with an unlikely NP component (median score 6, IQR 2.0; mean score 5.6, SD ± 1.4). The PD-Q's final results classify patients into no NP, unclear and NP. In 28.1% of patients (9/32), results were unclear (median score 6, IQR 2.0; mean score 5.6, SD ± 1.4); however a NP component might be present.

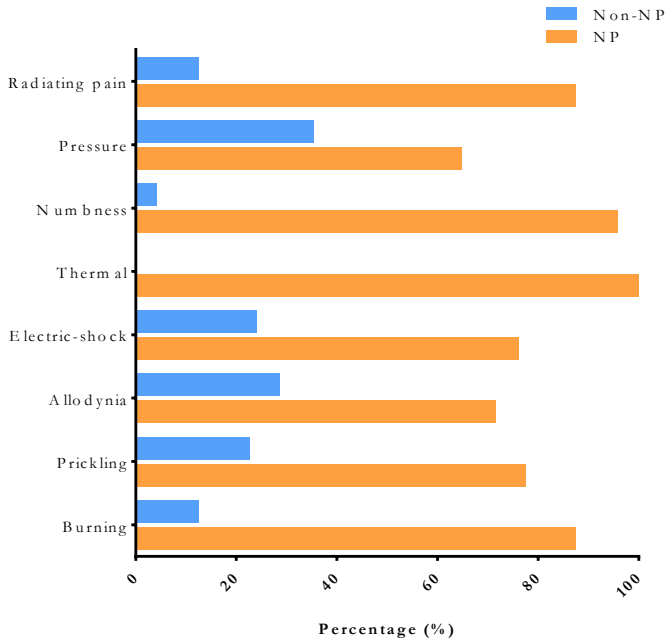

Figure 8.7. PD-Q scores in 32 leprosy patients with upper limb pain

Frequency of the PD-Q scores from 32 patients with upper limb pain, classified as non-neuropathic pain (8 patients) and neuropathic pain (24 patients).

A non-parametric analysis (Mann-Whitney two-sample statistic) between reported pain descriptors from patients classified as having non-NP and NP in upper limb using the PD-Q questionnaire was performed. The result showed that responses to questions 1 (burning sensations); question 2 (pins and needles); and question 6 (numbness) were significantly different between these two subgroups (p-value ≤ 0.05; more present in NP patients). When overall PD-Q questionnaire responses were considered in total points, there were also a difference between the two pain subgroups (p-value ≤ 0.001). When the analysis was repeated using binary coding for the PD-Q questionnaire responses in the upper limb instead of categorical coding, the findings were unchanged (Table 8.10).

Table 8.10. A comparison of symptoms detected by PD-Q in pain groups (n=32)

Q1-7: Clinical relevant complaint §	**Frequency of patients descriptor present**		
	Non-NP (n=10) (%)	NP (n=22) (%)	P- value
Q1, burning sensation	3 (30.0%)	17 (77.3%)	0.02*
Q2, prickling	7 (70.0%)	20 (90.9%)	0.01*
Q3, allodynia	2 (20.0%)	4 (18.2%)	0.90
Q4, electric shocks	6 (60.0%)	17 (77.3%)	0.31
Q5, thermal	0 (00.0%)	5 (22.7%)	0.10
Q6, numbness	1 (10.0%)	19 (86.4%)	0.001*
Q7, pressure	6 (60.0%)	9 (40.9%)	0.31

† A comparison of pain symptoms detected by PD-Q questionnaire for the two pain subgroups, using chi-squared test. § Q1-7: Question 1 to 7 of PD-Q questionnaire. *P-value ≤0.05

The responses to DN4 questionnaire had agreement with PD-Q responses when identifying neuropathic pain in 21 of the 32 patients with upper limb pain (NP: n = 13; Non-NP: n = 8), yielding a 65.6% agreement between questionnaire final results (Table 8.11). In all discordant (11 patients), a neuropathic pain component was detected by DN4 questionnaire, but not with the PD-Q.

By using the PD-Q final classification as having no neuropathic pain, unclear or neuropathic pain; the responses to DN4 questionnaire had agreement with PD-Q responses in 13 patients (Non-NP: n = 8, NP: n = 5), which yielded a 40.6% agreement.

Table 8.11. A comparison of NP detected by DN4 and PD-Q (n=32) †

		DN4		Total
		NP	No NP	
PD-Q	NP	13	0	13
	No NP	11	8	19
	Total	24	8	32
PD-Q	NP	5	0	5
	Unclear	8	0	8
	No NP	11	8	19
	Total	24	8	32

† A comparison of NP in 32 patients with hands pain detected by DN4 and PD-Q questionnaires. Two classifications for PD-Q were used: non-NP and NP; and non-NP, unclear and NP

Patient's responses to DN4 and PD-Q

In the 36 patients with pain present at the time of interview, DN4 had been evaluated as very easy by 2 (6.5%) patients, easy 21 (67.7%), and fair 8 (25.8%). Similarly, PD-Q was evaluated as very easy by 3 (9.7%) patients, easy 16 (51.6%), and fair 12 (38.7%) (Figure 8.8). No statistical difference between the two groups.

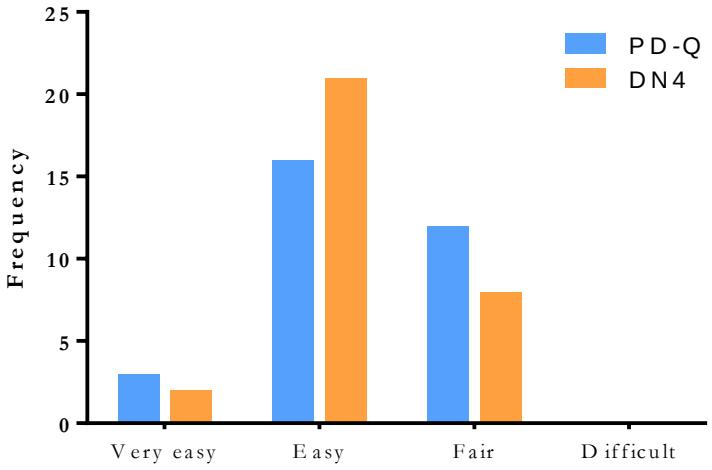

Figure 8.8. Patients' responses for the DN4 and PD-Q questionnaires (n=36)

8.4 Clinical examination findings

Clinical examination included the following: assessment of skin; evaluation of enlargement and tenderness of main peripheral nerves affected by leprosy (greater auricular (GA), median, ulnar, radial cutaneous, ulnar branch, lateral popliteal, posterior tibial, and sural nerves); nerve function assessment; and disability assessment.

8.4.1 Skin assessment

Seventy patients (77.78%) had skin lesions at the time of interview, Table 8.12. Of these 70 patients, 38 (54.29%) had old skin lesions: fully treated in 32 patients, and partially treated in 6.

Table 8.12. Distribution of skin lesions in leprosy patients (n=90)

Skin lesion	Number (%)
No skin lesion	20 (22.22%)
Single skin lesion (SSL)	12 (13.33%)
2-5 skin lesions	28 (31.11%)
6-10 skin lesions	16 (17.78%
More than 10	14 (15.56%)

8.4.2 Evaluation of enlargement and tenderness of main peripheral nerves

For the 90 studied patients, 1620 peripheral nerves were assessed for enlargement and tenderness in both right and left body side. Nerve enlargement was common (90% of the patients had one or more enlarged nerves), and 21% had tenderness of nerves on palpation. The ulnar nerves were found to be both the most frequently enlarged and tender nerves, followed by the posterior tibial, lateral popliteal, and superficial peroneal nerves. The prevalence of palpable nerve enlargement and tenderness on palpation in each nerve is shown in Table 8.13.

8.4.3 Nerve functions assessment

Nerve function assessments: sensory and muscle strength examination were completed for the 90 patients. Nerve function impairment of less than 6 months duration (new NFI) was reported for 10 patients (11.11%). A further 36% of patients reported that their impairment had been present for longer than 6 months (old NFI). In both old and new NFI, sensory loss was more frequent than motor loss or mixed loss. Sensory impairment was found in 62 (78%) patients, and motor impairment in 47 patients (59%); the ulnar nerve was the most commonly affected nerve.

The frequency of abnormal tendon reflexes or absent joint position sense in each nerve in this cohort was very few. The percentage of absent reflexes in each nerve as follow: right biceps (1.11%), right triceps (1.11%), left supinator (1.11%), right knee jerk (1.11%), and left ankle (2.22%). Two patients (2.22%) had absent JPS in their right index finger, and other two (2.22%) in their right big toe. Impaired JPS or reflexes were not associated with the presence of neuropathic pain or depression. 4 – 6

The frequency of ulnar neuropathy (sensory and motor impairment) detected by the different tests is shown in Table 8.14. Of 29 patients with no clinical evidence of neuropathy, 15 patients had subclinical neuropathy. Of these 15 patients, 14 patients (93.33%) had impairment of two or more QST parameters and classified as having subclinical neuropathy (Figure 8.13 – A and B, page – 214). Pooling results for right and left dermatomes C8 of the ulnar nerves, where a response was recorded, the QST parameters were abnormal in 112/176 (63.63%) of participants (Figure 8.10 – A and B, page – 208). The most frequently affected were CDTs and WDTs (thermal QST parameters). CDTs were affected as least twice as often as WDTs in the ulnar nerves in the subclinical group. This difference was less pronounced on the neuropathy and pain

groups. A discrepancy was found between the frequencies of ulnar nerve impairment detected by MF and QST thermal tests. This was particularly pronounced in the subclinical neuropathy group. For neuropathy and pain groups, WDTs and CDTs were significantly more often abnormal than MF and VMT (e.g. 31% versus 89% for the neuropathy and pain group, p-value<0.001). Interestingly, vibration sense in leprosy ulnar neuropathy were less frequently affected (15%) than other modalities. Overall, on the ulnar nerve tests, the sensation conducted by small fibres were the most frequently impaired. This confirms that small fibre neuropathy usually precedes large fibre damage.

Table 8.15 shows the concordance between ulnar neuropathy diagnosed with monofilament testing and results of quantitative sensory testing (thermal, vibration and combined QST parameters (two or more abnormal parameters)) in 88 patients. Combining results for right and left ulnar nerves, monofilaments and QST testing are both detected abnormality in 94 of the 176 nerves (ulnar nerve impaired: n= 30; no ulnar nerve impairment: n= 64); yielding 83.9% agreement. Concordance between monofilament results and QST parameters was best for CDTs and WDT. Unlike thermal tests, the VDT results were not concordant with the monofilament results. The highest positive concordance was seen between monofilament results and combined QST. Combining impairment of any of the QST parameters in one variable improved agreement with the monofilament test, over that of individual QST parameters, but negative concordance was substantially higher. Up to 50% of nerves with a normal MF result had one or more abnormalities in quantitative sensory testing. Similar results were observed for the motor assessments.

8.4.4 Disability assessment

Disability was assessed using the WHO disability criteria, which define grade 0 as no loss of sensation or visible deformity, grade 1 as loss of sensation without visible deformity, and grade 2 as presence of visible deformity. 55.56% of participants had physical impairment (28.9% grade 1 and 26.7% grade 2). Impairment was associated with the hand (46%), followed by 37% associated with the feet and 1% associated with eyes (grade 2).

Table 8.13. Prevalence of palpable nerve enlargement and tenderness (n=90)

	Greater A		Ulnar		Median		Radial		Uln. branch		LPN		Superficial		Post Tibial		Sural	
	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.
Enlarged	9%	12%	64%	73%	26%	22%	40%	37%	11%	10%	37%	56%	44%	51%	56%	48%	24%	24%
Tender*	0	0	17%	12%	4%	5%	8%	6%	0	0	6%	8%	15%	17%	14%	19%	23%	18%

*As the tender nerves were always enlarged, the denominator is the enlarged nerves

Table 8.14. Number and percentage of impaired ulnar nerves (n=90)

Test	No neuropathy		Subclinical neuropathy		Neuropathy		Neuropathy and pain	
	Ulnar nerve		Ulnar nerve (n=15)		Ulnar nerve (n=24)		Ulnar nerve (n=21)*	
	Right	Left	Right	Left	Right	Left	Right	Left
MF	0	0	0	0	10 (41.67%)	6 (25.00%)	6 (31.58%)	6 (31.58%)
VMT	0	0	0	0	14 (58.33%)	13 (54.17%)	13 (68.42%)	11 (57.89%)
WDT	0	0	5 (33.33%)	5 (33.33%)	17 (70.83%)	18 (75.00%)	17 (89.47%)	15 (78.95%)
CDT	0	0	10 (66.67%)	7 (46.67%)	15 (62.50%)	15 (62.50%)	15 (78.95%)	14 (73.68%)
VDT	0	0	0	0	3 (12.5%)	1 (4.17%)	3 (15.79%)	3 (15.79%)

*of the 24 patient's classified as neuropathy and pain over ulnar nerve territory, 3 patients had neuropathy and pain over skin lesion.

Table 8.15. Comparability of impairment by MF test and QST (n=88)

Test*	**Right Ulnar nerve (n = 88)**		**Left Ulnar nerve (n = 88)**	
	MF impaired (n=18)	MF not impaired (n=70)	MF impaired (n=12)	MF not impaired (n=76)
WDT impaired	94% (17)**	50% (35)	83% (10)	43% (33)
CDT impaired	89% (16)	40% (28)	92% (11)	41% (31)
Thermal impaired combined	100% (18)	63% (44)	92% (11)	68% (52)
VDT impaired	11% (2)	6% (4)	17% (2)	3% (2)
≥2 impaired QST parameters	100% (18)	56% (39)	100% (12)	57% (43)

*MF = monofilament test, WDT = warm detection threshold, CDT = cold detection threshold, VDT = vibration perception threshold

**Column % (number of nerves)

8.5 Quantitative Sensory Testing (QST) findings in leprosy patients

DFNS-QST database was used to transform QST raw scores into z-scores, and healthy controls data was used for statistical comparisons. The healthy controls, consisting of 52 age-matched participants, were recruited from the local community. The normative data from local population showed similar distribution to those held in DFNS database.

The results of the QST data analysis are presented as follows: the first part is the descriptive results, and comparison of the QST findings between all leprosy patients and healthy controls. The second part contains the somatosensory profiling, and the number of abnormal QST parameters in leprosy patients with no pain; followed by results for patients with pain. The last part describes the QST findings and comparisons of the leprosy patients with neuropathic pain.

8.5.1 QST observations in healthy control participants

From the 52 healthy volunteers investigated in this study, 102 locations in the upper limb (dermatome C8) and 8 locations in the lower limb (dermatome S1) were assessed. The measurements were analysed by z-score profiling (Chapter 6), and data was used for statistical comparisons.

8.5.2 QST observations in patients

For the 90 study patients, 27 990 QST data measurements were obtained from the affected and contralateral side and analysed by z-score sensory profiling.

8.5.3 Distribution of QST measures

Figure 8.9 illustrates distributions of QST data from the 52 healthy control subjects and 88 leprosy patients tested in the ulnar nerve territory (dermatome C8). DFNS-QST database was used to transform QST raw scores into z-scores, which adjusts for test site, gender and age. The horizontal axis (x-axis) demonstrates the QST parameters after z-transformation, and the vertical axis (y-axis) indicates the percentage of cases (patients or healthy controls). As paradoxical heat sensations and dynamic dynamic mechanical allodynia normally do not occur in healthy participants, z-transformation could not be calculated. Thus, data are shown as percentage of participants showing PHS and DMA.

For healthy control subjects, QST measures fell within the normal range of the DFNS-QST references (Chapter 7). QST measures for leprosy patients demonstrated similar distribution shapes compared to healthy control subjects, but with larger standard deviations indicating diverse sensory findings. For thermal and mechanical detection thresholds (non-nociceptive parameters: CDT, WDT, TSL, MDT, VDT), there were significant leftward shifts, suggesting the presence of hypoesthesia. For pain thresholds (nociceptive parameters: CPT, HPT, PPT, MPT, MPS, WUR), there were slight leftward shifts, suggesting the presence of hypoalgesia. The high prevalence of hypoethesia and hypoalgesia led to difficulties in performing WUR, which was the most frequently missing QST parameter in the cohort (21%). Overall, abnormal findings for loss of function (30.5%) across all QST parameters in patients with leprosy were more frequently observed than gain of function phenomenon (1.7%).

For thermal detection threshold (CDT, WDT, TSL), only sensory loss signs (thermal hypoethesia) were detectable in the affected area. For pain thresholds, negative sensory signs (thermal hypoalgesia) also dominated in 7.9% of the patients for CPT and in 31.8% for HPT. Sensory gain signs (thermal hyperalgesia) were absent in affected area for both CPT and HPT. Patient's measures of MDT demonstrated a broader distribution and showed a leftward shift compared to the healthy controls (Figure 8.9 - J). Thus indicating that the negative sensory sings (mechanical hypoesthesia) were frequent in the affected area. VDT, WUR and PPT patient's data exhibited similar distribution to the control's data.

For dynamic mechanical allodynia (DMA) and paroxysmal heat sensation (PHS), which are pathological phenomena and normally do not occur in healthy subjects, the occurrence in leprosy patients was rare (range between 2.3% for DMA and 13.6% for PHS). DMA was present in 2.3% of patients, but mostly of very mild intensity.

PHS in the affected area was reported in twelve patients, but it is not clear whether this phenomenon is part of sensory gain. In these twelve patients, PHS was reported once in three patients, twice in one patient, and three times in eight patients.

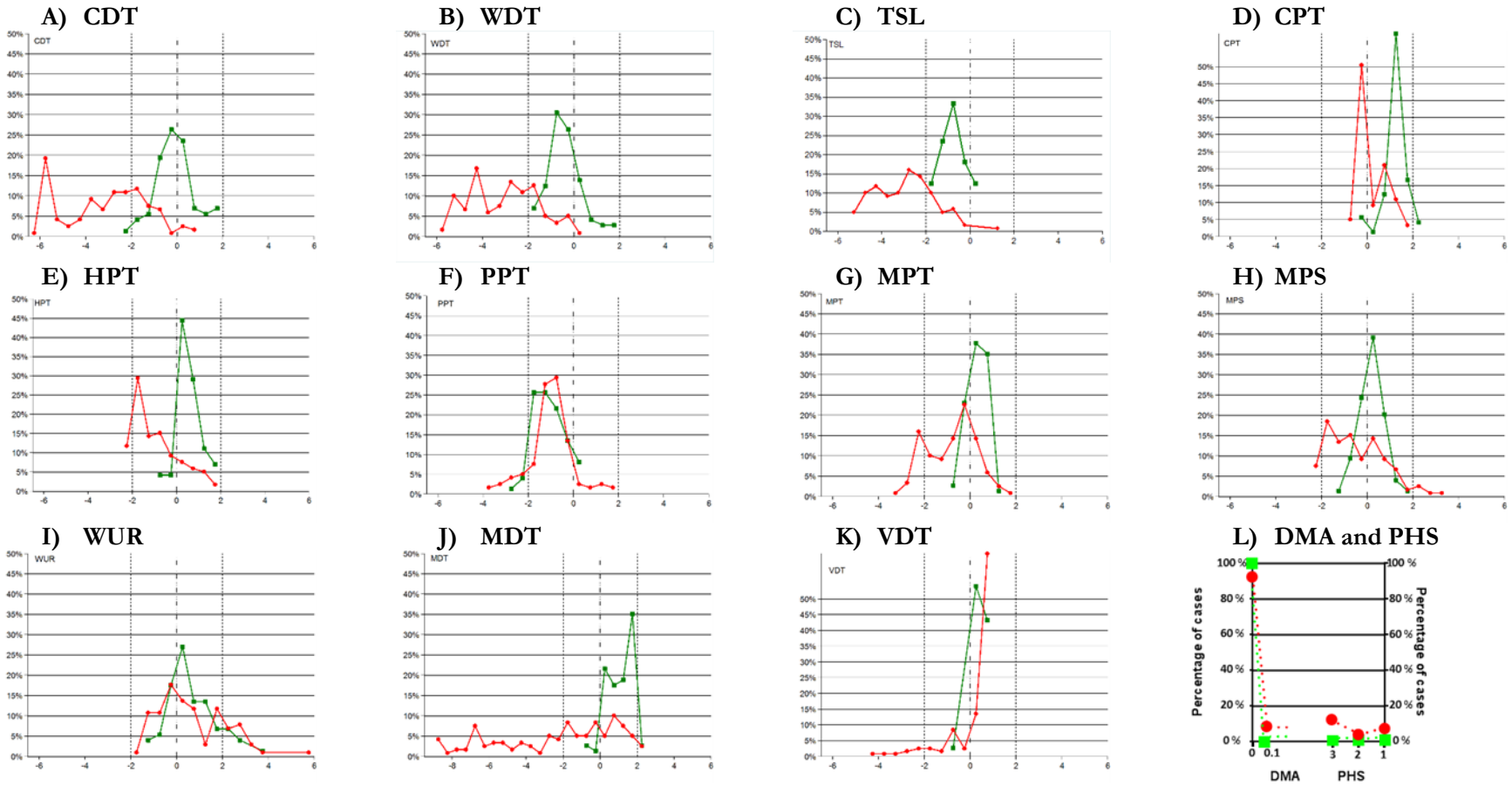

Figure 8.9. Distribution of the QST parameters after z-transformation

Distribution of the QST data using DFNS reference data. Affected ulnar nerve territory of all leprosy patients (n=88) (red circles/ solid line) in comparison with the controls (n=50) (green square/solid line). The y-axis indicates the percentage of cases (patients or controls). For PHS and DMA % are plotted versus original data: occurrences of PHS (0–3), log numerical ratings scale for DMA (0–100)

8.5.3.1 Frequencies of abnormal QST values

Of the 90 patients with leprosy, 86 patients had completed a full DFNS QST measures in the upper limbs, 4 patients in the lower limbs and 2 patients in both upper and lower limbs. The frequencies of abnormal QST values for each parameter was identified by absolute (outside 95% CI of DFNS reference data) and relative (side-to-side differences) sensory abnormalities (Figure 8.10). In these 88 patients tested in the ulnar nerve territories (dermatome C8), the abnormal sensory loss was highly prevalent, and significant rates were found primarily for non-nociceptive thresholds in approximately two third of the patients (60%) for thermal detection; and in about half of the patients for mechanical detection thresholds (46%), but rarely for vibration thresholds (8%). Almost no one had sensory gains for the non-nociceptive parameters.

For nociceptive parameters (pain), sensory loss (hypoalgesia) was frequent (range 7.9% - 42%), but sensory gain was rare (18%). Of these detected abnormalities, about one third of the patients with relative sensory loss were identified by side-to-side comparison (for different parameters between 2.3% – 15.9% additional patients), but again almost none with relative sensory gain for the nociceptive parameters. Remarkably, cold pain hypoalgesia was only detectable by side-to side comparison. Hypoalgesia was most frequently detected for pinprick, followed by heat, blunt pressure, and cold. Paroxysmal heat sensation was about as frequent as Wind up ratio. Dynamic mechanical allodynia was rare.

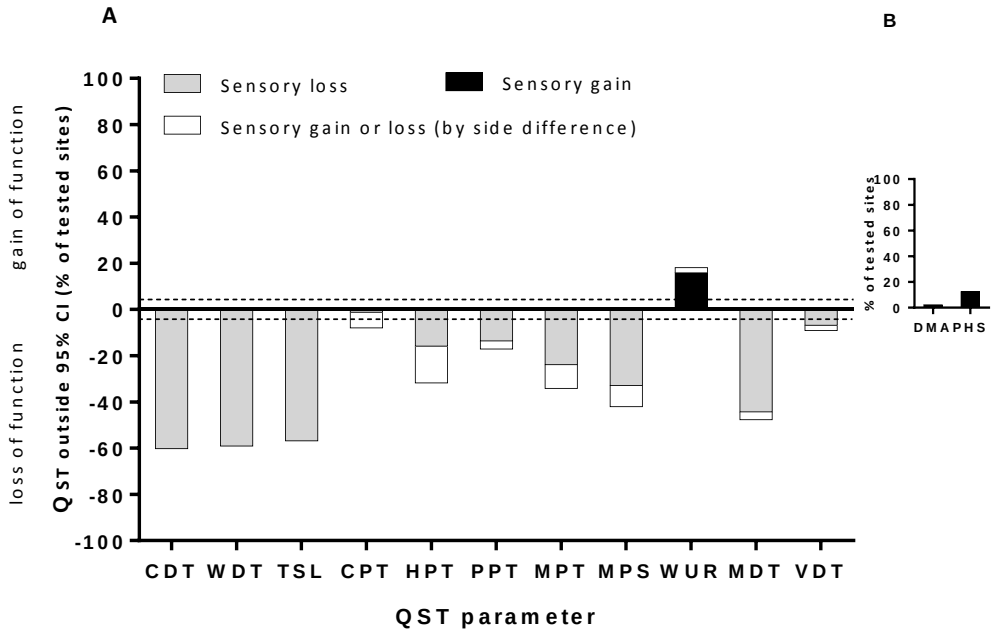

Figure 8.10. Frequencies of abnormal QST measures

Frequencies of abnormal QST measures (values outside the 95% CI of the reference data base) in the affected ulnar nerve site. Shaded areas of the bars illustrate percentage of abnormal findings according to absolute reference data, open areas of bars according to abnormal side-to-side difference. The y-axis shows percentage of patients (n = 88), with positive sensory signs plotted upwards and negative sensory signs plotted downwards. (A) QST parameters that display loss or gain of function (B) Parameters, which are absent in normal subjects and can only present as sensory gain as defined by DFNS.

8.5.3.2 Differences between patients with leprosy and healthy controls

There were significant differences between the patients with leprosy and healthy controls in all QST thermal measures (mean and standard deviation of the DFNS z-score); CDT, WDT, TSL, CPT and HPT (p-value <0.0001). Patients had increased cold and warm thresholds; and were less sensitive to heat, and cold pain stimuli. For QST mechanical measures, there were significant differences in MDT, MPT, and MPS (p-value <0.0001). No significant differences in VDT, WUR, or PPT were found between the two groups (p-value >0.5, p-value >0.6, and p-value >0.5, respectively) (Table 8.16, Figure 8.11 and Figure 8.12).

Table 8.16. A comparison of QST measures between patients and controls

QST Parameter	Controls (n=50)		Leprosy patients (n=88)		P value
	Mean	SD	Mean	SD	
CDT (°C)	-0.12	1.8	-2.94	0.89	<0.0001
WDT (°C)	-0.43	0.74	-2.84	1.52	<0.0001
TSL (°C)	-0.75	0.57	-2.82	1.39	<0.0001
CPT (°C)	1.24	0.48	0.30	0.65	<0.0001
HPT (°C)	0.55	0.53	-0.87	1.03	<0.0001
MDT	1.08	0.66	-1.69	2.86	<0.0001
MPT	0.27	0.38	-0.72	1.06	<0.0001
MPS	0.17	0.55	-0.43	1.21	<0.0001
WUR	0.62	1.02	0.59	1.44	0.45
VDT	0.48	0.28	0.17	0.98	0.49
PPT	-1.07	0.68	-1.05	0.90	0.62

† Means and standard deviation (SD) of QST parameters of leprosy patients tested on the ulnar area (C8) compared to controls tested on the same site (n=50). QST data are shown as mean for untransformed data (HPT, VDT) and transformed mean for log-normally distributed data.

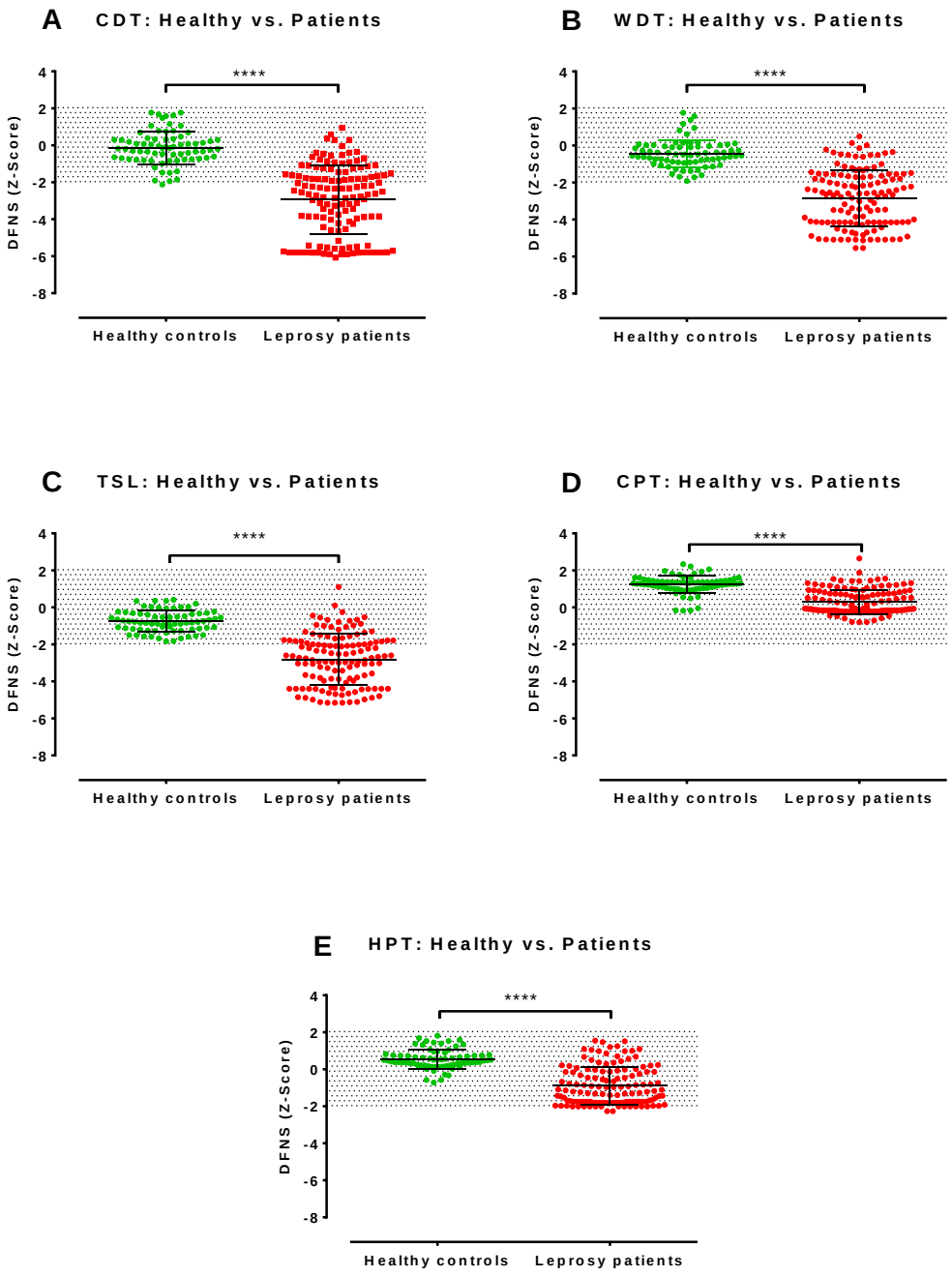

Figure 8.11. Thermal QST measures for patients (n=88) and controls (n=50)

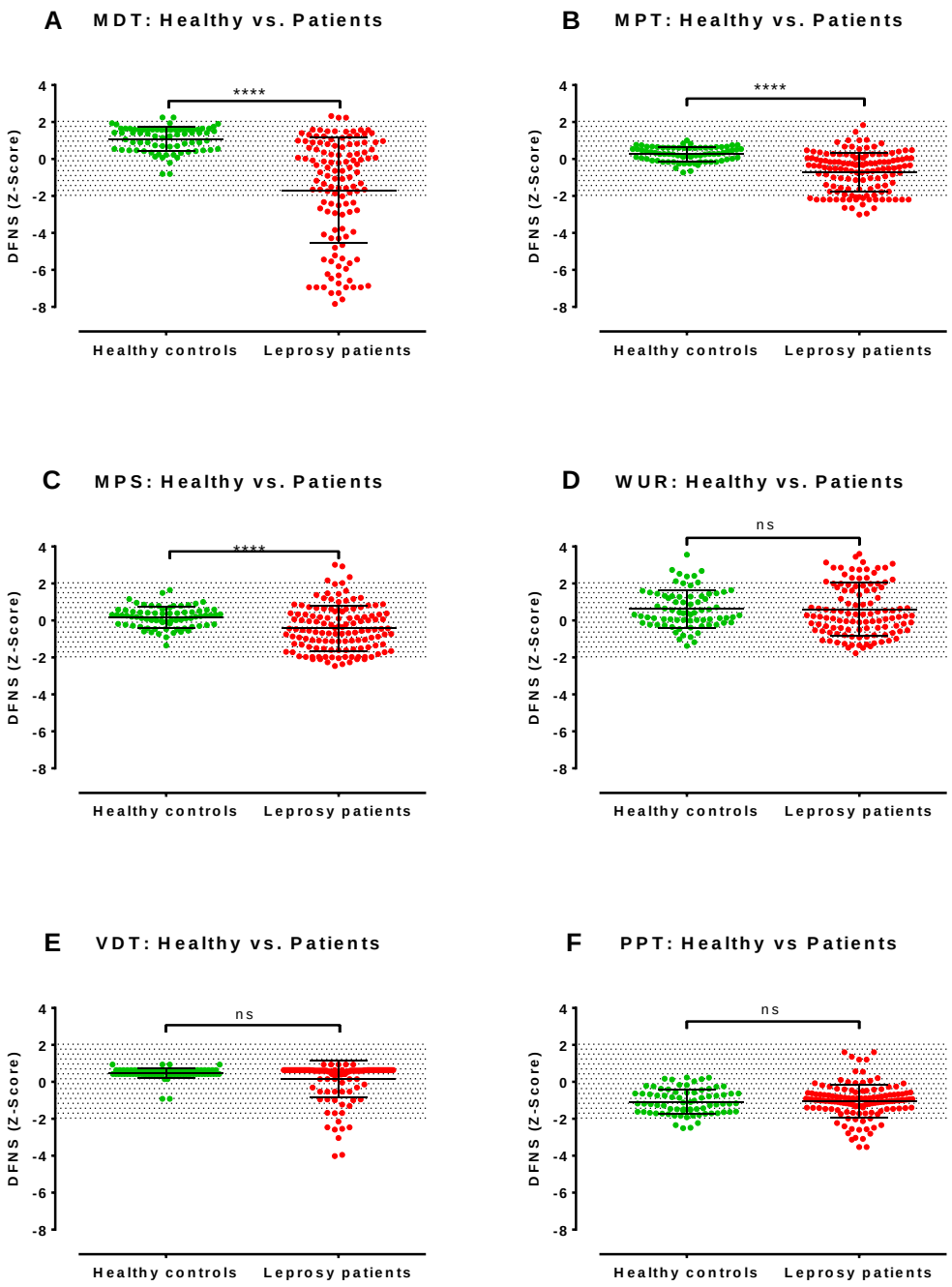

Figure 8.12. Mechanical QST measures for patients (n=88) and controls (n=50)

8.5.4 Somatosensory profiles of leprosy patients

8.5.4.1 Sensory profile and number of abnormal findings

Z-score sensory profiles of all leprosy patients compared to control

The QST sensory profiles for ulnar nerve territory (maximum pain area on dermatome C8) and by group (HC, patients with no pain, and patients with pain) shown as z-scores are presented in Figure 8.13 and Table 8.17. For the current study, the QST parameters are grouped into thermal and mechanical parameters; and to allow for easy visual comparison, the z-scores sensory profile are also shown for all patients by each group independently.

8.5.4.2 Distribution of QST measures in patients without pain

The z-score DFNS-QST sensory profiles for all thermal and mechanical parameters in patients with leprosy and no pain in the ulnar nerve territories (dermatome C8) are illustrated in Figure 8.13 and Table 8.17. For patients with no clinical evidence of neuropathy (Group 1), the mean values of all QST parameters were within the 95% confidence interval of the DFNS and local Indian healthy controls references (Figure 8.13 - A). Patients with no clinical evidence of neuropathy based on MFs and/ or MRC scale, but who showed abnormal nerve conduction study (NCS) or thermal testing were classified as "Subclinical neuropathy".

Of the 29 patients with no clinical evidence of neuropathy, 14 patients were identified as having subclinical neuropathy using the thermal testing compared to 15 patients using NCS (data for NCS were not presented), indicating that QST measures can differentiate neuropathy from no neuropathy (Figure 8.13 - A and B).

Patients with subclinical neuropathy (Group 2) and clinical evidence of neuropathy (Group 3) had z-scores beyond the 95% confidence interval of the DFNS and local Indian healthy controls references. Their sensory profiles were characterised predominately by a loss of function, indicated by increased thermal and mechanical thresholds (Table 8.17). In these two groups, a thermal loss of function was demonstrated for non-nociceptive CDT, WDT, TSL; and nociceptive parameters CPT, and HPT in the ulnar side compared to healthy controls (Figure 8.13 - B and C). For mechanical QST parameters, a loss of function was demonstrated for the non-nociceptive parameter MDT; and for the nociceptive parameters MPT, and MPS.

Although MPT, MPS, VDT, WUR, and PPT in the subclinical group; and VDT, WUR, and PPT in the neuropathy group, were abnormal in the affected side (Table 8.17) they did not reach statistical significance compared to healthy controls data (p-values >0.05). In both groups, there was no evidence of sensory gain.

The thermal and mechanical frequencies of z-score values outside the 95% confidence interval of the DFNS and HC group which indicating a loss of function (<- 1.96), for patients with subclinical neuropathy, were as follows: CDT (53.3%), WDT (40.0%), TSL (56.6%), CPT (6.7%), HPT (13.3%), MDT (26.7%), MPT (10.0%), MPS (30.0%), and PPT (30.0%) (Table 8.22). For the clinical evidence of neuropathy group, the frequencies of the abnormal values were as follows: CDT (53.3%), WDT (40.0%), TSL (56.6%), CPT (6.7%), HPT (13.3%), MDT (26.7%), MPT (10.0%), MPS (30.0%), and PPT (30.0%) (Table 8.22). WUR was not consistently present in any of the affected and/ or contralateral ulnar side. No patients had DMA in any of the affected and/ or contralateral ulnar side. PHS in the affected area was frequently reported in nine patients. In these nine patients, PHS was reported once in five patients, twice in two patients and three times in two patients (Table 8.22).

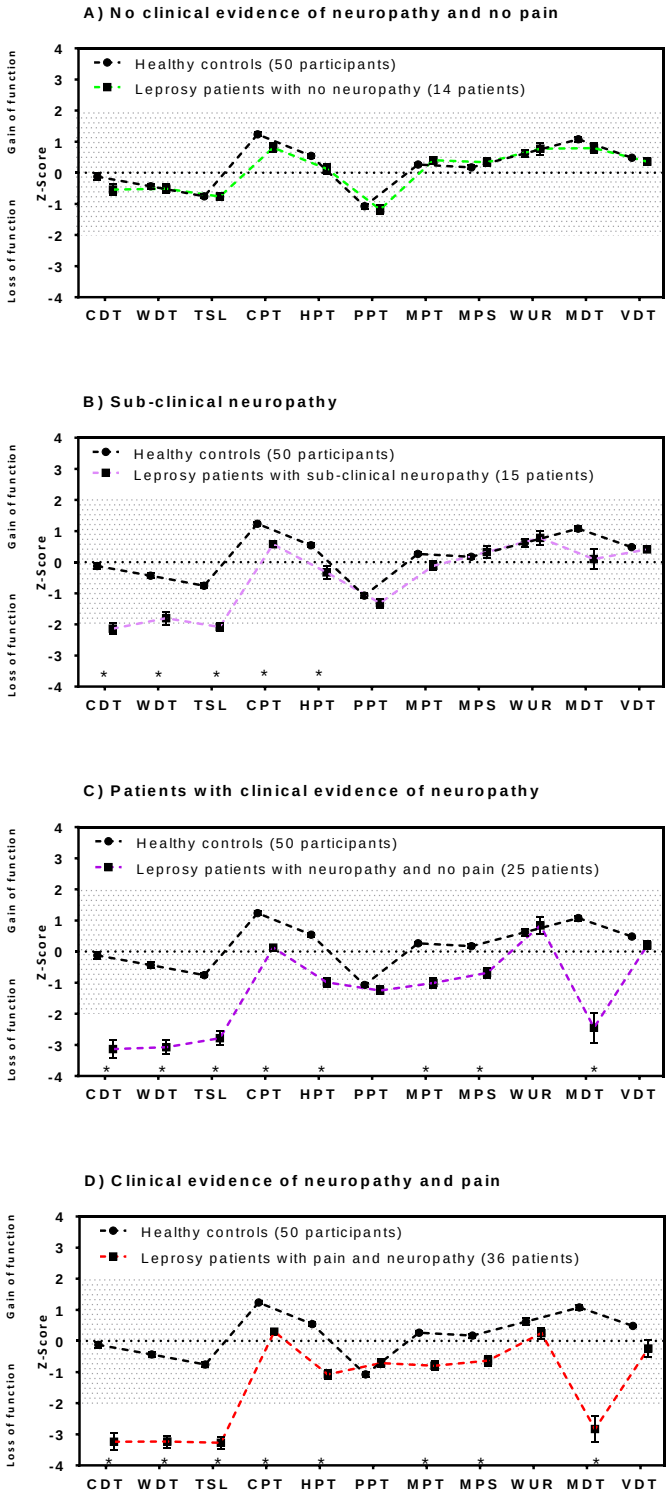

Figure 8.13. Leprosy sensory profiling

The z-score sensory profiles are shown of (A) patients with no clinical evidence of neuropathy (n=15), (B) patients with sub-clinical neuropathy (n=14), (C) patients with clinical evidence of neuropathy (n=25), and (D) patients with pain (n=32)

Table 8.17. Descriptive statistics for QST parameters †

QST Parameter †		Groups				
		Healthy control (n=50)	Patient (n=88)			
			Group 1	Group 2	Group 3	Group 4
Thermal QST parameters	CDT (°C)	-0.12 (0.89)	-0.54 (0.88)	-2.13 (1.01)*	-3.13 (2.06)*	-3.24 (1.99)*
	WDT (°C)	-0.43 (0.74)	-0.51 (0.75)	-1.80 (1.20)*	-3.07 (1.59)*	-3.23 (1.41)*
	TSL (°C)	-0.75 (0.58)	-0.77 (0.67)	-2.08 (0.77)*	-2.78 (1.55)*	-3.27 (1.34)*
	CPT (°C)	1.24 (0.48)	0.81 (0.77)	0.58 (0.56)*	0.13 (0.69)*	0.30 (0.62)*
	HPT (°C)	0.55 (0.53)	0.13 (0.84)	-0.33 (1.11)*	-0.99 (0.97)*	-1.08 (0.93)*
Mechanical QST parameters	MDT(mN)	1.08 (0.66)	0.80 (0.85)	0.10 (1.73)*	-2.44 (3.34)*	-2.83 (3.10)*
	MPT (mN)	0.27 (0.38)	0.41 (0.60)	-0.11 (0.80)	-1.00 (1.07)*	-0.80 (1.05)*
	MPS (0-100)	0.17 (0.56)	0.34 (0.68)	0.33 (1.12)	-0.68 (1.16)*	-0.63 (1.14)*
	VDT (x/8)	0.48 (0.28)	0.34 (0.59)	0.41 (0.47)	0.20 (0.89)	-0.24 (2.04)*
	WUR (ratio)	0.62 (1.02)	0.73 (1.07)	0.78 (1.29)	0.84 (1.75)	0.25 (1.19)
	PPT (kPa)	-1.07 (0.68)	-1.19 (0.68)	-1.31 (0.78)	-1.25 (0.90)	-0.71 (0.90)

† Means and standard deviation (SD) of QST parameters of healthy controls (HC), and leprosy groups (Group 1, 2, 3, and 4) in the maximum pain area (C8). QST data are shown as mean for untransformed data (HPT, VDT) and transformed mean for log-normally distributed data. *p-value <0.05.

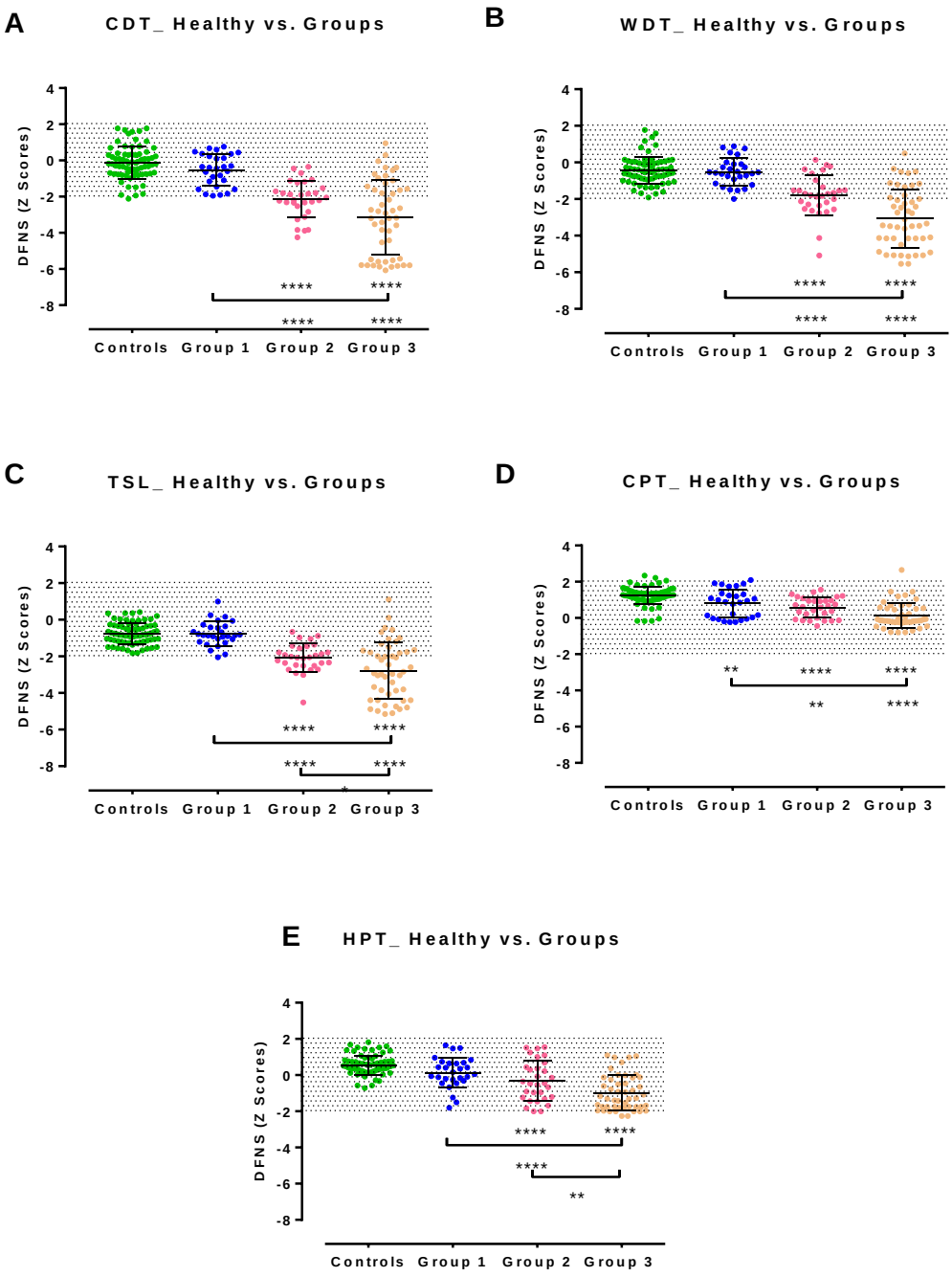

Figure 8.14. Thermal QST measures for leprosy patients with no pain (n=54)

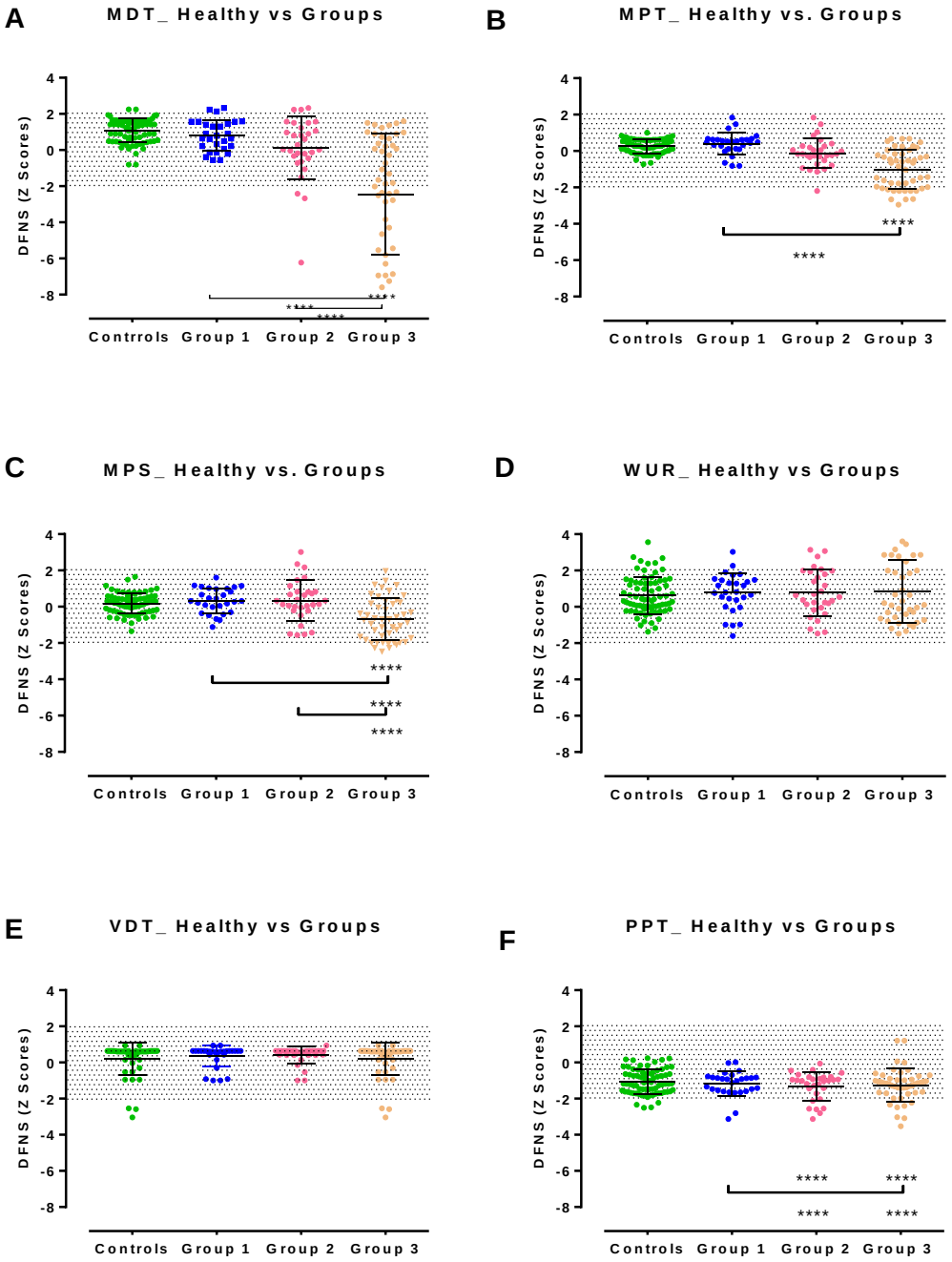

Figure 8.15. Mechanical QST measures for leprosy patients with no pain (n=54)

8.5.4.3 Distribution of QST measures in patients with pain

The z-score DFNS-QST sensory profiles for thermal and mechanical parameters in patients with leprosy and pain (Group 4) are illustrated in Figure 8.13 - D (above), Figure 8.16 and Figure 8.22 (below); and Table 8.18. Patients with leprosy and pain were further sub-grouped according to the DN4 score and neuropathy which was classified clinically by using MFs and/ or MRC scale (but no NCS), as follows: no neuropathy and DN4 <4 (2 patients); no neuropathy and DN4 ≥4 (2 patients); neuropathy and DN4 <4 (6 patients); and neuropathy and DN4 ≥4 (22 patients) (Table 8.18). In all these sub-groups patients had z-scores beyond the 95% confidence interval of the normal reference values for CDT, WDT, and TSL. The dominant sensory characteristics was a loss of function in the C8 area of the ulnar nerve territory. For mechanical QST parameters, a loss of function was demonstrated for the MDT and WUR in the no neuropathy subgroup (p-value <0.05) (Table 8.18); MDT, and MPS in patients with neuropathy and DN4<4; and MDT, and MPT in patients with neuropathy and DN4 ≥4.

In addition, few leprosy patients with any type of pain demonstrated signs of a gain of sensory function indicated by the presence of WUR and DMA. The former was present in eight (12.5%) patients. Two (3.1%) patient demonstrated DMA in the QST tested site (dermatome C8), but it was present nine (41.1%) patients along the ulnar nerve territory. PHS in the affected area was frequently reported in eleven (17.2%) patients. In these four patients, PHS was reported once in three patients, and three times in eight patients (Table 8.22).

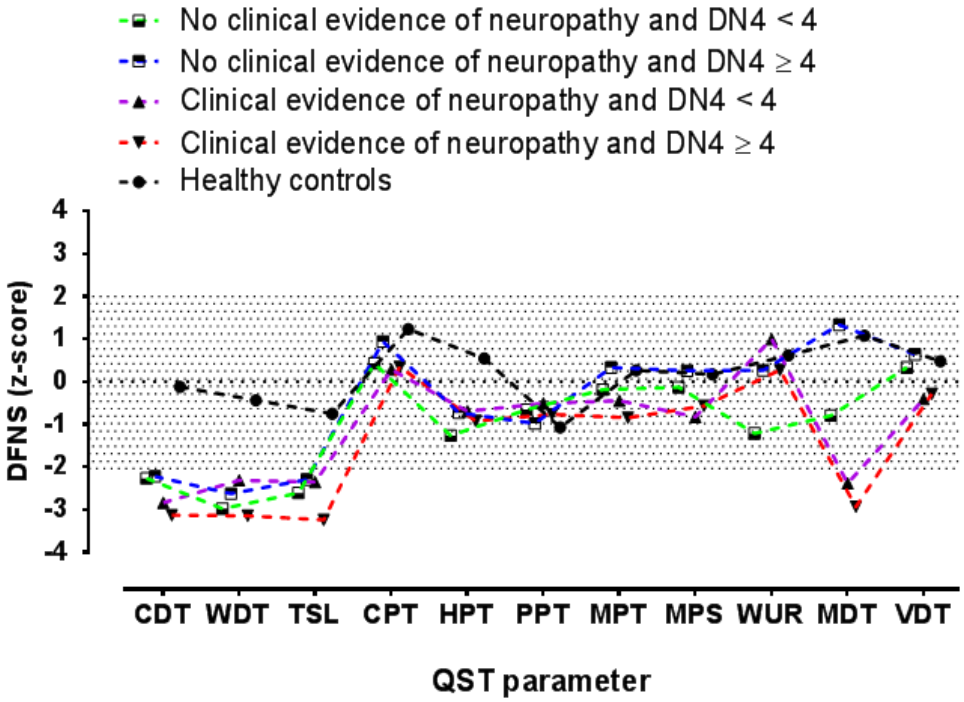

Figure 8.16. Sensory profiling for pain patients (n=32) †

The z-score sensory profiles of the ulnar tested sites are shown of patients with no clinical evidence of neuropathy and DN4 <4 (Green), or DN4 ≥4 (Blue); clinical evidence of neuropathy and DN4 <4 (Pink), or DN4 ≥4 (Red); and controls (Black)

Table 8.18. QST parameters for leprosy patients with pain †

QST parameter	Healthy controls (n=50)	Patients with pain in upper limbs (n=32)			
		No neuropathy		Neuropathy	
		DN4<4 (n=2)	DN4≥ (n=2)	DN4<4 (n=6)	DN4≥ (n=22)
CDT (°C)	-0.12 (0.89)	-2.26 (1.38)*	-2.22 (2.59)*	-2.84 (2.11)*	-3.13 (2.08)*
WDT (°C)	-0.43 (0.74)	-2.97 (1.29)*	-2.62 (1.57)*	-2.31 (1.97)*	-3.15 (1.39)*
TSL (°C)	-0.75 (0.58)	-2.61 (0.80)*	-2.29 (1.50)*	-2.36 (2.05)*	-3.24 (1.27)*
CPT (°C)	1.24 (0.48)	0.43 (0.70)	0.94 (0.66)	0.28 (0.71)*	0.35 (0.64)*
HPT (°C)	0.55 (0.53)	-1.27 (0.87)*	-0.73 (1.10)	-0.69 (1.12)*	-0.92 (1.03)*
MDT(mN)	1.08 (0.66)	-0.80 (1.06)*	-1.34 (0.04)	-2.38 (3.47)*	-3.13 (2.08)*
MPS	0.17 (0.56)	-0.13 (0.78)	-0.26 (0.79)	-0.82 (0.57)*	-0.57 (1.27)*
MPT (mN)	0.27 (0.38)	-0.18 (0.47)	0.33 (0.22)	-0.45 (0.72)	-2.94 (3.17)*
VDT (x/8)	0.48 (0.28)	0.33 (0.57)	0.64 (0.00)	-0.41 (1.64)	-0.28 (2.18)
WUR	0.62 (1.02)	-1.22 (0.10)*	0.27 (1.28)	1.00 (1.05)	0.27 (1.15)
PPT (kPa)	-1.07 (0.68)	-0.65 (0.11)	-0.98 (0.15)	-0.51 (0.74)	-0.76 (0.97)

† Means and standard deviation (SD) of QST parameters of leprosy patients with pain in the ulnar area (C8). QST data are shown as mean for untransformed data (HPT, VDT) and transformed mean for log-normally distributed data. *p value <0.05

8.5.4.4 Distribution of QST measures in patients with and without pain

Z-scores of sensory profiles of the patients with pain and without pain in the upper limbs are illustrated for each group (Table 8.19 and Figure 8.17). Healthy control participants are represented by a z-score of "zero". In both subgroups all QST parameters fell outside the 95% confidence interval of our healthy controls data (i.e. z-score >-1.96 or <1.96 standard deviation). QST measures cannot be used to differentiate leprosy patients with and without pain.

In patients with or without pain, thermal and mechanical detection thresholds; pain thresholds were significantly reduced on the affected side compared to the healthy control subjects (CDT: $p < 0.0001$, WDT: $p < 0.0001$, TSL: $p < 0.0001$, CPT: $p < 0.001$, HPT: $p < 0.001$, and MDT: $p < 0.0001$) (Figure 8.17). Other QST parameters (VDT, WUR and PPT) were not statistically significant compared to healthy control subjects in affected side. Although patients with and without pain both had QST parameters beyond 95% confidence interval of the references, these measures cannot be used to differentiate leprosy patients with and without pain (Table 8.19). In this study, QST results revealed that the number of sensory abnormalities did not differ between patients with and without pain.

Table 8.19. QST parameters in leprosy patients with and without pain †

QST parameter	Patients without Pain (n=54)		Patients with pain (n=32)		P-value
	Mean	SD	Mean	SD	
CDT (°C)	-3.74	2.13	-3.29	2.10	0.35
WDT (°C)	-3.62	1.36	-3.31	1.44	0.59
TSL(°C)	-3.10	1.66	-3.23	1.44	0.91
CPT (°C)	-0.10	0.49	0.34	0.66	0.35
HPT (°C)	-1.22	0.94	-1.02	1.06	0.81
MDT(mN)	-3.27	3.21	-2.76	3.36	0.37
MPT (mN)	-1.43	1.06	-0.92	1.13	0.34
MPS (0-100)	-1.08	1.16	-0.81	1.01	0.74
VDT (x/8)	0.08	1.03	-0.19	1.38	0.74
WUR (ratio)	1.10	1.72	0.17	1.26	0.08
PPT (kPa)	-1.34	0.10	-0.74	0.95	0.27

† Means and standard deviation (SD) of QST parameters are shown of leprosy patients with and without pain in the ulnar area (C8). QST data are shown as mean for untransformed data (HPT, VDT) and transformed mean for log-normally distributed data

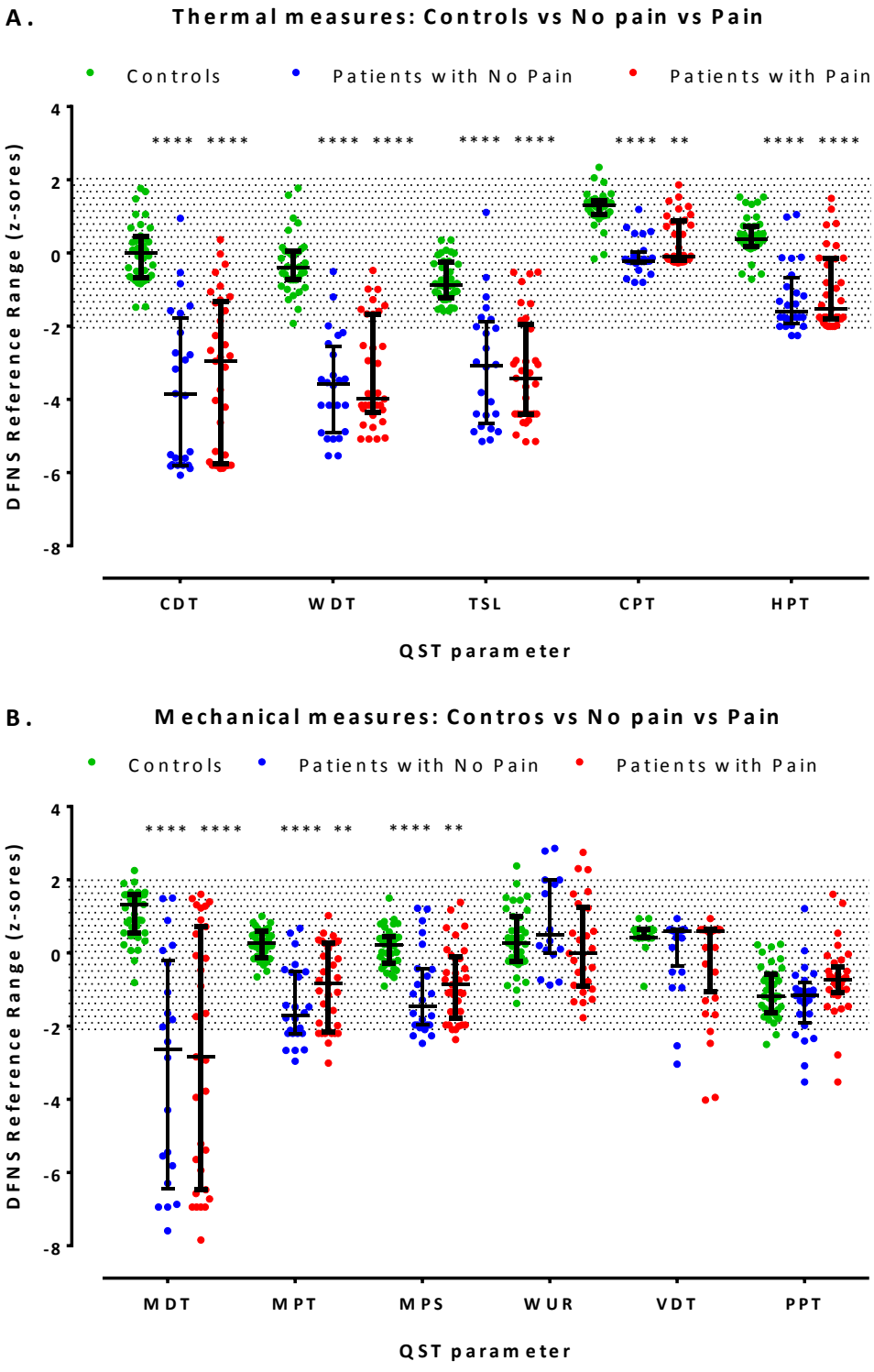

Figure 8.17. QST findings for leprosy patients (n=88)and controls (n=50)

8.5.4.5 QST findings in leprosy patients with neuropathic pain

Sensory phenotypes

Patients with leprosy NP demonstrated z-scores beyond the 95% confidence interval of the normal reference values in almost all QST parameters, except for VDT, PPT and WUR, in the maximum pain area over the ulnar nerve territory (dermatome C8) (Figure 8.18). Data analysis on the individual level for frequencies of abnormal values gave a similar findings (Figure 8.19 and Table 8.20). Two thirds of these findings were identified by direct comparison to reference data, which is defined as an absolute abnormality; and about one third by side-to-side difference i.e. relative abnormality (if a patient's values were abnormal in both tests, only abnormality with respect to absolute reference data was counted). Figure 8.19 shows the percentage of abnormal values in the leprosy patients presented with NP.

Of the twenty four patients with NP components in the ulnar nerve territory, three patients had NP in their skin lesions which were not tested as part of the QST protocol. In the remaining 21 patients, 84-94% had abnormal sensory loss and significant rates were found primarily for non-noxious detection for thermal detection transmitted by small nerve fibres (CDT (84.2%), WDT (89.5%), TSL (94.7%): p-value <0.0001); and in about one quarter of the patients for mechanical detection conducted by large nerve fibres (MDT (73.7%): p-value <0.0001). Remarkably, sensory loss was also frequent for pain parameters, in particular for pinprick (MPT (85.7%), MPS (78.9%): p-value <0.0001); and heat pain (HPT (52.6%): p-value <0.0001) (Table 8.18). Although patients had abnormal PPT, WUR and VDT in the affected side (VDT (26.3%), PPT (15.8%), and WUR (15.8%)) (Table 8.19 and Figure 8.17 - B), they were not significantly different from healthy controls data (PPT, WUR and VDT: p-values >0.05).

The sensory gain in patients with leprosy NP was not consistently present in the tested site (dermatome C8). The most prevalent findings of sensory gain was the presence of WUR in three (15.8%) patients, and in nine (47.4%) patients the thresholds was not detected as the patients did not feel the stimulus. Only one (5.3%) patient had pain to light touch (DMA) demonstrated in the QST tested site (dermatome C8). In addition, DMA was present in six (31.6%) patients along the ulnar nerve distribution, but not at the QST tested site. No abnormal hypersensitivity were found in all other pain

parameters. PHS in the affected area was frequently reported three times in 3 (15.8%) patients, but it is not clear whether this phenomenon is part of sensory gain.

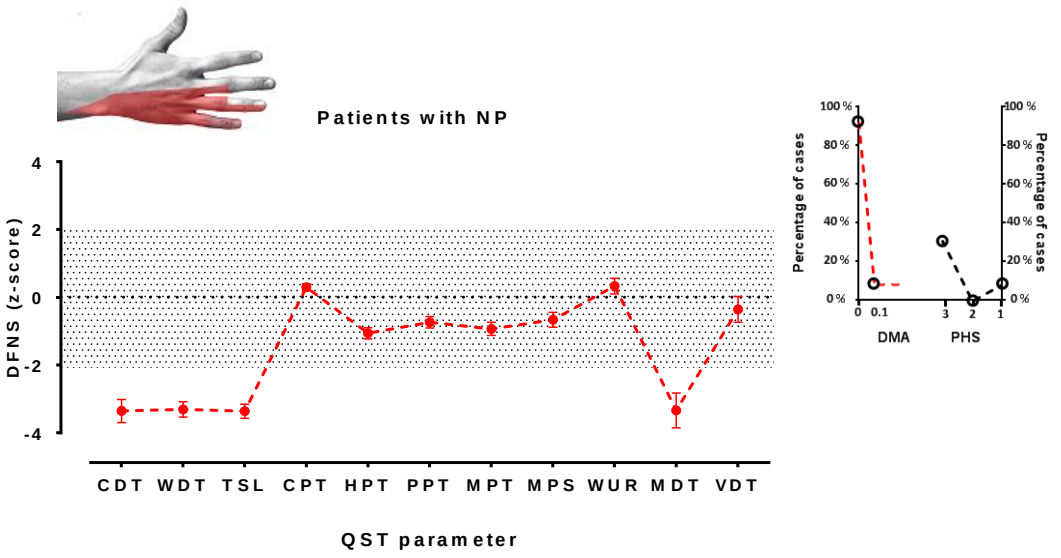

Figure 8.18. Leprosy neuropathic pain sensory profiling

QST profiles QST profile of 24 patients with clinical evidence of neuropathy and DN4≥4 in ulnar nerve territory (dermatome C8) (red symbols), using a QST test protocol according to the German Research Network on Neuropathic Pain (DFNS). Data are presented as z-scores, using the following expression: Z-value = (Value patients – Mean control) / SD control. Data of healthy control patients are represented by a z-score of "0"; patients' data are presented as positive or negative z-values. The grey area represents the confidence interval of healthy control patients. Values are defined as pathological when deviating more than two SD from the respective control sample (age- and sex-matched). This profile shows signs of sensory loss detected by increased thermal detection thresholds (CDT, WDT) and increased mechanical detection thresholds (MDT). No signs of sensory gain are found by pinprick hyperalgesia (MPT, MPS). QST quantitative sensory testing; SD standard deviation; CDT cold detection threshold; WDT warm detection threshold; TSL thermal sensory limen; CPT cold pain threshold; HPT heat pain threshold; PPT pressure pain threshold; MPT mechanical pain threshold; MPS mechanical pain sensitivity; WUR wind-up ratio; MDT mechanical detection threshold; VDT vibration detection threshold; NRS numerical rating scale; DMA dynamic mechanical allodynia; PHS paradoxical heat sensation.

The abnormal values from the QST testing were categorised with respect to loss (L) and gain (G) of sensation from reference data taking age and sex into account (Magerl et al., 2010). Loss of sensation was further categorised to L0: no loss, L1: thermal hypoaesthesia, L2: mechanical hypoaesthesia, L3: thermal and mechanical hypoaesthesia; and gain of sensations was G0: no hyperalgesia, G1: thermal hyperalgesia, G2: mechanical hyperalgesia, G3 thermal and mechanical hyperalgesia (Table 8.20 and Table 8.22). This defines the abnormal sensitization of unmyelinated cutaneous nociceptors (irritable nociceptors) phenotype as L0G1, L0G2, L0G3, L2G1, L2G2, and L2G3; and the abnormal sensation of complete deafferentation of both large and small diameter fibres "non-irritable nociceptor" phenotype as any combination including L1 or L3, and L0G0 and L2G (Fields et al., 1998). The sensory phenotypes of patients with leprosy neuropathic pain was characterised predominately by a loss of function, indicated by increased thermal and mechanical threshold in the affected areas. The most prevalent combinations characterising most of the patients were sensory loss for both thermal and mechanical stimuli, combined with no sensory gain (Table 8.20). Only 4/21 patients had some form of abnormal mechanical pain (19%). Thus mechanical hyperalgesia was very rare and no thermal hyperalgesia. Mechanical hyperalgesia, if present, was usually accompanied by thermal and mechanical sensory loss.

Based on the QST findings patients were grouped as follows: patients with pain without hyperalgesia or allpdynia "non-irritable nociceptor phenotype". In this group, which including most of the patients, profound loss of small and large diameter fibre functions was documented. The second group had pain associated with small fibre deafferenation. In these patients, which represent the minority of the study cohort, pain and temperature sensation were profoundly impaired but allodynia was present "irritable nociceptor phenotype".

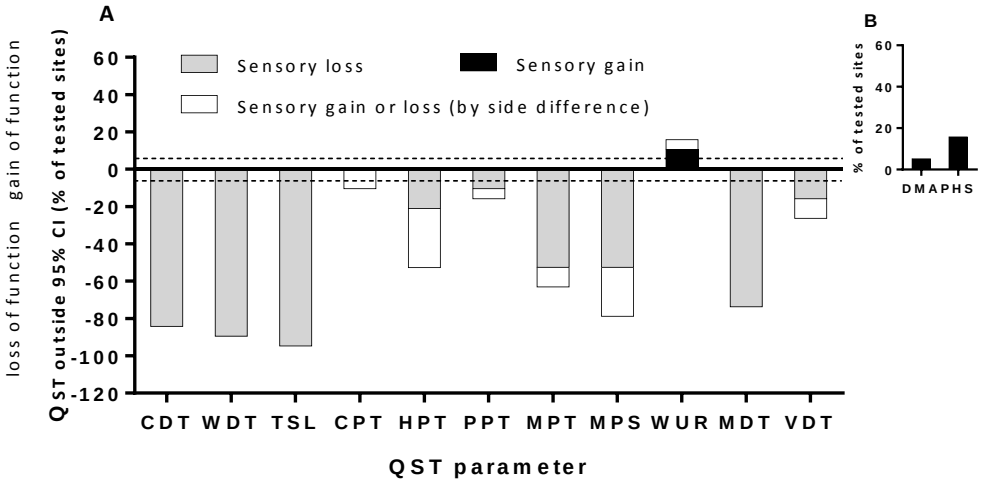

Figure 8.19. Percentages of abnormal QST values in NP patients

Percentages of abnormal QST values in 21 patients with NP in C8. Shaded areas of the bars illustrate percentage of abnormal findings according to absolute reference, open areas of bars according to abnormal side-to-side difference. (A) Parameters that display loss or gain of function (B) Parameters, which are absent in normal subjects and can only present as sensory gain as defined by DFNS.

Table 8.20. Frequency of abnormal values in NP (n=21) †

Loss (detection)	**Gain (pain)**				
	No gain (G0)	Thermal (G1)	Mechanical (G2)	Both (G3)	All
No loss (L0)	- (0%)	- (0%)	- (0%)	- (0%)	- (0%)
Thermal (L1)	- (0%)	- (0%)	- (0%)	- (0%)	- (0%)
Mechanical (L2)	- (0%)	- (0%)	- (0%)	- (0%)	- (0%)
Both (L3)	15 (86%)	- (0%)	4 (19%)	- (0%)	21 (100%)
All	15 (86%)	- (0%)	4 (19%)	- (0%)	21 (100%)

† Frequency of different combinations of abnormal values in 21 patients with NP in dermatome C8. L0: no loss, L1: thermal hypoaesthesia, L2: mechanical hypoaesthesia, L3: thermal and mechanical hypoaesthesia; G0: no hyperalgesia, G1: thermal hyperalgesia, G2: mechanical hyperalgesia, G3 thermal and mechanical hyperalgesia.

8.5.4.6 Comparison of sensory profiles between groups

Side-to-side comparison of QST sensory profiles (pain group)

Sensory profiles of the symptomatic and asymptomatic upper arms are illustrated for each pain subgroup (non-NP subgroup Figure 8.20 and NP subgroup Figure 8.21) in the maximum pain area. Healthy control subjects are represented by a z-score of "zero". In both subgroups QST parameters fell outside the 95% confidence interval of our healthy controls data. Compared to asymptomatic side, patients with painful neuropathy have lower thermal detection threshold and pain threshold (CPT, HPT). Remarkably, in these patients, the responses to QST stimuli can identify abnormalities in somatosensory system, but it cannot be used to differentiate leprosy patients with and without pain.

Patients with leprosy non-neuropathic pain

In patients with non-NP in upper limbs, all thermal detection thresholds; and pain parameters, in particular for heat, cold and pinprick pain thresholds were significantly reduced on the symptomatic side compared to the asymptomatic side in the tested area (p-value <0.05) (Figure 8.20).

Patients with leprosy neuropathic pain

Of the 24 patients with NP in upper limbs, 4 patients had NP in the skin lesions, one of them located in the tested site (dermatome C8). So, 21 patients with maximum pain in the dermatome C8 were included in this comparison. Of these 21 patients, six had bilateral pain and the remaining 15 had unilateral pain. In these 21 patients, all thermal detection thresholds; and pain parameters, in particular for heat, cold and pinprick pain thresholds were significantly reduced on the symptomatic side compared to the asymptomatic side in the tested area (p-value <0.05) (Fig). Side-to-side comparison of all other QST parameters (MDT, WUR, VDT and PPT) were not significant.

Figure 8.21 -B demonstrates the percentages of the occurrence of PHS (0-3) and DMA (log numerical rating scale 0-100). The reports of both were infrequent. One patient with NP demonstrated DMA, but none in the asymptomatic side. PHS was reported by one patient once; and by four patients three times on the symptomatic side. Two patients reported PHS three times on the asymptomatic side.

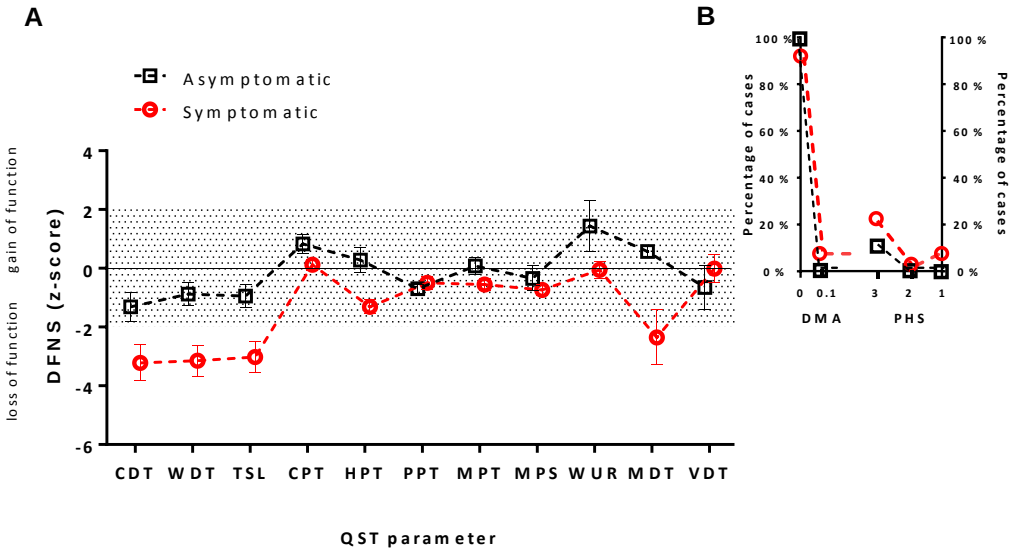

Figure 8.20. Somatosensory profiles in Non-NP patients

Somatosensory profiles (A), and occurrence of DMA and PHS (B) of the symptomatic (empty circle symbol "red") and asymptomatic (empty square symbol "black") side in 8 patients with leprosy non-neuropathic pain in ulnar nerve territory. Error bars indicate the standard error of measurement. Healthy control subject are represented by a z-score of "zero"

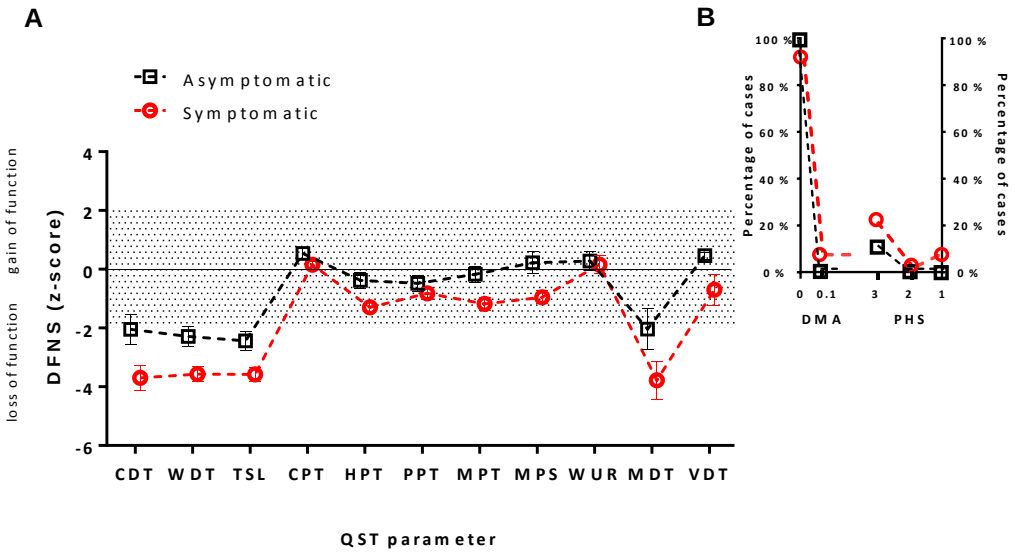

Figure 8.21. Somatosensory profiles in NP patients

Somatosensory profiles (A), and occurrence of DMA and PHS (B) of the symptomatic (empty circle symbol "red") and asymptomatic (empty square symbol "black") side in 21 patients with leprosy NP in ulnar nerve territory. Error bars indicate the standard error of measurement. Healthy control subject are represented by a z-score of "zero"

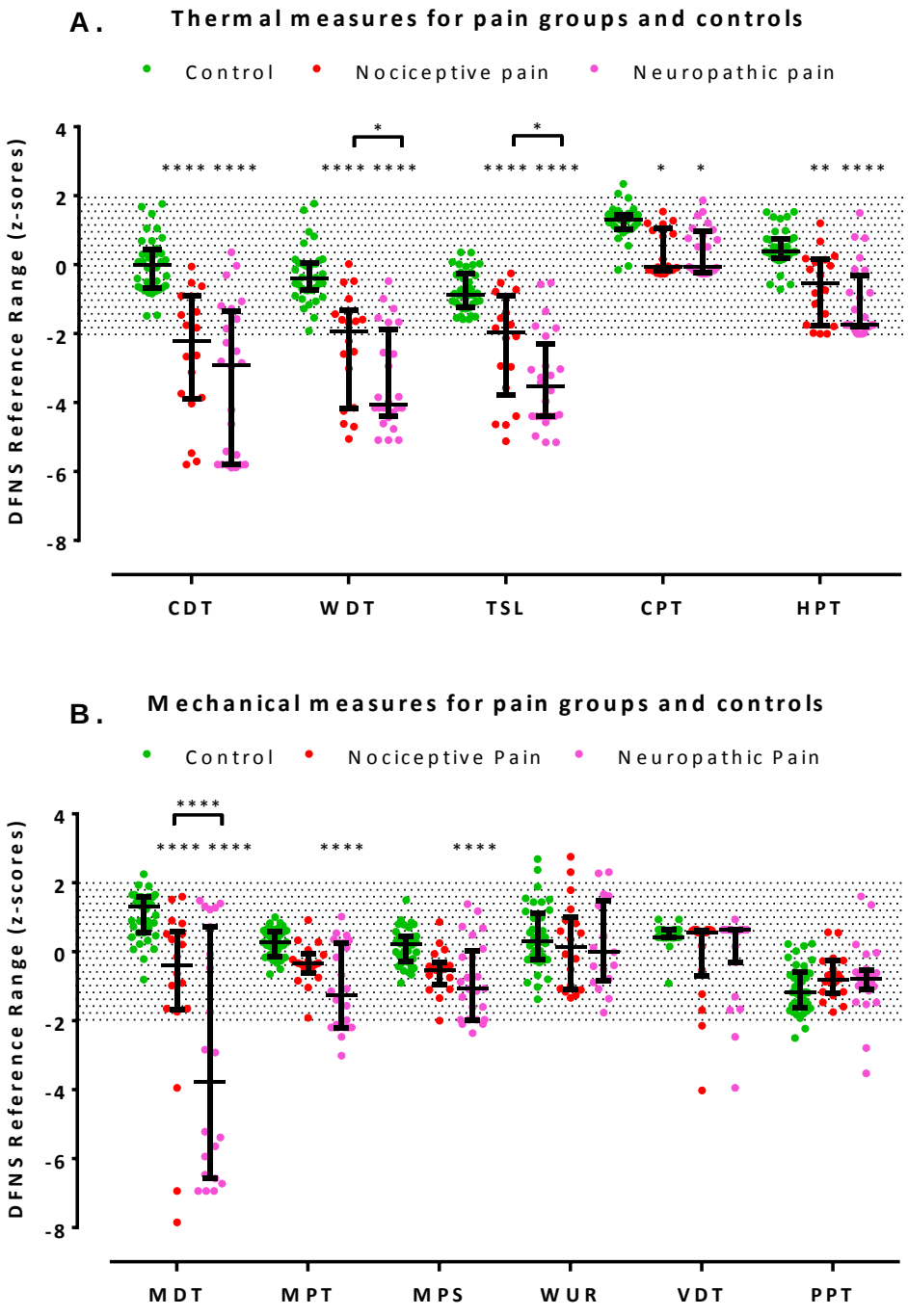

Figure 8.22. QST findings for patients with pain (n=32) and controls (n=50)

Table 8.21. Comparison between symptomatic and asymptomatic sides (n=21) †

QST parameter	Maximum pain area over ulnar nerve territory (C8)					
	Neuropathic pain			Non-neuropathic pain		
	Asymptomatic	Symptomatic	P-value	Asymptomatic	Symptomatic	P-value
CDT (°C)	-2.05 (1.89)	-3.70 (2.07)	0.018	-1.31 (0.98)	-3.23 (1.93)	0.088
WDT (°C)	-2.29 (1.23)	-3.57 (1.28)	0.001	-0.88 (0.77)	-3.15 (1.66)	0.024
TSL (°C)	-2.44 (1.24)	-3.58 (1.24)	0.009	-0.95 (0.80)	-3.02 (1.69)	0.039
CPT (°C)	0.54 (0.63)	0.15 (0.54)	0.052	0.83 (0.67)	0.12 (0.60)	0.075
HPT (°C)	-0.38 (1.01)	-1.30 (0.85)	0.005	0.28 (0.84)	-1.31 (0.76)	0.005
MDT (mN)	-2.04 (2.61)	-3.78 (3.21)	0.092	0.57 (0.34)	-2.35 (2.97)	0.079
MPT (mN)	-0.17 (1.02)	-1.18 (1.13)	0.009	0.08 (0.59)	-.55 (0.61)	0.102
MPS (NRS 0-10)	0.23 (1.34)	-0.96 (1.09)	0.006	-0.34 (0.85)	-0.74 (0.62)	0.350
WUR (ratio)	0.28 (1.14)	0.15 (1.28)	0.780	1.44 (1.74)	-0.06 (0.97)	0.058
VDT (x/8)	0.46 (0.43)	-0.70 (2.67)	0.117	-0.65 (1.47)	-0.01 (1.46)	0.470
PPT (kPa)	-0.48	-0.83	0.331	-0.69 (0.30)	-0.50 (0.74)	0.612

† Comparison between symptomatic and asymptomatic sides of 21 leprosy patients with neuropathic pain in the upper limbs using the QST parameters. Data are shown as mean for untransformed data (HPT, VDT) and retransformed mean for log-normally distributed data

Table 8.22. Distribution of abnormal findings in study population (n=142) †

			Patients without pain						**Patients with pain**			
QST Parameter	HC n=52		Group 1 n=14		Group 2 n=30 (two sites)		Group3 n=48 (two sites)		Non-NP n=10 (test site)		NP n=22 (test site)	
	Gain	Loss	Gain	Loss	Gain	Loss	Gain	Loss	Gain	Loss	Gain	Loss
CDT	0	0	0	0	0	16	0	33	0	5	0	16
WDT	0	0	0	0	0	12	0	38	0	6	0	17
TSL	0	0	0	0	0	17	0	34	0	6	0	18
CPT	0	0	0	0	0	2	0	4	0	1	0	2
HPT	0	0	0	0	0	4	0	17	0	3	0	10
MDT	0	0	0	1	0	8	0	23	0	2	0	15
MPT	0	0	0	0	0	3	0	22	0	2	0	12
MPS	0	0	0	0	0	9	0	19	0	1	0	14
WUR	0	0	4	0	8	0	13	0	0	1	0	3
VDT	0	0	0	0	0	0	0	3	0	1	0	5
PPT	0	0	0	0	0	0	0	13	0	1	0	3
DMA	0	0	0	0	0	0	0	0	1	0	1	0
PHS	0		0		1		9		1		3	

† Number of individuals within each group with z-score values outside the 95% confidence interval of healthy control participants (± 1.96 SD). HC: Healthy control participants; Group 1: No evidence of neuropathy and no pain; Group 2: Subclinical neuropathy and no pain; Group 3: Clinical evidence of neuropathy and no pain; Non-NP: Inflammotory/ nociceptive pain; NP: Clinical evidence of neuropathy and pain (DN4≥4). Gain: Number of patients with positive individual z-score values, indicating an increased sensitivity compared to normative data (>+ 1.96 standard deviation). Loss: Number of patients with negative individual z-score values, indicating a decreased sensitivity compared to normative data (>+ 1.96 standard deviation). As no DMA occurred in healthy subjects, z-score values could not be calculated. Data are shown as absolute number of participants showing DMA.

8.6 Pain intensity and quality assessment

Patients with pain were asked to rate their current pain and estimate a level for their worst and average pain in the previous week using the NRS and BPI. All patients with pain (36) completed pain questionnaire. The individual scores in total and scores within each pain subgroup are shown in Figure 8.23, Table 8.23, and Table 8.24.

Figure 8.23 shows the distribution of pain scores (worst, average and current pain). The worst pain scores were not normally distributed, and the Shapiro-Wilk test was significant (W = 0.94, p-value = 0.03). Kurtosis was 1.81 and skewness was 0.74, which confirms that worst pain score is not a form of normal distribution, as in a normal distribution, both values should be zero (Kim, 2013).

The mean of current pain scores was slightly worse at 5.9 than average pain, and the median was six (interquartile range from 3 – 10). The mean of the worst pain intensity experienced by patients in the last week was high at 7.5 out of 10 (maximum score), and the median was eight (interquartile range from 4 – 1). The mean of the average pain intensity reported by patients in the previous week was relatively high at 5.3. Descriptive statistics for pain intensity measures are presented in Table 8.23.

Table 8.24 and Figure 8.24 display the scores for the BPI severity measure. Mean and median scores are displayed as well as how the scores were distributed between the neuropathic and non-NP groups. The two groups were compared according to pain intensity. The Mann-Whitney U test (for worst pain) and mean comparison test (for average and current pain) were conducted. None of the test results showed a significant difference (p-values: 0.09, 0.85, and 0.5 respectively).

The proportions of men and women who reported pain were quite similar (40% of men, 38% of women) (p-value =0.8). Women were slightly more likely than men to report a pain score of 4 or more, indicative of pain severity. The mean pain value for women was 7.4 and for men was 7.6 (p-value=0.06). No differences in mean score for men and women who reported pain interference problems. The mean interference value for men was 37 and for women was 36.7 (p-value=0.9).

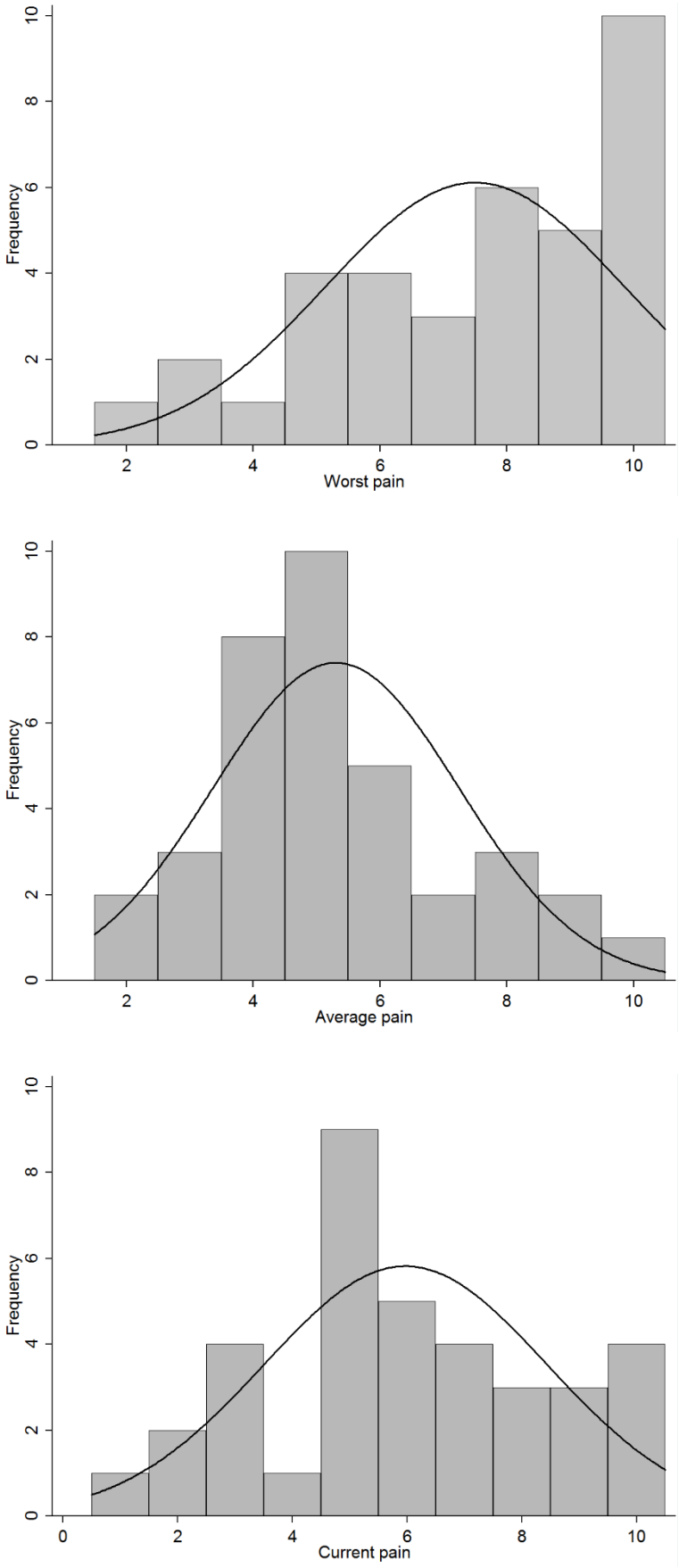

Figure 8.23. Distribution of pain scores (n=36)

Table 8.23. Descriptive statistics for pain intensity measures (n=36)

Pain measures	Mean	SD	95% CI	Median	Interquartile range
NRS current pain	5.97	2.47	5–7	6	3–10
NRS worst pain	7.50	2.35	7–8	8	4–10
NRS average pain	5.31	1.94	5–6	5	3-8

Table 8.24. Pain intensity between pain groups (n=36)

Variable	Non-NP group		NP group	
	Mean (SD)	Median (IQ)	Mean (SD)	Median (IQ)
NRS current pain	5.5 (2.42)	5.5 (5–7)	6.15 (2.51)	6 (5–8)
NRS worst pain	8.5 (2.01)	9.5 (7–10)	7.12 (2.01)	8 (5–9)
NRS average pain	2.49 (2.01)	5 (3–7)	5.35 (2.01)	5 (4–6)

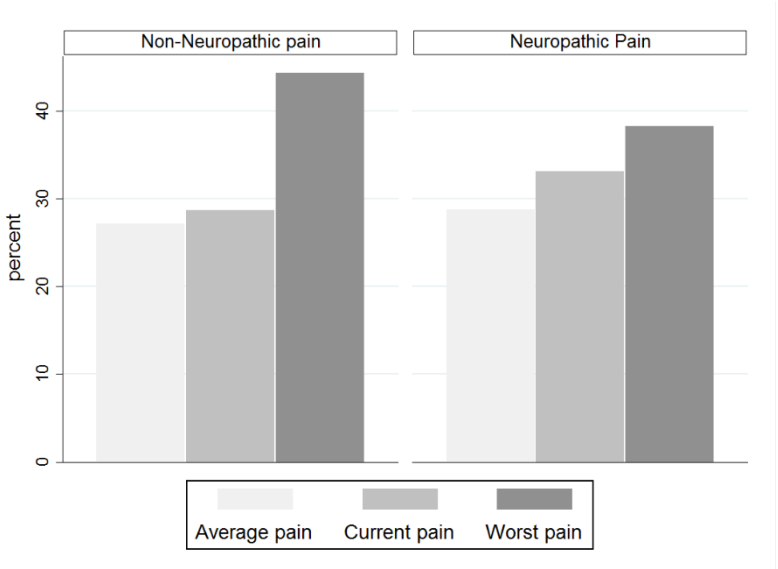

Figure 8.24. Pain intensity in NP and non-NP sub-groups (n=36)

8.7 Evaluation of psychological co-morbidity and HRQoL

8.7.1 Health related quality of life

8.7.1.1 Pain interference with daily life

The BPI is designated to evaluate pain interference over a variety of domains over the last 24 hours using a standard 0 – 10 Likert scale (0 = Does not interfere versus 10 = completely interferes). Patients were asked to rate how much their pain was interfering with aspects of daily life in the last 24 hours. Of the 36 patients with leprosy and pain, 35 (97%) patients completed the BPI related questions (Table 8.25).

Pain interference levels were moderate-to-severe, with the mean ranging from 4.1 to 6.0 across the selected daily life aspects. The collective patient group had a total interference score of more than four, which may be considered to be a high level of interference (Cleeland, 2009). Pain substantially interfered (≥4 on 0 – 10 scales) with normal work (mean 6.06, SD 3.11), sleep (mean 5.94, SD 3.30), and mood (mean 5.71, SD 3.22). Overall, patients reported variable levels of interference per domain; however, the highest levels of interference were observed in sleep, work, and mood. The lowest levels of interference were observed in walking ability (Figure 8.25). The former three vital aspects of daily life have been found to be affected due to leprosy patients feeling pain.

Table 8.25. Descriptive statistics for pain interference using BPI (n=35)

Pain interference	Mean	SD*	95% CI**	Median	IQ range
General activity	5.23	2.81	4–6	5	4–7
Mood	5.71	3.22	7–8	5	5–7
Walking ability	4.11	3.12	3–5	5	0–7
Normal work	6.06	3.11	5–7	7	3–9
Relations	4.26	3.51	3–5	4	0–7
Sleep	5.94	3.30	5–7	7	4–8
Enjoyment of life	5.69	2.98	5–7	6	4–8

*SD = standard deviation **CI = confidence interval

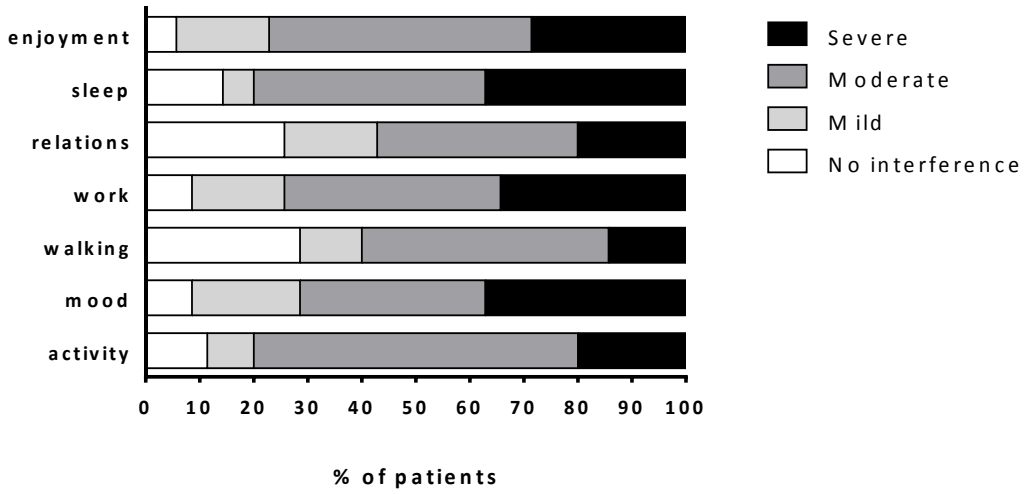

Figure 8.25. BPI Pain interference

Pain interference in various activities of daily life in 35 leprosy patients with pain

8.7.1.2 Comparing pain interference scores between pain groups

The NP and non-NP sub-groups were compared with pain interference on BPI. As expected, the BPI interference mean total score was significantly higher in the NP group (mean 41.5, SD 11.9) compared to the non-NP sub-group (mean 25.7, SD 17.8) (p-value <0.004). The high scores present in the NP group indicate that a patient's pain has an impact on their day-to-day living and quality of life.

The scores for each interference domain were normally distributed (the Shapiro-Wilk test W: 0.96 – 0.980, P-values: 0.19 – 0.90). The Mann-Whitney U test as well as mean comparison tests were conducted for each domain between the two pain sub-groups, and both showed consistent results. All of the test results were significantly different (p-value <0.05) except for mood (p-value = 0.07), walking ability (p-value = 0.47), and normal work (p-value = 0.17) when analysed by type of pain. These results indicate that NP in patients with leprosy has a greater negative impact on sleep (p-value <0.001), relations with other people (p-value <0.03), enjoyment of life (p-value <0.04), and compromised ability to perform general activities (p-value <0.05) compared to patients with non-NP (Figure 8.26). A further sub-analysis for the patients with upper limb pain showed that normal work–Including both work outside of the home and housework– was significantly different between pain sub-groups (p-value = 0.04), (Table 8.26).

Compared to the mild and moderate pain groups, patients in the severe pain group had higher ratings on the BPI interference items (mood, relations with others, sleep, and enjoyment of life), and the mean interference scores increased with increasing pain intensity. However, results of analysis of variance showed no statistical difference (p-value >0.05).

Overall, NP frequency was found to be high among leprosy patients. In addition, the patients' worst pain scores on average were high and severe. Furthermore, NP affected patients' life activities. Thus, the impact of NP on quality of life seems to be prevalent among leprosy patients. Its psychological effect on leprosy patients will be discussed in the following section.

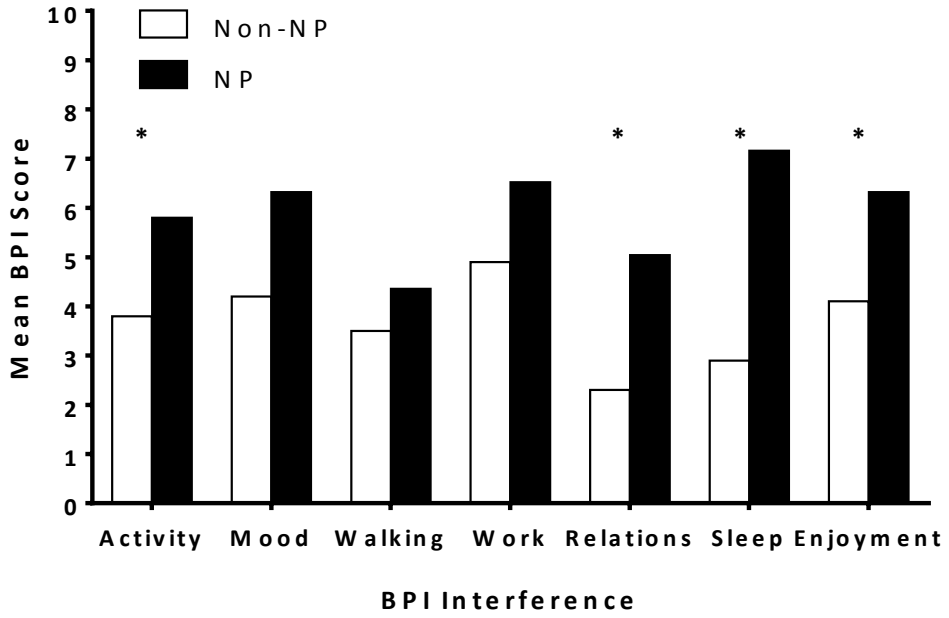

Figure 8.26. Mean BPI interference scores in patients with pain

Mean scores in BPI interference in patients with non-neuropathic pain (n=10, white bar) vs. neuropathic pain (n=25, black bar). **P-value* < 0.05

Table 8.26. BPI interference in pain groups

BPI interference		Non-NP (n=10)	NP (n=25)	P- value
BPI general activity	No interference	3	0	0.02
	Mild	1	0	
	Moderate	5	15	
	severe	1	6	
BPI mood	No interference	3	0	<0.01
	Mild	4	3	
	Moderate	0	9	
	severe	3	9	
BPI walking ability	No interference	3	5	0.80
	Mild	2	2	
	Moderate	4	11	
	severe	1	3	
BPI normal work	No interference	1	0	0.04
	Mild	3	2	
	Moderate	4	9	
	severe	2	10	
BPI relations with other people	No interference	6	2	0.03
	Mild	1	5	
	Moderate	2	8	
	severe	1	6	
BPI sleep	No interference	5	0	<0.01
	Mild	0	2	
	Moderate	4	10	
	severe	1	9	
BPI enjoyment of life	No interference	2	0	0.1
	Mild	3	3	
	Moderate	3	11	
	severe	2	7	

8.7.2 Psychological well-being

8.7.2.1 Evaluation of the psychological well-being with the GHQ-12

Descriptive analysis

A total of 89 patients (98.9%) completed the GHQ-12 questions in the study. Sixty six point three percent of the respondents had a GHQ-12 score of three or more. The overall mean score for the GHQ-12 of the patients was 3.52 (SD 2.11) (Table 8.27) and the median score was four (inter-quartile range 2–5). The distribution of scores obtained from men and women are shown in Figure 8.27. The median value for men was three and for women was 4.5. No significant differences were observed.

Over 57% of patients had a feeling of "under strain" and suffered from stress. The other most common symptoms were "feeling unhappy and depressed" (51.7%), sleep problems almost every night (43.8%), could not overcome difficulties (38.2%), and lost confidence (37.1%). In addition, 29 patients (32.6%) felt worthless, 24 patients (27%) were not feeling happy, and 20 patients (22.5%) could not face problems. Other symptoms of mental disorders were much less common, and included not enjoying activities (15.7%), could not make a decision (11.2%), could not concentrate (8.99%), and a feeling of "not playing a useful part" (6.7%). Thus, more than two-thirds of the patients were considered to have possible psychological distress (anxiety and depression).

In patients with no clinical evidence of neuropathy, the proportion of patients scoring three or higher using the GHQ-12 was 35.7% (mean 2.29, SD 1.94), compared to 66.7% (mean 3.07, SD 1.83) in the sub-clinical neuropathy group, 58% (mean 3.08, SD 1.97) in the neuropathy group, and 83.3% (mean 4.5, SD 2.01) in the pain group (Table 8.27). Patients with neuropathy and pain had a poorer mental health compared to other groups (p-value <0.001) (Figure 8.28).

Among patients with pain, 30 individuals (83.33%) had a GHQ score of three or more, compared to 29 (54.72%) among non-pain patients. 24 patients (92.31%) with NP had a GHQ score of three or more, compared to six patients (60%) in the non-neuropathic group. Figure 8.29 shows the distribution of GHQ-12 scores of three or more in leprosy patients with and without pain.

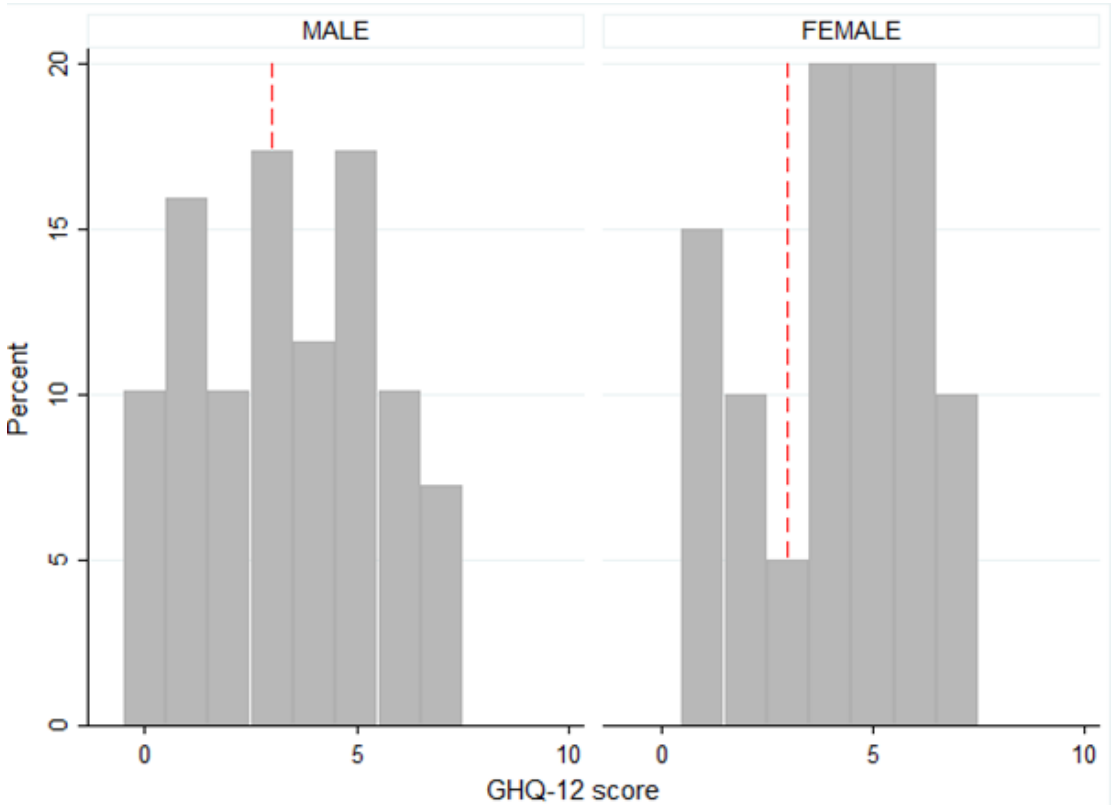

Figure 8.27. Distribution of GHQ-12 scores (n=89)

Distribution of GHQ-12 scores in men (median 3, above thresholds: 64%) and women (median 4.5, above thresholds: 75%)

Table 8.27. GHQ-12 scores †

GHQ-12 item	**Groups**				**Total scores (n=89)**
	Group1 (n=14)	Group2 (n=15)	Group3 (n=24)	Group4 (n=36)	
Could not concentrate	1.9 (0.5)	1.8 (0.7)	1.5 (0.7)	1.5 (0.7)	1.6 (0.7)
Lost sleep	2 (0.7)	2.5 (1.0)	2.3 (0.7)	2.6 (1.0)	2.4 (0.9)
Not playing a useful part	1.7 (0.5)	1.9 (0.5)	1.7 (0.7)	1.5 (0.6)	1.6 (0.6)
Could not make a decision	1.8 (0.6)	1.6 (0.6)	1.8 (0.7)	1.9 (0.7)	1.7 (0.7)
Felt under strain	1.9 (1.1)	2.1 (1.0)	2.5 (1.1)	2.7 (0.9)	2.4 (1.0)
Could not face difficulties	2.1 (0.7)	1.9 (0.9)	1.9 (1.0)	2.4 (0.9)	2.1 (0.9)
Not enjoying activities	1.9 (0.7)	2 (0.7)	1.8 (0.9)	1.5 (0.7)	1.7 (0.8)
Could not face problems	2.1 (0.7)	1.9 (0.6)	1.9 (0.9)	1.7 (0.7)	1.9 (0.8)
Unhappy and depressed	1.6 (0.9)	2.2 (1.2)	2.1 (1.1)	2.7 (1.0)	2.3 (1.1)
Lost confidence	1.9 (0.7)	2.1 (0.8)	1.8 (0.8)	2.4 (0.9)	2.1 (0.9)
Felt worthless	1.5 (0.8)	1.4 (0.8)	2 (0.9)	2.2 (0.9)	1.9 (0.9)
Not feeling happy	2.1 (0.8)	1.9 (0.8)	1.8 (0.8)	2.1 (1.0)	1.9 (0.9)
All GHQ-12 items	2.3 (1.9)	3.1 (1.8)	3.1 (1.9)	4.5 (2.0)	3.5 (2.1)

† A table displaying the scores for the GHQ-12 and how these scores were distributed between the groups (No neuropathy, sub-clinical neuropathy, neuropathy, and neuropathy and pain), as well as total scores. Mean values and SDs shown

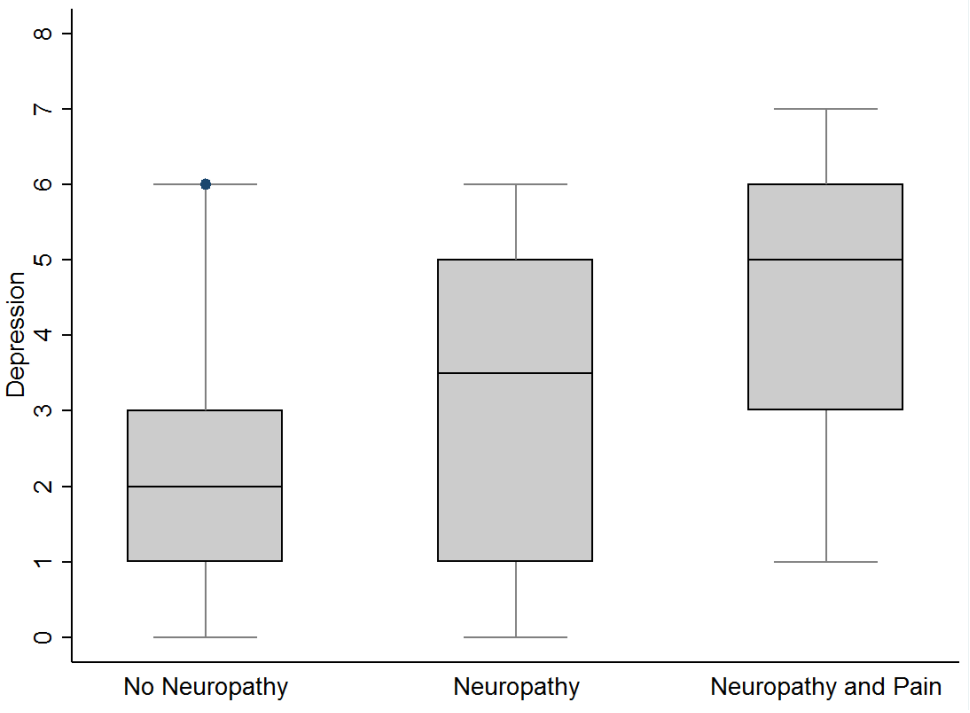

Figure 8.28. Overall score of GHQ-12 in 89 leprosy patients

The relation between the presence of neuropathy, pain and overall score of depression in 89 leprosy patients.

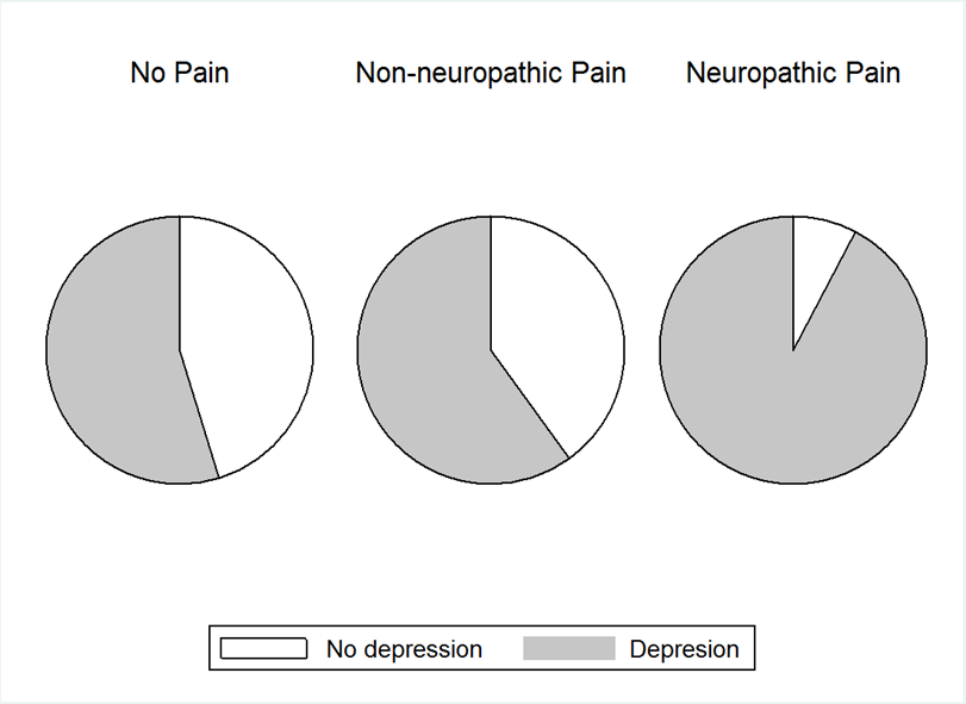

Figure 8.29. GHQ-12 score of 3 or more in 89 leprosy patients

Analysis

Univariate analysis

Univariate analysis was carried out for the association between the variables and mental health (depression) as an outcome. The following factors were strongly associated with the outcome: patients' motor nerve impairment, delay in presentation, WHO-disability classification, disease duration, and the presence of pain particularly neuropathic pain (p-value <0.001). There was, however, some evidence of an association between mental health status and educational qualifications (p-value = 0.04), disease duration (p-value = 0.05), presence of skin lesions on examination (p-value = 0.06), number of skin lesions on examination (p-value = 0.07), sensory nerve impairment (p-value = 0.08), and the presence of a reaction on examination (p-value = 0.1). Other variables showed no evidence of an association (p-value >0.2). Appendix 48 shows the distribution of GHQ-12 (above a threshold) cases by patients' characteristics and the odds ratios for each variable.

GHQ scores and social, clinical features and pain variables

In the following section the association between psychiatric morbidity and social and clinical findings are described.

Association between socio-demographic variables and GHQ scores

The prevalence of significant psychiatric morbidity between those in different age groups and sexes were not statistically different (Appendix 48). This may be due to age and gender match of the study population. However, at all ages and for both sexes, those who have some formal educational qualifications had better mental health than those who had no such qualifications. The difference between these two categories was more pronounced in the 20–29-year old age group. For men there was a statistically significant difference between those with and without qualifications in relation to their mental health. While those with no qualifications reported a higher prevalence of psychiatric morbidity in the youngest age groups, the differences were small and there was no difference at ages 30–39, 40–49 and >50. There was no difference for women across the five age bands. The odds ratios for educational level were found to be marginally significant (p-value <0.04). Married participants had approximately the same prevalence of psychological morbidity as single or separated, widowed, or divorced

participants. Of currently married participants, 67.8% had a higher GHQ-12 score, while 63.3% of the non-married group had a higher GHQ-12 score.

Association between clinical findings and GHQ scores

Patients who had clinical evidence of motor impairment were significantly more likely to have scored above the GHQ-12 threshold score (crude OR 3.13, 95% CI 1.20–8.18). Of patients with motor impairment, 78.26% obtained higher GHQ-12 scores, compared to 53.49% of patients who did not have motor impairment. In comparison with motor impairment, neither sensory impairment nor neuropathy (both sensory and motor) showed a statistical association with a GHQ-12 score, p-values 0.08 and 0.07 respectively. There was, however, a clear relationship between ulnar neuropathy and GHQ-12 score (crude OR 4.46, 95% CI 1.55–12.82).

There was a clear relationship between the presence of disability and GHQ-12 score. Patients who reported having a disability at diagnosis or at the time of interview were more likely than those who did not to have a GHQ-12 score of three or more. For respondents who had a disability at diagnosis, the figures were 82.9% and 17.1% respectively, and for those who had a current disability they were 75.5% and 55.0% (Appendix 48). Of those who had a previous reaction, 90% had a higher GHQ-12 score compared to 80% of patients who did not experience a reaction.

There was also a clear relationship between the reaction and GHQ-12 score. Patients who reported having a previous reaction were more likely than those who did not to have a GHQ-12 score of over three (crude OR 2.25, 95% CI 1.13–8.21).

Association between pain and GHQ scores

Large differences were evident when comparing those respondents who reported having pain symptoms and those who did not. Of the former, 83.3% had a GHQ-12 score of three or more, while the equivalent figures for the latter were 54.7%. Among those who had pain, respondents with symptoms and signs suggestive of neuropathic pain were more than nine times more likely to have an above-threshold GHQ-12 score than those with non-neuropathic pain (crude OR for neuropathic pain 9.93, 95% CI 2.13–46.35; crude OR for non-neuropathic pain 1.24, 95% CI 0.31–4.91). Twenty-four out of 26 patients (92.3%) with a presentation suggestive of NP using the DN4 questionnaire had a higher GHQ-12 scores compared to 60% of those patients presenting with complaints

of non-neuropathic pain, and 54.72% of the no pain group. The greatest difference was for men at age 20–29 and 30–39 where those with neuropathic pain were more likely to have a high GHQ-12 score than those in the non-neuropathic pain group. At the oldest female age group, smaller numbers obscure the pattern. Overall, there were clear relationships between the presence of neuropathic pain and GHQ-12 scores. Those who were diagnosed with neuropathic pain had the worst mental health.

Multivariate analysis

Logistic regression

Adjusted odds ratios for experiencing mental health disturbances were estimated using logistic regression. Stepwise logistic regression modelling was done (Appendix 49). The main social and clinical findings were included in the model for GHQ-12. This modelling allowed us to assess the association for each variable, adjusting for others, and to examine which factors affected the odds of having a high score on the GHQ-12.

All variables and not only those significantly associated variables (above a certain p-value in the univariate analysis), were considered for the multivariate regression model. For instance, gender and age group did not have a significant effect on the association, but were included in the multivariate regression model, as both are known universal confounders. Variables were retained in the final multivariate regression model when the model found significant evidence (p-value <0.05) with that variable included than without it, using a likelihood ratio test. In the model, the variable most significant in the univariate analysis was included first (forward regression). The next variable selected in the model for inclusion was then the one that best improved the model based on the LRT test until no additional variables improved the model significantly. In addition, all potential variables were included in the model first and then removed one-by-one starting with those least associated with the outcome (backward regression).

After adjusting for all other factors in the model, the odds of having significant psychiatric morbidity fell by more than one third (from 9.60 to 6.25). This result showed that the magnitude of the association decreased, but strong evidence of an association between psychiatric morbidity (anxiety and depression) and presence of neuropathic pain (p-value = 0.03) remained. There was strong evidence of reduced odds for the presence of neuropathic pain compared to patients with no neuropathic pain.

While there was a tendency for the presence of disability, particularly motor nerve impairments, to have higher psychiatric morbidity, there was no statistical significance (p-value 0.09). Neither socio-demographic factors nor disease duration were associated with mental health in either men or women.

The major determinant of mental health of the cohort was the presence or absence of chronic pain, "neuropathic pain", or presence of disability, "motor nerve impairment". The likelihood of psychiatric morbidity increased if neuropathic pain was present. The odds of psychiatric morbidity in those with neuropathic pain was 6.25 the odds of disorder in those without pain. At this stage in the study, we would suspect that those with chronic neuropathic pain were at a higher risk of developing worse mental health. This result would make sense, as patients with neuropathic pain are more likely to suffer from its impact on all quality of life modalities.

Chapter 9 Discussion

9.1 Introduction

The aim of this doctoral thesis was to investigate the clinical characteristics of patients with leprosy-associated NP and to establish the somatosensory profiles of such patients. Recent advancement of NP assessment has included two aspects. First, the identification and baseline profiling of patients with NP, including different dimensions of chronic pain problems, and second, the adaptation and development of a comprehensive clinical trial design for NP treatment. I hypothesised that:

i. Patients with painful neuropathy have a different sensory profile compared to patients with non-painful neuropathy
ii. Patients with NP endure a greater quality of life and psychological well-being burden than those with leprosy and neuropathy, but without NP.

These baseline comprehensive hypotheses were tested in a case-control study of a leprosy cohort consisting of patients with established pain and neuropathy, patients with pain-free and established clinical evidence of neuropathy, patients with no pain and no clinical evidence of neuropathy, and local healthy volunteers recruited in Mumbai, India.

9.2 Summary and discussion of the findings

Somatosensory profiles were compared to those from the DFNS-QST reference data and local Indian healthy control subjects. The pattern in all leprosy patients revealed a novel profile not previously seen in other NP conditions whereby cool and warm detection thresholds and also mechanical detection were lowered but vibration perception was preserved. This is somewhat different to profiles seen in other NP conditions. Patients with leprosy NP had a high rate of abnormal findings in almost all QST parameters when measured in the maximum pain area in the ulnar nerve territory. Their sensory profiles were categorised into two subgroups. The majority of patients have spontaneous pain with evidence of sensory loss, but no sign of sensory gain, these findings are consistent with peripheral neuronal damage. The second subgroup showed pain and temperature sensation to be profoundly impaired, but light mechanical stimuli produced pain (dynamic mechanical allodynia). Surprisingly, the obtained QST profiles in leprosy patients with pain were not significantly different from those patients without

pain. Patients with NP had poor quality of life and psychological well-being compared to those with pain-free neuropathy. Hence, the characterisation of patients with respect to the NP is of therapeutic significance.

9.2.1 Sociodemographic, clinical and epidemiological characteristics of study participants

The sociodemographic profile found in this study is comparable with those in other studies conducted in different parts of India, which point out gender bias, illiteracy, and a move to a city as constant characteristics of leprosy populations (Thakkar and Patel, 2014, Van Brakel et al., 2005a). The age profile of the patients was younger than the general population. In India more than 65% of the population are below the age of 35 years (WHO, 2014). Approximately one third of the population sample were in their third decade. The relatively few patients in either the under 20s age group or the above 50s age group probably reflect the sampling method and the nature of the disease.

In leprosy, the proportion of male to female is identical (1:1) up to puberty, then changes to 2:1 which reflects the natural history of the disease (Guinto and Rodriguez, 1936). In our cohort, the proportion of male and female patients was not evenly distributed across age groups and the ratio of 3:1 was also slightly different from that in the general leprosy population. This could be explained by the sampling method of the study. In many developing countries leprosy clinics are accessed by more men than women. In addition, bias in favour of men is also found in India (Hausmann, 2013). The high illiteracy and low educational level in our cohort reflects the strong association in most leprosy populations with complex variables of poverty such as income, housing quality hygiene and education. The geographical distribution of our cohort sample was also typical of the general leprosy population in India. In this study, half of the patients recruited at the BLP had moved from rural areas to Mumbai. This could be explained by the strong association between leprosy and poverty (Murto et al., 2013), as leprosy may be characterised by rural incidence and urban prevalence, i.e. cases move to cities.

Regarding clinical characteristics, it is worth noting that the high prevalence of MB cases associated with the high percentage of disability grade 2 at diagnosis is indicative of late diagnosis and lack of early detection of cases. Grade 2 disability at diagnosis, which is defined as the presence of visible deformity, is an indicator of the late diagnosis and severity of the disease. In our cohort, 10% of patients had disability grade 2 at diagnosis.

Our finding is similar to results from the INFIR cohort study (9.6%). The proportion of grade two disability in newly diagnosed leprosy cases in India reported by WHO at 3% (WHO, 2013b) this could be explained by the fact that the WHO figure included PB cases who usually have lower rates of disability. The high percentage of grade 2 disability at diagnosis in our cohort suggests that the risk of leprosy transmission is still ongoing in the study area. Delayed presentation is a known risk factor for disability in leprosy (Schreuder, 1998, Meima et al., 1999). A study from Thailand (Schreuder, 1998) has shown a highly significant correlation between the proportion of new cases with disability and delay in diagnosis. An Ethiopian study found an odds ratio of 2.1 for grade 2 disability when registration was delayed by more than 2 years (Meima et al., 1999). In this study, we found that more than 70% of the patients had had symptoms for more than 6 months before starting their MDT treatment. Data on the main reasons for this delay were related to misdiagnosis and patient's unawareness of the disease; other studies have found similar level of delay, explained by stigma and difficulties accessing services (Lockwood and Reid, 2001, Nicholls et al., 2003). These findings indicate that there is still more work to be done to prevent and manage disability in leprosy. A recent publication on the use of the WHO disability grading system by Cross and colleagues (Cross, 2014), used Delphi methods to reach a consensus among fifteen experts on the prevention of disability due to leprosy. The authors defined the terms more precisely and provided guidelines for use in the clinic, which can be immediately applied. There is limited time for the current global strategy, which proposed the target of reducing the rate of new cases with grade 2 disabilities per 100 000 population by at least 35% by the end of 2015, compared to the baseline at the end of 2010 (WHO, 2009a). However, the new guidelines may help to improve disability assessment, monitoring and successful leprosy burden reduction.

Twenty six patients (28.9%) had leprosy reactions at the time of examination, and previous history of reaction was reported by 40 patients (56%). Nociceptive joint pain is likely to be reaction associated. Pain associated with neuritis reaction, which is defined by the development of inflammation of a nerve sheath without abnormal findings in sensory testing, is considered to be of inflammatory origin and clinically defined as nociceptive pain (originating from nervi nervorum) (Bove and Light, 1997). However, if an inflammatory neuritis causes nerve damage then the pain, is by definition, neuropathic. Inflammatory pain is usually considered to be of nociceptive character, because it partly results from hyperexcitability of intact nociceptive dorsal root ganglion

neurons innervating inflamed tissue. However, chronic inflammatory pain is often characterized by positive signs such as allodynia, suggesting a possible neuropathic component. Recent studies have shown that inflammation-induced nociceptor hyperexcitability is sustained by C-nociceptors, which may contribute to inflammatory hyperalgesia (Flynn et al., 2014). This may also explain why in some inflammatory conditions nociceptive and NP may overlap. In our study, patients with reactions could have been over-represented, but this group is still attending leprosy services and therefore accessible to our recruitment tactics. The high prevalence of reactions in our cohort supports the growing evidence that the development of NP is probably immunologically mediated (Lund et al., 2007). The immune response in the peripheral nerves may recur and if it repeatedly affects the peripheral nerves, chronic-post inflammatory pain may result. Lockwood and colleagues (Lockwood et al., 2002) have shown that *M. leprae* protein and lipid antigens are present in skin and nerves at the time of acute reversal reactions. These data show the importance of reactions in pain among leprosy patients; they can be significant risk factors for the development of chronic NP.

The epidemiological profile in this cohort had a prevalence of leprosy neuropathy of 68%, with 60% of those reporting pain. NP was found in 28.8% of the patients. This finding is similar to the large epidemiological studies: In the INFIR cohort study, the neuropathy is consistently reported at around 40% (van Brakel et al., 2005b). New peripheral nerve damage is present in about 65% of cases. In our previous study in Ethiopia, pain was experienced in 60% of the patients who had completed their MDT within 18 months (Haroun et al., 2012). The prevalence of NP in this study is lower than other NP due to infectious disease, such as HIV-SN, which stand at 40%. Previous epidemiological studies on leprosy neuropathy and pain showed that NP occurs in up to 30% of patients in the long term (Hietaharju et al., 2000, Stump et al., 2004, Saunderson et al., 2008, Lasry-Levy et al., 2011, Haroun et al., 2012, Ramos et al., 2014). This supports the validity of the NP criteria used, and it is likely that these findings would be applicable to larger leprosy populations and in different settings. However, this study did not find some of the well-established risk factors for leprosy neuropathy and pain, such as reaction (Appendix 47). This could be because the case control study was powered against the sensory changes associated with risk of developing HIV neuropathy from the pain in HIV related neuropathy study (Phillips et al., 2014), and was not designed to elucidate these risk factors in the same way as larger epidemiological studies.

The HIV study is one of few studies to use quantitative sensory testing to assess sensory parameters in NP caused by infectious diseases.

9.2.2 Diagnostic tools

9.2.2.1 Case definition

The ability of health personnel in remote leprosy clinics to identify NP in patients with chronic pain is unclear. In this study, leprosy patients with NP were defined in a stepwise manner. First monofilaments and VMT, which are widely used in leprosy clinics, were used to confirm that some damage to the somatosensory sensory system along ulnar nerve territory had occurred. A sensory deficit in the innervation territory of a lesioned nerve is a diagnostic criterion of NP (Treede et al., 2008, Haanpaa et al., 2011a). Secondly, as the presence of nerve damage per se does not necessarily indicate that pain is neuropathic in origin, patients were further classified based on a score of ≥ 4/10 using the DN4 symptom descriptors questionnaire. Using this definition, would provide simplicity, validity, utility and affordability for use in most routine clinical practice in leprosy population. This indicates that our case definition may help to develop a new tool for the assessment of NP in leprosy that might be useful in resource-limited settings.

9.2.2.2 Pain symptoms

Screening tools are used to alert clinicians to the possibility of NP (Haanpaa et al., 2011a). In previous studies done in collaboration with the Bombay Leprosy Project in India, ALERT hospital in Ethiopia, and LSHTM we demonstrated that the DN4 questionnaire is valid in its application in the leprosy NP in different languages and settings (Lasry-Levy et al., 2011, Haroun et al., 2012). In this study, I used the DN4 questionnaire for the case definition of NP; a score of 4 or higher in patients with evidence of neuropathy. In addition, I used PD-Q to verify the DN4 result.

NP, based on the identification of common pain symptoms and sensory tests over the ulnar nerve territory (C8) obtained with the DN4 questionnaire, was identified in the pain group with mean scores of 5.6 out of 10, specifically with the presence of "numbness" in the NP and "aching or dull pain type" in non-NP patients. The presence of NP in patients with upper limb pain was identified in 24 patients out of 32. The number of DN4 sensory pain descriptor items described by those patients was higher

than that identified by examination of sensory function. Similar findings were also observed in a study by Bouhassira, who compared the clinical features of NP and non-NP in 160 patients in France (Bouhassira et al., 2005). In our study "tingling", "burning", and "numbness" were the sensory descriptors most widely used by NP patients. Hypoesthesia to touch and pin-prick were much more frequent in NP than in non-NP patients. These findings are consistent with previous studies on NP in Fibromyalgia (Petzke et al., 2003, Staud et al., 2003). The presence of "painful brush" sensation was also more frequent in NP compared to the non-NP group, although it was not statistically significant.

In this study clinical examination, and the DN4 questionnaire, were used for the case definition of leprosy NP. The PD-Q identified fewer patients (13 subjects) with NP components compared to DN4. Of 32 patients with upper limb pain, 24 patients were clinically classified by DN4 as definite NP, while PD-Q identified only 5 of these patients. There were inconsistent responses to the common questions between DN4 and PD-Q in 60% of cases. It is unclear if the lowered sensitivity of PD-Q in our cohort might be related to the validity of the questionnaire in this population and setting, as there are no previous studies documenting the clinical diagnostic accuracy and reliability of PD-Q in leprosy. Similar findings were also observed in patients with neck/upper limb pain by Tampin and colleagues (Tampin et al., 2013). In this study, the author investigated the application of LANSS and PD-Q in 152 patients with neck/upper limb pain. Both questionnaires failed to identify a large number of patients with clinically classified definite NP. These findings suggest that the application of PD-Q in patients with leprosy NP is limited.

Another potential observation regarding the differences between the DN4 and PD-Q is questionnaire design. For instance, the number and type of questions are different: the DN4 consists of 10 symptom and clinically-related questions; while PD-Q contains only seven symptom-related questions. The phrasing of the questions and the scoring method are also different. Whilst DN4 uses yes or no fixed scores for each question, sensory descriptor questions are score-weighted in PD-Q. The latter scoring may introduce bias, as responses could be vulnerable to subjective psychological factors, which potentially contribute to an overall higher score. These observations in questionnaire design and low sensitivity between the two instruments, support the use of DN4 as screening tools for leprosy NP.

Patients were asked to evaluate the administration of NP screening tools; no difference was found between DN4 and PD-Q. In a previous study, we documented that DN4 was easier to administer than the LANSS in patients with leprosy and NP (Haroun et al., 2012).

9.2.2.3 Clinical examination

The nine nerves commonly affected in leprosy, namely: greater auricular, median, ulnar, radial cutaneous, ulnar branch, lateral popliteal, superficial peroneal, posterior tibial, and sural nerves were assessed in a cohort of 90 patients with and without neuropathy and pain. Of these nine nerves, I compared the sensory and motor findings from ulnar nerve examinations between groups. I also compared the results of the QST tests against monofilament testing.

In this study, abnormal tendon reflex or JPS was present in very few patients (only around 2%). This is typical for leprosy, and accords with previous observations. Jennekens and colleagues, who examined 28 male leprosy patients, found abnormal JPS of one or more digits in 33% of the participants (Jennekens and Jennekens-Schinkel, 1992). In the INFIR cohort study around 2% of the 303 subjects had abnormal reflexes or JPS (van Brakel et al., 2005b). Ramadan and colleagues found 'diminished' reflexes in 45% of their patients and 'diminished joint and vibration sensation' in 33%. However, the patient group in the latter study was older and had longer histories of leprosy. In our study, the presence of abnormal reflexes or JPS could be explained by neuropathy of long duration (van Brakel et al., 1994b).

In the subclinical neuropathy group, the QST findings showed ulnar impairment in up to two third of the patients. This indicates that QST testing is a more efficient method of clinical detection than those currently used in leprosy neuropathy. A similar conclusion, that monofilament and VMT are not very sensitive methods in detecting neuropathy, was also observed by McKnight, who further analysed the data from the INFIR cohort study (McKnight, 2010). However, the use of monofilament and VMT in resource-limited setting is reliable (Brandsma et al., 2014). In Chapter 7, I showed that the use of monofilament in detecting touch sensation in healthy volunteers is comparable to electronic von Frey, but may be different in pathological conditions. The low sensitivity of clinical evidence of neuropathy in detecting ulnar impairment compared to QST in the subclinical neuropathy group can be explained by the fact that

thermal (warm and cold) sensation occurs early in leprosy, which cannot be detected by monofilament. Another explanation could be related to the scale used for the VMT grading range; 4 scores instead of 3 for abnormal limits (Van Brakel et al., 2007). The new grades of weakness are more difficult to assesses in comparison to no weakness (Brandsma, 2000).

In the current study, I found that all nerves classed as impaired on the monofilament test also had two or more QST based abnormal parameters. In the ulnar nerve the combined thermal tests were impaired in all right ulnar nerves, and in more than 90% of left ulnar nerve impaired according to the monofilament test. In addition, a substantial proportion (>60%) of the nerves had impaired thermal sensation, but normal touch sensation. These findings indicate that, if touch sensation is affected, one of the QST parameters will also be abnormal. Unlike the INFIR cohort study findings (Van Brakel et al., 2005a), our study showed that impaired thermal sensation may be detectable before touch sensation. Our findings could be explained by the fact that small, unmyelinated fibres are the first to be affected in leprosy (Shetty et al., 1988, Shetty et al., 1977).

In our cohort, the pattern assessing large afferent fibre using monofilament and vibration tests revealed a loss of touch sensation, but vibration perception was preserved. These findings were fully compatible with what might be expected from leprosy neuropathy, i.e., not all ulnar nerves with impaired touch had impaired vibration sense. This is similar to the findings for neuropathy assessment in the INFIR cohort study by Brakel and colleagues (Van Brakel et al., 2005a). The authors found high negative concordance between monofilament and vibration perception; if the monofilament test was normal, the vibration test was also normal in the great majority of nerves. This indicates that the vibration perception test is less sensitive for detecting sensory neuropathy in leprosy than monofilament testing.

9.2.2.4 Metabolic factors

In this cohort, the mean values of plasma level of vitamin B_{12} across the study group were high, unlike the healthy cohort where three volunteers with very low levels of B_{12} were identified. Vitamin B_{12} deficiency is an important factor in the development of peripheral neuropathies (Reynolds, 2014). The low vitamin B_{12} observed in our healthy volunteers could be explained by Indian dietary habits, as the majority of volunteers

were vegetarian. Higher plasma levels in our patients, particularly the neuropathy and pain group, could be explained by the fact that 60% of them were on vitamin supplementation. Vitamins are givens to all patients as a routine treatment at the BLP clinic.

9.2.3 Quantitative sensory testing

This is the first study to use the DFNS-QST protocol in a resource-limited setting and validates the Mumbai centre for the use of the QST. The QST machine (MSA Thermotest, Somedic) used in this study was easy to operate. The protocol is highly relevant in leprosy, because both small and large fibres are damaged.

QST results are interpreted on the basis of a DFNS reference data set that is stratified for age and gender (Rolke et al., 2006a, Magerl et al., 2010). It contains a description of somatosensory profile and, subsequently, refers to possible underlying mechanisms.

9.2.3.1 Differences between healthy controls and patients

Consistent differences in quantitative sensory testing results were observed between our local Indian samples of healthy control participants and patients with leprosy. The most frequent differences was sensory loss indicated by increased thermal detection thresholds (CDT, WDT) and increased mechanical and vibration detection thresholds (MDT, VDT) in leprosy patients compared to healthy controls. This highlights the fact that nerve damage is a characteristic of leprosy, even if there is no clinical evidence of neuropathy using monofilaments and/or voluntary muscle testing.

QST measurements in the current study revealed that patients with leprosy had a widespread loss of function in the tested site (dermatome C8) in most DFNS-QST thermal and mechanical sensory parameters, but also that vibration sense tend to be preserved. About two thirds of participants showed a loss of function of at least one sensory modality. The same was found for leprosy patients in the INFIR study by Van Brakel et al; loss of temperature sensation, but retained vibration perception (Van Brakel et al., 2005a). Vibration "sense" is mediated by large afferent Aαβ fibres (Light and Perl, 1993). VDT and monofilaments tests both assess large afferent fibre function, it was therefore expected that vibration test would also be affected. One explanation would be that the preserved vibration sense reflects the type of nerve fibres that are damaged in leprosy (i.e. there is a preservation of the large myelinated sensory fibres that transmit

vibration sense in leprosy). Another explanation for the preserved vibration in this cohort could be because vibration is transmitted by bone not skin which may not reflect abnormality in the cutaneous nervous system. Further explanation again would be the preserved spinal dorsal columns in leprosy. The supporting explanation for this may be that since the spinal dorsal columns are preserved in leprosy, one needs less intense afferent input to perceive vibration and the remaining sensory input is sufficient for vibration and yet not of other thermal and mechanical parameters.

In concordance with our hypothesis, patients with leprosy had localised sensory abnormalities in the tested ulnar site (negative sensory signs: reduced thermal and mechanical modalities), indicating a loss of small and large sensory fibre function. The main sensory finding was loss of function of the C and Aδ mediated sensory modalities of thermal non-nociceptive parameters (60%) and functions mediated by large fibres (Aβ) (46%), except for vibration sense (8%). This is similar to previous findings for leprosy patients in the INFIR study; loss of thermal sensation, but retained vibration sense (Van Brakel et al., 2005a, van Brakel et al., 2008a). In contrast, abnormal negative nociceptor QST parameters ranged from 7.9% (CPT) to 42% (MPS). The presence of these negative sensory findings is indicative of peripheral nerve damage (Hansson, 2002). Loss of function occurred in all sensory fibres tested (C, Aδ and Aβ), which is consistent with previous findings in patients with peripheral nerve damage and in patients with HIV sensory neuropathy (Kleggetveit and Jorum, 2010, Phillips et al., 2014).

9.2.3.2 Somatosensory profiles in patients with and without pain

Patients with and without pain had a similar sensory abnormalities for nociceptive and non-nociceptive QST parameters. Abnormality of thermal, and mechanical detection thresholds; and pain thresholds to the nociceptive parameters were common and similar in both patients groups compared to healthy controls. Although the cumulative frequency of abnormalities in any of the thermal and mechanical measures were higher in patients with painful neuropathy, it was not statistically significant. The QST findings showed a pattern of profound sensory loss in both groups. A similar distribution of QST profile in patients with and without pain has previously been reported in other conditions. In a recent study of HIV painful neuropathy, the results resemble those of the present study. In a QST profile study of 66 HIV infected participants, Phillips and colleagues (Phillips et al., 2014), reported no differences in regard to thermal and

mechanical perception thresholds between painful and non-painful sides of denervated skin. In addition, the authors found that patients with painful neuropathy had profound loss to vibration sense. The implications of our findings that leprosy patients with pain do not have significantly different QST profile from leprosy patient without pain is discussed in detail in section 9.3.6, page 276.

In this study, the differences in QST parameters between symptomatic and asymptomatic sides in 21 leprosy patients with symptoms and signs suggestive of NP and 10 patients with non-NP, was investigated. The QST findings demonstrated a significant loss of function mediated by nociceptive and non-nociceptive sensory fibres in both sides of the NP groups; these findings are consistent with the characteristics of NP (Haanpaa et al., 2011a). However, in patients with non-NP, the QST findings demonstrated a significant loss of function on the symptomatic side compared to the asymptomatic side. These findings indicate that unlike non-NP, in patients with NP there was no significant side-to-side difference in any QST parameters in the maximum pain area. Our findings could be explained by the fact that in NP patients, loss of thermal and mechanical detection may occur bilaterally. Contralateral loss of thermal detection has been observed in patients with nerve damage (Leffler and Hansson, 2008b, Jaaskelainen et al., 2005). In patients with trigeminal neuropathy, contralateral loss of thermal detection was associated with the presence of ipsilateral NP. This was explained by peripheral nerve damage induced inhibition or disturbed excitatory connections within the central pathways mediating non-noxious thermal information from the contralateral side (Jaaskelainen et al., 2005, Davis et al., 2011).

Our results indicate that the QST measures allow us to differentiate between patients with and without neuropathy, but cannot be used to differentiate between leprosy patients with and without pain, which is similar to the study by Phillips and colleagues (Phillips et al., 2014).

9.2.3.3 Somatosensory profiles in patients with NP

The description of the somatosensory profiles in patients with leprosy NP is the central focus of this doctoral thesis. As mentioned in the introduction, baseline profiling is an important step towards better understanding of pathophysiological mechanisms as well informed mechanism based prescribing, which in turn influences clinical trial design and drug responder defining NP treatment (Reimer et al., 2014).

To our knowledge, this is the first study to comprehensivly investigate the clinical presentation of NP in leprosy. A detailed description of the leprosy NP phenotype is given. As expected, the majority (90%) of leprosy NP patients showed sensory abnormalities at their ulnar affected side. This is similar to the findings for NP patients by Maier and colleagues (Maier et al., 2010): In this study, 1236 patients with NP of different aetilogies were investigated and somatosensory profiles of all patients were assessed, the authors reported a high percentage (92%) of patients with at least one QST abnormality. The most prevelant profiles were thermosensory and mechanical hypoesthesiac (in up to 41%).

In our study, across different thermal and mechanical modalities, the predominant profile in leprosy NP was loss of sensory function; 90% of leprosy NP patients showed a loss of function of at least one sensory modality. In concordance with our hypothesis, sensory loss of functions was predominately found in non-nociceptive parameters, with higher incidence for thermal function mediated by small nerve fibres (CDT 84.2%, WDT 89.5%, TSL 94.7%) and mechanical function mediated by large nerve fibres (MDT 73.7%), whereas loss of vibration sense mediated by dorsal column tract occurred in 26.3%. Similarly, sensory loss of function in nociceptive parameters occurred in most patients (MPT 85.7%, MPS 78.9%, and HPT 52.6%), except for pressure pain (15.8%), which reflects the innervation of deep muscles rather than cutaneous sensory receptors. On the other hand, sensory gain of functions for both non-nociceptive and nociceptive parameters was rare. 5.3% of the patients had DMA and 15.8% had abnormal WUR. 15.8% of the patients had PHS.

In patients with pain and neuropathy group, I found that 26.5% of them had increased vibration detection threshold (i.e. loss), while our finding of generalized retained vibration sense in non-NP patients is consistent with previous studies (Van Brakel et al., 2005a). Our demonstration of increased vibration detection threshold in patients with NP has not been reported in leprosy, but corresponds with other NP conditions (Maier et al., 2010, Konopka et al., 2012).

In studies conducted by Hammond and colleagues in India, the vibration thresholds, which were assessed using a biosthesiometer technique, were found useful for predicting the risk of plantar ulcer (Hammond and Klenerman, 1988), risk of tarsal disintegration (Klenerman et al., 1990), and for diagnosing sensory impairment in skin lesions

(Klenerman and Hammond, 1988). The authors showed that vibration sense was affected in 90% of feet at risk of ulceration.

This important findings, as it reflects that a considerable percentage of patients (26.5%) had impaired vibration sense, wich could be a potiential predictor for the development of NP in leprosy. This observation is again indicative of peripheral nerve damage.

Previous studies of patients with NP have shown that loss of sensory function is associated with central or peripheral nerve damage which may be complicated by ongoing pain via increased ectopic activity (Liu et al., 2000, Orstavik et al., 2006, Zhao et al., 2006, Vaso et al., 2014). This is usually associated with high incidence of thermal and mechanical loss of function. The frequent sensory loss found in leprosy NP patients may indicate peripheral nerve damage.

Although PHS in the affected area was frequently reported (15.8%), its consideration in regards to sensory function is still controversial: some believe it to be a sensory gain phenomena and others a sensory loss.

Interestingly, in this group of leprosy patients with NP I found an appreciable percentage of patients (5.3% and 19%) who had pain due to light moving mechanical stimuli (allodynia) in the tested site C8 and along the ulnar nerve territory, respectively. This finding is consistent with peripheral nerve damage. Sandkuhler had similar findings assessed behavioural hypersensitivity to stimuli after inducing a mechanical peripheral damage in animal models of NP; high rates of positive sensory signs, such as, blunt pressure pain, dynamic mechanical allodynia, and pinprick hyperalgesia were also found in patients with peripheral nerve damage (Sandkuhler, 2009).

The pathophysiological mechanisms of NP associated with leprosy are not well established. They may involve the development of peripheral nerve damage or central mechanisms, or both. In this study, the QST findings have shown that the majority of patients have spontaneous pain with evidence of sensory loss, but no signs of sensory gain (hyperalgesia or allodynia). Such patients characteristically have lost both small and large diameter fibres. In this group, the pain is possibly due to increased spontaneous activity in deafferented central neurons and/or reorganization of central connections (Wallace and Rice, 2008). A few other leprosy patients have abnormal sensitization of unmyelinated cutaneous nociceptors (irritable nociceptors). In these patients, the QST

results have shown that pain and temperature sensation are profoundly impaired but light mechanical stimuli often produce pain (allodynia). In these patients, allodynia may be due to the formation of new connections between non-nociceptive large-diameter primary afferents and central pain transmission neurons (Fields et al., 1998).

In summary, the profile of NP associated with leprosy shows signs of sensory loss by increased thermal detection thresholds (CDT, WDT) and increased mechanical and vibration detection thresholds (MDT, VDT). No signs of sensory gain are found by pinprick hyperalgesia (MPT, MPS), except for DMA and WUR. This sensory phenotype of sensory loss in patients with leprosy is likely to reflect the underlying pathology peripheral nerve damage.

9.2.4 Pain intensity and quality assessment

Self-reported pain intensity in leprosy patients was assessed using the BPI. Despite different pain distribution in NP and non-NP, the two groups reported similar pain intensity. Similar findings were also reported in PHN and LBP (Daniel et al., 2008). These finding support the evidence that patients with NP suffer to a similar extent to those with nociceptive pain (Haythornthwaite and Benrud-Larson, 2000). The average pain intensity among patients with NP was 5.4. Previous pain studies on NP describe "worst pain (rated as five or above)" as significant pain, and report it as contributing disproportionately to more functional impairment. In this study, around 40% of patients with NP rated their worst pain as five or more, which is lower than in the Ethiopian and Brazilian study of leprosy patients with NP (Haroun et al., 2012, Stump et al., 2004).

The genders different in responses to pain severity or pain-related functioning in patients with leprosy are not known. In this study I found that no significant sex differences in measures of pain and functioning (depression symptoms, pain severity or interference). A similar finding, no differences between men and women in their responses to pain, were reported by Racine in study from UK, USA and Canada. The authors used a cross-sectional design with a cohort of 747 women and 48 men with fibromyalgia syndrome referred to The Fibromyalgia Day Program (Racine et al., 2014) . These findings oppose the fact that women typically report more frequent and/or severe pain than men (Unruh, 1996). Our findings suggest that no important differences exist between men and women in the study. However, there might be a gender bias, as we know that more men than women develop leprosy. The inclusion of the differences

between men and women in how they view and cope with leprosy-related pain would add further knowledge to the overall concept of pain in leprosy.

9.2.5 Psychological co-morbidity and HRQoL

This study is the first to use validated structured instruments to evaluate the impact of pain on health-related quality of life and psychological state among leprosy patients with and without pain in India. The BPI interference subscale mean total score (5.29) was significantly higher in the patients with NP sub-group than the non-NP. This indicates that NP may cause substantial interference with the activities of daily living among leprosy patients. The domain of "Sleep" was identified as a major independent variable affected by pain in leprosy. The prevalence of psychological co-morbidity in this cohort was 66.3%. Our study has shown that anxiety and depression were highly prevalent in NP patients.

Overall, NP is associated with poor general health. In a French nationwide survey on the impact of NP on quality of life among 4,554 members of the general population, respondents who reported pain with neuropathic characteristics had a higher anxiety/depression score and higher degree of impairment in all dimensions relating to quality of life compared to those reporting pain without NP characteristics and those without pain (Attal et al., 2011a). Similarly, in a study from the UK population using SF-36 General Health Questionnaire, found that the quality of life was worse in the presence of NP than non-NP of the same severity (Smith et al., 2007). The same findings were also confirmed in a recent systematic review of health utilities on NP (Doth et al., 2010). The authors also found that the intensity of NP was more important in determining the extent of its health impact. Cognitive behavioural implications are important in the management of patients with chronic neuropathic pain (Daniel et al., 2008).

9.2.5.1 Health-related quality of life (HRQoL)

For the BPI interference scores, a measure of how the patients' pain interferes with every day activities, the greatest impact of pain on leprosy patients was in terms of "normal work", "sleep", and "mood". Between patients groups, there were significant differences of pain on the domain of "general activity", "relations with other people", "sleep" and "enjoyment of life". Patients in the NP group with upper limb pain had

significantly poor scores for all pain interference domains of the BPI except "mood" and "walking ability" compared to non-NP.

BPI interference has been previously measured in patients with leprosy NP in Ethiopia (Haroun et al., 2012). In our previous study, Ethiopian patients who had completed MDT within the past 18 months were selected. Results were compared with non-NP, and found that NP interfered in the domains of "general activity", "normal work", and "enjoyment of life".

Patients with leprosy NP show interference from pain and reduced quality of life compared to patients without NP across most domains of the BPI. Findings were comparable to the impact of NP on quality of life in other infectious painful neuropathies, but NP in leprosy appears to be associated with greater disability and poor overall perception of general health (van Brakel et al., 2012). In a study by Serpell, who investigated the burden of PHN in 152 patients from Britain aged 50 years or older using BPI, the interference score revealed a substantial impact of pain on the domains of "enjoyment of life", "mood", and "sleep" (Serpell et al., 2014). Phillips and colleagues (Phillips et al., 2014), who studied 66 HIV-infected patients, also reported that patients with painful neuropathy had higher BPI interference scores compared to pain-free neuropathy. The high BPI interference scores found in our study indicate that patients' pain is associated with a negative impact on their day to day living and their quality of life. These findings support the growing evidence that patients with NP have a strong association with the domains of HRQoL (Jensen et al., 2007). This indicates that leprosy NP has produced an additional quality of life burden over that of leprosy itself or leprosy with painless nerve damage. Therefore, there is a pressing need to further investigate specific consequences in patients with leprosy and to assess these HRQoL domains in NP clinical trials.

9.2.5.2 Psychological co-morbidity

NP was found to be the most important factor independently associated with psychological co-morbidity using logistic regression analysis. This finding supports previous observations of leprosy patients from Ethiopia, India and Brazil, in whom the prevalence of psychiatric illness is high and the presence of pain was significantly associated with psychological co-morbidity (Haroun et al., 2012, Lasry-Levy et al., 2011, Reis et al., 2013). This indicates that the concomitant chronic NP pain may exacerbate

existing psychological morbidity and challenges patients' adjustment and coping with their life.

Our findings of increased depressive symptoms in patients with and without neuropathy appear to extend those of our previous study (Haroun et al., 2012), in which we found a linear relationship between pain and psychological distress. Our study controls for the presence of clinical evidence of neuropathy differentiated patients with and without pain. Our study found that even patients with subclinical neuropathy and pain had greater psychological co-morbidity. NP and psychological co-morbidity association was also found in HIV painful neuropathy (Wright et al., 2008, Phillips et al., 2014). These findings support the importance of NP, not only as a physical symptom, but as a possible cause of psychological co-morbidity. A study on HIV-associated neuropathy in South East Asia found that 20% of patients had sensory neuropathy and 36% had depression (Wright et al., 2008). It is possible that association with psychiatric co-morbidity could be due to reverse causality, which cannot be fully discarded, since patients with psychological disturbance have been shown to have a decreased threshold for pain (Steer et al., 1993). The consistent and strong association found in this study between NP patients and psychological co-morbidity, suggests the need to find another way of understanding and treating NP. The utility of the biopsychosocial model developed by Novy and colleagues (Novy et al., 1995), which showed growing empirical support and acceptance, would be useful for understanding and treating leprosy NP. In this model, both physical and psychological factors are believed to contribute to the experience of pain. These findings also highlight the importance of an in-depth profiling of NP that includes psychological factors, particularly if tricyclic antidepressants were to be tested for efficacy in treating NP.

9.3 General discussion

Pain is a common problem among leprosy patients in clinical practice particularly in endemic countries. Leprosy-associated NP, which occurs as a result of persistent nerve damage in patients successfully treated with MTD, is now being recognised as an important long-term complication. Our leprosy group at LSHTM has recently shown in India and Ethiopia that 17-20% of treated leprosy patients cured of their infection but left with peripheral nerve damage, have significant NP (Lasry-Levy et al., 2011, Haroun et al., 2012). NP in leprosy leads to impaired quality of life, and increased use of health care, and is associated with more co-morbidity such as anxiety, depression, and sleep disturbances compared to non-NP (Schmidt et al., 2009). For individuals, life with such pain can be disabling even after their disease has been "cured".

The treatment of patients with NP remains a challenge (Finnerup et al., 2010). There are no disease-modifying therapies for NP yet. The current treatments are symptom control based, notably associated with variability of treatment response among patients with pain. For instance, patients with HIV-SN do not respond to pregabalin or amitriptyline treatment whereas many of those with other neuropathies do respond to these drugs. This may be explained by the heterogeneity of pain at clinical presentation, different underlying pain type or patterns and different aetiologies. In leprosy, pain is also heterogeneous with different clinical presentations, and associated with varying pain types and mechanisms. Different types of patients can be distinguished: those with pain associated with reactions "nociceptive pain" and those with NP; overlap of the two categories may occur. Improvement of treatment outcomes requires identification of such differences and the appropriate classification of patients with leprosy pain conditions. Recent developments in the treatment of NP have proposed that the somatosensory characterisations of these patients, with respect to distinguishing the type of pains, is of therapeutic relevance as NP requires a different treatment approach to non-NP (Baron et al., 2010a, Baron et al., 2012, Freeman et al., 2014). Recent developments have also shown that even within one underlying cause, the somatosensory profiles have different subgroups of patients with NP (Baron et al., 2009, Maier et al., 2010). In patients with radiculopathy, Baron and colleagues (Baron et al., 2010b) found that the individual differences in response to NP treatment were due to differences of somatosensory profiling, which may be associated with different underlying pain.

A recent guideline on the assessment of NP by IASP recommends the use of clinical tools such as NP screening questionnaires and QST testing (Haanpaa et al., 2011a). Unlike for NP caused by infectious diseases such as PHN (Pfau et al., 2014) and HIV (Phillips et al., 2014), there has been little work on the assessment of leprosy NP. The impact of NP in leprosy is also not well represented in the literature. The overall aim of this thesis was to accurately characterise patients with and without neuropathy; and patients with and without pain, with particular emphasis on pain and neuropathy. Pain subgroups were chosen as they have commonalities in their clinical pain characteristics.

In this section, the classification of pain in leprosy, the application and utility of the quantitative sensory testing used in this thesis for the somatosensory characterisation of leprosy patients with NP and interpretation of somatosensory profiling, is the focus for general discussion. The strengths and limitations of the study; reflective thoughts of how I would do the work if starting now, implications of the current work, and suggestions for future work, will also be presented.

9.3.1 Classification of pain in leprosy

This study used a recent NP definition and guidelines published by the IASP. However, there is currently no proper systematic classification of NP in leprosy, which led to inconsistency in the thesis. The definitions of the IASP were simple to use at the start of the study, but became difficult when I applied them. For the practical difficulties see the LePaIn flow chart (Figure 8.1). In particular, the definition and classification of neuritis in leprosy was practically difficult. According to the IASP definition, neuritis is inflammation of a nerve, but if this causes nerve damage then the pain, is by definition, neuropathic. In the field of leprosy, neuritis is defined as an acute loss of function (Wagenaar et al., 2012). This loss of function could be without pain, and that is why we regularly use the monofilaments and MRC grading system to identify patients who have got silent neuritis. It is not clear whether this neuritis is an acute neuropathic pain or neuropathic pain of different type. This indicates that a review of the classification of pain in leprosy is needed.

9.3.2 Somatosensory profiling

Quantitative sensory testing is a sophisticated measurement which assesses psychophysical responses to systematic and quantifiable sensory stimuli for the purpose of characterising somatosensory profiling. It can be simply described as follows: an

increasing and quantified sensory stimulus is applied to an individual, they are asked with specific questions to report either a perception or pain threshold. Therefore, participants' responses are potentially influenced by psychological components (Backonja et al., 2013, Backonja et al., 2009, Shy et al., 2003). In addition, there are different methods for both the stimulus application (such as mechanical stimuli, electrical stimuli, or contact heat stimuli) and for the response measures, which can be simple measures like pain threshold and intolerance or more complex processes, like temporal summation and conditional pain modulation. Furthermore, demographic factors (age and gender), site of test, environment, training of the instructor and instructions given to participants have an impact on QST measures (Magerl et al., 2010). Hence, standardisation of testing protocol is required to facilitate validity and comparison of QST data between studies. The German Network on NP has developed such a standardised DFNS-QST protocol (Rolke et al., 2006a, Rolke et al., 2006b). It has proved to be a useful tool in identifying the underlying sensory abnormalities in each patient groups and in identifying the differences between the groups in regard to their underlying pain type. The use of QST profiling was important to distinguish groups because the occurrence of nerve damage does not necessarily mean that any pain is neuropathic in origin (Landerholm et al., 2010). The DFNS-QST protocol was employed in this thesis.

In our study, I found that obtaining full DFNS-QST profiles in leprosy patients provided new insights beyond studies that only used thermal testing. Initially I considered whether leprosy patients or group of patients differ in their QST profiles from people who are not experiencing pain, and I found that a variety of differences occurred. The QST findings revealed profound signs of sensory loss through increased thermal detection thresholds (CDT, WDT) and increased mechanical and vibration detection thresholds (MDT, VDT). Also the findings showed a variety of thermal (HPT/CPT) pain stimuli and pricking mechanical pain (MPT, MPS). The QST findings of the differences between leprosy patients and healthy controls were statistically significant, except VDT, WUR and VDT; with patients showing higher sensory loss than pain-free controls. These patterns are the same for patients with and without pain. Thus, it can be seen that I have several QST parameters that distinguish leprosy patients with clinical evidence of neuropathy from patients with no evidence of neuropathy and controls.

Another issue that I considered is the possibility to subgroup leprosy patients with pain based on their responses to QST testing. I referred to a development by the DFNS group, who studied 1236 patients with NP due to different diseases and categorised their findings according to sensory loss and/or gain. They found that a minority of patients showed no sensory changes in their profile, but most showed some evidence of sensory perturbation: some showed only loss or negative signs, while some patients showed only gain or the positive signs. The remaining patients showed a combination of loss and gain sensory profile. The authors found that all subtypes are presented within each diagnosis. They concluded that if this reflects different pain mechanisms, a single pain treatment within the diagnosis is not helpful. Fortunately, they found commonalities across pain diagnosis. For instance, some patients with trigeminal neuralgia showed only sensory gain profile, while patients with polyneuropathy showed only sensory loss. Therefore, the authors concluded that these profiles might be better targets for treatment than the diagnosis of the condition. In the present study, I found that the somatosensory profile of leprosy NP could be categorised into two main subgroups. The first one is a patient who shows signs of predominant sensory loss only, where the profile shows signs of sensory loss through increased thermal detection thresholds (CDT, WDT and TSL) and increased mechanical and vibration thresholds (MDT and VDT), but no signs of sensory gain (hyperalgesia and/ or allodynia). The second group is patients with a combination of symptoms and signs. In this subgroup, the profile shows both sensory loss and gain. The pain and temperature are profoundly impaired, but the condition is associated with light mechanical touch pain (dynamic mechanical allodynia) occurred in 5.3% and WUR 15.8%.

Finally, I would like to discuss the implication of these findings along with a recent clinical case report published by Baron and colleagues (Westermann et al., 2012), which I think points towards future work. They report on a patient with bilateral burning and prickling pain in the T9-11 (at-level pain) following spinal cord injury. Pain on both sides was described the same way by the patient; burning, pricking, and severe in nature. On the right side, the QST findings showed a normal sensory profile and cold hyperalgesia, suggesting central NP mechanism. On the left side, there was a loss of thermal and mechanical sensation, suggesting peripheral nerve damage mechanism (deafferenation). There was also more loss of IENFD on the left side compared to the right. The patient was treated with pregabalin, and the result was unilateral pain relief only in the area with remaining sensory function, but not the pain on the left. In spite of

the fact that this a single case report, I think the scenario could also be relevant in leprosy patients with NP. This somatosensory profile for leprosy NP may assist researchers in designing clinical trials for targeting more specific management for these patients. I recommend that leprosy patients with dominant sensory loss profile be treated differently from patients who have combined sensory loss and gain.

9.3.3 Strengths and limitations

The principle strength of the current study is the comprehensiveness of the profiling measures employed to investigate NP in patients with leprosy. In contrast to studies using QST as a stand-alone test for characterisation, this study explored the multiple facets of NP including symptoms and sensory signs, metabolic dysfunction and psychological state. This facilitated the differentiation of subgroups of NP in leprosy pain and provided valuable new insights for treatment.

Limitations to this study related to the recruitment of participants; choice of assessment instruments; communication using patient's pain terminology; and QST-related methodological considerations.

A relatively small number of participants with NP were enrolled, particularly patients with sensory gain. As the ulnar nerve is the most commonly affected by leprosy, this site was deliberately chosen for the QST test of the C8 dermatome. However, this limited the recruitment of patients with NP. Patients with leprosy experience pain in multiple locations. During testing it was found that some patients had painful areas that were not precisely confined to the QST test site (multiple pain areas). For instance, patients with NP over treated skin lesion or skin lesion over the dermatome C8 proved extremely difficult to recruit. Out of 36 clinically examined patients with leprosy and pain, four patients had skin lesion pain over ulnar territory. Of these four patients, only one fulfilled the criteria of our QST site, which may have been insufficient for analysis. QST testing over the affected area in these patients may have been useful. Similarly, it was found that pain associated with light mechanical touch (allodynia) was confined to the ulnar nerve territory, but not QST tested site. In retrospect, including assessment of the entire ulnar nerve territory in our study would have been useful. As the sample size for patients with combined sensory gain and loss was small, any subgroup in the statistical analysis was not necessarily significant, due to loss of power. This meant that the logistic regression model had a very wide CI (95%). The small sample size also limits the

conclusions that can be drawn from the impact of NP on health related-quality of life. A larger subgroup of patients with combined sensory gain and loss was necessary for statistical analysis.

A potential limitation also relates to the sampling process used in the study. Since more than 80% of the study cohort were selected from one centre this may have introduced bias and may reduce the generalisability of our results to the larger population of patients with leprosy. Similarly, patients with leprosy reactions were over-represented in our study. Those patients were attending leprosy service at BLP clinic and therefore accessible to our recruitment. This could be a source of recruitment bias. In addition, it was less likely to recruit cured patients who have no ongoing symptoms of nerve damage and will not be attending a clinic. It would have been ideal to recruit patients from different study sites.

In this study the diagnosis of leprosy neuropathy was based on clinical evidence; no additional techniques were used to investigate neuropathy. This study used Semmes-Weinstein monofilaments to evaluate abnormal sensory nerve function. Semmes-Weinstein monofilaments have limited sensitivity and specificity; to reach the definitive diagnosis of neuropathy, an additional measure of abnormal nerve function such as NCS would have contributed to the accurate identification of neuropathy and increased the accuracy of the diagnosis of NP. Measures of abnormal finding by NCS were used only for patients in the subclinical group as part of the TENLEP study (Wagenaar et al., 2012); to carry out more detailed NCSs in such a setting is challenging. In addition, autonomic nervous testing of nerve function was not performed in this study; this might have increased the number of patients with neuropathy.

Another potential limitation related to the health-related quality of life instruments. Recent recommendations in the IASP guidelines concerning NP assessment (Haanpaa et al., 2011a), suggests using a generic HRQoL measure such as medical outcome short survey (SF-36). This study used the BPI measure which while also recommended by the IASP, is a condition-specific instrument appropriate for detection of treatment response, whereas the SF-36 measure is suitable for evaluating the impact of pain on the common elements of health (Brazier et al., 1992).

In this study the diagnosis of psychological disorder was based on assessment by GHQ-12 questionnaire; no additional techniques were used to assess anxiety and depression.

In addition, the influence of pain catastrophising on impact of NP is not considered (Phillips et al., 2014). It influences chronic perceptions of one's pain (Lame et al., 2005). Such data may have further supported the interpretation of the impact of leprosy NP on quality of life and allowed for comparison with the quality of life changes in other pain conditions; any specific consequences; and whether or not the findings really contributed to overall health. This study used GHQ-12 to assess symptoms and signs suggestive of depression (i.e. a score of three or more); for more objective diagnosis of anxiety syndromes and depression an additional measure of clinical criteria would have contributed to the accurate identification of psychological status.

Communicating with patients regarding their pain complaints was difficult in this study. The use and interpretation of the word "pain" is dependent on local cultural context and language, which changes from one setting to another. For example, many people in South Africa and India interpret the word "numbness" to mean "nothing" (Haroun, 2014). Additionally, communicating through a third person increases the risk of misunderstanding. To overcome this, communication was limited to a few sentences at a time and detailed examples were used to illustrate meaning. This strategy was developed from prior experience in communicating with leprosy patients through a third person in a study from Ethiopia, which helped to convey the desired message during the current study.

Another potential limitation also related to the fact that patients were using medication for their pain relief, which may contribute to variability in responses obtained and may decrease levels of pain. This may be considered as a confounding factor in the data analysis.

The main limitations of the QST were the onerous technical requirements. The time needed to complete the full DFNS-QST protocol during our study was extensive; it took 30 minutes to complete a single QST test on one ulnar site and one hour for both. In addition, the questionnaires and clinical examination assessment completed prior to QST, required an additional 45-60 minutes.

Other methodological design limitations were related to the QST procedure: the high number of tests, and methods of limits. While QST is used to assess somatosensory function thresholds using 13 parameters, perhaps not all these parameters provide additional information compared with standard assessment of pain patients. If the QST

protocol were abbreviated, the duration of the procedure would shorten. Specifically, excluding mechanical pain sensitivity would have made testing easier and faster. The methods of limits algorithm used in this study provided highly reliable threshold results, but took a long time to complete, particularly in patients with long standing disease of the hand. In such situations, the test could take more than an hour per site to complete.

Another limitation of the QST method is that the repeated testing in one area could lead to sensitisation that would confound the QST-Data results. In study from Germany by Grone and colleges (Grone et al., 2012), who investigated the effect of testing order on the results of QST. Twenty healthy subjects were tested twice, 1 week apart with 2 different QST testing orders: the standardized testing order according to the German Research Network on Neuropathic Pain and a modified testing order in which mechanical stimuli were applied before thermal stimuli. The authors found that preceding mild thermal stimulation might lead to a sensitization to mechanical stimuli and thus to mechanical hyperalgesia. Alternative habituation mechanisms in the modified testing order resulting from repeated pinprick stimulation at the beginning should also be debated. I personally, believe that in theory we should do thermal testing second, but since the DFNS-QST protocol has always done in the other order it is best to keep to that.

Another potential limitation also relates to the fact that QST uses psycho-physical methods which require the attention and cooperation of the subject. For instance, the subject's concentration, motivation, reaction time and ability to respond quickly using the hand clicker can influence the results. Hence, the subjective character of the data collected through this method reduces acceptance. In addition, our cohort expectation was high in terms of demonstrating their problem. Participants may exaggerate the response and bias towards a bad outcome in order to get more attention and treatment. However, there is no algorithm of psychophysical testing that can reliably overcome the bias toward showing abnormality found in patients who wish to demonstrate more disability than they have, for whatever reason (Dyck et al., 1998). These observations emphasise the limitation of QST which cannot be considered as a single test to provide full somatosensory profile in patients with NP (Pfau et al., 2012), but it should be thought of as an additional tool to map the area of interest in terms of standard bedside sensory testing (Hansson et al., 2007).

Despite these limitations, our study used stringent criteria for NP, which in turn proved that the diagnosis of NP may be considered optimal. The study still provided an in-depth characterisation of somatosensory profile of patients with leprosy NP and view of the impact of pain upon quality of life.

9.3.4 Practical considerations in doing research in resource-limited settings

9.3.4.1 QST battery high technical requirements

Nerve damage is a frequent complication in leprosy patients with and without pain. The DFNS-QST battery provides a comprehensive assessment of this impairment; however, the practicality of using such techniques in resource-limited settings were, prior to this study, unknown. The DFNS-QST protocol and skin biopsy were used to characterise somatosensory profiles in 90 leprosy patients and 52 healthy volunteers in India. The ulnar nerve territory (dermatome C8) was tested. The QST findings were comparable with a study on HIV painful neuropathy done in London (Phillips et al., 2014). This study suggests that the use of DFNS-QST protocol in resource-limited settings is technically feasible. While I was not sure of the DFNS-QST protocol feasibility in resource-limited settings, it appears to be valid because the findings from our study were consistent with the DFNS database and other studies (Rolke et al., 2006a). However, there were some practical considerations with environment, local idiom, and logistics.

The testing environment caused the greatest challenge. For instance, ambient room temperature (around 31.2 ^{0}C in Mumbai during August 2012) is critical for the MSA thermal stimulator machine, as well as maintaining temperature distribution across the thermode surface over the tested skin site. In addition, some of devices, such as, pinprick are highly sensitive to dust. Furthermore, the DFNS-QST protocol required patients' concentration, which in turn depends on the size and quietness of the room. Given the high number of patients and associated co-patients in the leprosy clinic, problems with noise were unavoidable.

Although our study was carried out in a well-established centre, the Foundation for Medical Research, the erratic electricity supply still remains a potential limitation to the feasibility of using QST. We encountered frequent loss of electricity supply and power cuts due to overburden of the system and the thermal electrode of the QST device is sensitive to fluctuating electric current. To re-calibrate the device after sudden power cut was time consuming.

Another potential challenge to the feasibility was the lack of knowledge of the local idiom. Although the full DFNS-QST protocol was translated and back translated into the local languages (Hindi and Marathi), the need for knowledge of local social conditions is considerable. Training on social conditions (local idiom) may encourage the introduction of novel technology into a new setting.

Finally, logistics and costs must be considered when implementing QST in resource-limited settings. The rules and regulations for the importing of machinery and the bureaucracy of taxation are logistically extensive. The initial set up cost of approximately £15 000 is considerable. In addition, the QST kit requires maintenance after being established, adding to the expenses.

This study is the first to present a detailed assessment of the challenges facing the use of the DFNS-QST protocol in a developing setting, and validates the Mumbai centre for the use of QST. The lessons learned with this particular setting of patients emphasise the importance of understanding the local language and customs.

The way forward in minimizing the QST high technology requirements is better knowledge of local-society, and development of resources and tools. Without human resources, willingness to learn and understanding of the benefit, it will be difficult in practice. The identified challenges may be overcome through improved capacity and increased motivation. Potentially the development of battery operated QST, would overcome other challenges.

9.3.4.2 Tissue biopsy and IENFD challenges

Intra-epidermal nerve fibre density (IENFD) is a technique for measuring the endings of small peripheral nerve fibres in the epidermis. It provides anatomical data regarding the sensory nervous system, whereas QST provides functional/physiological data. Both are useful and complementary tools. IENFD has been used for identifying the presence of nerve damage in other peripheral neuropathies (Haanpaa et al., 2011a). IENFD in affected skin is measured by a skin biopsy taken from patients with suspected small fibre neuropathy (Sommer and Lauria, 2007, Holland et al., 1998). Skin biopsy (3mm punch biopsy) is a safe and reliable technique and has therefore become a widely used tool to investigate IENF (Lauria et al., 2005).

This study was designed to assess the IENFD in leprosy patients in line with the recent NeuPSIG guidelines on the assessment of NP (Haanpaa et al., 2011a). I hypothesised that skin biopsy examination of patients with NP would show significant loss of intra-epidermal fibres in affected sites compared to asymptomatic sites.

A total of 200 biopsy samples were collected: 170 samples from 85 patients and 30 samples from 30 healthy participants. Each sample was divided into 2 pieces. These samples were processed and stored frozen at -80 ^{0}c in FMR. While it was planned to transfer the samples to Oxford, UK, the administrative practicality of this process proved difficult within the timeframe of the study. Tissue transfer permission is not granted, and the decision on how to process the biopsy is under review.

9.3.5 If I had to start now, this is what I would do differently

I qualified in using the DFNS-QST protocol application and now I have data from my leprosy study. I had a lot to learn in the beginning, but I quickly learned what I needed, in particular to apply this advanced technology in a resource-limited settings. However, I always felt that if I worked in leprosy neuropathy and pain, I would have started off with an in-depth foundation. I am happy with what I obtained, but if I could start over again, I would probably chose to have a shorter protocol with more patients. It would have been useful to develop a simpler version of the DFNS-QST protocol that could be applied in routine clinical examinations to diagnose small-fibre neuropathies, requiring less psychophysical patient collaboration, having lower cost, maintaining features of high accuracy and rapidity, and with applicability to poor psychomotor performance. Such a tool would be more practical, particularly in resource-limited settings.

In hindsight, the use of the QST protocol according to the DFNS represents a comprehensive protocol of somatosensory profiling and was very useful in leprosy; however, identification of new neurological abnormalities to differentiate patients with and without pain is not yet possible. It would have been useful if to examine other possibilities such as skin biopsy and IENF density.

In hindsight, the use of the BPI measure is appropriate for detection of treatment response in patients with NP. It would have been useful if to use the SF-36 measure for evaluating the impact of pain on HRQoL.

The recruitment of leprosy patients with NP to the study was not representative of all types of pain in those patients (i.e. pain in nerve affected territory and pain in skin lesions). It would have been useful if I had powered the study to the NP patients in each subgroup. This would have given a sample size of 15 patients with NP in each.

I wish I had tested the entire ulnar nerve territory and/or other pain location. This would have given further positive sensory gain findings. Similarly testing the QST parameters in the skin lesions would have been of great value.

9.3.6 What contributions has this study made to our knowledge?

In the literature I reviewed, I found that while the concept of sensory profiling using tools such as QST was well established in NP field, it was not evident in leprosy NP, hence there has been a contribution to knowledge in the later practice through this study.

This is the first study using the DFNS-QST protocol in a resource-limited setting and validates the Mumbai Centre's for the use of the QST. Normative QST data are generated by evaluating somatosensory function in healthy volunteers, a process in which one body area is assessed using the QST measures according to the DFNS protocol. This study contributed to the DFNS reference database with normative data from the dermatome C8 of non-Caucasian population.

To facilitate the identification of leprosy patients with NP, a simple case definition was introduced in this thesis using the DN4 questionnaire and clinical examination, by which the patient's pain could be categorised as NP or non-NP pain. This case definition aimed to identify a leprosy patients with NP in a resource-limited setting. Our findings showed the utility of this simple case definition, and it could be introduced in other leprosy populations.

Furthermore, the QST investigative tool methodology for sensory profiling, is still emerging as a field of research; therefore, new questions investigating practice have come from this research. Firstly, why do leprosy patients with pain not have significantly different QST profiles than leprosy patients without pain? This observation is interesting given recently increased use of QST worldwide. One could argue that the way this study was designed and implemented actually caused this results, but because this study was three-way case controlled with age and gender matched control (i.e.

controls were selected correctly from the study population), this is not likely. All methods were carefully planned to improve the study design. In addition, the QST testing was carried out by a trained and qualified candidate according to the DFNS criteria (Geber et al., 2009), ensuring that protocol of QST laboratories was properly used. The second concern of the investigating practice being proposed by thesis, is: how specific are QST measures in identifying phenotypical abnormalities of leprosy patients with neuropathy that is associated with pain? In this context, if investigating somatosensory changes contribute to the presence or absence of pain could also be valuable.

In the current study the QST measures did not identify new abnormalities for patients with and without pain. Similar findings were also obtained by Phillips in HIV-related painful neuropathy (Phillips et al., 2014), unlike other studies in patients with pain, where the QST tool has identified abnormalities. Maier and colleagues studied sensory abnormalities in 1236 patients with NP due to different underlying diseases (Maier et al., 2010). In this large cohort of patients, DFNS-QST measures showed that 92% of all patients with proven neuropathy had at least one sensory abnormality compared with the contralateral unaffected body area or with the reference data obtained from healthy controls. Pfau and colleagues also showed the applicability of the DFNS-QST protocol in identifying abnormalities in PHN (Pfau et al., 2014). In all these studies, age and gender match healthy controls were designed. These studies were therefore similar to ours in study design. It is suggested that a shorter protocol in more leprosy patients may be the best options for leprosy NP. In this context, the current study has shown that investigating leprosy patients using the DFNS-QST protocol was time-consuming and demanding for both-investigators and patients. The protocol needs to be simplified to become a regular screening tool in resource-limited settings. Therefore, there is a pressing need to identify the most sensitive QST measures to determine somatosensory abnormalities for each NP entity in leprosy.

The findings from the current study will contribute to clinical practice in leprosy NP. I demonstrated that, by using the DFNS-QST measures from the healthy controls, the interpretation of sensory findings for patients with NP may be different compared to an un-affected contralateral side, which is usually used as a reference in clinical practice. I have shown that in leprosy patients with unilateral NP, bilateral sensory changes occur too. This observation of bilateral sensory abnormalities in leprosy patients with

unilateral NP is of great importance clinically, because it indicates that the mirror unaffected side should be used carefully as a reference side in sensory examinations in clinical practice (Konopka et al., 2012). In addition, this work validate thermal abnormalities and preserved JPS and vibration in leprosy patients. This may help clinicians to differentiate leprosy from other peripheral neuropathies; if vibration and/or JPS are preserved in patients with peripheral neuropathy, think of leprosy.

Through my doctoral investigation, although I have not found differences between patients with and without pain in terms of their detailed sensory profiles, this tells us that another tool is needed to identify neurological abnormalities in those patients. It could be said that my thesis made a contribution to knowledge about the implications of the current work (i.e. the investigation approach of leprosy NP). Thus, tools such as skin biopsy and its IENF density are now being proposed by this piece of work since it is vital to explore other possible differences. IENF density provides anatomical data regarding the sensory nervous system, whereas QST provides functional and physiological data. Therefore, doing the biopsies is very important, as it might indicate what other tools need to be used in future.

Another contribution from this work that still needs further research is the identification of patients who are at risk of developing pain. This work highlights the question, as temperature abnormalities are a marker of neurological abnormality in pain, why do all leprosy patients not have pain? Furthermore, the thermal abnormality found in this study indicates the need for a field friendly temperature testing, for example apps applications. This will help early detection and treatment of neuropathy in leprosy.

The findings of our profiling measures in leprosy neuropathy are also of relevance for routine clinical use and clinical trials in resource-limited settings. For instance, the selection of sub-groups based on specific QST parameters for the clinical evaluation of drugs will improve trial sensitivity. Moreover, including simplifying sensory and symptom profiles of patient responses to various sensory stimuli such as heat and pressure will empower post-hoc analysis of responders/non-responders, which will then be used to enable efficient prescribing to patients likely to respond to the drug when the intervention is introduced into clinical practice. In addition, knowledge gained in profiling this patient population could also help to determine a mechanism-based therapy for NP.

Finally, the study contributions included development of skills of the health facility staff at collaborating centres. They improved their skills in identifying leprosy patients with NP using clinical examinations and highly specialised techniques. These are generic skills that can be transferred to other settings in India, including non-leprosy NP diseases such as diabetic and HIV-painful neuropathy. In addition, this study may have an impact on policy makers, as there are many governmental and non-governmental leprosy experts in India who can contribute to policy guidelines. I think even highlighting the issues around NP in leprosy would move quickly into priority in treatment. Hence, this work contributed to the academic work in India and policy benefits will follow.

9.3.7 Future perspectives

The DFNS-QST protocol enables a standardised approach to be used when assessing patients with NP. A simple and robust diagnostic tool in identifying neurological abnormalities in leprosy patients with NP can be developed. This would help to answer the question, "why do leprosy patients with pain not have significantly different profiles than leprosy patients without pain?" or "who is at risk of developing leprosy NP?" The tool would help to accurately identify patients for both large epidemiological studies in resource-limited settings and for future clinical trials.

The identification of stratified sub-groups of leprosy patients with NP through this doctoral thesis has established important steps for the future therapeutic efficacy approach. However, findings are not yet sufficient. New therapeutic concepts based on sub-group characteristics of NP leprosy patients with a dominant sensory loss profile and patients who have combined sensory loss and gain need to be developed. Possibly, this sub-grouping approach needs further modification to better assign patients to interventions, but indeed, the two sub-groups should receive different treatments.

Chapter 10 Conclusions and Recommendations

10.1 Conclusions

This study aimed to establish the somatosensory characteristics of leprosy patients with persistent neuropathy, both with and without neuropathic pain. The QST parameters were effective in detecting neuropathy, but were not able to distinguish between patients with and without neuropathic pain. A major finding of this thesis demonstrates that leprosy patients with persistent neuropathy have a unique somatosensory profile compared to other conditions.

10.2 Recommendations

Based on the research findings presented in this thesis and the acknowledged limitations, the following steps are recommended:

1. A clear classification of leprosy related neuropathic pain should be developed. Neuropathic pain can present in a number of ways in leprosy. For instance, acute pain may be the presenting symptom in a patient with leprosy who is seeking treatment. In this setting, the pain may be nociceptive in nature, usually due to reactions. However, the type of acute pain from neuritis or other leprosy nerve involvement is not well classified. Acute pain in leprosy can be classified into acute pain with reactions and neuropathic pain. The classification should also involve the newly developed grading system for the assessment of neuropathic pain (Treede et al., 2008). The grading system of neuropathic pain proved to be useful for the identification of neuropathic pain in patients with neck-arm pain (Tampin et al., 2013). Leprosy patients with pain can be classified as having probable, possible, or definitive neuropathic pain. This would add further help to the identification of leprosy related neuropathic pain.
2. Understanding of the pathophysiology of leprosy neuropathy and in particular, the unique feature of loss of one Aβ fibre mediated sensory modality (mechanical detection threshold) accompanied by preservation of another (vibration detection threshold) requires further elucidation which will have physiological implications for understanding other conditions as well as the opportunity to develop specific diagnostic tools.

3. Future research should investigate the methods of self-reporting pain in determining the prevalence and impact of neuropathic pain in leprosy patients using pain questionnaires. Self-reported pain relies on two factors: the description questionnaire used and cultural barriers to reporting or not reporting pain. Leprosy is global disease, but the same terms cannot be used in different settings.
4. Psychological distress was found significantly higher in leprosy patients with neuropathic pain than those with painless neuropathy, as well as the additional quality of life burden that leprosy neuropathic pain has produced over that of leprosy itself or leprosy with painless nerve damage. Future studies should consider these observations for the identification and treatment of neuropathic pain in leprosy.
5. Future research should include the development of new tools for identifying leprosy neuropathic pain to inform the appropriate treatment. Given that the full QST battery is beyond the feasibility of most centres in poorer leprosy-endemic countries, a simple and robust diagnostic tool is required. The new tools should include a specific QST parameters such as thermal and vibration testing and requiring less psychophysical patient collaboration, having lower cost, maintaining features of high accuracy and rapidity, and with applicability to poor psychomotor performance. Such tools need to be validated, tested, and deployed in clinical settings. Once established as valid and reproducible, tools for neuropathic pain may be used to identify patients for clinical trials that may be developed in the future.
6. A future study should consider a stratified grouping of somatosensory findings: patients with a dominant sensory loss profile and patients who have combined sensory loss and gain, for a future therapeutic efficacy approach. The differentiation between the somatosensory profile of sensory loss and sensory gain could help to predict responses to treatment.

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Appendices

Appendix A

Ethical Approvals

Appendix 1. LSHTM Ethical approval

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636
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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Diana Lockwood
Professor of Tropical Medicine
CRD/ITD
LSHTM

12 July 2012

Dear Professor Lockwood,

Study Title: **The development of new tools for the investigation of neuropathic pain in leprosy: a pilot study**
LSHTM ethics ref: **6181**

Thank you for your letter of 25 June 2012, responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered by the Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

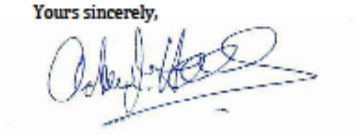
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	
Protocol	V3.2	21/06/2012
Information Sheet	V1.0	04/04/2012
Consent form	V1.0	04/04/2012

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor Andrew J Hall
Chair
ethics@lshtm.ac.uk
http://intra.lshtm.ac.uk/management/committees/ethics/

Appendix 2. Imperial College London Ethical approval

Imperial College London

Imperial College Research Ethics Committee

Imperial College London
G02 Sir Alexander Fleming Building
South Kensington Campus
SW7 2AZ
Tel: +44 (0)207 594 1770 Fax: +44 (0) 207 594 1792

researchethicscommittee@imperial.ac.uk

03 March 2011

Professor Andrew Rice,
Section of Anaesthetics,
Department of Surgery and Cancer,
Imperial College London,
Chelsea and Westminster Campus,
369 Fulham Road,
London,
SW10 9NH

Dear Professor Rice,

Study Title: Healthy Volunteer Quantitative Sensory Testing (QST); Quality Control Study

ICREC reference: ICREC_11_2_3

CI: Professor Andrew Rice

The above study was approved by your HoD on 17th February 2011 and by the Joint Research Office on the 1st March 2011.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents

The documents reviewed were:

- ICREC Application form
- Participant Information Sheet V2
- Consent form for healthy volunteers
- Recruitment Invitation email

Yours sincerely,

Gary Roper,
Head of Regulatory Compliance,
Imperial College London

Appendix 3. FMR Ethical approval

THE FOUNDATION FOR MEDICAL RESEARCH

DR. KANTILAL J. SHETH MEMORIAL BUILDING, 84-A, R.G. THADANI MARG, WORLI, MUMBAI-400 018, INDIA

Trustees :
Mr. J. N. Godrej (Chairman)
Mrs. A. V. Sheth
Mr. V. K. Sheth
Mr. N. B. Godrej
Dr. N. F. Mistry (Director)

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E-mail : fmr@fmrindia.org/fmrmum@gmail.com
Website : www.fmrindia.org

2nd November 2012

IEC No – FMR/IEC/LEP/04/2012

TO WHOMSOEVER IT MAY CONCERN

We have reviewed the project entitled **"THE DEVELOPMENT OF NEW TOOLS FOR THE INVESTIGATION OF NEUROPATHIC PAIN IN LEPROSY: A PILOT STUDY IN MUMBAI, INDIA"**. This is a collaborative study submitted by the 'London School of Hygiene and Tropical Medicine', United Kingdom to the 'Ethics Committee of The University of London' and was approved by the Ethics Committee (LSHTM Ethical Ref no : 6181) . The Foundation for Medical Research is one of the collaborating centers.

Documents approved by the Ethics Committee are as follows:

Documents	Version	Date
Protocol	V3.3	21/06/2012
Information sheet in Hindi, Marathi &English	V1.0	04/04/2012
Consent form in Hindi, Marathi & English	V1.0	04/04/2012

As members of the Ethics Committee we have no objection to this project being conducted at The Foundation for Medical Research. We find that the project satisfies the pertinent ethics issues involved in the execution of this project and there will be no infringement with regards to involvement of human subjects. **This Project will be reviewed on the basis of defined criteria until its termination.**

Members of the Ethics Committee, The Foundation for Medical Research

Mr. N. B. Godrej
(Chairperson)

Prof A.S. Desai

Dr. N.F. Mistry

Dr. S. Rougan

Appendix B

Participant Recruitment, Information Sheets and Consent Forms

Appendix 4. Healthy volunteer's recruitment invitation letter

Healthy volunteers study: Recruitment invitation, email

This email has been approved by the ICREC Number: 11_2_3

Dear All,

We are seeking volunteers to participate in a study examining the way the skin sense touch, temperature, pressure and pain sensation using a well established technique called Quantitative Sensory Testing (QST). This is essentially a sophisticated clinical examination of the skin and would take about 1.5 hours of your time.

Volunteers should be in good general health.

If you would like more information or would like to volunteer please let me know. Please feel free to pass this invitation on to colleagues within Imperial Collage or LSHTM who might be interested in taking part.

Many thanks
Dr Omer Haroun
+447411220020
+447536136026

Version 1.0 <15.02.11>

Appendix 5. Healthy volunteer's recruitment invitation in Hindi

स्वयंसेवक की जरूरतः

क्वान्टीटेटीव्हसेंसरी टेस्टींग और स्कीन बायोप्सी से: त्वचा का स्पर्श, तापमान, दबाव और दर्द संवेदना जानने की परीक्षा करनेवाले अध्ययन में, जो भाग ले सके उन स्वयंसेवक की हमें तलाश है.

ये एक त्वचा की रोगविषयक परिक्षण है जिसे १.५ घंटे लगेंगे.

स्वयंसेवकों की सेहत अच्छी होने चाहिए.

अगर आपको और जानकारी चाहिए या आप हिस्सा लेना चाहते है तो कृपया मुझे बताइए. कृपया ये जानकारी आपके अन्य दोस्तों को और रिश्तेदारों को दीजिये जो इस अध्ययन में भाग लेना चाहेंगे.

शुक्रिया,

डॉ. ओमर हारुन

Tel: ९८१९०७९०१४

Appendix 6. Healthy volunteer's recruitment invitation in Marathi

स्वयंसेवक आवश्यक

चांगल्या सिद्ध पद्धती, क्वान्टीटेटिव्ह सेन्सरी टेस्टिंग (QST) व त्वचा जीवोटक परीक्षा, ह्यांचा वापर करून आम्हीं स्पर्श, तापमान, दबाव आणि वेदना संवेदना ह्या बाबीसंबधी त्वचेची जाण, ह्या अभ्यासात भाग घेण्यासाठी आम्हीं स्वयंसेवक शोधत आहोत. त्वचेची ही अत्याधुनिक चिकित्साविषयक तपासणी आहे व अद्दमात्ते तुमचा दीड तास जाईल.

स्वयंसेवकांचे आरोग्य हे सर्वसाधारण असावे.

तुम्हांला अधिक माहिती हवी असल्यास किंवा तुम्हांला स्वयंसेवक व्हावयाचे असेल तर कृपया मला सांगा. तुमची मित्रमंडळी, नातेवाईक ज्यांना सहभाग घ्यावयाचा असेल तर आपण हे आमंत्रण त्यांना देऊ शकता.

मनःपूर्वक आभार

डॉ. ओमर हरूना

दूरध्वनी: ९८९०७९०१४

Appendix 7. Healthy volunteer information sheet

Participant Information Sheet

QST_IN_LEP

STUDY PARTICIPANT INFORMATION SHEET

The development of new tools for the investigation of neuropathic pain in leprosy: a pilot study in Mumbai, India

Healthy Volunteer Quantitative Sensory Testing (QST) and Skin biopsy

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Part 1: Tells you the purpose of this study.

Part 2: Gives you more detailed information about the conduct of the study and what will happen to you if you take part.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

PART 1

What is the purpose of this study?

The purpose of the study is to obtain sensory perception measurements in healthy people. We will also use the data from these measurements to provide "normal values" for the leprosy and other studies.

Why have I been chosen?

You have been invited to participate in the study as you are not pregnant, over 16 yrs of age and do not suffer from:

- Migraine headaches
- Lower back pain
- Acute or chronic pain conditions

Continue…

Participant Information Sheet

QST_IN_LEP

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

PART 2

What will happen to me if I take part?

If you are interested in taking part in the study, an appointment with the investigator will be made at a time convenient for you. For the 24 hour period prior to the QST measurements we ask that you take no pain-killer medications if possible. If you do take pain-killers in this period please let the research investigator know.

Quantitative Sensory Testing and skin biopsy of hands and feet ~ 1.5 hrs

This is a detailed method of testing the function of the sensory nerve in your skin, which normally detects changes in temperature, pressure, sharpness and touch.

Your ability to sense changes in temperature is measured using a small probe applied to your skin which changes temperature, i.e. becomes cool or warm. You will be asked to say when you can feel any change.

Your ability to detect light touch is determined using very fine filaments, again you will be asked to say when you can feel them.

For sharpness a small probe, designed not to puncture the skin, is applied to your skin. You are asked to say when it begins to feel sharp.

A blunt pressure gauge is used to apply pressure. You will be asked to say when the pressure just begins to become uncomfortable.

We shall also conduct some measurements, which might cause slight discomfort, However you will be able to stop at any point if you are not happy.

Continue…

Participant Information Sheet

QST_IN_LEP

What if something goes wrong?

The technique of Quantitative Sensory Testing (QST) is in routine clinical and research use in our laboratory and others. We have not seen any adverse events in the hundreds of people examined to date. London School of Hygiene and Tropical Medicine hold insurance policies, which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that London School of Hygiene and Tropical Medicine are at fault.
This does not affect your legal rights to seek compensation. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator **Dr O Haroun; tel: 07536136026 / Local number xx** or **email: omer.haroun@lshtm.ac.uk** . If you are still not satisfied with the response, you may contact the **London School of Hygiene and Tropical Medicine Clinical Trials QA Manager.**

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Data from this aspect of the study will be kept in an anonymous form. Initially the information will be stored on secure computers at BLP centre. We will then send this anonymised data to University computers at LSHTM for analysis and also include it in computer databases which are used to store and analyze data about neuropathy and pain; these are the London Pain Consortium and the German Neuropathic Pain Network databases.

What will happen to the results of the research study?

The results from this data will be used to assess the QST as a clinical tool for the diagnosis of neuropathic pain in leprosy context. Subsequent research conducted in the QST_IN_LEP study will be disseminated by the normal process of publication in scientific journals and presentation at professional conferences. If you wish to be informed of these publications we can arrange for that. No data will be identifiable as from you in the publications.

Who is organizing and funding the research?

This study is being organised by Clinical Research Department, Faculty of Tropical and Infectious Disease, London School of Hygiene and Tropical Medicine. The Hospital and Homes of St. Giles (HHSG) is the charity that is funding this research.

Who has reviewed the study?

This study was given approving ethical opinion for conduct in the BLP centre by Foundation Medical Research Ethics Committee (FMREC) number xx and London School of Hygiene and Tropical Medicine Ethical Committee (LSHTM) number xx.

Contact for Further Information:

For further information regarding this study please contact the study investigator **Dr Omer Haroun tel: +44(0) 07536136026 / Local number x or email: omer.haroun@lshtm.ac.uk.**

Appendix 8. Healthy information sheet – German version

Prof. Dr. med. R.-D. Treede
Lehrstuhl für Neurophysiologie
Zentrum für Biomedizin und Medizintechnik Mannheim
Medizinische Fakultät Mannheim
der Universität Heidelberg
Ludolf-Krehl-Str.13-17
68167 Mannheim

Deutscher
Forschungsverbund
Neuropathischer
Schmerz

Probandenaufklärung

Untersuchung der Funktion und Eigenschaften des somatosensorischen Nervensystems mit Hilfe der quantitativen sensorischen Testung (QST)
im Rahmen des Deutschen Forschungsverbundes Neuropathischer Schmerz (DFNS)

Sehr geehrte/r Proband/in!

Wir möchten Sie bitten, an einer wissenschaftlichen Untersuchung teilzunehmen, die die Ursachen von einer veränderten Empfindlichkeit der Haut infolge von Nervenverletzungen (neuropathische Schmerzen), Hautkrankheiten oder anderen Ursachen erforschen soll. Während der Untersuchung wird ihre Empfindung auf Temperatur-, Berührungs- und Schmerzreize getestet, was sie teilweise als unangenehm empfinden könnten. Eine Schädigung der Haut ist dabei nicht zu befürchten.

Minderjährige Patienten sind grundsätzlich von den Untersuchungen ausgeschlossen.

1. Ziele der Untersuchung
Es soll ein Profil der Empfindlichkeit Ihrer Haut erstellt werden, um Unterschiede in der Empfindlichkeit zwischen unterschiedlichen Patientengruppen und gesunden Kontrollprobanden erkennen zu können. Hierzu möchten wir Sie mittels standardisierter Untersuchungsmethoden genau untersuchen. Später soll diese Untersuchung (quantitative sensorische Testung) als Routinediagnostik bei Patienten durchgeführt werden können.

2. Der Deutsche Forschungsverbund Neuropathischer Schmerz (DFNS)
Der DFNS ist ein Verbund aus 27 deutschen Universitätskliniken, Städtischen Kliniken, Rehabilitationskliniken und Instituten. Die Hauptziele des DFNS sind, das Wissen auf dem Gebiet der Schmerzen, die nach einer Nervenverletzung entstehen (neuropathische Schmerzen, z.B. Schmerzen nach einer Gürtelrose, schmerzhafte Polyneuropathie) in Deutschland zugänglicher zu machen und die klinische und experimentelle Forschung durch Koordination, Kooperation und verbesserte Kommunikation entscheidend zu verbessern. Dieses Projekt wird hierbei vom Bundesministerium für Bildung und Forschung gefördert. Mit ihrer Teilnahme unterstützen Sie dieses Projekt und leisten einen Beitrag zur angestrebten Verbesserung der Situation aller Patienten mit einer veränderten Empfindlichkeit der Haut oder Schmerzen aufgrund verschiedener Erkrankungen.

Continue…

3. Ablauf der Untersuchungen
Die Untersuchungsdauer beträgt ca.

- ☐ 30 min
- ☐ 60 min
- ☐ 90 min
- ☐ 120 min
- ☐ 150 min
- ☐ 180 min.

Untersucht werden die folgenden Körperareale: _____

(A) Die quantitative sensorische Testung (QST)

Zu Beginn werden Sie körperlich auf neurologische Symptome hin untersucht. Darauf folgt eine Untersuchung mittels im Folgenden beschriebener Methoden, um Vergleichsdaten zu Patienten zu erheben. Dabei findet keine Hautverletzung statt.
Zunächst wird Ihre Warm- und Kaltempfindung sowie Ihre Wahrnehmung von Kälte- und Hitzeschmerzreizen geprüft. Hierfür wird Ihnen eine ca. 13 cm^2 große Metallfläche auf die Haut gelegt. Diese hat eine Ausgangstemperatur von 32°C, die in einer festgelegten Reihenfolge ansteigt oder abfällt. Sobald Sie Temperaturveränderungen oder Schmerzempfindungen an der Auflagefläche wahrnehmen, bitten wir Sie, eine Stop-Taste zu drücken, woraufhin die Metallfläche ihre Ausgangstemperatur wieder erreicht. Dieser Vorgang wiederholt sich insgesamt 2-mal für jede Temperaturänderung in jedem Testareal. Es folgt die Prüfung Ihrer Wahrnehmungsschwellen für Berührungsreize und Nadelreize, die mittels eines Haares und einer Nadel unterschiedlichen Auflagedrucks auf der Haut geprüft wird. Darauffolgend wird untersucht, ob bei Ihnen Schmerzen durch Berührung, eine sogenannte Allodynie, bestehen. Hierzu wird mit einem Wattebausch, einem Q-Tip sowie einem standardisierten Pinsel die Haut bestrichen bzw. leichter Druck auf die Haut ausgeübt. In einer weiteren Untersuchung wird ein Einzelreiz mit einer stumpfen Nadel auf die Haut aufgebracht. Im Abstand von zehn Sekunden folgt eine Serie von zehn identischen Nadelreizen innerhalb desselben Hautareals. Unmittelbar nach dem Einzelreiz sowie erneut im Anschluss an die nachfolgende Reizserie erfolgt eine zusammenfassende Beurteilung der Empfindungsstärke mit Hilfe einer numerischen Skala von 0-100. Zur Untersuchung der Vibrationsschwelle wird eine Stimmgabel auf die Haut über einem Knochenvorsprung (z.B. an den Füßen über Innenknöchel, an den Händen über dem Handgelenk, am Kopf seitlich über der Schläfe) platziert. Zur Prüfung der Wahrnehmung der Druckempfindlichkeit der Muskulatur wird über definierten Muskeln ein Druckstimulator aufgesetzt (z.B. an den Füßen über der Fußinnenmuskulatur, an den Händen über dem Daumenballen, am Gesicht über der Schläfenregion). Mittels einer aufsteigenden Druckintensität kann die Druckschmerzschwelle über den entsprechenden Muskeln bestimmt werden.

(B) Erfassung krankheitsspezifischer Daten mittels Fragebögen
Sie werden gebeten, verschiedene Fragebögen auszufüllen. Diese erfassen Informationen hinsichtlich möglicher Schmerzen, aber auch Informationen zu einer möglichen Beeinträchtigung Ihres Alltagslebens und Ihrer allgemeinen Befindlichkeit.

4. Datenverarbeitung und Datenschutz

Die im Rahmen dieser Studie erhobenen Daten werden auf einer mit Ihren persönlichen Daten versehenen Krankenakte in der Abteilung für Neurophysiologie im Zentrum für Biomedizin und Medizintechnik Mannheim gespeichert. Zur Auswertung der erhobenen Daten können diese Daten anonymisiert mit einer Probandennummer, d.h. ohne Namensnennung, innerhalb des Deutschen Forschungsverbundes Neuropathischer Schmerz an die beteiligten Institutionen für wissenschaftliche Zwecke weitergeleitet werden. Alle im Rahmen dieser Studie erhobenen Daten unterliegen der ärztlichen Schweigepflicht und werden strikt vertraulich gemäß dem Datenschutz behandelt.
Ihre Daten sollten für die Durchführung des Projektes langfristig gespeichert werden. Sie können aber jederzeit ohne Angabe von Gründen Ihr Einverständnis widerrufen und die Löschung Ihrer Daten verlangen. Ihr Ansprechpartner ist in diesem Fall der die Untersuchung durchführende Mitarbeiter, den Sie über die Telefonnummer 0621-3839926 erreichen.

Continue…

5. Versicherungsschutz

Für die beschriebenen Untersuchungen besteht eine Unfall-/Wegeversicherung.
Der Versicherer ist der Badische Gemeinde-Versicherungs-Verband, Durlacher Allee 56, 76131 Karlsruhe (Telefonnummer 0721 660-0), die Vertragsnummer ist V1087106. Versichert sind Unfälle, von denen Sie als versicherte Person auf den direkten Fahrten von Ihrer Wohnung zu der Untersuchungsstätte und zurück betroffen werden. Der Versicherungsschutz besteht ausschließlich während der Fahrten. Er beginnt auf dem Hinweg mit dem Verlassen der Wohnung bzw. auf dem Rückweg mit dem Verlassen der Untersuchungsstätte zum Zwecke des Antritts der Fahrt und endet mit der Ankunft an der Untersuchungsstätte bzw. mit der Rückkehr in die Wohnung. Der Versicherungsschutz entfällt, wenn die normale Dauer des Weges verlängert oder der Weg selbst durch rein private und eigenwirtschaftliche Maßnahmen (z.B. Einkauf, Besuch von Wirtschaften zu Privatzwecken) unterbrochen wird.

Um den Versicherungsschutz im Bedarfsfall nicht zu gefährden, sind gewisse Bedingungen zu erfüllen.
Bitte berücksichtigen Sie folgende Punkte (Auszug aus den Allgemeinen Unfallversicherungsbedingungen 2001; Punkte 7 und 8 Obliegenheiten des Versicherten):

7. Was ist nach einem Unfall zu beachten (Obliegenheiten)?

Ohne Ihre Mitwirkung und die der versicherten Person können wir unsere Leistung nicht erbringen.

1. Nach einem Unfall, der voraussichtlich eine Leistungspflicht herbeiführt, müssen Sie oder die versicherte Person unverzüglich einen Arzt hinzuziehen, seine Anordnungen befolgen und uns unterrichten.
2. Die von uns übersandte Unfallanzeige müssen Sie oder die versicherte Person wahrheitsgemäß ausfüllen und uns unverzüglich zurücksenden; von uns darüber hinaus geforderte sachdienliche Auskünfte müssen in gleicher Weise erteilt werden.
3. Werden Ärzte von uns beauftragt, muss sich die versicherte Person auch von diesen untersuchen lassen. Die notwendigen Kosten einschließlich eines dadurch entstandenen Verdienstausfalls tragen wir.
4. Die Ärzte, die die versicherte Person – auch aus anderer Anlässen – behandelt oder untersucht haben, andere Versicherer, Versicherungsträger und Behörden sind zu ermächtigen, alle erforderlichen Auskünfte zu erteilen.
5. Hat der Unfall den Tod zur Folge, ist uns dies innerhalb von 48 Stunden zu melden, auch wenn uns der Unfall schon angezeigt war. Uns ist das Recht zu verschaffen, gegebenenfalls eine Obduktion durch einen von uns beauftragten Arzt vornehmen zu lassen.

8 Welche Folgen hat die Nichtbeachtung von Obliegenheiten?

Wird eine nach Eintritt eines Unfalls zu erfüllende Obliegenheit verletzt, verlieren Sie den Versicherungsschutz, es sei denn, Sie haben die Obliegenheit weder vorsätzlich noch grob fahrlässig verletzt.
Bei grob fahrlässiger Verletzung behalten Sie insoweit den Versicherungsschutz, als die Verletzung weder Einfluss auf die Feststellung des Leistungsfalls noch auf die Bemessung der Leistung gehabt hat.
Bei vorsätzlicher Verletzung behalten Sie in diesen Fällen den Versicherungsschutz insoweit nur, wenn die Verletzung nicht geeignet war, unsere Interessen ernsthaft zu beeinträchtigen oder wenn Sie kein erhebliches Verschulden trifft.

Kontaktpersonen für Fragen:

Dr. Doreen Pfau

Telefonnummer: 0621-3839926

Appendix 9. Healthy volunteer information sheet – Hindi version

अध्ययन सहभागी जानकारी पत्र.

परियोजना का नाम: कुष्ठरोग में होनेवाले तंत्रिक विकृति दर्द को जाँचने के लिए नया साधन तैयार करना: मुंबई, भारत में मार्गदर्शक जाँच

निरोगी स्वयंसेवक क्वान्टीटेटीव्ह सैंसरी टेस्टींग और चमड़ी ऊतकों की जाँच (biopsy)

आपको इस संशोधन अध्ययन में भाग लेने के लिए आमंत्रित किया गया है. निर्णय लेने से पहले, आपको ये संशोधन क्यों किया जा रहा है और इसमें क्या होगा ये समझना जरूरी है. कृपया आगेकी जानकारी ध्यान से पढ़े और इच्छा होनेपर दूसरों से चर्चा करें.

भाग १: आपको इस अध्ययन का उद्देश बताया जायेगा.

भाग २: आपको अध्ययन के बारे में अधिक जानकारी दी जायेगी और अगर आप हिस्सा लेना चाहते है तो क्या होगा ये बताया जायेगा.

अगर आपको कुछ समझ नहीं आया हो या आपको अधिक जानकारी चाहिए हो तो आप हमें पूछ सकते है. आप इसमें भाग लेना चाहते है की नहीं ये तय करने के लिए आप अपना समय लीजिये.

ये पढने के लिए शुक्रिया.

भाग १:

इस अध्ययन का उद्देश्य क्या है?

निरोगी स्वयंसेवकों से संवेदनात्मक अवबोधन का मापन प्राप्त करना इस अध्ययन का उद्देश्य है. हम इस मापन से मिली जानकारी को कुष्ठरोग और दूसरे अध्ययन में 'साधारण मूल्य' प्रदान करने के लिए उपयोग करेंगे.

मुझे क्यों चुना गया है?

आपको इस अध्ययन में शामिल करने के लिए आमंत्रित किया गया है क्योंकि आप १६ से ऊपर के उम्र के है, आप गर्भवती नहीं है और आपको नीचे दी गए बीमारियाँ नहीं है:

- सरदर्द
- कमर दर्द
- प्रखर या ज्यादा समय का दर्द

क्या मेरा सहभागी होना जरूरी है?

ये आपको तय करना है की आप भाग लेना चाहते है की नहीं. अगर आप भाग लेने का निर्णय लेते है तो आपको ये जानकारी पत्र रखने के लिए दे जायेगा और आपको सहमति पत्र पर दस्तखत करना होगा. अगर आप भाग लेने का निर्णय लेते है तो भी आप किसी भी वक्त, बिना कोई कारण दे अपने आप को इस अध्ययन से निकाल सकते है.

भाग २:

अगर मैं भाग लेता/लेती हूँ तो मेरा क्या होगा?

अगर आप इस अध्ययन में भाग लेना चाहते है, तो आपके सुविधा के अनुसार आपको अन्वेषक के साथ नियुक्ति (appointment) की जाएगी. आपके QST माप्ण के २४ घंटे पहले हम आपसे दरख्वास्त करेंगे की आप किसी दर्दके लिए कोई दवा ना ले. अगर आप दर्द की दवा लेते तो कृपया ये बात अन्वेषक को बता दिजीये.

Continue…

क्वान्टीटेटीव्ह सँसरी टेस्टींग और हाथ और पैर के चमड़ी ऊतकों की जाँच (biopsy) - १.५ घंटे:
यहाँ आपको आपके त्वचा की संवेदनात्मक नस (sensory nerve) मापने के बारे में जानकारी दी जाएगी; जो साधारण तापमान, दबाव, तीव्रता और स्पर्श में होनेवाले बदल का पता लगाता है.

एक छोटा यंत्र आपके त्वचा पर रखा जायेगा जिससे आपकी तापमान में होनेवाले बदलाव जानने की क्षमता जानी जायेगी. इस यंत्र में तापमानी बदल होंगे: ठंडा या उष्ण. आप कोई बदल महसूस कर रहे है के नही ये आपको पुछा जायेगा.

बारिकी तंतु से आपका हल्का स्पर्श जानने के क्षमता जाँची जायेगी और फिर से आपको वो महसूस हो रही की नहीं ये पुछा जायेगा.

तीव्रता के लिए न चुभनेवाला एक छोटा यंत्र, आपपर रखा जायेगा. आपको जब तीव्रता महसूस होती है तब बताने की सूचना दी जाएगी.

एक बिना धारवाला दबावयंत्र दबाव देने के लिए इस्तेमाल किया जायेगा. जब दबाव असुविधाजनक हो जाता है तभी आप अन्वेषक को बताइये ऐसे आपको पुछा जायेगा.

हम कुछ गायन करेंगे जो थोडीसी असुविधा निर्माण कर सकती है. परंतु अगर आप खुश नहीं है तो आप किसी भी वक्त वह बंद कर सकते हैं

हम एक चमड़ी ऊतकों की जाँच (biopsy) आपके हाथ और पैर में से ३ मिलिमीटर छेदक यंत्र से करेंगे.

हम आपको एक वैध प्रश्नावली का जवाब देने के लिए कहेंगे जिसका नाम है जनरल हेल्थ कुएर्शोनेर - १२, (सामान्य स्वास्थ्य प्रश्नावली)

इस अध्ययन में भाग लेने से क्या नुकसान और खतरे हैं:
इसका मुख्य नुकसान है कि आपको अपना साधारण १.५ घंटा इसमें भाग लेने के लिए देना पड़ेगा. विपरीत घटनाए घड़ने की संभावना नहीं है क्योंकि हम वैध पद्धती इस्तेमाल कर रहे है.

इस अध्ययन में भाग लेने से क्या लाभ हो सकते है?
अगर आप इस अध्ययन मे भाग लेते है तो आप हमे निरोगी स्वयंसेवकों का विवरण जमा करने में मदद करेंगे जिसे हम हमारे कुष्ठरोग सहभागी विवरण से तुलना कर सकेंगे. आपको कोई सीधा लाभ नहीं है.

अगर कुछ गलत हो गया तो?
क्वान्टीटेटीव्ह सँसरी टेस्टींग (QST) एक नियमित रोगविषयक और अन्वेषण की निपुणता है जिसका उपभोग हम हमारे और दूसरों की प्रयोगशाला में करते है. हमने अभी तक सैकड़ों लोगों में कोई विपरीत घटना देखी नहीं है. लन्दन स्कूल ऑफ़ हायजिन अॅण्ड ट्रॉपिकल मेडिसीन इस अध्ययन पे लागू होनेवाले बीमा युक्ति रखती है. अगर इस अध्ययन में भाग लेकर आपको कोई हानि या चोट पहुँचती है तो आप लन्दन स्कूल ऑफ़ हायजिन अॅण्ड ट्रॉपिकल मेडिसीन की गलती को साबित किये बगैर मुआवजा मांगने के लिए निर्वाच्य होते है.

Continue…

ये आपके मुआवज़ा मांगने के कानूनी हक़ को प्रभावित नहीं करता. अगर आपको किसीके लापरवाही के कारण नुकसान होता है तो आप कानूनी कार्यवाही कर सकते है. इसके बावजूद अगर आपको कोई तकरार या आपसे किये गए इस अध्ययन के दरम्यियान बर्ताव के बारे में चिंता हो तो आप तुरंत अन्वेषक डॉ. ओमर हारून, नंबर:
०७५३६१३६०२६/ देशीय नंबर: XXXX या ईमेल:
omer.haroon@lshtm.ac.uk से संपर्क कर सकते है. अगर आप फिर भी संतुष्ट नहीं है तो अप लन्दन स्कूल ऑफ़ हायजिन अँण्ड ट्रॉपिकल मेडिसीन के रोगविषयक परख (Clinical Trial) QA व्यवस्थापक से संपर्क कर सकते हैं.

क्या मेरी जानकारी गुप्त रखी जाएगी?

इस अध्ययन के दरमियान आपसे ली हुई सभी जानकारी सख्ती से गुप्त रखी जाएगी. इस अध्ययन की जानकारी गुप्त रूप में रखी जायेगी. पहले ये जानकारी BLP केंद्र में सुरक्षित कंप्यूटर में रखी जायेगी. इस ये गुप्त जानकारी LSHTM के महाविद्यालय के कंप्यूटरों को विश्लेषण के लिए भेजेगे और दूसरे कंप्यूटरों को जो तंत्रिकविकृति दर्द की जानकारी को इकट्ठा और इसका विश्लेषण करते है: ये लन्दन पेन कंसोर्टियम और जर्मन न्युरोपथीक पेन नेटवर्क के कंप्यूटर होंगे.

इस अध्ययन के अंतिम परिणाम का क्या होगा?

इस जानकारी से मिले अंतिम परिणाम QST को कुष्ठरोग में होनेवाले तंत्रिक विकृति दर्द को निदान करने का एक रोगविषयक साधन होने में मदद करेंगे. इससे होनेवाले QST IN LEP में अन्वेषक साधारण तरीके से शास्त्रीय पत्रिका में प्रकाशित होंगे और वृतिक सभा में प्रस्तुत किये जायेंगे. अगर आपको इन प्रकाशितों के बारे में जानना है तो हम इसकी व्यवस्था कर सकते है. प्रकाशितों में कोई जानकारी आपसे ली गयी है ये अभिज्ञेय नहीं होगा.

इस अध्ययन को किसने आयोजित किया और मूलधन किसने दिया है?

ये अन्वेषक क्लिनीकल रिसर्च डिपार्टमेन्ट, फैकलटी ऑफ ट्रॉपिकल अँण्ड इन्फेक्शियस डिझीज, लन्दन स्कूल ऑफ हायजिन अँण्ड ट्रॉपिकल मेडिसीन ने आयोजित किया है. हॉस्पिटल अँण्ड होम्स ऑफ सत.गिल्स(HHSG) इस अन्वेषक को मूलधन देनेवाला सेवागृह है.

इस अध्ययन का किसने निरीक्षण किया है?

इस अध्ययन को BLP केंद्र में करने की अनुमोदित नैतिक राय फौन्डेशन फॉर मेडिकल रिसर्च एथीक्स कमिटी (FMREC) अंक XXX और लन्दन स्कूल ऑफ़ हायजिन अँण्ड ट्रॉपिकल मेडिसीन एथिकल कमिटी अंक XXX ने दी है.

अधिक जानकारी के लिए संपर्क:

इस अध्ययन के बारे में अधिक जानकारी के लिए कृपया अध्ययन अन्वेषक डॉ. ओमर हारून नंबर:
+44(0) 07536136026/ 0091 9819079014
या
मैत्रेयी निगवेकर - नंबर: 0091 9820936534

Appendix 10. Healthy volunteer information sheet – Marathi version

अभ्यास सहभागी माहिती पत्रक
शीर्षक:कुष्ठरोगामध्ये होणाऱ्या चेतारुग्णी (neuropathic) वेदनांचा तपास करणारे नवे साधन: मुंबई, भारत येथील पथदर्शी अभ्यास

निरोगी स्वयंसेवकांसाठी क्वान्टिटेटिव्ह सेन्सरी टेस्टींग (QST) आणि त्वचा जीवोतक परीक्षा

संशोधन अभ्यासामध्ये सहभागी होण्याकरिता तुम्हांला येथे आमंत्रित केले गेले आहे. तुम्ही निर्णय घेण्याआधी, हे संशोधन का केले जात आहे व त्यामध्ये कोणत्या गोष्टी सामील आहेत हे तुम्हीं जाणून घेणे महत्वाचे आहे. कृपया खालील माहिती काळजीपूर्वक वाचा व गरज वाटल्यास इतरांशी चर्चा करा.

भाग १: इथे ह्या अभ्यासामागील हेतू तुम्हांला सांगितला आहे.
भाग २: इथे तुम्हांला हा अभ्यास कशा प्रकारे केला जाईल ह्याची तपशीलवार माहिती दिली गेली आहे. व तुम्हीं ह्यात सहभागी झाल्यावर काय घडेल हे सांगण्यात आले आहे.

तुम्हांला ह्यातील कोणतीही बाब न समजल्यास वा अधिक माहिती हवी असल्यास कृपया आम्हांला विचारा. तुम्हांला ह्यात सहभाग घ्यावयाचा आहे वा नाही हे ठरवण्यासाठी तुम्हीं तुमचा वेळ घ्या.

हे वाचल्याबद्दल तुमचे आभार.

भाग १
ह्या अभ्यासामागील उद्देश्य काय आहे ?

निरोगी माणसांमधील संवेदनात्मक तसज नोंदणी प्राप्त करणे हे ह्या अभ्यासामागील उद्देश्य आहे. तसेच ह्या नोंदणीमधून प्राप्त झालेली माहिती आम्हीं कुष्ठरोग व इतर अभ्यासांसाठी 'सामान्य मूल्य' पुरवण्यासाठी वापरू.

माझी निवड का करण्यात आली आहे ?

तुम्हीं पारोदर नाही आहात, वय वर्षे सोळा तुम्हीं ओलांडीले आहे आणि तुम्हांला खालील कुठलाही आजार नाही:

इथे दुखने
खालचे पाठीचे दुखणे
तीव्र किंवा जुनाट वेदना स्थिती

मला सहभाग घेणे जरुरीचे आहे काय ?
सहाभाग घ्यावयाचा किंवा नाही हे सर्वस्वी तुम्हांला ठरवायचे आहे. सहभाग घेण्याचे जर तुम्हीं ठरविले तर हा माहिती कागद तुम्हांला तुमच्याकडे ठेवण्यासाठी देण्यात येईल आणि सही करण्यासाठी तुम्हांला संमती प्रपत्र दिले जाईल. सहभाग घेण्याचा निर्णय घेतल्यावर देखील कोणत्याही क्षणी व कोणतेही कारण न देता नाव काढून घेण्याचे तुम्हांला स्वातंत्र्य आहे.

Continue…

भाग २

मी जर सहभाग घेण्याचे ठरवले तर माझे काय होईल ?

अभ्यासात भाग घेण्याचे तुम्ही ठरवले तर तुमच्या सोयीनुसार अन्वेषकाबरोबर तुमच्या भेटीची वेळ निश्चित केली जाईल. शक्य असल्यास QST मोजणीच्या २४ तास आधी कुठलेही वेदनानाशक औषध तुम्ही घेऊ नये असे आम्ही तुम्हांला सांगू. ह्या कालावधीत जर तुम्ही वेदनानाशक औषध घेतले तर कृपया संशोधन अन्वेषकाला तरी सांगा.

हात व पाय यांची संवेदनात्मक (sensory) गुणात्मक चाचणी व त्वचा जीवोतक परीक्षा
तुमच्या त्वचेतील संवेदनात्मक अज्जातंतूचे परीक्षण करण्याचा हा तपशीलवार अभ्यास आहे, ज्यातून तापमान, दाब, तीक्ष्णता आणि स्पर्श ह्यातील बदल शोधले जातात.
तापमान बदलणारे म्हणजेच थंड व गरम होणारे छोटे साधन तुमच्या त्वचेवर लावून तापमानातील बदल जाणून घेण्याची तुमची क्षमता मापली जाईल. तुम्हांला कुठलाही बदल जाणवला की सांगा अशी तुम्हांला सांगण्यात येईल.
हलका स्पर्श जाणून घेण्याची तुमची क्षमता अतिशय सूक्ष्म तंतू वापरून ठरवली जाईल. ह्या वेळी देखील तुम्हांला काही जाणवले की सांगा असे वीचान्यात येइल .

तीक्ष्णता समजून घेण्यासाठी जिच्यामुळे तुमच्या त्वचेला हानी पोचणार नाही अशे छोटे साधन तुमच्या त्वचेवर लावली जाईल. ज्यावेळी तुम्हांला तीक्ष्णता जाणवेल त्यावेळी सांगा असे तुम्हांला वीचान्यात येइल.

दबाव टाकण्यासाठी बोथट मापक वापरले जाईल. ज्या क्षणी दबाव असुखाकारक होऊ लागेल त्यावेळी तुम्ही ते सांगा असे तुम्हांला सांगितले जाईल.

जी मापने तुम्हांला थोडी अस्वस्थता आणेल अशी काही मापने देखील वापरली जातील. जर तुम्हाला परिक्षनात पुढे जायचे नसेल तर कृपया आम्हाला सांगा.

३ मिली मीटर छिद्रक त्वचा जीवोतक वापरून तुमचे हात आणि पाय ह्यांची त्वचा जीवोतक चाचणी देखील केली जाईल. आम्ही तुम्हांला वैध सामान्य आरोग्य प्रश्नावली १२ ची उत्तरे देण्याची देखील आम्ही तुम्हांला विनंती करू.

सहभाग घेण्यात काय धोके व त्याचे काय तोटे आहेत ?

तुम्हाला आम्हांला अंदाजे दीड तास थांबा लागेल हा सर्वात मोठा तोटा आहे. प्रतिकूल काही प्रसंग उद्भवेल ह्याची शक्यता नाही कारण आम्ही वैध पद्धती वापरीत आहोत.

सहभाग घेण्याचे फायदे काय आहेत ?

सहभाग घेऊन तुम्ही आम्हांला निरोगी स्वयंसेवक नियंत्रण माहिती गोळा करण्यास मदत करणार आहात. आम्ही ही प्रमाणानुसार संदर्भ माहिती, कुष्ठरोग सहभागी माहिती बरोबर तुलना करू शकू. तुम्हाला थेट फायदा नाही आहे.

Continue…

काही विपरीत घडले तर ?

ही चिकीत्सालयीन (clinical) आणि संशोधन यामधील नित्याची मापात्मक (qualitative) संवेदनात्मक (sensory) परीक्षा (QST) आहे. आजपर्यंत शेकडो लोकांच्या तपासणी वेळी काही विपरीत घडलेले नाही. लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल यांचे मेडिसिन विमा धोरण आहे जी ह्या अभ्यासामध्ये येते. ह्या अभ्यासामध्ये भाग घेताना जर तुम्हांला काही इजा झाली तर लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल ह्यांची काही चुकी झाली आहे हे सिद्ध न करता देखील तुम्ही त्या धोरणाचा फायदा घेण्यास पात्र ठरता.

भरपाई घेण्याच्या तुमच्या कायदेशीर हक्कांमध्ये कोणतीही बाधा येत नाही. कोणाच्या हलगर्जीपणामुळे तुम्हांला काही इजा पोहोचली तर तुम्ही कायदेशीर कारवाई करू शकता. तरी देखील तुम्हांला काही तक्रार करावयाची असेल किंवा तुमचे इथे उपचार चालू असताना जे तुम्हांला दिल्या जाणाऱ्या वागणुकीबाबत तुम्हांला काही तक्रार करावयाची असेल तर तुम्ही तात्काळ अन्वेषक (investigator) डॉ. ओ हरून, दूरध्वनी: ०७५३६१३६०२६/ स्थानिक क्र. XX किंवा इ मेल: omer.haroun@lshtm.ac.uk जर तुम्हांला मिळालेल्या प्रतिसादाबाबत तरी देखील तुम्ही समाधानी नसाल तर तुम्ही लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल मेडिसिन क्लिनिकल ट्रायल्स QA मॅनेजर ह्यांच्याशी संपर्क साधू शकता.

ह्या अभ्यासातील माझ्या सहभागाविषयी गुप्तता पाळली जाईल का ?

संशोधन चालू असताना जी माहिती गोळा केली जाईल ती पूर्णत: गुप्त राखली जाईल.

ह्या संशोधनातून मिळालेल्या निकालाचे पुढे काय होईल ?

ह्या माहिती साठ्याची अंतिम निष्पत्ती कुष्ठरोग संदर्भातील चिकित्सालयीन उपकरण म्हणून QST ची योग्यता जोखण्यासाठी करण्यात येईल.

संशोधनाला कोण आर्थिक सहाय्य करीत आहे व संशोधन कोण संपटीत करीत आहे ?

हे संशोधन क्लिनिकल रिसर्च डीपार्टमेंट, फॅकल्टी ऑफ ट्रॉपिकल अॅण्ड इन्फेक्शस डिझीझ, लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल मेडिसिन ह्यांनी संघटीत केला आहे.

दी हॉस्पिटल अॅण्ड होम्स ऑफ सेंट. गिल्स (HHSG) ह्या संशोधनाला अर्थसहाय्य करीत आहे.

ह्या संशोधनाचे समालोचन (review) कोणी केले आहे ?

फॉंडेशन मेडिकल रिसर्च एथिक्स कमिटी (FMREC) क्र. XX आणि लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल मेडिसिन एथिक्स कमिटी (LSHTM) क्र. XX ह्यांनी ब्ल्यू सेंटर मध्ये हे संशोधन होण्यास नीतीपूर्ण (ethical) मान्यता दिली आहे.

अधिक माहितीसाठी संपर्क साधा:

ह्या संशोधनासंबंधित अधिक माहितीसाठी कृपया अन्वेषक (investigator) डॉ. ओमर हरून दूरध्वनी क्र. ४४(०) ०७५३६१३६०२६ / स्थानिक क्र. 9819079014 किंवा पुढील पत्त्यावर इ मेल पाठवा: omer.haroun@lshtm.ac.uk

Appendix 11. Patient's recruitment in Hindi

रोगी भर्ती मापदंड:

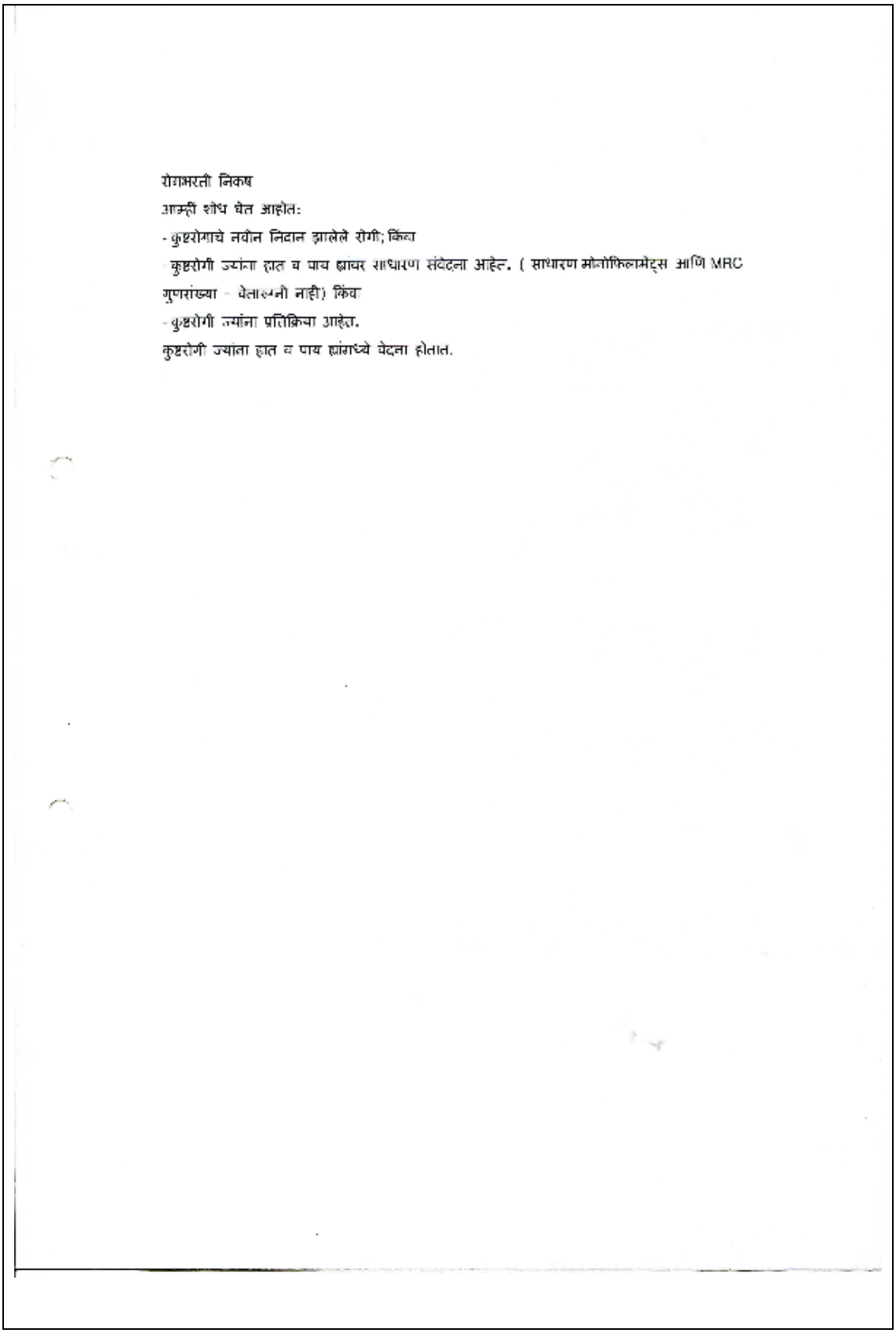
हमे इसकी तलाश है:

- कुष्ठरोग के नए निदान किये हुए या
- कुष्ठरोग के नए रोगी जिन्हें हाथ और पैर में साधारण संवेदन है

(साधारण मोनोफिलामेंट्स और MRC हिसाब - जिन्हें तांत्रिक विकृति नहीं है) **या**

- कुष्ठरोगी जिन्हें प्रतिक्रिया है **या**
- कुष्ठरोगी जिन्हें हाथ और पैर में दर्द है.

Appendix 12. Patient's recruitment in Marathi



रोगभरती निकष

आम्ही शोध चेत आहोत:

- कुष्ठरोगाचे नवीन निदान झालेले रोगी; किंवा

कुष्ठरोगी ज्यांना हात व पाय ह्यावर साधारण संवेदना आहेत. (साधारण मोनोफिलामेंट्स आणि MRC गुणसंख्या - चेतासंनी नाही) किंवा

- कुष्ठरोगी ज्यांना प्रतिक्रिया आहेत.

कुष्ठरोगी ज्यांना हात व पाय ह्यांमध्ये वेदना होतात.

Appendix 13. Patient information sheet

PATIENT INFORMATION SHEET

Information about a Research Project

Title: the development of new tools for the investigation of neuropathic pain in leprosy: a pilot study in Mumbai, India

Background:

Leprosy is a curable disease, but even so people with leprosy may develop pain, because leprosy may damage their nerves. Peripheral neuropathy may occur as a result of nerve damage, most often in the feet and hands, and changes the way that skin senses touch, temperature, pressure, and pain. One type of pain affecting leprosy people is called Neuropathic Pain.

Objective and methods:

Neuropathic pain is a common problem in leprosy. We would like to assess this pain among leprosy patients in India. This study is being undertaken by a researcher at London School of Hygiene and Tropical Medicine.

The main objective of the project is to develop a simple tool for the assessment of neuropathic pain in leprosy for future use in larger multi-centre studies. This study may help to treat the problem probably.

The Maharasha region of India was selected for this study because the record showed that there is increased number of leprosy patients. Bombay Leprosy Project (BLP) clinic is the leprosy referral centre for the Maharasha region.

You have been invited to take part in this study because you may have complications of leprosy. The study will involve an interview and clinical examination assessing your nerve function and your pain symptoms. These methods can tell us about the type of pain that you may be experiencing. Interviews will take place at the BLP clinic and are expected to last approximately two hours and 45 min.

Participations:

Your participation is entirely voluntary, and should you agree to take part you may withdraw at any time without given a reason. If you do not wish to take part it will not in any way affect your current treatment. Should you agree to participate, we would like to collect some routine information from your hospital notes. We shall ask you to answer validated pain questionnaires. We shall do a very thoroughly examination of your skin and nerves using qualitative sensory test, and if needed will do urine examination. We shall do skin biopsy from your lesion using 3 mm punch skin biopsy.

There are no risks to you in participating in this study. The study will not be of any direct benefits to you, but will provide important results as it will assess the neuropathic pain problem among leprosy patients in India. Such information can help doctors in deciding how best to treat pain and it is useful for researchers to understand and manage this chronic pain condition seen in leprosy patients and give an important contribution to care after cure.

Confidentiality:

All information that is collected about you during the course of the research will be kept strictly confidential. Data from this aspect of the study will be kept in an anonymous form and will be available only to the research workers listed below. Initially the information will be stored on secure computers at London School of Hygiene and Tropical Medicine. We will then send this anonymised data to the university computers for analysis and also include it in computer databases which are used to store and analyse data about neuropathy and pain; these are the London Pain Consortium and the German Neuropathic Pain Network databases. Please note that we intend to disseminate our final results to other researcher by publishing it in international journals, but we will not identify any of the participants by name, and therefore, we will maintain your privacy, and anonymity and confidentiality of information will be preserved.

Further information:

The project is funded by the Hospital and Homes of St. Giles (HHSG), a registered charity in UK. It is being conducted by Dr. Omer Haroun of London School of Hygiene & Tropical Medicine, and is supervised by Professor Diana Lockwood (Chief consultant, LSHTM). And collaborators from the BLP and the Foundation for Medical Research (FMR) India, Professor Andrew Rice (Imperial Collage London), Dr David Bennett, Kings College London (KCL) and the German Network on Neuropathic Pain (DFNS); Professor Christoph Maier and Professor Rolf-Detlef Treede.

This study has been reviewed and approved by the Ethical Review Committee in India (IERC), number XXX and LSHTM Research Ethics Committee number XXX; contact person is Professor Andy Hall, email address: ethics@lshtm.ac.uk.

Contact for further information:

Should you have any questions that are not answered here or require any further information or explanation, please contact Dr. Omer Haroun at the address below

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Thank you for taking time to read this information leaflet. If you think you will take part in the study please read and sign the consent form.

Appendix 14. Patient information sheet – Hindi version

रुग्ण जानकारी पत्र
अन्वेषण अध्ययन के बारे में जानकारी.

परियोजनाका नाम: कुष्ठरोग में होनेवाले तंत्रिकविकृति दर्द को जाँचने के लिए नया साधन तैयार करना: मुंबई, भारत में मार्गदर्शक जाँच

पृष्ठभूमि: (background)

कुष्ठरोग एक इलाज होनेवाला रोग है, परन्तु जिन्हें कुष्ठरोग हुआ है उन्हें कभी कभी दर्द हो सकता है क्योंकि ये रोग नसों को नुकसान पहुँचाता है. नसो के नुकसान के कारण परिधीय (peripheral) तंत्रिक विकृति हाथ और पैरों में निर्माण हो सकती है, और ये त्वचा कि स्पर्श, तापमान, दबाव और दर्द की समझ बदल सकता है. एक प्रकार का दर्द जो कुष्ठरोगियों को होता है उसे तंत्रिकविकृति दर्द कहते है.

उद्देश्य और ढंग:

तंत्रिकविकृति दर्द कुष्ठरोग में एक सामान्य समस्या है. हमें ये दर्द भारत के कुष्ठरोगियों में जाँचना है. ये अध्ययन लन्दन स्कूल ऑफ हायजीन अॅन्ड ट्रॉपीकल मेडिसीन के एक अन्वेषक ने शुरू किया है. इस अध्ययन का मुख्य उद्देश्य कुष्ठरोग में होनेवाले तंत्रिक विकृति दर्द को जाँचने के लिए साधारण साधन तैयार करना है जिसका भविष्य में विशाल रूप से उपयोग हो सके. ये अध्ययन शायद इस समस्या के उपचार में मदद करेगा.

इस अध्ययन के लिए भारत में महाराष्ट्र प्रदेश चुना गया क्योंकि दस्तावेज (record) दिखाते हैं कि कुष्ठरोगों का प्रमाण बढ़ रहा है. मुंबई के लिए मुंबई लेप्रसी प्रोजेक्ट चिकित्सालय कुष्ठरोग संप्रेषण केंद्र है. आपको इस अध्ययन में भाग लेने के लिए आमंत्रित किया गया है क्योंकि कुष्ठरोग के कारण आपको उलझने हो सकती है. इस अध्ययन में आपकी मुलाकात और रोगविषयक जाँच की जाएगी जिससे आपके नस कृत्य (nerve functor) और आपके दर्द के लक्षण, आकलन होंगे. आपको किस प्रकार का दर्द हो रहा है वह ये जाँच हमें बता सकेगी. मुलाकाते और परिक्षण फौंडेशन फॉर मेडिकल रीसर्च चिकित्सालय में की जायेंगी और लगभग चार घंटे पैंतालीस मिनट चलेंगे.

सहयोग:

आपका सहयोग पूर्ण तरीकेसे स्वैच्छिक है. आप सहमति देने के बाद में भी, कभीभी बिना कारण दिए वापस जा सकते है. अगर आप सहभाग नहीं लेना चाहते तो भी आपके चालू इलाज पर कोई असर नहीं पड़ेगा. अगर आप सहभाग लेने का निर्णय लेते है तो हम आपके अस्पताल की जानकारी से कुछ सामान्य जानकारी लेंगे. हम आपको दर्द के वैध प्रश्नावली भरने के लिए पूछेंगे. हम आपके त्वचा और नस की पूरी तरह से क्वान्टीटेटीव्ह सँसरी टेस्ट और मूत्र परीक्षा करेंगे. हम आपकी त्वचा ऊतकों (Biopsy) की जाँच तीन मिलीमीटर के छेदक यंत्र से करेंगे.

इस अध्ययन में सहयोग लेने के कोई खतरें नहीं है. ये अध्ययन आपके लिए कोई सीधे फायदेमंद नहीं है, परन्तु आप भारत में जो कुष्ठरोग में होनेवाले तंत्रिकविकृति दर्द के गराले का हल निकालने में मदद करेंगे. इस प्रकार की जानकारी, डाक्टरोंको को इस दर्द को बहतो अच्छे तरीके का उपचार करने में मदद कर सकती है. अन्वेषको के लिये ये जानकारी महत्वपूर्ण है क्योंकि वह इस दर्द को समझ सकते है और ये स्थायी दर्द जो कुष्ठरोगों में देखी जाती है इसके इलाज के बाद के देखभाल में एक महत्वपूर्ण योगदान कर सकते है.

Continue…

गोपनीयता:

इस अध्ययन के दरमियाँ आपसे पायी हुई सब जानकारी सख्ती से गुप्त रखी जाएगी. इस अध्ययन की जानकारी गुप्त रूप में रखी जायेगी और सिर्फ नीचे लिखे गए अन्वेषकों को उपलब्ध होगी. शुरू में ये जानकारी लन्दन स्कूल ऑफ़ हायजिन अॅन्ड ट्रॉपिकल मेडिसीन में सुरक्षित कंप्यूटरों में रखी जायेगी. हम ये गुमनाम जानकारी महाविद्यालय के कंप्यूटरों को और जो कंप्यूटर तंत्रिकविकृति दर्द की जानकारी को रखते है और विश्लेषण करते है उन्हें भेजेंगे: ये लन्दन पेन कंसोर्टियम और जर्मन न्युरोपथीक पेन नेटवर्क के कंप्यूटर होंगे. कृपया ये ध्यान में रखे कि हमारे अंतिम परिणाम हम दुसरे अन्वेषक को अंतरराष्ट्रीय पत्रिका में प्रकाशित करने के लिए भेजेंगे, परन्तु हम किसी भी सहभागी को नाम से नहीं पहचानेंगे और इस तरह हम आपकी गोपनीयता, और गुमनामी सुरक्षित रखेंगे.

अधिक जानकारी:

इस परियोजना का पैसा हॉस्पिटल अॅन्ड होम्स ऑफ़ सैंट.गिल्स (HHSG) जो युनायटेड किंगडम की एक पजीकृत हुई सेवायह है. ये अध्ययन लन्दन स्कूल ऑफ़ हयजीन हायजिन अॅन्ड ट्रॉपिकल मेडिसीन के डॉ. ओमर हारुन कर रहे है और इसका निरीक्षण प्राध्यापिका डागना लोकवूड (मुख्य सलाहकार, LSHTM) कर रही है. इस अध्ययन में बॉम्बे लेप्रसी प्रोजेक्ट और फौन्डेशन फॉर मेडिकल रिसर्च (FMR), भारत, प्राध्यापक अॅन्डरु राईस (ईम्पीरिअल कॉलेज लन्दन), डॉ. डेविड बेनेट, किंग्स कॉलेज लन्दन (KCL) और जर्मन नेटवर्क ऑन न्युरोपथीक पेन (DFNS); प्राध्यापक क्रिस्टोफर मायर और प्राध्यापक रोल्फ - देतलेफ ट्रीड सहयोगी है.

ये अध्ययन को एथीकल रिव्हू कमिटी इन इंडिया (IERC), अंक XXX और लश्तम रिसर्च कमीटी अंक XXX ने निरीक्षण और अनुमोदित किया गया है और संपर्क साधने के लिए प्राध्यापक अॅन्डरु राईस, ईमेल पता है: ethics@lshtm.ac.uk.

अधिक जानकारी के लिए संपर्क:

अगर आपके किसी प्रश्नों का जवाब आपको नहीं मिला है या आप अधिक जानकारी चाहते है, तो कृपया नीचे दी गए पते पर डॉ. ओमर हारुन से संपर्क कीजिये.

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या

डैडेरी बिगवेकर - नंबर - ००९१ ९८२०९३६५३४

इस जानकारी पत्र को पढने के लिए वक्त निकालने के लिए शुक्रिया. अगर आपको इस अध्ययन में भाग लेना है तो कृपया सहमति पत्र पढ़िए और उसपर दस्तखत कीजिये.

Appendix 15. Patient information sheet – Marathi version

Patient Information Sheet

शीर्षक: कुष्ठरोगात होणाऱ्या वेदनांची चेतारुग्णी (neuropathic) करण्याऱ्या नव्या साधनांतील प्रगती : मुंबई, भारत येथील मार्गदर्शी अभ्यास

पार्श्वभूमी:
ह्या संशोधनाचे मुख्य उद्देष्ट्य असे आहे की, कुष्टरोग एक बरा होण्यासारखा रोग आहे. परंतु, कुठरोगमुळे माणसाला वेदना सुरु होऊ शकतात कारण त्यांच्या मज्जातंतूंना नुकसान पोहोचलेले असते.
मज्जातंतूंचे नुकसान झाल्याकारणाने बहुधा पाय व हात ह्यांना Peripheral neuropathy (परिसराचे) उद्भवू शकते. आणि त्यामुळे तापमान, दाब आणि वेदना ह्या न्यानौन्दर्य संबंधातील त्वचेच्या जागीना बदलू शकतात. कुष्ठरोग्यांना होणाऱ्या वेदनेच्या एका जाणीवेला चेतारुग्णी (न्यूरोपाथिक) वेदना असे संबोधले जाते.

उद्दिष्ट आणि पद्धती: चेतारुग्णी वेदना ही कुष्ठरोगामधील एक सामान्य समस्या आहे. आम्ही, भारतातील कुष्ठरोग्यांमधील ह्या वेदनेचे मुल्यांकन करू इच्छितो. लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल मेडिसिन ह्यामधील अन्वेशाकाने हे संशोधन अंगीकृत केले आहे. (हाती घेतले आहे)
कुष्ठरोगामधील चेतारुग्णी (न्यूरोपाथिक) वेदनांचे मूल्यमापन करण्यासाठीचे साधन उपकरण विकसित करणे हे ह्या संशोधनाचे मुख्य उद्दिष्ट्य आहे. बहुधा हे संशोधन समस्येला उपचार करण्यास मदत करेल.
भारतातील महाराष्ट्र प्रदेशामधे कुष्ठरोगात वाढ झालेली दिसून आल्याकारणाने संशोधनासाठी हा प्रदेश निवडला गेला. Bombay Leprosy Project (प्रकल्प) हे महाराष्ट्र विभागातील संदर्भित केंद्र आहे. संशोधनाकरीता तुम्हांला आमंत्रित केले गेले आहे कारण कदाचित तुमच्यामध्ये कुष्ठरोगाची वेदनासंकुलना (complication) असू शकते. ह्यामध्ये तुमची मुलाखत. तुमच्या मज्जातंतूंची कार्यपद्धतीचे मोजमाप व तुमची वेदना लक्षणे ह्यांचा समावेश असेल. ही पद्धती तुम्हांला ज्या वेदना होत आहेत त्यांचा प्रकार ओळखण्यास आम्हांला मदत करेल. मुलाखती अदमारे २ तास ४५ मिनिटे चालतील व परिक्षनाला ३ तास लागेल.

सहभाग:
तुमचा सहभाग हा पूर्णत: ईच्छिक आहे आणि कोणतेही कारण न देता तुम्ही कधीही ह्यातून आपला सहभाग काढून घेऊ शकता. तुम्ही तुमचा सहभाग काढून घेतला तरीही तुमच्या सध्या चालू असलेल्या उपचारामध्ये कुठल्याही प्रकारची बाधा येणार नाही. तुम्ही सहभागी होण्याची परवानगी दिल्यानंतर तुमच्या रुग्णालयातील नोंदीमधून काही नेहेमीची माहिती आम्ही घेऊ इच्छितो. तुलच्या वेदनेबाबत आम्ही तुम्हांला काही वैध (validated) प्रश्न विचारू. संवेदनात्मक (sensory) गुणात्मक चाचणी वापरुन आम्ही तुमची त्वचा व तुमच्या मज्जातंतू ह्यांची कसून पहाणी करू, व गरज पडल्यास लघवी परीक्षा (तपासणी) करू. क्षत स्थळावर (lesion) त्वचा जीवोतक छिद्रक वापरून आम्ही तुमची त्वचा जीवोतक परीक्षा (biopsy) करू (चमडिचा तुकडा घेऊ).

Continue…

ह्या संशोधनामध्ये सहभागी होण्यात कोणत्याही प्रकारचा तुम्हाला धोका नाही. ह्यातून तुम्हांला कोणत्याही प्रकारचा प्रत्यक्ष फायदा नसला तरीही ह्या परिक्षनामुळे पुढच्या कुष्ठरोगींना मदत होउ शकते. ह्या संशोधनामुळे वेदनांवर सर्वात चांगल्या पद्धतीने कोणते उपचार केले जावेत ह्या संबधातील निर्णय घेण्यास डॉक्टरांना मदत होऊ शकेल. तसेच संशोधकांस ह्या कुष्ठरोगांमधील दीर्घकालीन (जुनाट-chronic) वेदना स्थिती समजून घेण्यास व त्यांना ताब्यात ठेवण्यावरील अभ्यास करण्यास मदत करू शकेल. बरे झाल्यानंतर घेण्यात येणारी खबरदारी (care) विषयक अभ्यासात हा तुमचा फार महत्त्वचा हातभार (योगदीक्षा) ठरेल.

गोपनीयता:
संशोधन करीत असता मिळालेली तुमच्याविषयक संपूर्ण माहिती ही काटेकोरपणे गुप्त राखली जाईल.

अधिक माहिती:
ह्या प्रकल्पाला युनायटेड किंगडममधील नोंदणीकृत धर्मादाय, हॉस्पिटल्स अॅण्ड होम्स ऑफ सेंट. गिल्स (HHSG) ह्यांचे आर्थिक पाठबळ लाभले आहे. लंडन स्कूल ऑफ हायजीन अॅण्ड ट्रॉपिकल मेडिसिन येथील डॉ. ओमर हरून हे हा प्रकल्प चालवणार आहेत व प्राध्यापक डायना लॉकवूड ह्यांचे पर्यवेक्षण असेल. आणि BPL आणि फौंडेशन फॉर मेडिकल रिसर्च (FMR) भारत, प्राध्यापक अॅण्ड्रू राईस (इम्पेरिअल कॉलेज लंडन). डॉ. डेव्हिड वेनेट, किंग्स कॉलेज लंडन (KCL), द जर्मन नेटवर्क ऑन न्यूरोपथिक पेन (DFNS); प्राध्यापक क्रिस्तोफ मेयात आणि प्राध्यापक रॉल्फ-डेटलेफ ट्रीड ह्यांचा सहभाग असेल.
ह्या अभ्यासास एथिकल रेव्ह्यू कमिटी इन इंडिया, क्र. XXX आणि LSHTM रिसर्च एथिक्स कमिटी क्र. XXX, ह्यांनी समालोचन (review) करून संमती दिली आहे. संपर्क करिण्यासाठी प्राध्यापक अॅण्डी हॉल, इ-मेल पत्ता: ethics@lshtm.ac.uk.

अधिक माहितीसाठी स्पर्क साधा:तुमच्या कोणत्याही प्रश्नांना येथे उत्तर दिले गेले नसेल किंवा तुम्हाला काही अधिक माहिती वा स्पष्टीकरण हवे असेल तर कृपया खालील पत्त्यावर डॉ. ओमर हरून ह्यांच्याशी संपर्क साधा.

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तुम्ही पेज वाढून हे माहितीपत्रक वाचले ह्याबद्दल धन्यवाद. ह्या संशोधनात तुम्ही जर सहभागी होऊ इच्छित असाल तर कृपया संमती पत्रक वाचा व त्यावर सही करा.

Appendix 16. Healthy volunteer consent form

Consent form

Imperial College London

CONSENT FORM FOR HEALTHY VOLUNTEER

ICERC Number: xxx

Healthy Volunteer Quantitative Sensory Testing (QST)

Chief investigators: Prof Andrew Rice Professor Diana Lockwood
Study organizer: Dr O Haroun

Please initial the boxes next to statements you are in agreement with.

	Please initial Box
1. I confirm that I have read and understood the participant information sheet dated ……..…version ……..…for the above study, and I have had the opportunity to ask questions which have been fully answered.	☐
2. I understand that my participation is voluntary and I am free to withdraw at anytime, without my medical care or legal rights being affected.	☐
3. The compensation regulations have been discussed with me.	☐
4. I agree to take part in this research study	☐

.....	.....	.....
Name of participant	Signature	Date
.....	.....	.....
Name of Person taking consent (If not the Principle investigator)	Signature	Date
.....	.....	.....
Principle Investigator	Signature	Date

1 copy for patient and 1 copy for principle investigator

Appendix 17. Healthy volunteer consent form – German version

Prof. Dr. med. R.-D. Treede
Lehrstuhl für Neurophysiologie
Zentrum für Biomedizin und Medizintechnik Mannheim
Medizinische Fakultät Mannheim
der Universität Heidelberg
Ludolf-Krehl-Str.13-17
68167 Mannheim

Deutscher
Forschungsverbund
Neuropathischer
Schmerz

Einverständniserklärung

Ich, _____ , wurde vollständig über Art, Umfang und Bedeutung der klinischen Studie:

Untersuchung der Funktion und Eigenschaften des somatosensorischen Nervensystems mit Hilfe der quantitativen sensorischen Testung (QST)
im Rahmen des Deutschen Forschungsverbundes Neuropathischer Schmerz (DFNS)

aufgeklärt. Ich hatte die Möglichkeit, den aufklärenden Arzt _____ ausführlich zu befragen.

Dabei wurden u.a. Studienziel und Studienlänge, studienbedingte Erfordernisse und mögliche Nebenwirkungen der Studienbehandlung besprochen. Die Probandeninformation sowie ein Exemplar der Einverständniserklärung habe ich gelesen und verstanden sowie eine Kopie von beidem erhalten. In diesem Zusammenhang bestehende Fragen wurden besprochen und beantwortet. Ich hatte ausreichend Zeit, mich für oder gegen eine Teilnahme an dieser Studie zu entscheiden. Über die vorliegende Probandenversicherung wurde ich informiert, ein Auszug aus den Allgemeinen Versicherungsbedingungen wurde mir ausgehändigt.

Ich bestätige durch meine Unterschrift, dass ich mich mit der vorgenannten Prüfung und ihrer Durchführung einschließlich der dafür notwendigen ärztlichen Untersuchungen einverstanden erkläre.

Ich bin mit der im Rahmen der Studie erfolgenden Aufzeichnung von personenbezogenen Untersuchungsdaten, auch in elektronischer Form, und ihrer Weitergabe sowie Verarbeitung in anonymisierter Form im Rahmen des Deutschen Forschungsverbundes Neuropathischer Schmerz (DFNS) entsprechend der Probandeninformation einverstanden. Alle im Rahmen dieser Studie erhobenen Daten unterliegen der ärztlichen Schweigepflicht und werden vertraulich gemäß dem Datenschutz behandelt. Das zugehörige Kapitel "Datenverarbeitung und Datenschutz" (Seite 3 der Probandeninformation zu dieser Studie) habe ich gelesen und stimme dem beschriebenen Vorgehen zu.

Ich weiß, dass diese Studie in erster Linie der medizinischen Wissenserweiterung dient und gegebenenfalls keinen persönlichen Vorteil für mich bringen kann.
Ebenso weiß ich, dass meine Teilnahme freiwillig ist und ich jederzeit meine Einwilligung ohne Angabe von Gründen widerrufen kann, ohne dass in irgendeiner Weise ein Nachteil für mich entsteht. Ich kann die Untersuchung jederzeit abbrechen. Auch der Arzt kann aufgrund seiner ärztlichen Erfahrung die Prüfung jederzeit beenden.

Ort, Datum Unterschrift des Probanden

Ort, Datum Unterschrift des Arztes

Appendix 18. Healthy volunteer consent form – Hindi version

निरोगी स्वयंसेवकों के लिए सहमति पत्र :

नैतिक अनुमोदन अंक:

परियोजना का नाम: कुष्ठरोग में होनेवाले तंत्रिक विकृति दर्द को जॉचने के लिए नया साधन तैयार करना: मुंबई, भारत में मार्गदर्शक जाँच

निरोगी स्वयंसेवक क्वान्टीटेटीव्ह सैंसरी टेस्टींग और चमड़ी ऊतकों की जाँच (biopsy)
प्रमुख अन्वेषक: प्रोफ. डायना लॉकवूड, प्रोफ. आन्द्रू राईस और डॉ.वनजना शेट्टी

अन्वेषक का नाम: डॉ. ओमर हरून

कृपया इस भाग में आपके आद्याक्षर लिखकर नीचे दस्तखत कीजिये.

1) मैं ये सहमति देता/देती हूँ कि मैंने पढ़ा है या मुझे अर्थ बताया गया है और मैं ये जानकारी पत्र दिनांक ..... वृतान्त ..... समझता/समझती हूँ और मुझे इस अध्ययन की एक प्रतिलिपि रखने के लिए दी जाएगी. मुझे ये जानकारी समझाने के लिए और प्रश्न पूछने के लिए मौका दिलाया गया और मेरे प्रश्नों के उत्तर संतोषजनक ढंग से दिए गए है. ☐

२) मैं ये समझता/समझती हूँ कि मेरा सहभाग स्वैच्छिक है और मैं बिना कारण दिए जब चाहे वापसी ले सकता/सकती हूँ और मेरे चिकित्सक या कानूनी अधिकारों पर कोई असर नही होगा. ☐

३) मुझे मुआवजों के नियम समझाए गए है. ☐

४) मैं अन्वेषण समूह को चमड़ी ऊतकों के दो जांच करने की सहमति देता/देती हूँ. ☐

५) मैं मेरा मांसतंतु फौन्डेशन फॉर मेडिकल रिसर्च और किंग्स कॉलेज लन्डन, यूनाइटेड किंगडम में विश्लेषण और बचाए रखने के लिए अनुमति देता/देती हूँ. ☐

६) मैं इस अन्वेषण अध्ययन में भाग लेने के लिए अनुमति देता/देती हूँ. ☐

सहभागी का नाम	दस्तखत	दिनांक
सहमति लेनेवाले का नाम	दस्तखत	दिनांक
प्रमुख अन्वेषक	दस्तखत	दिनांक

Appendix 19. Healthy volunteer consent form – Marathi version

निरोगी स्वयंसेवकांसाठी संमती प्रपत्र

नीतीपूर्ण अनुमती अंक:

प्रकल्प शीर्षक: कुष्ठरोगात होणाऱ्या वेदनांची चेतारुग्णी (neuropathic) करण्याऱ्या नव्या साधनांतील प्रगती : मुंबई, भारत येथील मार्गदर्शी अभ्यास

निरोगी स्वयंसेवकांसाठी क्वान्टिटेटिव्ह सेन्सरी टेस्टींग (QST) आणि त्वचा जीवोतक परीक्षा

प्रमुख अन्वेषक: प्रा. डायना लॉकवूड, प्रा. ॲण्ड्रू राइस आणि डॉ. वनजा शेट्टी
संशोधकाचे नाव: डॉ. ओमर हरून

कृपया तुमची संमती असलेल्या निवेदनापुढील चौरसांमध्ये तुमची आद्याक्षरे भरा.

१) मी ही खात्री देते/देतो की मी सहभागी होण्याबाबतचे हे माहिती पत्र दिनांक .....वाचले आहे, किंवा मला समजावले गेले आहे, आणि मला, रुपांतर..... कळले आहे, त्याची प्रतिलिपि मला देण्यात आली आहे. मला ह्या माहितीवर विचार करण्यासाठी, प्रश्न विचारण्यासाठी संधी दिली गेली आहे आणि माझ्या प्रश्नांना समाधानकारक उत्तरे दिली गेली आहेत. ☐

२) मला समजावण्यात आले आहे की माझा सहभाग ऐच्छिक आहे आणि मी कधीही कारण न देता माघार घेऊ शकते/शकतो व त्यामुळे माझ्या वैद्यकीय आणि कायदेशीर हक्कांवर काही परिणाम होणार नाहीत. ☐

3) मोबदल्याचे नियंत्रण माझ्याबरोबर मला समजावले गेले आहेत. ☐

४) मी अध्ययन संघला दोन चामडीचे जीवोतक परीक्षा करायला अनुमति देते. ☐

५) मी माझं ऊति फौन्देशन ऑफ़ मेडिकल रीसर्च आणि किंग्स कॉलेज लन्दन,युनायटेड कींगडम, ह्याना विश्लेषण आणि साठवन्यासाठी परवानगी देते. ☐

६) मी या संशोधनात भाग घ्यायला सहमती देते. ☐

सहभागी व्यक्तीचे नाव	सही	दिनांक
संमती घेणाऱ्या व्यक्तीचे नाव	सही	दिनांक
प्रमुख अन्वेषक	सही	दिनांक

ह्या संशोधनामध्ये सहभागी होण्यासाठी मी माझी अनुमती देत आहे.

Appendix 20. Patient consent form

Patient's consent form For Ethical approval **Bombay leprosy centre _ BLP India**

CONSENT FORM

Title of Project: The development of new tools for the investigation of neuropathic pain in leprosy: a pilot study in Mumbai, India

Name of Researcher: Dr Omer Haroun

Chief investigators: Prof Diana Lockwood, Prof A. Rice and Dr Vanaja Shetty

Please complete this section by initialling the boxes and then signing at the bottom

Patient consent to study protocol		
1.	I confirm that I have read, or had explained to me, and understand the information sheet dated _____ version_____ concerning the above study and have been given a copy to keep. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at anytime, without giving any reason, without my medical care or legal rights being affected	☐
3.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from LSHTM or pain research team. I give permission for these individuals to access my records.	☐
4.	I agree with the study team that skin biopsies being taken.	☐
5.	I agree for my tissue to be analysed and stored at Foundation for Medical Research (FMR) India and King's College London, London, UK.	☐
6.	I agree to take part in this research study.	☐

.....	.....	.....
Name of participant	**Signature**	**Date**
.....	.....	.....
Name of Person taking consent (If not the Principle investigator)	**Signature**	**Date**
.....	.....	.....
Principle Investigator	**Signature**	**Date**

1 copy for participant; 1 copy for Principle Investigator; 1 copy to be kept with BLP notes

Version v2.0 08.02.12

Appendix 21. Patient consent form – Hindi version

सहमति पत्र

परियोजना का नाम: कुष्टरोग में होनेवाले तंत्रिक विकृति दर्द को जाँचने के लिए नया साधन तैयार करना: मुंबई, भारत में मार्गदर्शक जाँच

अन्वेषक का नाम: डॉ. ओमर हरून
प्रमुख अन्वेषक: प्रोफ. डायना लौकवूड, प्रोफ. आन्द्रू राईस और डॉ. वनजना शेट्टी

कृपया इस भाग में आपके आद्याक्षर लिखकर नीचे दस्तखत कीजिये.

रुग्ण सहमति पत्र

1) मैं ये सहमति देता/देती हूँ कि मैंने पढा है या मुझे अर्थ बताया गया है और मैं ये जानकारी पत्र दिनांक ..... वृतान्त ..... समझता/समझती हूँ और मुझे इस अध्ययन की एक प्रतिलिपि रखने के लिए दी जाएगी. मुझे ये जानकारी समझने के लिए और प्रश्न पूछने के लिए मौका दिलाया गया और मेरे प्रश्नों के उत्तर संतोषजनक ढंग से दिए गए है. ☐

२) मैं ये समझता/समझती हूँ कि मेरा सहभाग स्वैच्छिक है और मै किसी भी वक्त बिना कारण दिए वापसी ले सकता/सकती हूँ और मेरे चिकित्सक या कानूनी अधिकारों पर कोई असर नहीं होगा. ☐

३) मैं ये समझता/समझती हूँ की इस अध्ययन के दरमियान मेरे इकट्ठे किये हुए चिकित्सक व्याख्या के उचित भाग और दी हुयी सामग्री सिर्फ जिम्मेदार LSHTM के व्यक्ति या अन्वेषण समुह देखेंगे. मैं इन व्यक्तियोंको मेरे अभिलेख अभिगम करने की अनुमति देता/देती हूँ. ☐

४) मैं अन्वेषण समूह को चमड़ी की जीवित ऊतकों की जाँच करने की सहमति देता/देती हूँ. ☐

५) मैं मेरा मांसतंतु फौन्डेशन फॉर मेडिकल रिसर्च और किंग्स कॉलेज लन्दन, यूनाइटेड किंगडम में विश्लेषण और बचाए रखने के लिए अनुमति देता/देती हूँ. ☐

६) मैं इस अन्वेषण अध्ययन में भाग लेने के लिए अनुमति देता/देती हूँ. ☐

सहभागी का नाम	दस्तखत	दिनांक
सहमति लेनेवाले का नाम	दस्तखत	दिनांक
प्रमुख अन्वेषक	दस्तखत	दिनांक

Continue…

मैं ये सहमति देता/देती हूँ की मैंने मेरी तस्वीर लेने की अनुमति दी हुई है.

मैं समझता/समझती हूँ की इस सामग्री को शिक्षासंबंधी मूल्य है.
मैं ये सामग्री समुचित व्यवसायी कर्मचारी और शिक्षासंबंधी प्रकाशित ग्रंथ, दैनिक पत्र, अध्ययन - पुस्तक और दुनियाभर की अन्य रूप या माध्यम में, हर तरह के इलेक्ट्रोनिक प्रकाशितों में वितरित किये जाने की अनुमति देता/देती हूँ.
इस कारण मैं ये समझता/समझती हूँ की ये सामग्री सामान्य जनता को दिखाई जा सकती है.
इसमें से सब या कुछ सामग्री अन्य तस्वीर,चित्र, वीडियो टेप, ध्वनीलेखन या अन्य रूप के चित्र के साथ इस्तेमाल किये जाएंगे.

मेरी पहचान गुप्त रखने का प्रयास किया जाएगा परंतु इसकी कोई गारन्टी नहीं है.

सहभागी का नाम दस्तखत दिनांक

Appendix 22. Patient consent form – Marathi version

संमती प्रपत्र

प्रकल्पाचे नाव: कुष्ठरोगात होणाऱ्या चेतारुग्णी (neuropathic) वेदनांचा तपास करण्याऱ्या नव्या साधनातील प्रगती : मुंबई, भारत येथील मार्गदर्शी अभ्यास

संशोधकाचे नाव: डॉ. ओमर हरून

प्रमुख अन्वेषक: प्राध्यापक डायना लॉकवूड, प्राध्यापक अँण्ड्रू हाईस आणि डॉ. वनजा शेट्टी

कृपया चौरस भरून प्रपत्र पूर्ण भरा आणि सर्वात शेवटी सही करा.

खऱ्याच्या मूळ नोंदी अभ्यास करण्यासाठी संमती:

१) मी ही खाली देते/देतो की ही या तपशीलाणीवरून वाचले आहे, किंवा मला समजावले गेले आहे, आणि मला हे माहितीपत्र, दिनांक ..... रुपांतर..... कलले आहे, त्याची सबकल मला देण्यात आली आहे. मला या माहितीवर विचार करण्यासाठी, प्रश्न विचारण्यासाठी संधी दिली गेली आहे आणि माझ्या प्रश्नांना समाधानकारक उत्तरे दिली गेली आहेत. ☐

२) मला समजावण्यात आले आहे की माझा सहभाग ऐच्छिक आहे आणि मी कधीही कारण न देता माघार घेऊ शकते/शकतो व त्यामुळे माझ्या वैद्यकीय आणि कायदेशीर हक्कांवर काही परिणाम होणार नाहीत. ☐

३) मला समजावण्यात आले आहे की माझी वैयक्तीय नोंदणी आणि जमा केलेली माहिती LSHTM च्या जबाबदार व्यक्ति किंवा वेदना संशोधन संघ/पथक सबतील. मी या व्यक्तींना माझी माहिती वापरण्यासाठी परवानगी देते/देतो. ☐

४) मी त्वचेच्या जीवोतक परीक्षेसाठी अनुमति देते/देतो. ☐

५) फॉन्डेशन ऑफ मेडिकल रिसर्च अँन्ड किंग्स कॉलेज लंडन, युनायटेड किंग्डम, यांना माझ्या ऊति, विश्लेषण आणि साठवण्यासाठी मी परवानगी देते/देतो. ☐

६) मी या संशोधनात भाग घेण्यास सहमती देते/देतो. ☐

Continue…

सहभागी व्यक्तीचे नाव सही दिनांक

संमती घेणाऱ्या व्यक्तीचे नाव सही दिनांक

प्रमुख अन्वेषक सही दिनांक

माझे फोटो काढण्यासाठी मी माझी परवानगी दिली आहे ह्याला मी येथे अनुमती देत आहे.
योग्य व्यावसायिक कर्मचारी वर्गामध्ये साहित्य दाखवले जाईल आणि शैक्षणिक प्रकाशने, नियतकालिके, पाठ्यपुस्तके, तसेच इतर माध्यमांमध्ये, कम्प्यूटरशी संबंधित इतर प्रकाशने, ह्यांमध्ये हे साहित्य प्रकाशित केले जाईल व जगभर कुठेही ह्याचे वितरण होईल ह्यासाठी मी माझी अनुमती देत आहे.
मला हे माहित आहे की त्यामुळे सर्वसाधारण लोकांच्या नजरेत हे साहित्य येऊ शकेल.
इतर छायाचित्रे, रेखाचित्रे, व्हिडीयोटेप इमेजेस, ध्वनिमुद्रण, किंवा चित्राचे इतर प्रकार ह्यांमध्ये ह्यातील काही भाग वा हे संपूर्ण वापरले जाईल.
माझे नाव गुप्त राखण्यासाठी प्रयत्न केले जातील परंतु, पूर्ण गोपनीयतेची खात्री देता येणार नाही.

सहभागी व्यक्तीचे नाव सही दिनांक

Appendix C

Patient Screening Forms and Clinical Assessment Forms

Appendix 23. Patients record form (PRF)

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

LePaIn: _____

Patient Record Form

For

Study: QST_IN_LEPROSY

Bombay Leprosy Project Clinic
Mumbai, India

Date: _____

Start time: __:__
End time: __:__

Investigators:
Dr. Omer Haroun
Dr. V. V Pai
Dr. Ashish Khodke
Dr. Vanja Shetty
Prof. Andrew Rice
Prof. Diana Lockwood

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

FORM 1: RECRUITMENT SHEET

Advice on the completion of the PRF

Completion of the PRF:

1. Complete PRF in black ink (not pencil)
2. Write clearly and concisely in English
3. Do not use ditto marks
4. If the answer is "zero" do not leave the field blank
5. If the answer to a question is unknown, write "NK" or Not Known or "8"
6. If a requested test has not been done, write "ND" or Not Done
7. If a question is not applicable, write "NA" or Not Applicable
8. All dates in this PRF take the format dd/mm/yyyy. Note that 'dd', 'mm' and 'yyyy' should be filled in with numbers
9. If a date is partially known (e.g. year only) enter that part which is known and NK for the rest of the information
10. If a mistake is made please correct in the following way:
    - Cross through with a single straight line
    - Write the correct value clearly above or to the side
    - Initial and date the correction
    - If appropriate, add an explanation

Patient work flow

Summary:

1. Patient identified at Bombay Leprosy Clinic
2. Patient informed about study, and recruited with consent
3. Full history and examination by study investigator
4. Patients sent for laboratory investigations
5. Patients screened for neuropathy using MFs and MRC
6. Patient reviewed by study investigator
7. Patient given review date and time

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Schedule of events:

Protocol activities and Forms to be completed	Screen days			Test day
Patient information and Consent	x			
Screening form	x			
Clinical assessment	x			
Urine analysis		x		
Complete blood count		x		
HbA1c (Blood glucose)		x		
Blood sample for VitB12 level		x		
Blood sample for serology (Syphilis and HIV test)		x		
Neuropathy assessment	x			
Leprosy assessment	x			
Assessment of leprosy reactions	x			
Pain assessment (pain intensity)			x	
Clinical neurological examination		x		
DN4 Questionnaire			x	
Pain detect questionnaire			x	
GHQ-12 Questionnaire				X
BPI Questionnaire				X
Quantitative sensory testing (QST)				X
3 mm skin punch biopsy				X

Patient screening and registration

Complete Address of the patient

Name: _____ _____
Last name First name

Contact details/Mobile: _____
Contact details /Landline: _____
Province/Region: _____
District: _____
Location: _____
Village: _____

Name of the Head of Household: _____ _____
Last name First name

Please note: This section must remain at site

EQuiSTA code number: |__|__|__| **Patient Initials:** |__|__|__|

SCREENING: DAY 0
(Screening may last more than one day)

Consent

Did the patient consent to participate in the study? Yes (1) No (0) [__]
Date of Consent (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]

Did the patient consent for sample collection and lab investigation? Yes (1) No (0) [__]
Date of Consent (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]

Did the patient consent for storage of sample for future use? Yes (1) No (0) [__]
Date of Consent (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]

Demography

Date of Birth (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
OR
Age of the patient (in years): (estimate) [__|__]
Gender: Male (1) Female (2) [__]
Date sample taken (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Results: Positive (1) Negative (0) [__]

History of Symptoms on the day of interview:

Please indicate if the patient reported a presence of the following symptoms as Yes (1) No (0) Unknown (8). If yes, complete the duration as the number of months and/or days: where the duration is less than 1 month, complete [0|0] in "months" column.

Description of problem	Yes (1) No (0) unknown (8)	Months
Pain	[__]	[__|__]
Skin changes	[__]	[__|__]
Reactions	[__]	[__|__]
No problem	[__]	[__|__]

Concomitant disease

Does the patient have any clinically significant concomitant diseases at baseline?
Yes (1) No (0) Unknown (8) [__]
If yes Specify _____
_____
_____
For every mentioned condition requiring treatment, please write the medication.

Does the patient have alcohol? Yes (1) No (0) [__]
If yes; what's the type (Beer (1), Wine (2), Whisky (3), other _____) [__]
Duration of Alcohol consumptions: _____ Years
Frequency of Alcohol consumption: (Daily (1), weekly (2), occasionally (3)) [__]
Estimate Alcohol consumption in glasses per weeks: _____ glass/wk

EQuiSTA code number: |__|__|__| **Patient Initials:** |__|__|__|

SCREENING: DAY 0

Clinical assessment

Date measurements taken (dd/mmm/yyyy) [__|__| / |__|__|__| / |__|__|__|__]

Weight: [__|__|__]•[__] Kg

Height [__|__|__] cm

Body Mass Index - BMI [__|__] kg/m²

Haematologic Examination

Date sample taken (dd/mmm/yyyy) [__|__| / |__|__|__| / |__|__|__|__]

Haemoglobin [__|__|_•_|__] g/dL

Clinical Chemistry Examination

Date sample taken (dd/mmm/yyyy) [__|__| / |__|__|__| / |__|__|__|__]

HbAc1 [__|__|•|__] mmol/L
B12 level [__|__|__|•|__] ng/L

Serological test for syphilis and HIV

Date sample taken (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
(Results will be reported separately)

Urinalysis (Dipstick Test)

Date sample taken (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Please record one of the following numeric codes for the result on the +, ++, +++ scale.
Negative (0) + (1) ++ (2) +++ (3)

Glucose [__]

Urine for pregnancy test:

Negative (0) Positive (1) [__]

If positive:

Duration in months [__]
Last menstrual period: (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Last child birth: (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Screening for neuropathy:

Baseline peripheral neuropathy assessment

Right			Movement	Left		
Dura#	Imp Y/N	MRC		MRC	Imp Y/N	Dura#
			Little finger abduction (ADM)			
			Index finger abduction (IDI)			
			Thumb abduction (ABP)			
			Wrist extension			
			Foot dorsiflexion (DF)			
			Extension big toe (EHL)			
			Flexion big toe (EHL)			
			Toe fanning (TF)			
			Closes eyes (strong and gentle closure)			

Does the patient have motor neuropathy at baseline? Yes (1) No (0) [__]

Monofilament assessments (Scoring and defining impairment by monofilament)							
Right side				Left side			
Site	MED	ULN			Site	MED	ULN
1.					1		
2.					2		
3.					3		
Total					Total		
Imp (Y/N)					Imp (Y/N)		
Site	RCN	Ubr			Site	RCN	Ubr
1.					1.		
2.					2.		
3.					3.		
Total					Total		
Imp (Y/N)					Imp (Y/N)		
Site	Post. Tibial				Site	Post. Tibial	
1.					1.		
2.					2.		
3.					3.		
4					4		
Total					Total		
Imp (Y/N)					Imp (Y/N)		
Site	SURAL N				Site	SURAL N	
1.					1.		
2.					2.		
3.					3.		
Total					Total		
Imp (Y/N)					Imp (Y/N)		

Does the patient have sensory neuropathy at baseline? Yes (1) No (0) [__]

Does the patient have neuropathy at baseline? Yes (1) No (0) [__]

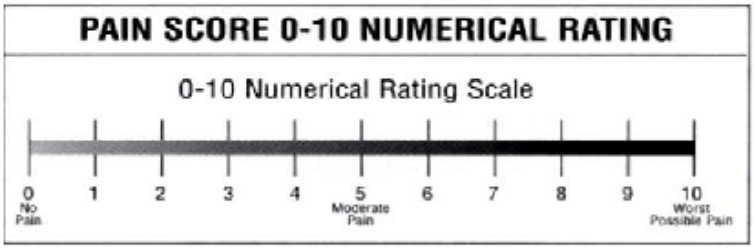
EQuiSTA code number: |__|__|__| **Patient Initials: |__|__|__|**

Does the patient have pain? Yes (1) No (0) [__]

If yes, please indicate:

1. Duration of pain symptoms in months? [__|__]
2. The pain intensity score using 11-point Likert scale [__]

Please mark the scale below to show how intense your pain is.
A zero (0) means no pain, and ten (10) means extreme pain.



3. The DN4 score [__]

Please answer yes or no for each item of the following four questions.

- **Question 1:**
  - Does the pain have one or more of the following characteristics?
    - Burning Yes (1) No (0) [__]
    - Painful cold Yes (1) No (0) [__]
    - Electric shocks Yes (1) No (0) [__]
- **Questions 2:**
  - Is the pain associated with one or more of the following symptoms in the same area?
    - Tingling Yes (1) No (0) [__]
    - Pins and needles Yes (1) No (0) [__]
    - Numbness Yes (1) No (0) [__]
    - Itching Yes (1) No (0) [__]
- **Question 3:**
  - Is the pain located in the area where the physical examination may reveals one or more of the following characteristics?
    - Hypoethesia to touch Yes (1) No (0) [__]
    - Hypoethesia to pinprick Yes (1) No (0) [__]
- **Question 4:**
  - In the painful area, can the pain be caused or increased by:
    - Brushing Yes (1) No (0) [__]

YES = 1 point NO = 0 points
Patient's score __/10 [__]

How did you find this questionnaire? [__]
(Very easy (1) / easy (2) / fair (3) / difficult (4) / very difficult (5))

EQuiSTA code number: |__|__|__| **Patient Initials:** |__|__|__|

SCREENING: DAY 0

Please complete the boxes with Yes (1) No (0) Not applicable (3) as appropriate. Patients should meet all of the inclusion criteria and none of the exclusion criteria

Inclusion

1. Written informed consent to participate [__]
2. Aged between 16 and 65 years (inclusive) who are able to comply with the protocol [__]

Exclusion

3. Known to be Diabetes Mellitus [__]
4. Have positive serological test for syphilis [__]
5. Serum B12 level outside the normal range for age and gender [__]
6. Have any history of alcohol abuse (Have suffered from alcoholism for 10 or more years or who drink excessive amounts of alcohol regularly [__]

If answer YES to any of questions 3-7, the patient **must NOT** be entered into the QST study

Investigator signature: _____

Date (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]

Inclusion as:

Indicate inclusion number according to the table below: [__]

Number	Inclusion as
1.	Leprosy patients with established pain and clinical neuropathy
2.	Leprosy patients with established pain and no clinical evidence of neuropathy
3.	Leprosy patients with pain free neuropathy
4.	Leprosy patients with no pain and no clinical evidence of neuropathy

Check list for painful neuropathy:

The following answers has to be "yes"	Yes	No
- Proved evidence of clinical neuropathy by MFs and MRC.	☐	☐
- Pain with neuropathy-type of location and evidence of neuropathic pain based on a score of ≥ 4/10 using the DN4 questionnaire	☐	☐
- Pain since more than 3 months	☐	☐
- Current pain intensity >2 (NRS 0-10)	☐	☐

Check list for painless neuropathy:

The following answers has to be "yes"	Yes	No
- Proved evidence of clinical neuropathy by MFs and MRC	☐	☐
- No pain of any type	☐	☐

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 1: Registration and Demographic details of the patient

Registration:

Lepain patient ID (EquiSTA code number ###) [__|__|__]
Registration date (interview date: dd/mmm/yyyy) [__|__| / |__|__|__| / |__|__|__|__]
Clinic record card number: [__|__| __|__]
Centre name: BLP (1) FMR (2) [__]
PHC name: [__]
(Bhabha Hospital Bandra (1), J.J Hospital (2), Dharavi Urban Health Centre (3), Worli BDD-45 (4), Borivali (5), BLP Clinic (6), Narmada Complex Panvel Clinic (7), other (8))
Start time: [__|__| / |__|__]
End time: [__|__| / |__|__]

Demographic details of the patient:

Date of Birth (dd/mmm/yyyy) [__|__| / |__|__|__| / |__|__|__|__]
OR
Age of the patient (in years): (estimate) [__|__]
Gender: Male (1) Female (2) [__]
Language: Hindi (1) Marathi (2) English (3) [__]
Religion: Hindu (1)/ Muslim (2)/ Christian (3)/ Jain (4)/ Other _____ [__]
State: Maharashtra (1)/ Uttar Pradesh (2)/ Gujarat (3)/ Other _____ [__]
Dominant hand: Right (1) Left (2) [__]
Marital status
- Single 1 [__]
- Married 2 [__]
- Widowed 3 [__]
- Divorced 4 [__]

Education
- Illiterate 1 [__]
- Primary 2 [__]
- Secondary 3 [__]
- High school 4 [__]
- Higher secondary 5 [__]
- College and above 6 [__]
- Other (specify) _____ 7 [__]

Occupation
- None 1 [__]
- Housewife 2 [__]
- Labour 3 [__]
- Farmer / skilled labour 4 [__]
- Office worker / Teacher / Business 5 [__]
- Student 6 [__]
- Other (specify) _____ 7 [__]
- Not known 8 [__]

Smoking status
- Current smoker 1 [__]
- Former smoker 2 [__]
- Occasionally 3 [__]
- Never smoked 4 [__]
- Not known 8 [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 2: History of the disease

History of the disease

(Patient first symptoms of the disease help seeking and the reasons behind the delay of staring the treatment)

Is it new or old case? New (1) old (2) [__]

First symptoms: Yes (1) No (0) [__]

If yes

Skin lesion(s)	Yes (1) No (0)	[__]
Anaesthesia	Yes (1) No (0)	[__]
Loss of warm sensation	Yes (1) No (0)	[__]
Burning / Tingling	Yes (1) No (0)	[__]
Loss of muscle strength	Yes (1) No (0)	[__]
Symptom of T1R	Yes (1) No (0)	[__]
Symptom of T2R	Yes (1) No (0)	[__]
Other (specify)	Yes (1) No (0)	[__]

Skin lesions Yes (1) No (0) [__]

- Type: Patches (1), Nodules (2), Primary neuritis (3), Don't know (8) [__]
- Location of lesion (Site)

Face	Yes (1) No (0)	[__]
Ears	Yes (1) No (0)	[__]
Upper extremities unilateral	Yes (1) No (0)	[__]
Upper extremities bilateral	Yes (1) No (0)	[__]
Lower extremities unilateral	Yes (1) No (0)	[__]
Lower extremities bilateral	Yes (1) No (0)	[__]
Trunk	Yes (1) No (0)	[__]
Buttock	Yes (1) No (0)	[__]
All over	Yes (1) No (0)	[__]

- Number of skin lesions

SSL	Yes (1) No (0)	[__]
2 – 5	Yes (1) No (0)	[__]
6-10	Yes (1) No (0)	[__]
Diffused lesions >10	Yes (1) No (0)	[__]
Don't know	8	[__]

- Appearance (lesion description)

Hypo-pigmented (Pale)	Yes (1) No (0)	[__]
Reddish lesions (erythematic)	Yes (1) No (0)	[__]
Diffuse	Yes (1) No (0)	[__]
Anaesthetic	Yes (1) No (0)	[__]

Date of first symptoms: [__|__| / |__|__|__|__] / |__|__|__|__|

Did you recognise the possibility of leprosy? Yes (1) / No (0) / don't know (3) [__]

Date of leprosy diagnosis: [__|__| / |__|__|__|__] / |__|__|__|__|

How many months it is since became aware of the first sign or symptoms of leprosy? [__]

Where was the first place the patient went to get help? [__]

[Pharmacist (1), Traditional healer (2), Alternative medicine practitioner (3), Private or health service clinic/doctor (4), Leprosy hospital or clinic (5), Person affected by leprosy (6), other – specify (7)]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

What's the main reason for delay in diagnosis and start of treatment?

_____
_____
_____
_____

Duration of disease (presumably, if not known)

- ☐ < 6 months
- ☐ 6 months up to 1 year
- ☐ more than 1 year up to 5 years
- ☐ longer than 5 years
- ☐ unknown

Result of slit skin smear at diagnosis: +ve (1) -ve (0) NA (3) [__]
Bacterial Index (BI) at diagnosis: [__]

Type of leprosy (WHO classification): PB (1) MB (2) [__]
Type of leprosy (R.J classification):
TT (1)/BT (2)/BB (3)/BL (4)/LL (5)/PN (6)/Indeterminate (7) or not known (8) [__]

WHO Disability grading for six body areas at diagnosis:
(Enter using standard 0/1/2 coding for each area)

Right		Left
[__]	Eyes	[__]
[__]	Hands	[__]
[__]	Feet	[__]

Disability at diagnosis Yes (1) No (0) [__]
If yes,
Complete Disability Record (CDR) at diagnosis:
C = clawed Yes (1) No (0) [__]
 = wound or open crack Yes (1) No (0) [__]
—— = shortening level Yes (1) No (0) [__]

Started MDT: Yes (1) No (0) [__]
If yes,
Date of MDT (started): [__|__| / |__|__|__|__| / |__|__|__|__|]
MDT treatment: MB-MDT (1) PB-MDT (2) Other _____ [__]
Completed MDT: Yes (1) No (0) [__]
If yes,
Date of MDT (completed): [__|__| / |__|__|__|__| / |__|__|__|__|]
Total duration of MDT received: [__|__] months
Did the patient ever have MDT prescribed in the past but he/she did not complete the treatment? Yes (1) / No (0) / don't know (3) [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 3: History of current illness

Skin changes

- Time of onset [__]
  < 6 months (1), 6 months up to 1 yr (2), > 1 yr up to 2 yrs (3), Longer than 2 years (4), Unknown (8)
- Type
  - Patches Yes (1) No (0) [__]
  - Nodules Yes (1) No (0) [__]
  - Primary neuritis Yes (1) No (0) [__]
- Location of lesion (Site)
  - Face Yes (1) No (0) [__]
  - Ears Yes (1) No (0) [__]
  - Upper extremities unilateral Yes (1) No (0) [__]
  - Upper extremities bilateral Yes (1) No (0) [__]
  - Lower extremities unilateral Yes (1) No (0) [__]
  - Lower extremities bilateral Yes (1) No (0) [__]
  - Trunk Yes (1) No (0) [__]
  - Buttock Yes (1) No (0) [__]
  - All over Yes (1) No (0) [__]
- Number of skin lesions
  - SSL Yes (1) No (0) [__]
  - 2 – 5 Yes (1) No (0) [__]
  - 6-10 Yes (1) No (0) [__]
  - Diffused lesions >10 Yes (1) No (0) [__]
  - Don't know 8 [__]
- Appearance (lesion description)
  - Hypo-pigmented Yes (1) No (0) [__]
  - Reddish lesions (erythematic) Yes (1) No (0) [__]
  - Diffuse Yes (1) No (0) [__]
  - Anaesthetic Yes (1) No (0) [__]
  - Not applicable 8 [__]
- Active skin lesion(s) Yes (1) No (0) [__]
- Total number of active skin lesions (if No, then #=0) [__]

Do you notice loss of sensation? Yes (1) No (0) [__]

If yes, area of sensory loss

- Over skin lesion Yes (1) No (0) [__]
- On the hands Yes (1) No (0) [__]
- On the feet Yes (1) No (0) [__]
- Uncertain Yes (1) No (0) [__]

Did you notice any new loss of sensation in your hands or feet during the past month? [__]

Did you notice any new dryness of your hand palms or foot soles during the past month? [__]

Did you notice any new weakness in your hands or feet during the past month? [__]

Did you notice any new weakness in your eye during the past month? [__]

Did you notice any new sensations of pin and needles or 'insects crawling' in your hands or feet during the past month? [__]

Did you notice any new pain sensations, such as burning or shooting pain in your hands or feet during the past month? [__]

(If a question is answered positively, the patient will be asked which limb is affected. This should be recorded on the assessment form.)

Do you have any pain around your nerve? Yes (1) No (0)

Have you noticed any painless cuts or blisters? Yes (1) No (0) [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 4: Leprosy reactions

Leprosy reactions:

Is the patient on reaction now? Yes (1) No (0) [__]
Is reaction diagnosed or new? Yes (1) No (0) [__]
If yes,
How diagnosed?
Skin lesion: Yes (1) No (0) [__]
If yes,
Red Yes (1) No (0) [__]
Swollen Yes (1) No (0) [__]
Tender Yes (1) No (0) [__]
Nerve: Yes (1) No (0) [__]
If yes,
Swollen Yes (1) No (0) [__]
Painful, tende Yes (1) No (0) [__]
reduced func Yes (1) No (0) [__]
New lesions appear Yes (1) No (0) [__]
Fever and malaise Yes (1) No (0) [__]
Tibial tenderness Yes (1) No (0) [__]
Orchitis Yes (1) No (0) [__]
Oedema Yes (1) No (0) [__]
If yes,
Face Yes (1) No (0) [__]
Hands Yes (1) No (0) [__]
Feet Yes (1) No (0) [__]

Type of reaction is:
TIRs (1) ENL (2) Neuritis (3) uncertain (8) [__]

Date of onset of reactions: [__|__| / |__|__|__] / |__|__|__|__]
Current treatment of reaction:
Steroid (Prednisolone) (1)/ Clofazimine (2)/ Thalidomide (3) other (7) [__]
Dose: _____
Date of reaction's treatment started: [__|__| / |__|__|__] / |__|__|__|__]
Duration of treatment: _____ weeks

History of reactions:

Have you had previous reactions? Yes (1) No (0) [__]
If yes,
Number of previous reactions: _____
Months taken for steroid treatment: _____

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

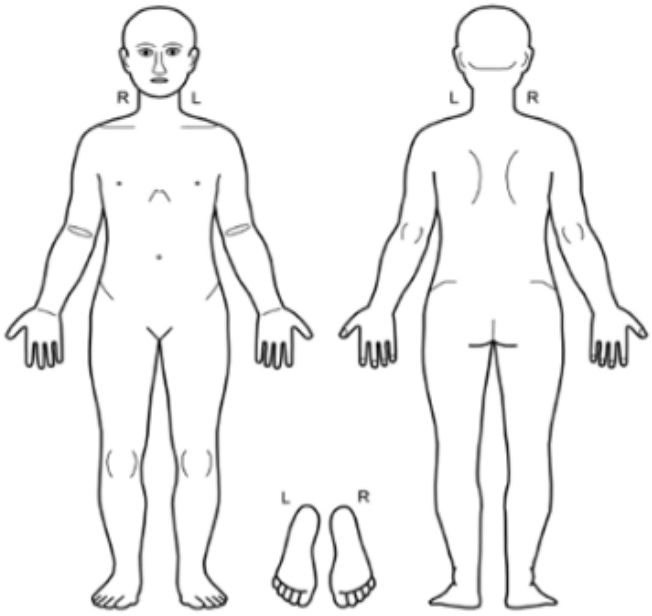
Form 5: Pain assessment

Pain assessment:

Do you have pain now?

Yes (1) No (0) [__]

Please, draw pain on body map



Area of pain: skin (1), nerve (2), area of sensory loss (3), other (4) [__]

Specify Area of pain:

Skin:	Yes (1)	No (0)	[__]
If yes,			
Active untreated lesions	Yes (1)	No (0)	[__]
Treated lesions	Yes (1)	No (0)	[__]
Nerve (neuritis)	Yes (1)	No (0)	[__]
Pain in area of sensory loss	Yes (1)	No (0)	[__]
Other:	Yes (1)	No (0)	[__]
If yes,			
Joint pain	Yes (1)	No (0)	[__]
Ulcer	Yes (1)	No (0)	[__]

Onset of the symptoms: [__|__| / |__|__| / |__|__|__|__]

When do you feel the pain? [__]

All the time (1)/ some hour every day (2)/ At least once a wk (3)/ only occasionally (4)/ uncertain (8)

How long you have pain (presumably, if not known): [__|__| months

Pain grade on a 4 point scale: [__]

Absent (0)

Mild – only aware intermittently; does not limit activity (1)

Moderate – sleep disturbed and/or activities (including work) diminished (2)

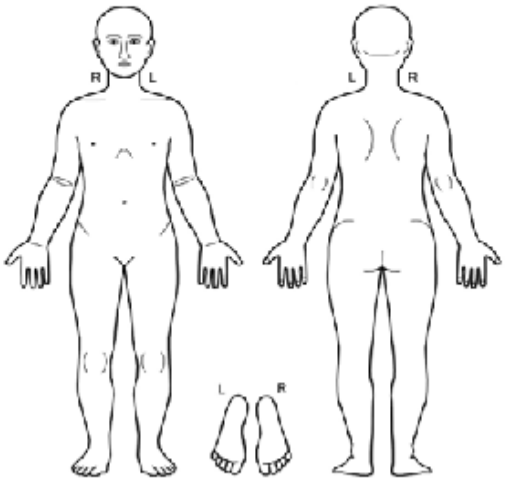
Severe – incapacitating (3)

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Does the patient have **numbness?**

Yes (1) No (0) [__]

Please, draw numbness on body map



How long you have numbness (presumably, if not known): [__|__] months

Numbness grade on a 4 point scale: [__]

Absent (0)

Mild – only aware intermittently; does not limit activity (1)

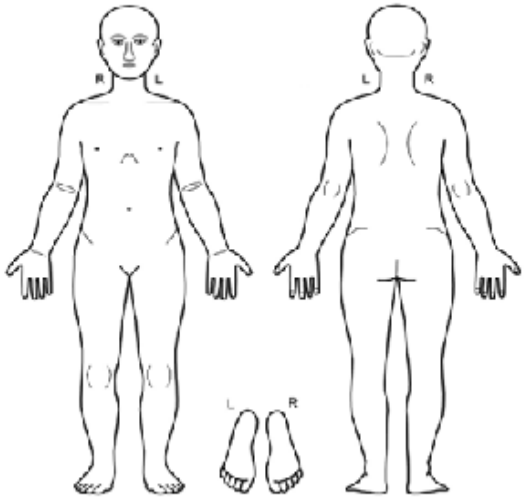
Moderate – sleep disturbed and/or activities (including work) diminished (2)

Severe – incapacitating (3)

Does the patient have **pins and needles / paraethesia?**

Yes (1) No (0) [__]

Please, draw pins and needles / paraethesia on body map



EQuiSTA code number: |__|__|__| **Patient Initials: |__|__|__|**

How long you have Pins and needles/ parethesia (presumably, if not known): [__|__| months
Paraethesia grade on a 4 point scale: [__]

Absent (0)

Mild – only aware intermittently; does not limit activity (1)

Moderate – sleep disturbed and/or activities (including work) diminished (2)

Severe – incapacitating (3)

Pain treatment (current and previous treatment):

Current pain medication: Yes (1) No (0) [__]

If yes, what treatment

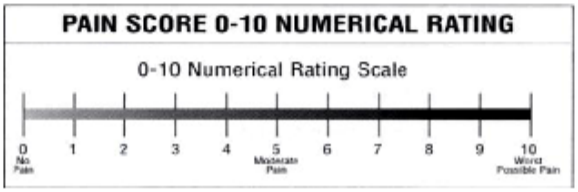
Drug: _____

Dose: _____

How often you take it: _____

Is your pain relived by medical treatment? Yes (1) No (0) [__]

How much does it relieve your pain?



Past pain medication: Yes (1) No (0) [__]

If yes, what treatment in the past?

Drug: _____

Dose: _____

How often you take it: _____

Duration of time under pain medication (months): [__|__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 6: Psychological problems associated with leprosy and pain

Problems associated with leprosy and pain

Are you happy or unhappy?	Happy (1)	unhappy (0)	[__]
If you are feeling unhappy or depress what do you think the reasons?			
_____			
Is it due to (you can check more than one):			
Pain	Yes (1)	No (0)	[__]
Leprosy	Yes (1)	No (0)	[__]
General life	Yes (1)	No (0)	[__]
Uncertain	(8)		[__]
Have you told anyone about the leprosy diagnosis?		Yes (1) No (0)	[__]
If yes, who already knows?			
Spouse	Yes (1)	No (0)	[__]
Family	Yes (1)	No (0)	[__]
Education/work	Yes (1)	No (0)	[__]
Friends	Yes (1)	No (0)	[__]
Neighbours	Yes (1)	No (0)	[__]
Community	Yes (1)	No (0)	[__]
Are you willing to tell other?		Yes (1) No (0)	[__]
If yes, who you are willing to tell?			
Spouse	Yes (1)	No (0)	[__]
Family	Yes (1)	No (0)	[__]
Education/work	Yes (1)	No (0)	[__]
Friends	Yes (1)	No (0)	[__]
Neighbours	Yes (1)	No (0)	[__]
Community	Yes (1)	No (0)	[__]
Who you do not want them to know?			
Spouse	Yes (1)	No (0)	[__]
Family	Yes (1)	No (0)	[__]
Education/work	Yes (1)	No (0)	[__]
Friends	Yes (1)	No (0)	[__]
Neighbours	Yes (1)	No (0)	[__]
Community	Yes (1)	No (0)	[__]
Has the diagnosis of leprosy already caused a problem?		Yes (1) No (0)	[__]
If yes, problems in/with:			
Marriage	Yes (1)	No (0)	[__]
Family members	Yes (1)	No (0)	[__]
Education/work	Yes (1)	No (0)	[__]
Friends	Yes (1)	No (0)	[__]
Neighbours	Yes (1)	No (0)	[__]
Community	Yes (1)	No (0)	[__]
May it cause a problem in the future?		Yes (1) No (0)	[__]
If yes, problems in/with:			
Marriage	Yes (1)	No (0)	[__]
Family members	Yes (1)	No (0)	[__]
Education/work	Yes (1)	No (0)	[__]
Friends	Yes (1)	No (0)	[__]
Neighbours	Yes (1)	No (0)	[__]
Community	Yes (1)	No (0)	[__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 7: Past medical history

Past medical history:

_____
_____
_____

Drug history (past and present):

Current drug therapy:

_____
_____
_____

Previous drug treatment (potentially neuropathy inducing agents:

_____
_____
_____

Family history of neuropathy: Yes (1) No (0) [__]

Data relevant to peripheral neuropathy from medical records if present

_____
_____
_____

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 8: Current clinical examination

Clinical examination:

❖ **Assessment of skin:**

Skin lesions: Yes (1) No (0) [__]

If yes,

Nature of lesion (new (1) / old (2)) [__]

Number of lesions: [__]

(SSL (1)/ 2-5 (2)/ 6-10 (3)/ >10 Diffused lesions (4)/ PN (5))

Type of lesion [__]

(Untreated (1) / partially treated (2) / fully treated (3))

Distribution of any lesion: (use body chart)

Face	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Ears	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Upper extremities unilateral	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Upper extremities bilateral	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Lower extremities unilateral	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Lower extremities bilateral	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Trunk	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
Buttock	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]
All over	Yes (1) No (0)	[__]
	If yes: few (1)/ many (2)/ not known (3)	[__]

Is the lesions symmetrically distributed? Yes (1) No (0) [__]

Type of lesions:

Macules	Yes (1) No (0)	[__]
Papules	Yes (1) No (0)	[__]
Nodules	Yes (1) No (0)	[__]
Plagues	Yes (1) No (0)	[__]
Infiltration	Yes (1) No (0)	[__]

Hypo pigmented lesion count: None (1) / some (2) / all (3) / not known (8) [__]

Any shiny skin lesions: None (1) / some (2) / all (3) / not known (8) [__]

Any erythrematous lesions: None (1) / some (2) / all (3) / not known (8) [__]

Are there any reactional signs on the skin lesions? Yes (1) No (0) [__]

If yes,

Oedema Yes (1) No (0) [__]

Any anaesthetic lesions: None (1) / some (2) / all (3) / not known (8) [__]

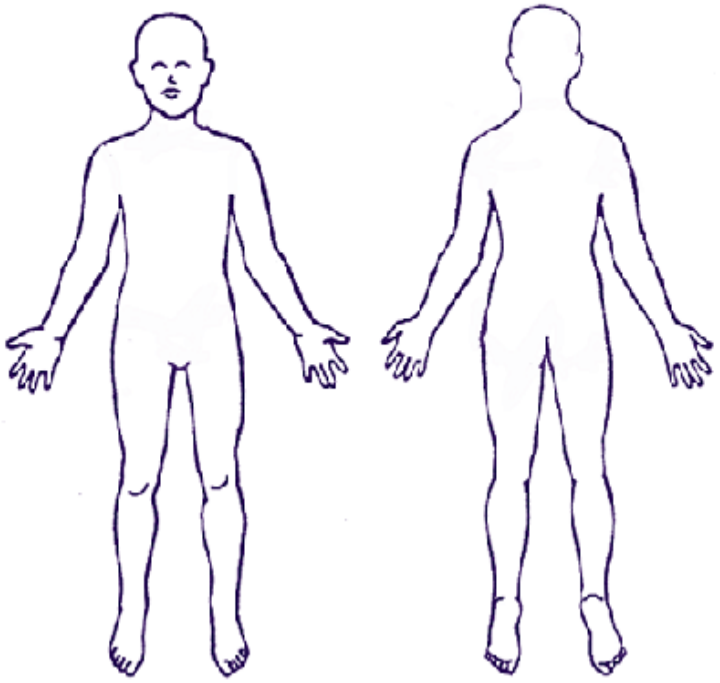
Sensory examination over the skin lesions, MFs gradients;

0.05gm 0.2gm 2gm

4gm 10gm 300gm A^0 [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Please, draw skin lesion on body map



Skin lesions overlying nerves: Yes (1) No (0) [__]

If yes,

Skin lesions overlying nerves and the MFs gradient	Right:		Left:	
	Y/N	MFs	Y/N	MFs
Skin lesion overlying or in distribution area of facial nerve? Yes/ No, if yes:				
Skin lesion overlying or in distribution area of the ulnar nerve? Yes/ No, if yes:				
Skin lesion overlying or in distribution area of the median nerve? Yes/ No:				
Skin lesion overlying or in distribution area of the radial cutaneous nerve? Y/ N				
Skin lesion overlying or in distribution area of the lateral popliteal nerve? Y/ N				
Skin lesion overlying or in distribution area of the posterior tibial nerve? Y/ N				
Skin lesion overlying or in distribution area of the sural nerve? Yes/ No, if yes:				

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Nerve examination:

A. Nerve palpation:

a. Nerves involved Yes (1) No (0) [__]

If No, skip to (nerve function)

Name of Enlarged Nerve	Right Yes (1) / No (0) / Not done (8)	Left Yes (1) / No (0) / Not done (8)
Upper limb (Yes/No) [__]	[__]	[__]
Greater auricular	[__]	[__]
Ulnar nerve	[__]	[__]
Radial Cutaneous	[__]	[__]
Ulnar branch	[__]	[__]
Median	[__]	[__]
Total upper [__]	[__]	[__]
Lower limb (Yes/No) [__]	[__]	[__]
Lateral popliteal	[__]	[__]
Superficial peroneal	[__]	[__]
Sural	[__]	[__]
Posterior tibial	[__]	[__]
Total lower [__]	[__]	[__]

Number of enlarged nerves, if No, then #=0 [__|__] right [__|__] left [__|__]

b. Nerve tenderness Yes (1) No (0) [__]

If No, skip to (nerve function)

Name of Tender Nerve	Right Yes (1) / No (0) / Not done (8)	Left Yes (1) / No (0) / Not done (8)
Upper limb (Yes/No) [__]	[__]	[__]
Greater auricular	[__]	[__]
Ulnar nerve	[__]	[__]
Radial Cutaneous	[__]	[__]
Ulnar branch	[__]	[__]
Median	[__]	[__]
Total upper [__]	[__]	[__]
Lower limb (Yes/ No)	[__]	[__]
Lateral popliteal	[__]	[__]
Superficial peroneal	[__]	[__]
Sural	[__]	[__]
Posterior tibial	[__]	[__]
Total lower [__]	[__]	[__]

Number of tender nerves affected, if No, then #=0 [__|__] right [__|__] left [__|__]

B. Nerve function:

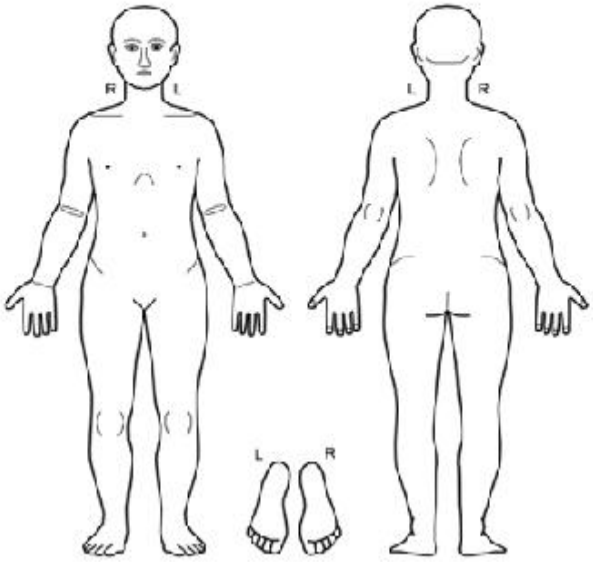
Muscle assessment using Modified 5-point MRC scale for muscle strength scoring

Movements and muscles tested (see page 8).

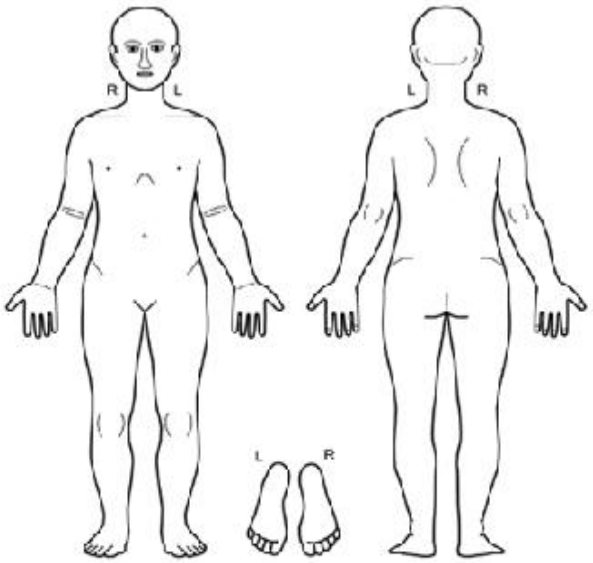
EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

A. Sensory testing:

- Testing light touch: Sensory level using cotton wool. **Normal (0)/ Abnormal (1) [__]**



- Pin-prick sensation: Sensory level using disposable pins. **Normal (0)/ Abnormal (1) [__]**



EQuiSTA code number: |__|__|__| **Patient Initials: |__|__|__|**

- Joint position sense: **Normal (0)/ Abnormal (1) [__]**

	Right Normal (0)/ Abnormal (1)	Left Normal (0)/ Abnormal (1)
Upper limb		
Index finger	[__]	[__]
Lower limb		
Great toe	[__]	[__]

A. **Reflexes:** **Normal (0)/ Abnormal (1) [__]**

	Right Normal (0) / Absent (1)/ Increased (2)	Left Normal (0) / Absent (1)/ Increased (2)
Upper Limb: Normal (0)/ Abnormal (1) [__]		
Biceps	[__]	[__]
Triceps	[__]	[__]
Supinator	[__]	[__]
Lower Limb: Normal (0)/ Abnormal (1) [__]		
Knee	[__]	[__]
Ankle	[__]	[__]
Ext planter	Dorsiflexion of the big toe Yes / No	Dorsiflexion of the big toe Yes / No

Current WHO Disability grading for six body areas:
(Enter using standard 0/1/2 coding for each area)

Right		Left
[__]	Eyes	[__]
[__]	Hands	[__]
[__]	Feet	[__]

Current Disability Yes (1) No (0) [__]
If yes,
Current Complete Disability Record (CDR):
C = clawed Yes (1) No (0) [__]
 = wound or open crack Yes (1) No (0) [__]
—— = shortening level Yes (1) No (0) [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 9: Pain Questionnaires

DN4 questionnaire

DN4 completed Yes (1) No (0) [__]
Date DN4 completed (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Start time: [__|__| / |__|__]
End time: [__|__| / |__|__]

DN4 score [__|__]
DN4 patient's result Yes ≥4 (1) No ≤3 (0) [__]

PainDETECT questionnaire

PainDETECT completed Yes (1) No (0) [__]
Date PainDETECT completed (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Start time: [__|__| / |__|__]
End time: [__|__| / |__|__]

PainDETECT score [__|__]
PainDETECT patient's score Yes (1) No (0) [__]

Form 10: Quality of life and Psychological

General Health Questionnaire (GHQ-12):

GHQ-12 completed Yes (1) No (0) [__]
Date GHQ-12 completed (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Start time: [__|__| / |__|__]
End time: [__|__| / |__|__]

GHQ-12 score [__|__]
GHQ-12 patient's result Yes ≥4 (1) No ≤3 (0) [__]

Brief Pain Inventory Questionnaire

BPI: Yes (1) No (0) [__]
Date GHQ-12 done (dd/mm/yyyy) [__|__| / |__|__| / |__|__|__|__]
Start time: [__|__| / |__|__]
End time: [__|__| / |__|__]

BPI score: [__|__]
BPI patient's result Yes (1) No (0) [__]

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 11: Quantitative Sensory Testing

QST testing	Yes (1)	No (0)	[__]
Date QST testing done (dd/mm/yyyy)	[__|__| / |__|__| / |__|__|__|__]		
Start time: [__|__| / |__|__]			
End time: [__|__| / |__|__]			
Site of QST			
RIGHT Hand C8	Yes (1)	No (0)	[__]
LEFT Hand C8	Yes (1)	No (0)	[__]
RIGHT Foot S1	Yes (1)	No (0)	[__]
LEFT Foot S1	Yes (1)	No (0)	[__]
Number of QST tested sites			[__]

Form 12: Skin biopsy

Skin biopsy taken	Yes (1)	No (0)	[__]
Date skin biopsy taken (dd/mm/yyyy)	[__|__| / |__|__| / |__|__|__|__]		
Start time: [__|__| / |__|__]			
End time: [__|__| / |__|__]			
Biopsy site			[__]
RIGHT Hand C8	Yes (1)	No (0)	[__]
LEFT Hand C8	Yes (1)	No (0)	[__]
RIGHT Leg	Yes (1)	No (0)	[__]
LEFT Leg1	Yes (1)	No (0)	[__]
Number of skin biopsy taken			[__]
Skin biopsy code: _____			
Date skin biopsy sends to KCL:	(dd/mm/yyyy)	[__|__| / |__|__| / |__|__|__|__]	
Date skin biopsy received at KCL:	(dd/mm/yyyy)	[__|__| / |__|__| / |__|__|__|__]	
Biopsy report 1:			[__]
Normal IENFD	1		
Increased IENFD	2		
Decreased IENFD	3		
Missing	9		
Biopsy report 2:			[__]
Normal IENFD	1		
Increased IENFD	2		
Decreased IENFD	3		
Missing	9		
Biopsy report 1:			[__]
Normal IENFD	1		
Increased IENFD	2		
Decreased IENFD	3		
Missing	9		
Biopsy report 2:			[__]
Normal IENFD	1		
Increased IENFD	2		
Decreased IENFD	3		
Missing	9		

Other findings or remarks: _____.

EQuiSTA code number: |__|__|__| Patient Initials: |__|__|__|

Form 13: investigations

Date sample taken: _____ Date result received: _____

No	Description	Res	NR	No	Description	Res	NR
1	CBC			5	Hormones		
	Erythrocyte				T3		*70-204ng/dl*
	RBCs count		*4.7-6mill/c.mm*		T4		*3.2-12.6µg/dl*
	Hb		*13.5-18g/dl*		TSH		*0.45-4.5µlU/ml*
	PCV		*42-52%*	6	VitB12 level		*211-911pgml*
	MCV		*78-100fl.*	7	Pregnancy test		
	MCH		*27-31pg*	8	HIV-DUO		
	MCHC		*32-36g/dl*		Non reactive		*0.0-1.0 index*
	RDW		*11.5-14%*		Reactive		*Above 1.0 index*
	RBC Morph:		*(Normal)*	9	Urine Exam.		
	Hypochromia				***General Exm:***		
	Microcytosis				Volume		*mL*
	Anisocytosis				Colour		*Pale yellow*
	Poikliocytosis				Appearance		*Clear*
	Macrocytosis				Deposit		*Absent*
	Polychromasia				Reaction (Ph)		*4.5-8.0*
	Others				Specific gravity		*1.01-1.03*
	Leucocytes:				***Chemical Exm:***		
	TWBC count		*4000-10500/c.m*		Albumin		*Absent*
	Neutophils		*40-80%*		Sugar		*Absent*
	Lymphocytes		*20-40%*		Acetone		*Absent*
	Monocytes		*2-10%*		Bile pigments		*Absent*
	Esinophils		*1-6%*		Bile salts		*Absent*
	Basophils		*0-2%*		Urobilinogen		*Normal*
	Platelets:				Nitrates		*Negative*
	Platelets count		*150-450X1000/c*		***Micro Exm:***		
	MPV		*6-9.5cum*		Red blood cells		*Absent*
	PCT		*0.2-0.5%*		Pus cells (WBCs)		*0.0-5.0/hpf*
	PDW		*9-17%*		Epithelial cells		*0.0-4.0/hpf*
2	ESR		*0-15%mm/hr*		Crystals		*Absent*
3	HbA1C		*mg/dl*		Cast		*Absent*
	eAG				Ddeposits		*Absent*
4	Syphilis (sero)				Bacteria		*Absent*
	Non reactive		*Below 1.0 index*		Trichomonas Vag		*Absent*
	Reactive		*Above 1.0 index*		Yeast cells		*Absent*

Appendix 24. Modified 5 - points MRC scale for muscle strength scoring

Study code: |__|__|__|__| Study number: |__|__|__| Patient Initials: |__|__|__|

Form A: Voluntary muscle testing

QST_IN_LEPROSY STUDY

ID number _____ Date _____

Muscle assessment

Modified 5-point MRC scale for muscle strength scoring (Grading criteria for the VMT)

HANDS AND FEET	MRC GRADE
Full range of movement	5
Full range of movement, reduced resistance	4
Full range of movement, no resistance	3
Reduced range of movement, some joint movement	2
Flicker only	1
Full paralysis	0

*in addition, eyelid gap in mm is measured and recorded

Movements and muscle tested per nerve

Nerve	Movement	Muscle/Muscle group
Ulnar	Little finger abduction	abductor digiti minimi
Ulnar	Index finger abduction	1st dorsal interosseos
Median	Thumb abduction	abductor pollicis brevis
Radial	Wrist extension	Wrist extensors
Lateral popliteal	Foot dorsiflexion	Foot dorsiflexors
Lateral popliteal	Extension big toe	Extensor hallucis longous
Lateral popliteal	Toe fanning	Intrinsic muscle of the foot
Facial	Closes eyes (strong and gentle closure tested)	Orbicularis oculi

If any particular muscle could not be tested (e.g. because of joint stiffness or previous surgery), a missing value (9) will be recorded for the nerve score. Similarly, if test data are not available for any particular follow-up time, a missing value will be recorded.

Criteria for motor impairment was any muscle scoring, 4.

This form modified from: Notes for completing leprosy neurological assessment, developed by Prof Diana Lockwood, Hospital for Tropical Diseases, London

1

Appendix 25. Sensory testing using Semmes-Weinstein monofilaments

Study code: |__|__|__|__| **Study number:** |__|__|__| **Patient Initials:** |__|__|__|

Form B: Sensory testing using Semmes–Weinstein monofilaments (MF)

Use the nylon monofilaments on the marked sites on hands and feet

Palms **Soles**

R L R L

Hands-do full range Feet – omit 0.05 gm / 0.2 gm

Perform the evaluation in the sequence listed below, and document the first nylon which has a positive response				
Nylon colour	Approx. Force	Interpretation	Score Hands	Score Feet
Green	(0.05 gm)	Sensation within normal limits for the hand and foot	0	-
Blue	(0.2 gm)	Diminished light touch sensation in the hand with difficulty in the fine tactile discrimination. Within normal limits for the foot	1	-
Purple	(2.0 gm)	Diminished protective sensation in the hand but sufficient to prevent injury.	2	0
Dark Red	(4.0 gm)	Loss of protective sensation of the hand, in some cases for the foot. Usually loss of temperature discrimination	3	1
Orange	(10.0 gm)	Definite loss of protective sensation of the foot. Continues to feel deep pressure and pain in both hands and feet.	4	2
Bright red	(300.0 gm)	Able to feel deep pressure and pain	5	3
No response	(....)	Loss of deep pressure sensation. Usually does not feel pain.	6	6
Missing/unable to test			U	U

Criterion for sensory impairment

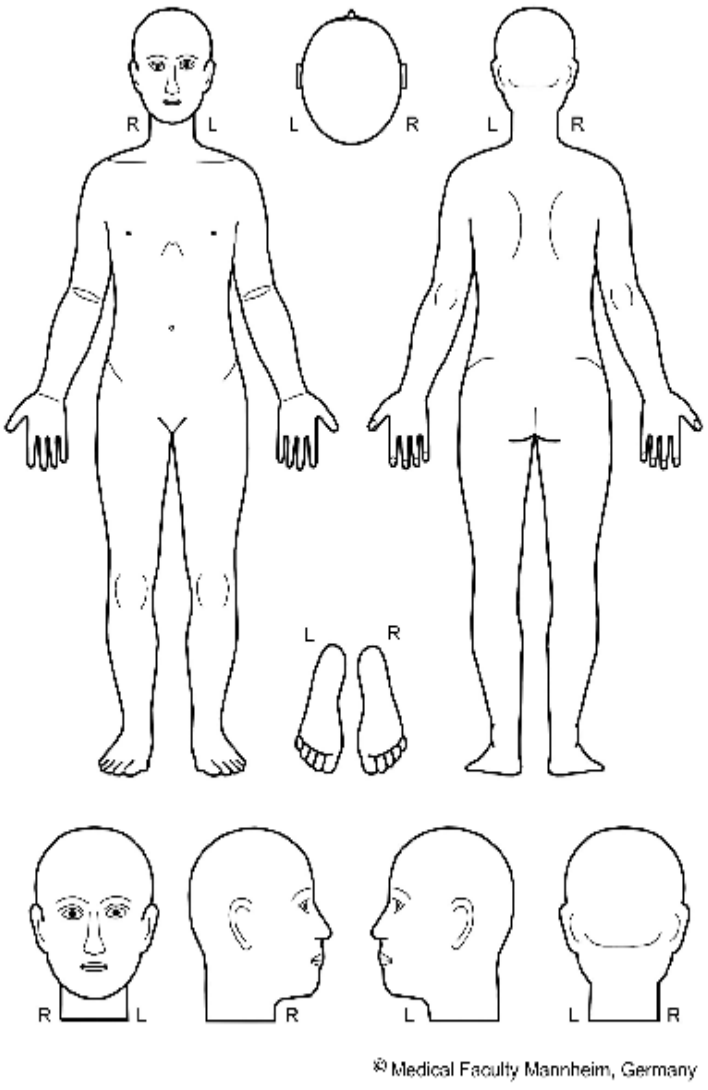
If a patient scores 3 or more for any nerve, the nerve had sensory impairment. The normal sensation level for all sites on the hand is 0.05mg; the normal sensation level for all sites on the foot is 2g.

This form modified from: Notes for completing leprosy neurological assessment, developed by Prof. Diana Lockwood, Hospital for Tropical Diseases, London

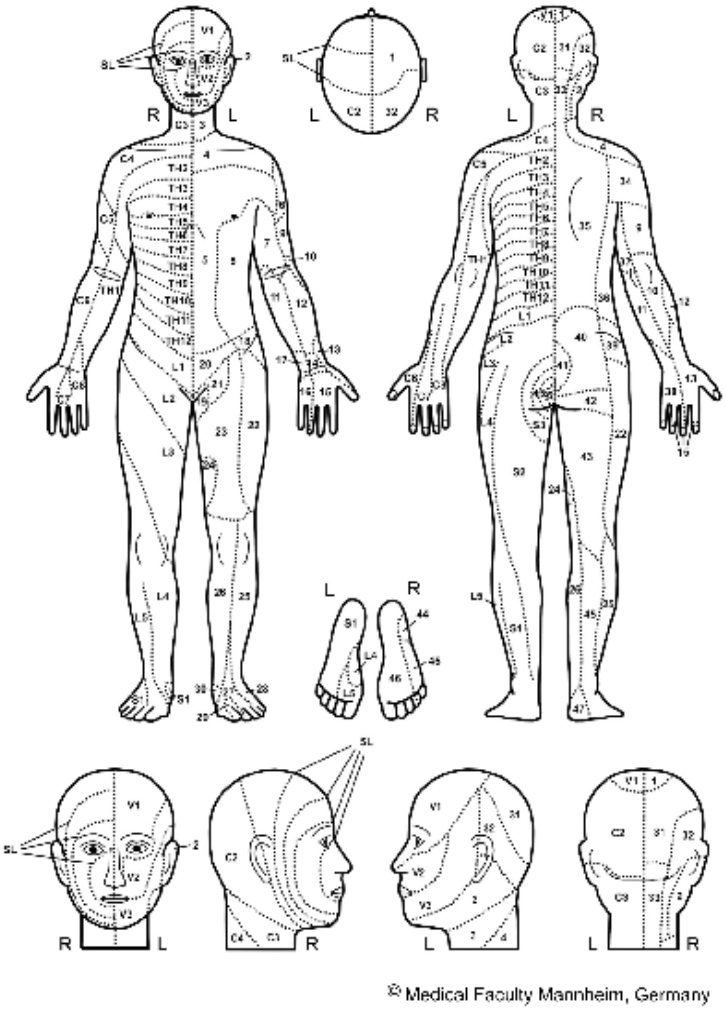
Study code: |__|__|__|__| **Study number:** |__|__|__| **Patient Initials:** |__|__|__|

1

Appendix 26. Body chart



Appendix 27. Dermatomes of the body



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Appendix D

Questionnaires

Appendix 28. DN4 Questionnaire

DN4 – QUESTIONNAIRE

To estimate the probability of neuropathic pain, please answer yes or no for each item of the following four questions.

INTERVIEW OF THE PATIENT

QUESTION 1:

Does the pain have one or more of the following characteristics?	YES	NO
Burning	❑	❑
Painful cold	❑	❑
Electric shocks	❑	❑

QUESTION 2:

Is the pain associated with one or more of the following symptoms in the same area?	YES	NO
Tingling	❑	❑
Pins and needles	❑	❑
Numbness	❑	❑
Itching	❑	❑

EXAMINATION OF THE PATIENT

QUESTION 3:

Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?	YES	NO
Hypoesthesia to touch	❑	❑
Hypoesthesia to pinprick	❑	❑

QUESTION 4:

In the painful area, can the pain be caused or increased by:	YES	NO
Brushing?	❑	❑

YES = 1 point
NO = 0 points

Patient's Score: /10

Appendix 29. DN4 Questionnaire – Hindi vesrion

Patient Initial :-
code :-
Start time :-
End time :-

डी एन ४ - फ़ार्म (DN 4 QUESTIONNAIRE)

अपके तंत्रिकाकृति दर्द का अनुमान लगाने के लिए, कृपया अगले चार प्रश्नोंके 'हां' या 'ना' में जवाब दीजिये:

रोगी की मुलाकात:

प्रश्न १:

क्या आपके दर्द की एक या ज्यादा नीचे लिखी हुई विशेषताएं हैं?

	हाँ	नहीं
जलना	☐	☐
दर्दनाक ठंड	☐	☐
बिजली के झटके जैसा	☐	☐

प्रश्न २:

क्या आपका दर्द नीचे लिखे एक या ज्यादा लक्षण से मिलता जुलता हैं?

	हाँ	नहीं
झुनझुनी जैसा	☐	☐
सूई और चुभने जैसा	☐	☐
सुन्न हो जाना	☐	☐
खुजली जैसा	☐	☐

प्रश्न ३:

क्या आपका दर्द ऐसे जगहपर है जहाँ शारीरिक परिक्षण के बाद नीचे लिखे गए एक या ज्यादा दर्द दिखते हैं?

	हाँ	नहीं
स्पर्श का कम अनुभव	☐	☐
चुभने का कम अनुभव	☐	☐

प्रश्न ४:

क्या वह दर्दनाक जगहपर, नीचे लिखी क्रिया करनेपर दर्द शुरू होता या बढ़ता है?

	हाँ	नहीं
झड़ना	☐	☐

हाँ = १
नहीं = ०

रोगी का अंक = /१०

आपको ये प्रश्नावली कैसा लगा?
(बहुत आसान (१)/आसान (२)/मध्यम (३)/कठीन (४)/बहुत कठीन (५)) – ☐

Appendix 30. DN4 Questionnaire – Marathi version

DN4 प्रश्नावली (Questionnaire)

चेतारुग्णी वेदनेची संभाव्यता (probability) जाणून घेण्यासाठी खालील चार प्रश्नांमधील मुद्द्यांचे कृपया हो किंवा नाही स्वरूपात उत्तर द्या.

रुग्णाची मुलाखत

प्रश्न १:

वेदनेची खालील एक किंवा अधिक लक्षणे आहेत का ?

	हो	नाही
जळजळ	☐	☐
वेदनामय थंड	☐	☐
विद्युत झटका	☐	☐

प्रश्न २:

वेदना होत असलेल्या भागात खालील लक्षणे देखील वाटत आहेत का ?

	हो	नाही
मुंग्या येणे (tingling)	☐	☐
टाचणी आणि सुई	☐	☐
बधीर	☐	☐
खाज	☐	☐

रुग्णाची तपासणी

प्रश्न ३:

खाली दिलेल्यातील एक व अधिक लक्षणे दिसून येतील अशा ठिकाणी वेदना होत आहेत का ?

स्पर्शाची जाणीव कमी	☐	☐
टाचणीची टोच कमी		

प्रश्न ४:

वेदनामय जागी खालील क्रिया केल्यानंतर वेदना वाढते व सुरु होते का?

☐	☐

घासणे ?

हो = १ गुण

नाही = ० गुण

रुग्णाचे गुण /१०

तुम्हाला हा प्रश्नावली कसा वाटला ?

(खुपच सोप्पा (1)/सोप्पा (2)/गडबड (3)/कठीण (4)/खुपच कठीण (5))- ☐

Appendix 31. PainDETECT Questionnaire

painDETECT PAIN QUESTIONNAIRE

Date : _____ Patient: Last name: _____ First name: _____

How would you assess your pain now, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the strongest pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the pain during the past 4 weeks on average?

0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain :

- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your main area of pain

Does your pain radiate to other regions of your body? ☐ yes ☐ no

If yes, please draw the direction in which the pain radiates

Do you suffer from a burning sensation in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g. with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

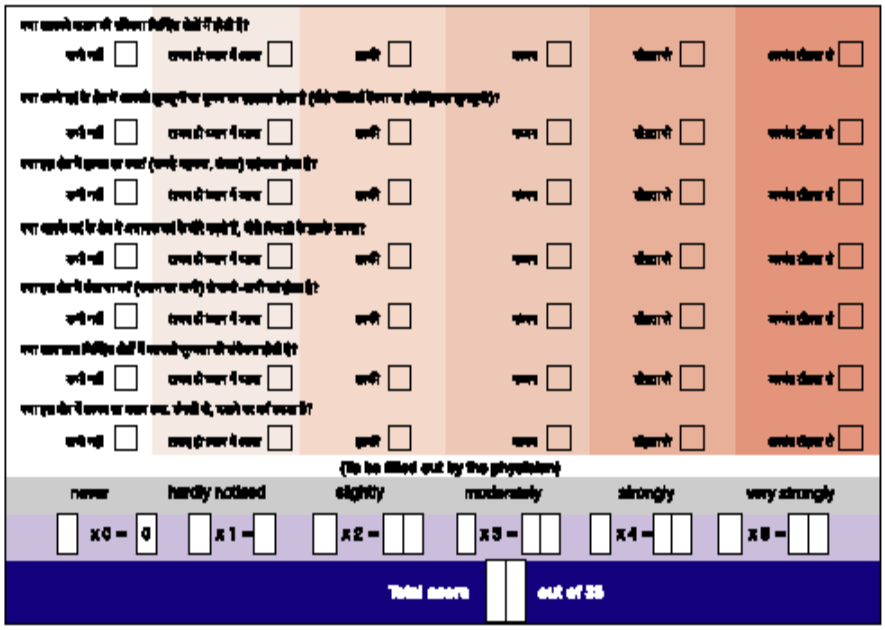
Total score ☐☐ out of 35

LYR_06_0073

Development/Reference : B. Freynhagen, R. Baron, U. Gockel, T. R. Tölle / Curr Med Res Opin, Vol. 22, No.10 (2006)

Appendix 32. PainDETECT Questionnaire – Hindi version

painDETECT दर्द प्रश्नावली



Appendix 33. PainDETECT Questionnaire – Marathi vesrion

painDETECT वेदना प्रश्नावली

never | hardly noticed | slightly | moderately | strongly | very strongly

x 0 = 0 | x 1 = | x 2 = | x 3 = | x 4 = | x 5 =

Total score ___ out of 35

Development/Reference : R. Freynhagen, R. Baron, U. Gockel, T. R. Tölle / Curr Med Res Opin, Vol. 22, No.10 (2006)

Appendix 34. Brief Pain Inventory Questionnaire (BPI)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

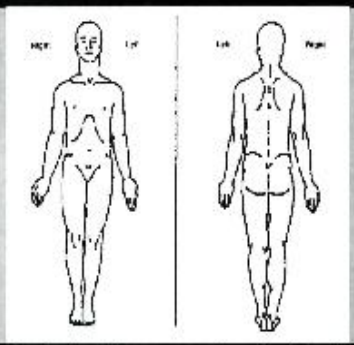
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

   1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Continue…

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

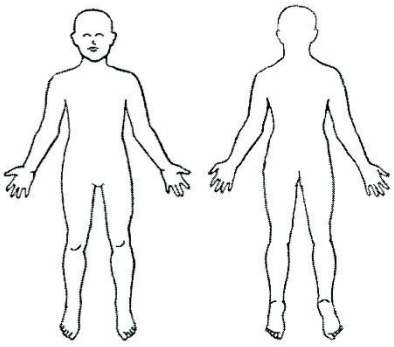
G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Appendix 35. Brief Pain Inventory Questionnaire – Hindi version

Brief Pain Inventory

इस चित्रकारी पर, जहाँ आपको दर्द महसूस होता है वहाँ निशान लगाइये. जहाँ आपको सबसे ज्यादा दर्द हो रहा है वहाँ 'X' लिखिए.



१) कृपया जो अंक आपके पिछले हफ्ते का सबसे दर्दनाक अनुभव का वर्णन करता है उस अंक को गोल कीजिये.

१ २ ३ ४ ५ ६ ७ ८ ९ १०

दर्द नहीं सबसे दर्दनाक

२) कृपया जो अंक आपके मध्यम तौर पर होनेवाले दर्द का वर्णन करता है उस अंक को गोल कीजिये.

१ २ ३ ४ ५ ६ ७ ८ ९ १०

दर्द नहीं सबसे दर्दनाक

३) कृपया जो अंक आपको इस वक्त होनेवाले दर्द का वर्णन करता है उस अंक को गोल कीजिये.

१ २ ३ ४ ५ ६ ७ ८ ९ १०

दर्द नहीं सबसे दर्दनाक

Continue…

हस्तक्षेप मापन

जो अंक पिछले हफ्ते होनेवाले दर्द की वजहसे आपके काम में हस्तक्षेप का वर्णन करता है उस अंक को कृपया गोल कीजिये.

अ) साधारण हलचल

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

ब) मनोदशा

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

क) चलने की क्षमता

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

ड) सामान्य काम (घर के और बाहर के)

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

इ) दुसरे लोगोंके साथ संबंध

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

फ) नींद

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

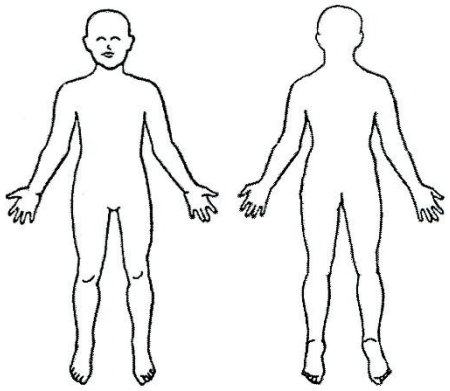
ग) ज़िन्दगी से आनंद

० १ २ ३ ४ ५ ६ ७ ८ ९ १०
कोई हस्तक्षेप नहीं पूरी तरह से हस्तक्षेप

Appendix 36. Brief Pain Inventory Questionnaire – Marathi version

वेदनेचे तीव्रता मूल्यमापन (Brief pain inventory)

आकृतीमध्ये ज्या जागी तुम्हाला वेदना होत असतील त्या जागा भरा. सर्वात जास्त जिथे वेदना होत असतील तिथे 'X' अशी खुण करा.



१) गेल्या आठवड्यातील तुमच्या सर्वात असह्य वेदनांना गुणमान देण्यासाठी, कृपया खालील एका आकड्याला गोल करा.

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

वेदना नाहीत असह्य वेदना

२) तुमच्या मध्यम स्वरूपाच्या वेदनांना गुणमान देण्यासाठी, कृपया खालील एका आकड्याला गोल करा.

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

वेदना नाहीत असह्य वेदना

३) आत्ता ह्या क्षणाला तुम्हांला होणाऱ्या वेदनांना गुणमान देण्यासाठी, कृपया खालील एका आकड्याला गोल करा.

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

वेदना नाहीत असह्य वेदना

Continue…

<u>हस्तक्षेप मोजमापन</u>

जो आकडा, गेल्या आठवड्यातील तुमच्या वेदनांनामुळे तुमच्या कामांमध्ये अडथळा निर्माण झाला हे सांगतो कृपया त्या आकड्याला गोल करा:

अ) सर्वसाधारण कामकाज

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

ब) वृती

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

क) चालण्याची क्षमता

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

ड) रोजचे काम (घराबाहेरील आणि घरातील कामे)

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

ई) इतर लोकांबरोबरचे संबंध

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

फ) झोप

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

ग) आयुष्यातील आनंद

० १ २ ३ ४ ५ ६ ७ ८ ९ १०

बाधा नाही संपूर्ण बाधा

Appendix 37. General Health Questionnaire (GHQ-12)

General Health Questionnaire (GHQ-12)

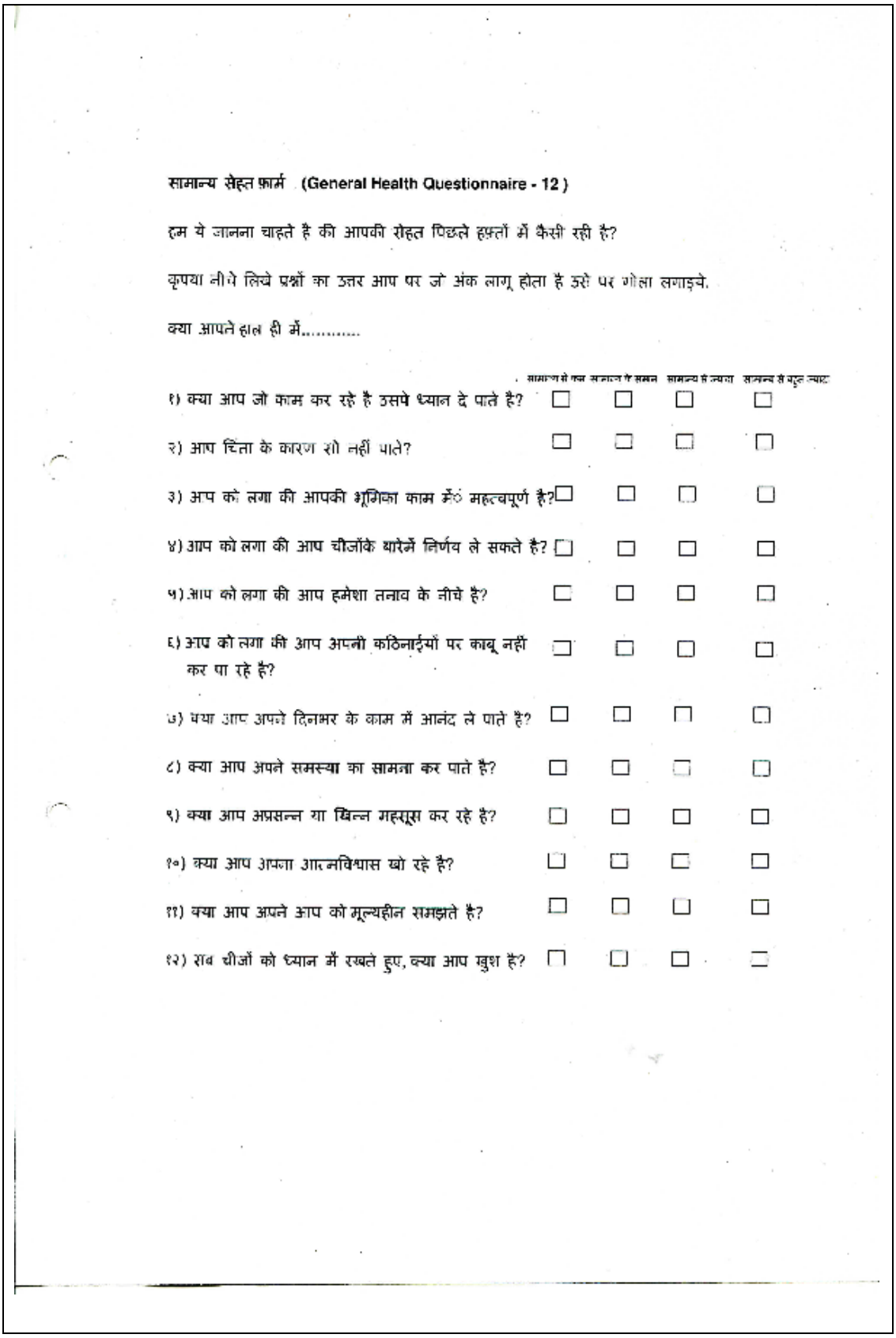
We would like to know how your health has been in general, over the past few weeks.

Please answer the following questions by circling the number that best applies to you.

Have you recently...,

	much less than usual	same as usual	more than usual	much more than usual
Been able to concentrate on whatever you are doing?	○	○	○	○
Lost much sleep over worry?	○	○	○	○
Felt that you were playing a useful part in things?	○	○	○	○
Felt capable of making decisions about things?	○	○	○	○
Felt constantly under strain?	○	○	○	○
Felt that you couldn't overcome your difficulties?	○	○	○	○
Been able to enjoy your normal day-to-day activities?	○	○	○	○
Been able to face up to your problems?	○	○	○	○
Been feeling unhappy and depressed?	○	○	○	○
Been losing self-confidence in yourself?	○	○	○	○
Been thinking of yourself as a worthless person?	○	○	○	○
Been feeling reasonably happy, all things considered?	○	○	○	○

Appendix 38. General Health Questionnaire – Hindi version



सामान्य सेहत फ़ार्म (General Health Questionnaire - 12)

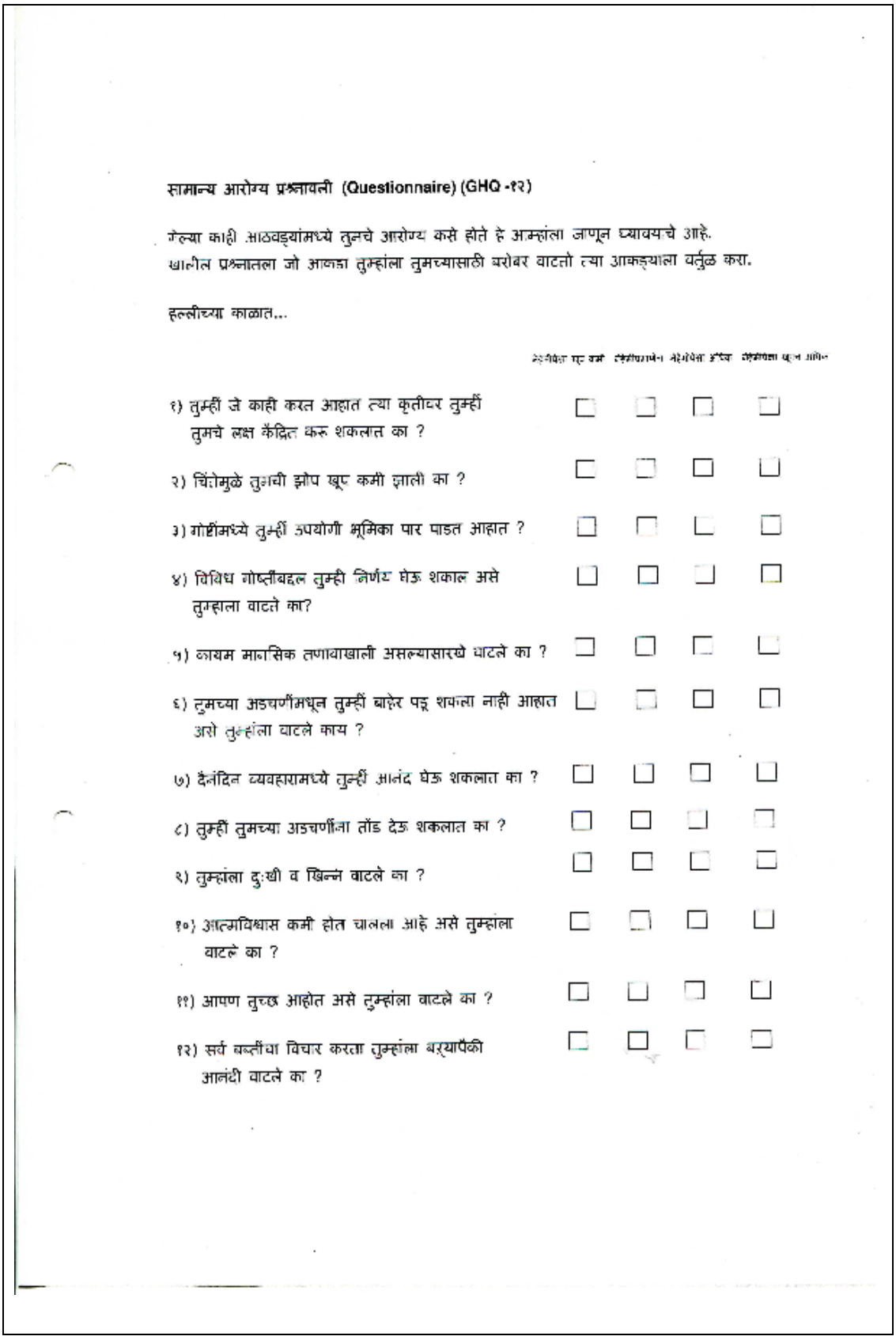
हम ये जानना चाहते है की आपकी सेहत पिछले हफ़्तों में कैसी रही है?

कृपया नीचे लिखे प्रश्नों का उत्तर आप पर जो अंक लागू होता है उसी पर गोला लगाइये.

क्या आपने हाल ही में.....

	सामान्य से कम अनुपात में समान	सामान्य से ज्यादा	सामान्य से बहुत ज्यादा
१) क्या आप जो काम कर रहे है उसपे ध्यान दे पाते है?	☐	☐	☐
२) आप चिंता के कारण सो नहीं पाते?	☐	☐	☐
३) आप को लगा की आपकी भूमिका काम में महत्वपूर्ण है?	☐	☐	☐
४) आप को लगा की आप चीजोंके बारेमें निर्णय ले सकते है?	☐	☐	☐
५) आप को लगा की आप हमेशा तनाव के नीचे है?	☐	☐	☐
६) आप को लगा की आप अपनी कठिनाईयों पर काबू नहीं कर पा रहे है?	☐	☐	☐
७) क्या आप अपने दिनभर के काम में आनंद ले पाते है?	☐	☐	☐
८) क्या आप अपने समस्या का सामना कर पाते है?	☐	☐	☐
९) क्या आप अप्रसन्न या खिन्न महसूस कर रहे है?	☐	☐	☐
१०) क्या आप अपना आत्मविश्वास खो रहे है?	☐	☐	☐
११) क्या आप अपने आप को मूल्यहीन समझते है?	☐	☐	☐
१२) सब चीजों को ध्यान में रखते हुए, क्या आप खुश है?	☐	☐	☐

Appendix 39. General Health Questionnaire – Marathi version



सामान्य आरोग्य प्रश्नावली (Questionnaire) (GHQ -१२)

गेल्या काही आठवड्यांमध्ये तुमचे आरोग्य कसे होते हे आम्हांला जाणून घ्यावयाचे आहे.
खालील प्रश्नातला जो आकडा तुम्हांला तुमच्यासाठी बरोबर वाटतो त्या आकड्याला वर्तुळ करा.

हल्लीच्या काळात...

१) तुम्ही जे काही करत आहात त्या कृतीवर तुम्ही तुमचे लक्ष केंद्रित करू शकलात का ?	☐	☐	☐	☐
२) चिंतेमुळे तुमची झोप खूप कमी झाली का ?	☐	☐	☐	☐
३) गोष्टींमध्ये तुम्ही उपयोगी भूमिका पार पाडत आहात ?	☐	☐	☐	☐
४) विविध गोष्टींबद्दल तुम्ही निर्णय घेऊ शकाल असे तुम्हाला वाटते का?	☐	☐	☐	☐
५) नायम मानसिक तणावाखाली असल्यासारखे वाटले का ?	☐	☐	☐	☐
६) तुमच्या अडचणींमधून तुम्ही बाहेर पडू शकत्या नाही आहात असे तुम्हांला वाटले काय ?	☐	☐	☐	☐
७) दैनंदिन व्यवहारामध्ये तुम्ही आनंद घेऊ शकलात का ?	☐	☐	☐	☐
८) तुम्ही तुमच्या अडचणींना तोंड देऊ शकलात का ?	☐	☐	☐	☐
९) तुम्हांला दुःखी व खिन्न वाटले का ?	☐	☐	☐	☐
१०) आत्मविश्वास कमी होत चालला आहे असे तुम्हांला वाटले का ?	☐	☐	☐	☐
११) आपण तुच्छ आहोत असे तुम्हांला वाटले का ?	☐	☐	☐	☐
१२) सर्व बाबींचा विचार करता तुम्हांला बऱ्यापैकी आनंदी वाटले का ?	☐	☐	☐	☐

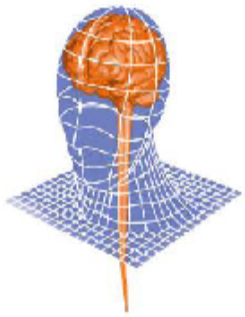
Appendix E

DFNS-QST Protocol

Appendix 40. Verbal instructions for performing QST-DFNS protocol

QST
QUANTITATIVE SENSORY TESTING

Version 2.1 - 08.07.2010



Short form - Instructions

A standardized battery of Quantitative Sensory Testing
according to the protocol of the
German Research Network on Neuropathic Pain (DFNS)

R. Rolke, K. Andrews, W. Magerl, R.-D. Treede

Version 2.1 revised by:

D. Pfau, T. Klein, J. A. Blunk, C. Geber, E. Krumova, C. Limbeck, W. Magerl,
C. Maier, A. Westermann, S. Schuh - Hofer, W. Tiede, R.-D. Treede

Continue…

General instructions for the volunteers/patients

"In the following tests, we will explore, using various procedures, how you perceive temperature changes as well as touch and vibration stimuli. In addition, we will examine, from what point on different test stimuli are felt as being painful. The results of these tests are compared to normative data gained from healthy volunteers. To make this possible, these tests are always performed in the same manner. To ensure this, among others, the test instructions will be read to you aloud.

If you have not understood the test instructions, please always feel free to immediately ask for clarification."

a.) Thermal detection thresholds and thermal pain thresholds

Demonstration of the test procedure

"The device placed on your skin is able to either warm or cool the skin. In addition you are given a stop button that enables you to immediately stop the ongoing test stimulus at any time. For every test I will explain to you when to use the stop button.

Please tell me, whether the device on your skin feels warm, cool or neutral.

Please do not look at the computer screen during the test procedures."

CDT *"First we will test your ability to perceive cold sensations. Please press the stop button immediately once you perceive a change in temperature to cool/cooler for the first time. Subsequently, the thermode will warm up again, until it reaches the baseline temperature. This procedure will start in a few seconds."*

WDT *"Now we will test your ability to perceive warm sensations. Please press the stop button immediately once you perceive a change in temperature to warm/warmer for the first time. Subsequently, the thermode will cool down again, until it reaches the baseline temperature. This procedure will start in a few seconds."*

TSL *"Now we will test how well you are able to discern between successive temperature changes. Please press the stop button immediately once you feel a temperature change towards "warm" or "cold" sensations, and tell us explicitly whether you felt the temperature change as "warm" or "cold". It may well be that some of the temperature changes are felt as "hot" or "painfully hot"."*

CPT *"Now we will test as to when you perceive the cooling of the thermode as painful. Your skin will be slowly cooled. At some point in time you will feel a second sensation on top of the usual "cold" sensation. The impression of "cold" will change its quality towards an additional impression of a "burning", "stinging", "drilling" or "aching" sensation. Please press the stop button immediately once you perceive such a change. Please **DO NOT** wait to press the stop button until the sensation has become unbearably painful. Subsequently, the thermode will warm up again, until it reaches the baseline temperature. This procedure will start in a few seconds."*

HPT *"Now we will test as to when you perceive the warming of the thermode as painful. Your skin will be slowly warmed. At some point in time you will feel a second sensation on top of the usual "warm" or "hot" sensation. The impression of "warmth" or "heat" will change its quality towards an additional impression of a "burning", "stinging", "drilling" or "aching" sensation. Please press the stop button immediately once you perceive such a change. Please **DO NOT** wait to press the stop button until the sensation has become unbearably painful. Subsequently, the thermode will cool down again, until it reaches the baseline temperature. This procedure will start in a few seconds."*

Continue…

Testing within the control and test site

Please tell me, whether the device on your skin feels warm, cool or neutral."

CDT *"Just as we have done in the practice round, you will first perceive a cooling of the skin. Please press the stop-button immediately as soon as you first feel a change of temperature to "cool or cooler".*
This procedure will be performed a total of 3 times."

WDT *"Please press the stop-button immediately as soon as you first perceive a warming of the skin. Again this procedure will be performed a total of 3 times."*

TSL *"Please press the stop-button immediately as soon as you first perceive any kind of temperature change. Please state, whether the sensation was "cold", "warm", "hot" or "painfully hot". This procedure will be performed a total of 6 times."*

CPT *"Please press the stop-button immediately as soon as the "cold" sensation changes its quality to an additional sensation of "burning", "stinging", "drilling" or "aching". This procedure will be performed a total of 3 times."*

HPT *"Please press the stop-button immediately as soon as the "warm" or "hot" sensation changes its quality to an additional sensation of "burning", "stinging", "drilling" or "aching". This procedure will be performed a total of 3 times."*

b.) Tactile detection thresholds

Demonstration of the test procedure

MDT *"This is a test of your ability to detect light touch. Please do not look at the skin area we are testing at any time during the test procedures. I will now touch your skin with these thin hairs. Please say "yes" as soon as you perceive a touch sensation"*

Testing within the control or test site

MDT *"Please say "yes" as soon as you perceive a touch sensation."*

Continue…

c.) Mechanical pain threshold

Familiarization – Demonstration of the test procedure

MPT *"This is a test of your ability to perceive "sharp", "pricking" or "stinging" stimuli. Various fine metal rods that are able to exert different pressure intensities will be carefully placed onto your skin.*

Please say "sharp" as soon as you no longer perceive only a touching sensation on your skin, but experience an additional "sharp", "pricking" or "stinging" sensation.

Please say "blunt" when you only feel a touching sensation.

Under no circumstances, you should look at the skin area we are testing during the test procedure!"

Testing within the control or test site

MPT *Please say "sharp" as soon as you not only perceive a touching sensation on your skin, but an additional "sharp", "pricking" or "stinging" sensation.*
Please say "blunt" when you only perceive a touching sensation.

d.) S/R-(Stimulus/Response) functions: Mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA)

Familiarization – Demonstration of the test procedure

MPS *"As in the test before, blunt fine metal rods will be carefully pressed against your skin with varying pressure.*

DMA *In between these punctual stimuli your skin will occasionally be touched by a cotton wisp, a Q-tip, and a brush. Some of these stimuli may be accompanied by a "sharp", "pricking", "stinging" or "burning" sensation. Other stimuli may only be perceived as a touching sensation, others may not be perceived at all.*

Please rate the painfulness of each stimulus by giving a number between "0" and "100". Any "sharp", "pricking", "stinging" or "burning" sensation should be defined as being painful and given a rating value above "0". You may also use decimals.

"0" meaning: No pain, no "sharp", "pricking", "stinging" or "burning" sensation.
"100" meaning: Most intense pain sensation imaginable.

Under no circumstances, you should look at the skin area we are testing during the test procedure!

(Should the subject/patient give a rating of "100", please ask:

Are you sure that this was the most intense pain sensation imaginable for you?")

Testing within the control or test site

MPS *"Again, please rate the painfulness of each stimulus by giving a number between "0" and "100".*

DMA *"0" meaning: No pain, no "sharp", "pricking", "stinging" or "burning" sensation.*
"100" meaning: Most intense pain sensation imaginable."

(Should the subject/patient give a rating of "100", again please ask:

"Are you sure that this was the most intense pain sensation imaginable for you?"

If applicable: *"Then we will no longer use this or any other of the more severe stimuli."*)

QST instructions according to the protocol of the German Research Network on Neuropathic Pain (DFNS)
Version 2.1 - 08.07.2010

Continue…

e.) Wind-up ratio

Familiarization – Demonstration of the test procedure

WUR

"Like in the former test I will now press a single fine metal rod against your skin. Please rate the painfulness of this single stimulus by giving a number between "0" and "100" Any "sharp", "pricking", "stinging" or "burning" sensation should be defined as being painful and given a rating value above "0" You may also use decimals.

"0" meaning: No pain, no "sharp", "pricking", "stinging" or "burning" sensation.
"100" meaning: Most intense pain sensation imaginable.

Now I will apply a series of 10 stimulations with the same metal rod at 1 second intervals on your skin. Once the entire series is over, please rate its average painfulness by giving a number between "0" and "100".

"0" again meaning: No pain, no "sharp", "pricking", "stinging" or "burning" sensation.
"100" meaning: Most intense pain sensation imaginable."

Testing within the control or test site

WUR *"The whole procedure of applying one single stimulus followed by the stimulus series will be carried out within this area and will be repeated 5 times. Please rate again how painful this single stimulus was on a scale of 0 to 100.*

"0" meaning: No pain, no "sharp", "pricking", "stinging" or "burning" sensation.
"100" meaning: Most intense pain sensation imaginable.

Please rate again how painful the stimulus series was on a scale of 0 to 100."

f.) Vibration detection threshold

Familiarization – Demonstration of the test procedure

VDT *"This procedure tests your ability to perceive "vibrations". I will now place this vibrating tuning fork on your skin. Please tell me if you are able to feel the vibrations?*

Please immediately say "NOW" as soon as you are no longer able to feel any further vibrations!

You may hear the vibrations of the tuning fork as a sound. Please try to pay attention only to the vibration, and not to the sound."

Testing within the control and test site

VDT *"A series of 3 consecutive tests will now be carried out within the control and the test site. I will now place this vibrating tuning fork on your skin. Please tell me if you are able to feel the vibrations?*

Please immediately say "NOW" as soon as you are no longer able to feel any further vibrations!"

Continue…

g.) Pressure pain threshold

Familiarization – Demonstration of the test procedure

PPT *"This procedure tests your ability to feel pressure pain above muscles.*

I will press this pressure measuring device against one of your muscles. Please immediately say "NOW" as soon as the usual sensation of pressure changes towards an additional sensation of "burning", "stinging", "drilling" or "aching"."

Testing within the control and test sites

PPT *"Again, I will press this pressure measuring device against one of your muscles. Please immediately say "NOW" as soon as the usual sensation of pressure changes towards an additional sensation of "burning", "stinging", "drilling" or "aching"."*

This procedure will be carried out a total of 3 times."

Appendix 41. QST-DFNS protocol – Hindi version

Hindi Version

Appendix
General instructions for the volunteers/patients:

"अगले परिक्षण में हम विविध प्रक्रिया इस्तेमाल करके ये जाँच लेंगे कि आप तापमान में होनेवाले बदल, स्पर्श और कंपन उत्तेजन को किस प्रकार समझते है. उसी तरह हम ये जाँच लेंगे कि किस स्तर से आपको विविध परिक्षण उत्तेजन दर्दनाक महसूस होते है. इस परिक्षण के अंतिम परिणाम, निरोगी स्वयंसेवकों से इकट्ठा की हुई जानकारी से तुलना की जाएगी. ये मुमकिन करने के लिए ये परिक्षण हमेशा एक ही प्रकार से किया जाएगा. ये सुनिश्चित करने के लिए ये सूचना आपको पढकर समझायी जाएगी.

अगर आपको परिक्षण की सूचना समझ में नहीं आए है तो कृपया आप तुरंत या कभी भी स्पष्टीकरण माँग सकते है."

A) Thermal detection thresholds and thermal pain thresholds:
Demonstration of the test procedure:

"आपकी त्वचा पर रखा गया यंत्र, उष्ण या ठंडा होता है. इस यंत्र के साथ आपको एक बंद करने का बटन दिया गया है जो आप किसी भी वक्त परिक्षण उत्तेजन रोकने के लिए इस्तेमाल कर सकते है. मैं आपको समझाऊंगी कि हर परिक्षण के लिए आपको कब ये बंद करने का बटन इस्तेमाल करना है.

कृपया मुझे बताईये कि आपकी त्वचा पर रखा गया यंत्र आपको उष्ण, ठंडा या निष्क्रिय लगता है.

कृपया परिक्षण प्रक्रिया शुरू होने पर कंप्यूटर के परदे को ना देखे."

CDT - "पहले हम आपकी ठंड संवेदन महसूस करने की क्षमता जाँच लेंगे. कृपया जब आपको तापमान में पहिले बार ठंडा/अधिक ठंडा बदल महसूस हो तब बंद बटन को तुरंत दबाईये. इसके पश्चात ये यंत्र सामान्य तापमान पर आ जाएगा. ये प्रक्रिया कुछ सेकंडो में शुरू होगी."

WDT - "अब हम आपकी उष्ण संवेदन महसूस करने की क्षमता जाँच लेंगे. कृपया जब आपको तापमान में पहिले बार उष्ण/अधिक उष्ण बदल महसूस हो तब बंद बटन को तुरंत दबाईये. पश्चात ये यंत्र सामान्य तापमान पर आ जाएगा. ये प्रक्रिया कुछ सेकंडों में शुरू होगी."

TSL - "तापमान में होनेवाले बदल आप कितनी अच्छी तरह से परख सकते है ये हम अब देखेंगे. कृपया जब आपको तापमान में 'उष्ण' या 'ठण्ड' बदल महसूस हो तब बंद बटन तुरंत दबाईये और हमें स्पष्ट बताईये कि तापमान में 'उष्ण' या ठण्ड' बदल महसूस हुआ. कभी कभी आपको ये तापमान गरम या दर्दनाक गरम महसूस हो सकता है."

CPT - "अब हम ठंडा स्पर्श कब दर्दनाक होता है इसका परिक्षण करेंगे. आपकी त्वचा धीरे धीरे ठंडी की जाएगी. एक समय ऐसा आएगा जब साधारण ठंड संवेदन के ऊपर और संवेदन होगा. ये ठंडा संवेदन बदलकर इसके ऊपर आपको जलने, डंक, बेधनीय या वेदना जैसे लगेगा. जब आपको ये बदल महसूस होगा तब कृपया तुरंत बंद बटन दबाईये. कृपया ये संवेदन असहनीय दर्दनाक होने तक ना रुके और तुरंत बंद बटन दबाईये. पश्चात ये यंत्र सामान्य तापमान पर आ जाएगा. ये प्रक्रिया कुछ सेकंडों में शुरू होगी."

HPT - "अब हम उष्ण स्पर्श कब दर्दनाक होता है इसका परिक्षण करेंगे. आपकी त्वचा धीरे धीरे गरम की जाएगी. एक समय ऐसा आएगा जब साधारण उष्ण संवेदन के ऊपर और संवेदन होगी. ये उष्ण संवेदन बदलकर इसके ऊपर आपको जलने, डंक, बेधनीय या वेदना जैसे लगेगा. जब आपको ये बदल महसूस होगा तब कृपया तुरंत बंद बटन दबाईये. कृपया ये संवेदना असहनीय दर्दनाक होने तक ना रुके और तुरंत बंद बटन दबाईये. पश्चात ये यंत्र सामान्य तापमान पर आ जाएगा. ये प्रक्रिया कुछ सेकंडों में शुरू होगी."

Continue…

Testing within the control and test site:

"कृपया मुझे बताईये कि आपकी त्वचा पर रखा गया यंत्र आपको उष्ण, ठंडा या निष्पक्ष लगता है."

CDT - "जैसे हमने पहले किया है, वैसे आपकी त्वचा पर शुरू में ठंडा स्पर्श होगा. कृपया जब आपको पहले तापमान में ठंडा/अधिक ठंडा बदल महसूस हो तब बंद बटन को तुरंत दबाईये. ये प्रक्रिया तीन बार की जाएगी."

WDT - "कृपया जब आपको पहले तापमान में उष्ण/अधिक उष्ण बदल महसूस हो तब बंद बटन को तुरंत दबाईये. ये प्रक्रिया तीन बार की जाएगी."

TSL - "कृपया जब आपको तापमान में कोई भी बदल महसूस हो तब बंद बटन तुरंत दबाईये. कृपया हमें स्पष्ट बताईये कि तापमान में 'उष्ण', 'ठण्ड', 'गरम' या 'दर्दनाक गरम' बदल महसूस हुआ. ये प्रक्रिया ६ बार की जाएगी."

CPT - "कृपया जब 'ठण्ड' संवेदन के ऊपर आपको जलने, डंक, बेधनीय या वेदना जैसे लगने लगता है तब बंद बटन तुरंत दबाईये. ये प्रक्रिया तीन बार की जाएगी."

HPT - "कृपया जब 'उष्ण' या 'गरम' संवेदन के ऊपर आपको जलने, डंक, बेधनीय या वेदना जैसे लगने लगता है तब बंद बटन तुरंत दबाईये. ये प्रक्रिया तीन बार की जाएगी."

) Tactile detection thresholds:
Demonstration of the test procedure:

MDT - "ये परिक्षण आपका हलका स्पर्श जानने की क्षमता के लिए है. कृपया त्वचा के जिस हिस्से पर हम जाँच कर रहे हैं, उस हिस्से को परिक्षण के समय ना देखे. मैं अब आपको इन पतले केश से स्पर्श करुंगी. कृपया 'हाँ' बोलिए जिस समय आपको इस स्पर्श की अभिज्ञता होती है."

Testing within the control or test site:

MDT - "जिस समय आपको इस स्पर्श की अभिज्ञता होती है उस समय कृपया 'हाँ' बोलिए ."

C) Mechanical pain threshold:
Familiarization - Demonstration of the test procedure:

MPT - "ये परिक्षण आपके तीव्र, चुभना, और डंक के उत्तेजन को समझने की है. तरह तरह धातू के छोटे पिन आपकी त्वचा पर सावधानी से विविध दबाव मात्र में रखे जाएंगे. कृपया 'शार्प' ऐसे बोलिए जब आपको त्वचा पर मामूली स्पर्श महसूस होनेके अतिरिक्त तीव्र, चुभना, और डंक जैसे महसूस होता है.

जब आपको सिर्फ मामूली स्पर्श महसूस होता है तब कृपया 'ब्लंट' ऐसे कहिये.

किसी भी परिस्थिति में आप के त्वचा के जिस जगह पर परीक्षा हो रही है वहाँ न देखे."

Testing within the control or test site:

MPT - "कृपया 'शार्प' ऐसे बोलिए जब आपको त्वचा पर मामूली स्पर्श महसूस होनेके अतिरिक्त तीव्र, चुभना, और डंक जैसे महसूस होता है.

कृपया 'ब्लंट' ऐसे कहिये जब आपको सिर्फ मामूली स्पर्श महसूस होता है."

Continue…

D) S/R - (Stimulus/Response) Functions: Mechanical pain sensitivity (MPS) and Dynamic mechanical allodynia (DMA):
Familiarization - Demonstration of the test procedure:

MPS - "पहले परिक्षण के समान, तरह तरह की धातू के छोटे पिन आपके त्वचा पर सावधानी से विविध दबाव मात्र में रखे जाएंगे.

DMA - इस परिक्षण के बीच में आपके त्वचा पर रूई, रूई बड (q tip) या ब्रश रखा जाएगा. इस में से कुछ उत्तेजक आपको तीव्रता, चुभना, जलन और डंक जैसे स्पर्श देंगे. कुछ उत्तेजक आपको एक हल्का स्पर्श देंगे और कुछ उत्तेजक शून्य स्पर्श देंगे.

कृपया हर उत्तेजक आपको कितना दर्दनाक होता है उसे १ से १०० तक गुणमान दीजिये. किसी भी तीव्रता, चुभन, जलन और डंक जैसे स्पर्श को दर्दनाक कहकर शून्य के ऊपर गुणमान दीजिये. आप दशमलव पद्धति का इस्तेमाल कर सकते है.

"०" का अर्थ दर्दरहित, तीव्रताहीन, न चुभना, न जलना, और न डंक जैसा स्पर्श होता है.
"१००" का अर्थ सबसे अधिक दर्द संवेदन कल्पनीय.

किसी भी परिस्थिति में आप जिस जगह पर परीक्षा हो रही है वहां न देखे."

If the patient/volunteer gives a score of 100, please ask them:

"क्या आप निश्चित है कि ये आपको होनेवाला सबसे अधिक दर्दनाक है?"

Testing within the control or test site:

MPS - "फिर से, कृपया हर उत्तेजक आपको कितना दर्दनाक होता है उसे १ से १०० तक गुणगान दीजिये.

DMA - "०" का अर्थ दर्दरहित, तीव्रताहीन, न चुभना, न जलना, और न डंक जैसा स्पर्श होता है.
"१००" का अर्थ सबसे अधिक दर्द संवेदन कल्पनीय.

If the patient/volunteer gives a score of 100, please ask them:

"क्या आप निश्चित है कि ये आपको होनेवाला सबसे अधिक दर्द है?"

If applicable: "फिर हम इस तरह कि तीव्र उत्तेजक का इस्तेमाल नही करेंगे."

E) Wind up ratio:
Familiarization - Demonstration of the test procedure:

WUR - "पहले परिक्षण की तरह, मैं एक धातु की छोटी पिन आपके त्वचा पर रखूँगी. कृपया ये उत्तेजक आपको कितना दर्दनाक होता है उसे १ से १०० तक गुणमान दीजिये. किसी भी तीव्रता, चुभना, जलन और डंक जैसे स्पर्श को दर्दनाक कहकर शून्य के ऊपर गुणमान दीजिये. आप दशमलव पद्धति का इस्तेमाल कर सकते है.

"०" का अर्थ दर्दरहित, तीव्रताहीन, न चुभना, न जलना, और न डंक जैसा स्पर्श होता है.
"१००" का अर्थ सबसे अधिक दर्द संवेदन कल्पनीय.

अब मैं एक सेकंड के अंतर पे यही धातु की छोटी पिन का उत्तेजक १० बार आपके त्वचा पर रखूँगी. यह १० उत्तेजक की क्रिया समाप्त होने पर कृपया इस दर्द को ० से १०० तक मध्यगवर्ती गुणगान दीजिये.

"०" का अर्थ दर्दरहित, तीव्रताहीन, न चुभना, न जलना, और न डंक जैसा स्पर्श होता है.
"१००" का अर्थ सबसे अधिक दर्द संवेदन कल्पनीय.

Continue…

Testing within the control or test site:

WUR - "ये पूर्ण एक उत्तेजक की क्रिया और उसके बाद १० उत्तेजक की क्रिया इस भाग में की जाएगी और ५ बार की जाएगी. कृपया इस उत्तेजक आपको कितना दर्दनाक होता है उसे १ से १०० तक गुणमान दीजिये.

"०" का अर्थ दर्दरहित, तीव्रताहीन, न चुभना, न जलना, और न डंक जैसा स्पर्श होता है
"१००" का अर्थ सबसे अधिक दर्द."

कृपया इस उत्तेजक आपको कितना दर्दनाक होता है उसे १ से १०० तक गुणमान दीजिये.

F) Vibration detection threshold:
Familiarization - Demonstration of the test procedure:

VDT - "ये प्रक्रिया आपकी कंपन मर्यादा समझने के लिए है. अब मैं इस कंपन यंत्र को आपके त्वचा पर रखूँगी. कृपया मुझे बताईए की क्या आपको कंपन महसूस हो रहे है?

कृपया जिस समय आपको कंपन महसूस होना बंद होता है तभी तुरंत "अभी" ऐसे कहिये.

आपको शायद कंपन की आवाज सुनाई देगी. कृपया आपका संपूर्ण ध्यान आवाजपर ना रखकर सिर्फ कंपन पर रखिये."

Testing within the control or test site:

VDT - "अब ३ परिक्षण एक के बाद एक आपके त्वचा पर किये जायेंगे. अभी मैं इस कंपन यंत्र को आपके त्वचे पर रखूंगी. कृपया मुझे बताईए की क्या आपको कंपन महसूस हो रहे है?

कृपया जिस समय आपको कंपन महसूस होना बंद होता है तभी तुरंत "अभी" ऐसे कहिये.

G) Pressure pain threshold:
Familiarization - Demonstration of the test procedure:

PPT - "ये परिक्षण आपकी मांसपेशी के ऊपर दबाव से दर्द का मापन करेगी. मैं ये दबाव मापन यंत्र आपके एक मांसपेशी पर दबाऊँगी. कृपया जिस समय साधारण दबाव जलन, तीव्रता, बेधनीय, या वेदनामय में बदलता है उस समय तुरंत "अभी" ऐसे कहिये.

Testing within the control or test site:

PPT - "मैं फिर से ये दबाव मापन यंत्र आपके एक मांसपेशी पर दबाऊँगी. कृपया जिस समय साधारण दबाव जलन, तीव्रता, बाधनीय, या वेदनामय में बदलता है उस समय तुरंत "अभी" ऐसे कहिये.

ये क्रिया ३ बार की जाएगी."

Appendix 42. QST-DFNS protocol – Marathi version

Marathi Version

Appendix

General instructions for the volunteers/patients:

"पुढील परीक्षणांमध्ये, विविध पद्धती वापरून तापमानातील बदल तसेच स्पर्श व कंपन उत्तेजन. तुम्हांला काय प्रकारे जाणवते हे आपण समजून घेऊ.

तसेच आपण परीक्षण करू की कुठल्या स्थितीपासून वेगवेगळे उत्तेजक तुम्हांला वेदना देऊ लागतात.

ह्या परीक्षणाचे निकाल निरोगी स्वयंसेवकांच्या परीक्षणाबरोबर तोलले जातील.

हे शक्य होण्यासाठी ह्या परीक्षा नेहेमीच एकाच पद्धतीप्रमाणे केल्या जातील. हे खातरजमा करण्यासाठी परीक्षेच्या सुचना स्पष्ट शब्दांमध्ये तुम्हांला समजावल्या जातील.

जर तुम्हांला त्या राजजल्या नाहीत तर कृपया मोकळ्या मनाने लगेच आम्हांला विचारा करा."

A) Thermal detection thresholds and thermal pain thresholds

Demonstration of the test:

तुमच्या त्वचेवर ठेवले गेलेले यंत्र हे तुमची त्वचा थंड किंवा उष्ण करेल. त्या यंत्राबरोबरच ही प्रक्रिया, गरज पडल्यास थांबवण्यासाठी तुम्हांला एक बटण दिले गेले आहे. प्रत्येक परीक्षेराठी, त्या बटणाचा वापर कधी करायचा आहे हे मी तुम्हांला समजावेन.

कृपया तुमच्या त्वचेवर ठेवले गेलेले यंत्र तुम्हांला थंड, उष्ण किंवा तटस्थ वाटत आहे.

कृपया कम्प्युटरच्या पडद्याकडे बघू नका."

CDT - "पहिल्यांदा आपण तुमची थंड संवेदनाची समर्थतेचे परीक्षण करू. कृपया जेव्हां तुम्हांला तापमानात पहिल्यांदा थंड आणि अती थंड बदल जाणवेल तेव्हा लगेच बंद करण्याचे बटण दाबा. पश्यात हे यंत्र पुन्हां साधारण तापमानावर येईल. ही प्रक्रिया काही सेकंदांमध्ये सुरु होईल."

WDT - "आता आपण तुमची उष्ण संवेदनाची समर्थतेचे परीक्षण करू. कृपया जेव्हां तुम्हांला तापमानात पहिल्यांदा उष्ण आणि अती उष्ण बदल जाणवेल तेव्हा लगेच बंद करण्याचे बटण दाबा. पश्यात हे यंत्र पुन्हा साधारण तापमानावर येईल. ही प्रक्रिया काही सेकंदांमध्ये सुरु होईल."

TSL - "तापमानातील बदल तुम्ही किती चांगल्या प्रकारे ओळखू शकता हे आपण आता बघू. कृपया जेव्हां तुम्हाला तापमानामध्ये थंड किंवा उष्ण बदल जाणवेल, तेव्हां तातडीने बंद बटण दाबा, आणि आम्हांला तापमानातील हा थंड किंवा उष्ण बदल स्पष्टपणे सांगा. कदाचित हे बदल तुम्हाला गरम किंवा वेदनापूर्ण गरम जाणवतील."

Continue…

CPT - "आता आपण थंड बदल कधी वेदनामय होतो, हे तपासुया. तुमची त्वचा हळूहळू थंड करण्यात येईल. कधीतरी एका क्षणानंतर तो थंड स्पर्श तुम्हांला वेदनामय होऊ लागेल. हा थंड स्पर्श बदलेल आणि तुम्हाला जळजळ, डंख, गिरमिट, किंवा ठणकण्यासारखा जाणवू लागेल. कृपया हा बदल असह्य होईस्तोवर थांबू नका. लगेच बटण दाबा. बटण दाबल्यानंतर, ते यंत्र पुन्हां साधारण तापमानावर येईल. ही प्रक्रिया काही सेकंदांमध्ये सुरू होईल."

HPT - "आता आपण उष्ण बदल कधी वेदनामय होतो, हे तपासुया. तुमची त्वचा हळूहळू गरम करण्यात येईल. कधीतरी एका क्षणानंतर तो उष्ण स्पर्श तुम्हांला वेदनामय होऊ लागेल. हा उष्ण स्पर्श बदलेल आणि तुम्हाला जळजळ, डंख, गिरमिट, किंवा ठणकण्यासारखा जाणवू लागेल. कृपया हा बदल असह्य होईस्तोवर थांबू नका. लगेच बटण दाबा. बटण दाबल्यानंतर, ते यंत्र पुन्हां साधारण तापमानावर येईल. ही प्रक्रिया काही सेकंदांमध्ये सुरू होईल."

Testing within the control and test site:

"कृपया तुमच्या त्वचेवर ठेवले गेलेले यंत्र तुम्हांला थंड, उष्ण किंवा तटस्थ वाटत आहे."

CDT - 'जसे आपण आधी बघितले तसे तुम्हांला पहिल्यांदा थंड संवेदना होईल. जेव्हा तुम्हांला तापमानातील बदल थंड किंवा अति थंड वाटतो तेव्हां कृपया लगेच बंद बटण दाबा. ही प्रक्रिया तीन वेळा केली जाईल."

WDT - "जसे आपण आधी बघितले तसे तुम्हांला पहिल्यांदा उष्ण संवेदना होईल. जेव्हा तुम्हांला तापमानातील बदल उष्ण किंवा अति उष्ण वाटतो तेव्हां कृपया लगेच बंद बटण दाबा. ही प्रक्रिया तीन वेळा केली जाईल."

TSL - "ज्या क्षणी तापमानामध्ये तुम्हांला बदल जाणवू लागेल तेव्हां कृपया लगेच बंद बटण दाबा. कृपया ही संवेदना थंड, उष्ण, गरम की वेदनापूर्ण गरम होता हे स्पष्ट सांगा. ही प्रक्रिया सहा वेळा केली जाईल."

CPT - "कृपया 'बंद बटण' लगेच दाबा ज्या क्षणी थंड संवेदनाच्या वर तुम्हांला जळजळ, डंख, गिरमिट, किंवा ठणकण्यासारखा जाणवू लागेल. ही प्रक्रिया तीन वेळा केली जाईल."

HPT - 'ज्या क्षणी उष्ण संवेदनाच्या वर तुम्हांला जळजळ, डंख, गिरमिट, किंवा ठणकण्यासारखा जाणवू लागेल तेव्हा कृपया बंद बटण लगेच दाबा. ही प्रक्रिया तीन वेळा केली जाईल."

Continue…

B) Tactile detection thresholds

Demonstration of the test procedure:

MDT - "ही परीक्षा तुमची हलका स्पर्श ओलाखन्याची परीक्षण आहे. कृपया त्वचेचा जो भाग तपासला जात आहे तिथे परिक्षेच्या वेळी बघू नका. मी आता ह्या बारीक टाचण्यांनी तुम्हांला स्पर्श करेन. कृपया, ज्यावेळी तुम्हांला तो स्पर्श जाणवेल त्यावेळेस 'हो' असे म्हणा."

Testing within the control and test site:

MDT - "कृपया, ज्यावेळी तुम्हांला तो स्पर्श जाणवेल त्यावेळेस 'हो' असे म्हणा."

C) Mechanical pain threshold

Familiarization - Demonstration of the test procedure:

MPT - "ही परीक्षा तीक्ष्ण, टोचणे, किंवा इंख ह्यांची ओळख आपल्याला होत आहे की नाही हे सांगू शकेल.
तुमच्या त्वचेवर विविध धातूंच्या छोट्या पिना वेगवेगळ्या दबावाने ठेवल्या जातील.
जेव्हां हा स्पर्श साधा न रहाता तीक्ष्ण, टोचणे, किंवा इंख असा होतो तेव्हां कृपया 'शार्प' असे सांगा.
कृपया जेव्हां साधारण स्पर्श होईल त्यावेळी 'ब्लंट' असे सांगा.
कुठल्याही परिस्थितीत तुमच्या त्वचेच्या ज्या जागी ही परीक्षा होत आहे, तिथे बघू नका."

Testing within the control and test site:

MPT - "जेव्हां हा स्पर्श हलका न रहाता तीक्ष्ण, टोचणे, किंवा इंख असा होतो तेव्हां कृपया 'शार्प' असे सांगा.
कृपया जेव्हां साधारण स्पर्श होईल त्यावेळी 'ब्लंट' असे सांगा."

Continue…

D) S/R (Stimulus/Response) Functions: Mechanical pain sensitivity (MPS) and Dynamic mecahnical allodynica (DMA)

Familiarization - Demonstration of the test procedure:

MPS - "जसे आधीच्या परिक्षेमधे तसे विविध धातूंच्या छोट्या पिना तुमच्या त्वचेवर विविध दाबाचे दाबले जातील."

DMA - "ह्या परिक्षेमधे तुमच्या त्वचेवर, अधूनमधून कापूस, कापूस बड (q tip), किंवा ब्रश दाबले जाईल. ह्यामधील काही उत्तेजक तुम्हांला तीक्ष्ण, टोचणे, डंख किंवा जलजलण्याचा अनुभव देतील. इतर उत्तेजक फक्त हलक्या संवेदनाचा अनुभव देतील आणि काही उत्तेजक शून्य जाणीव देतील.

कृपया प्रत्येक उत्तेजकाला तुमच्या वेदनेनुसार ० ते १०० मध्ये गुणमान द्या. कोणतेही तीक्ष्ण, टोचणे, डंख किंवा जलजलण्याचा अनुभव हे वेदनादायक असे सांगितले जावे आणि त्याचे गुणमान ० च्या वर दिले जावे. तुम्ही दशमान पद्धत वापरू शकता.

० चा अर्थ वेदनाविरहित, न तीक्ष्ण, न टोचणे, न डंख किंवा न जलजलण्याचा असा होतो.

१० चा अर्थ कल्पना करू शकू अशा असह्य वेदनेच्या संवेदना असा होतो.

कुठल्याही परिस्थितीत तुमच्या त्वचेच्या ज्या जागी हे परीक्षण होत आहे, तिथे बघू नका."

(Should the subject/patient give a rating of "100", please ask : 'तुम्हांला खात्री आहे का की ह्या वेदना तुमच्यासाठी असह्य आहेत ?')"

Testing within control and test site:

MPS - "आता पुन्हा कृपया प्रत्येक उत्तेजकाला तुमच्या अनुभवानुसार ० ते १०० मध्ये गुणमान द्या."

DMA - "० चा अर्थ वेदनाविरहित, न तीक्ष्ण, न टोचणे, न डंख किंवा न जलजलण्याचा असा होतो. १०० चा अर्थ कल्पना करू शकू अशा असह्य वेदनेच्या संवेदना असा होतो."

(Should the subject/patient give a rating of "100", please ask : 'तुम्हांला खात्री आहे का की ह्या वेदना तुमच्यासाठी असह्य आहेत ?')"

If applicable : ('मग आपुढे कुठलेही वेदनादायक उत्तेजक वापरण्यात येणार नाही.')

Continue…

E) **Wind - up ratio**

Familiarization - Demonstration of the test procedure:

WUR - "आधीच्या परीक्षणासारखी मी आता एका धातूची छोटी पिन तुमच्या त्वचेवर ठेवेन. कृपया ह्या एका उत्तेजकाने दिलेल्या वेदनेला ० ते १०० मध्ये गुणमान द्या.

कोणतेही तीक्ष्ण, टोचणे, दुंख किंवा जळजळणे अनुभव हे वेदनादायक असे सांगितले जावेत आणि त्याचे गुणमान ० च्या वर दिले जावे. तुम्ही दशमान पद्धत वापरू शकता.

० चा अर्थ वेदनाविरहित, न तीक्ष्ण, न टोचणे, न दुंख किंवा न जळजळणे असा होतो.

१०० चा अर्थ कल्पना करू शकू अशा असह्य वेदनेच्या संवेदना असा होतो."

आता मी एका सेकंदाच्या अंतरावर, हे उत्तेजक दहा वेळा तुमच्या त्वचेवर ठेवेन. ही पूर्ण दहा उत्तेजकांची क्रिया संपल्यावर कृपया ह्या वेदनांचे ० ते १०० ह्या दरम्यान मध्यमान गुणमान करा.

० चा अर्थ वेदनाविरहित, न तीक्ष्ण, न टोचणे, न दुंख किंवा न जळजळणे असा होतो.

१०० चा अर्थ कल्पना करू शकू अशा असह्य वेदनेच्या संवेदना असा होतो."

Testing within the control and test site:

WUR - "आता जी आपण एक उत्तेजक आणि दहा उत्तेजकांची क्रिया केली ती ह्या जागी पाच वेळा करण्यात येईल. कृपया एक उत्तेजक, किती वेदनामय होता त्याचे ० ते १०० ह्या दरम्यान गुणगान करा.

० चा अर्थ वेदनाविरहित, न तीक्ष्ण, न टोचणे, न दुंख किंवा न जळजळणे असा होतो.

१०० चा अर्थ कल्पना करू शकू अशा असह्य वेदनेच्या संवेदना असा होतो."

कृपया धातू उत्तेजक दहा वेळा दाबल्यानंतर त्या वेदनांचे ० ते १०० ह्या दरम्यान मध्यमान गुणमान करा."

F) **Vibration detection threshold**

Familiarization - Demonstration of the test procedure:

VDT - "ही प्रक्रिया तुमची कंपन संवेदना सामर्थतेचे परीक्षण करेल. आता मी कंपन यन्त्र तुमच्या त्वचेवर ठेवेन. तुम्हांला कंपन जाणवत आहे किंवा नाही हे तुम्ही कृपया मला सांगा. कृपया ज्या क्षणाला तुम्हांला कंपन जाणवेनासे होईल त्या क्षणी तुम्ही 'आता' अरो सांगा. तुम्हांला कदाचित कंपनाचा आवाज ऐकू येईल. कृपया तुमचे पूर्ण लक्ष आवाजावर न ठेवता फक्त कंपनावर ठेवा."

Continue…

Testing within the control and test site:

VDT - "आता 3 लागोपाठ परीक्षा घेतली जातील. आता मी कंपन यन्त्र तुमच्या त्वचेवर ठेवेन. तुम्हांला कंपन जाणवत आहे किंवा नाही हे तुम्हीं कृपया मला सांगा.
कृपया ज्या क्षणाला तुम्हांला कंपन जाणवेनासे होईल त्या क्षणी तुम्हीं 'आता' असे सांगा."

G) Pressure pain threshold

Familiarization - Demonstration of the test procedure:

PPT - "ही परीक्षा तुमच्या स्नायूंवरील दबाव वेदना मर्यादाची चाचणी घेईल.
मी दबाव मापन उपकरण तुमच्या स्नायूंवर दाबेन. कृपया ज्यावेळी साधारण दबावावर, जळजळ,इंख,गिरमिट किंवा ठणकणे होऊ लागते त्यावेळी लगेच 'आता' असे सांगा."

Testing within the control and test site:

PPT - "पुन्हां मी दबाव मापन यंत्र तुमच्या स्नायूंवर दाबेन. कृपया ज्यावेळी साधारण दबावावर, जळजळ,इंख,गिरमिट किंवा ठणकणे होऊ लागते त्यावेळी लगेच 'आता' असे सांगा. ही क्रिया तीन वेळा केली जाईल."

Appendix 43. Participant's state of health

Questionnaire for healthy participants _ Template for the investigator
Prof. A Rice Imperial College of Science, Technology and Medicine

Instructions for the investigator: The grey marked answers in the template are not definitive exclusion criteria. However, the investigator should check again by an extensive exploration and an extensive clinical neurological/ internistic examination, if the subject can be enrolled in the study as a "healthy subject".

Questionnaire about the participant's state of health

1. In the past 3 months have you suffered from strong pain, lasting for more than 24 hours?
   - ◻ no
   - ◻ yes, on less than 3 days
   - ◻ yes, on more than 3 days

   a. If yes, what was the reason for your pain (multiple answers possible):
      - ◻ trauma
      - ◻ operation
      - ◻ pain during a flue
      - ◻ period pain
      - ◻ alcohol consumption („hangover")
      - ◻ injury/ aching muscles after sports
      - ◻ other: _____
      - ◻ headache
      - ◻ back pain
      - ◻ stomach ache
      - ◻ painful joints
      - ◻ neuralgia

2. In the last 3 months have you taken medication for your pain?
   - ◻ no
   - ◻ yes, less than 3 tablets/ month
   - ◻ yes, 4-10 tablets/ month
   - ◻ more often

   a. If yes, what was the reason for your medication (multiple answers possible):
      - ◻ trauma
      - ◻ operation
      - ◻ pain during a flue
      - ◻ period pain
      - ◻ alcohol consumption („hangover")
      - ◻ injury/ aching muscles after sports
      - ◻ other: _____
      - ◻ headache
      - ◻ back pain
      - ◻ stomach ache
      - ◻ painful joints
      - ◻ neuralgia

3. Have you ever (more than 3 months ago) suffered from diseases accompanied by long lasting pain (longer than 3 months)?
   - ◻ no
   - ◻ yes

   If yes:

   b. If yes, what was the reason for your pain (multiple answers possible):
      - ◻ trauma
      - ◻ operation
      - ◻ pain during a flue
      - ◻ period pain
      - ◻ alcohol consumption („hangover")
      - ◻ injury/ aching muscles after sports
      - ◻ other: _____
      - ◻ headache
      - ◻ back pain
      - ◻ stomach ache
      - ◻ painful joints
      - ◻ neuralgia

   a. How long time ago did this happen?
      - ◻ 3-12 months ago
      - ◻ 1-3 years ago
      - ◻ 3-5 years ago
      - ◻ 5-10 years ago
      - ◻ more than 10 years ago

Healthy Volunteers Study Version 1.0 <15_02_11>

Continue…

Questionnaire for healthy participants _ Template for the investigator
Prof. A Rice Imperial College of Science, Technology and Medicine

Instructions for the investigator: The grey marked answers in the template are not definitive exclusion criteria. However, the investigator should check again by an extensive exploration and an extensive clinical neurological/ internistic examination, if the subject can be enrolled in the study as a "healthy subject".

4. Have you ever sought professional help for your pain (from a doctor, holicstic therapist, psychiatrist/ psychotherapist, physiotherapist or chiropractor etc)?
   ◻ no ◻ yes

5. In the past 5 years have you had any psychological or psychiatric treatment?
   ◻ no ◻ yes, only for a short time ◻ yes, for a longer period

6. How often have you been signed off work due to pain in the last 3 years?
   ◻ not applicable (i.e. retired or not actively working)
   ◻ never
   ◻ only a couple of days (overall max. 7 days)
   ◻ once (duration max. 7 days)
   ◻ more frequently

7. Do you smoke?
   ◻ no ◻ yes: how much? _____ for how many years? _____
   ◻ not at the moment, but I used to smoke: when did you quit? _____

Instructions for the investigator: If the subject smokes more than 39 cigarettes per day, she/ he should be excluded.

8. How often and how much do you drink alcohol?
   ◻ never ◻ regularly, in moderation
   ◻ occasionally, in moderation ◻ regularly, a lot
   ◻ occasionally, a lot ◻ often, beyond the proper amount

   a. Please specify on average how much exactly you drink alcohol: _____
   _____
   _____
   _____

9. How do you consider your behaviour concerning the intake of medication?
   ◻ I don't take ever medication
   ◻ I take medication only seldom
   ◻ I take medication often
   ◻ I take too much medication

   a. Which medication in what dose have you taken in the last 4 weeks regularly or on demand (on prescription, over the counter and homeopathic/ herbal medication)?

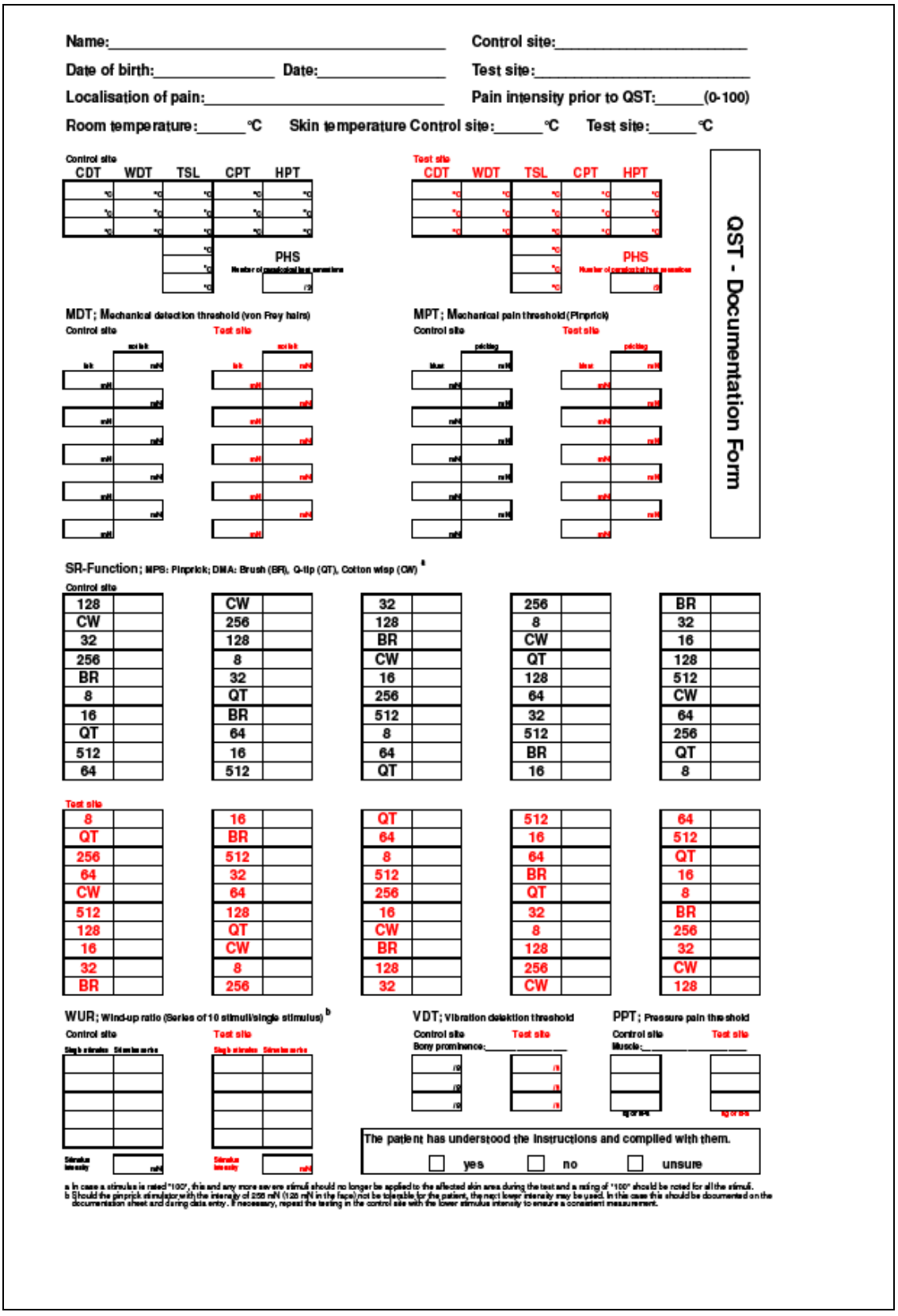
Continue…

Questionnaire for healthy participants _ Template for the investigator
Prof. A Rice Imperial College of Science, Technology and Medicine

Do you suffer from any other illnesses or disorders? In the table below are groups of conditions including examples. Please underline any of these which apply. Then please indicate how much this condition interferes with your everyday life where 0 implies no interference and 3 represents a high degree of interference.

Tumour, cancer Which condition:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Disorder of the nervous system, brain, or spinal cord eg. Epilepsy, MS, Parkinsons, nerve injury, polyneuropathy, spinal cord injury, paralysis, neuralgia, stroke, cranial nerve injury Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Disorder of the respiratory system e.g. Asthma, chronic bronchitis, emphysems, pneumothorax, tuberculosis or inflammation of the lungs Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Disorder of the heart or circulatory system e.g. Coronary heart disease, coronary arrhythmia, thrombosis, embolism, aneurysm, high blood pressure, myocardial infarction Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Gastrointestinal disorder e.g. Gastric reflux disorder, Crohn's disease, ulcerative colitis, haemmorrhoids, incontinence of faeces, duodenal ulcers, irritable bowel syndrome, incidence of stomach or intestinal haemorrage Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Disorder of the liver, gall bladder or pancreas e.g. chronic inflammation of the liver (=hepatitis), cirrhosis of the liver, gall stones, gall bladder inflammation, pancreatic inflammation Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Disorder of the kidneys or urinary system e.g. chronic kidney failure, urinary tract inflammation, bladder weakness, endometriosis, condition following renal colic or kidney stones, sexual disturbance Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Metabolic disorder e.g. Disrupted sugar metabolism, hyper- or hypo- glandular function, elevated blood lipid values Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Muculoskeletal disorder e.g. Chronic polyarthritis, rheumatic muscular inflammation, scoliosis, osteoporosis, arthritis in the knee, hip or shoulder Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Mental health disorder e.g. Depression, clinical anxiety, panic attacks, anorexia, chronic fatigue and exhaustion, addiction or dependence, psychosis Other:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Other disorders or conditions:	□ yes	□ no		
	No [0]	Interference [1]	[2]	High degree [3]
Risk factors e.g. Haemophilia, hepatitis, HIV Other:	□ yes	□ no		
Allergies e.g. Plasters, house dust, domestic/ cleaning products, cosmetics, pollen	□ yes	□ no		

Appendix 44. Recording sheet for QST



Name:_____ Control site:_____

Date of birth:_____ Date:_____ Test site:_____

Localisation of pain:_____ Pain intensity prior to QST:_____(0-100)

Room temperature:_____°C Skin temperature Control site:_____°C Test site:_____°C

Control site

CDT	WDT	TSL	CPT	HPT
°C	°C	°C	°C	°C
°C	°C	°C	°C	°C
°C	°C	°C	°C	°C
		°C		
		°C	PHS	
		°C	Number of paradoxical heat sensations	
			/9	

Test site

CDT	WDT	TSL	CPT	HPT
°C	°C	°C	°C	°C
°C	°C	°C	°C	°C
°C	°C	°C	°C	°C
		°C		
		°C	PHS	
		°C	Number of paradoxical heat sensations	
			/9	

QST - Documentation Form

MDT; Mechanical detection threshold (von Frey hairs)

Control site

	mN
lok	mN
mN	mN
mN	mN
mN	mN
mN	mN
mN	

Test site

	mN
lok	mN
mN	mN
mN	mN
mN	mN
mN	mN
mN	

MPT; Mechanical pain threshold (Pinprick)

Control site

	mN
picklig	
Mue	mN
mN	mN
mN	mN
mN	mN
mN	mN
mN	

Test site

	mN
picklig	
Mue	mN
mN	mN
mN	mN
mN	mN
mN	mN
mN	

SR-Function; MPS: Pinprick; DMA: Brush (BR), Q-tip (QT), Cotton wisp (CW) [a]

Control site

128	
CW	
32	
256	
BR	
8	
16	
QT	
512	
64	

CW	
256	
128	
8	
32	
QT	
BR	
64	
16	
512	

32	
128	
BR	
CW	
16	
256	
512	
8	
64	
QT	

256	
8	
CW	
QT	
128	
64	
32	
512	
BR	
16	

BR	
32	
16	
128	
512	
CW	
64	
256	
QT	
8	

Test site

8	
QT	
256	
64	
CW	
512	
128	
16	
32	
BR	

16	
BR	
512	
32	
64	
128	
QT	
CW	
8	
256	

QT	
64	
8	
512	
256	
16	
CW	
BR	
128	
32	

512	
16	
64	
BR	
QT	
32	
8	
128	
256	
CW	

64	
512	
QT	
16	
8	
BR	
256	
32	
CW	
128	

WUR; Wind-up ratio (Series of 10 stimuli/single stimulus) [b]

Control site

Sing le stimulus	Stimulus series
Stimulus intensity	mN

Test site

Sing le stimulus	Stimulus series
Stimulus intensity	mN

VDT; Vibration detektion threshold

Control site

Bony prominence:_____	
/9	
/9	
/9	

Test site

/9	
/9	
/9	

PPT; Pressure pain threshold

Control site

Muscle:_____	
kg or kPa	

Test site

kg or kPa	

The patient has understood the instructions and complied with them.

☐ yes ☐ no ☐ unsure

a In case a stimulus is rated "100", this and any more severe stimuli should no longer be applied to the affected skin area during the test and a rating of "100" should be noted for all the stimuli.
b Should the pinprick stimulator with the intensity of 256 mN (128 mN in the face) not be tolerable for the patient, the next lower intensity may be used. In this case this should be documented on the documentation sheet and during data entry. If necessary, repeat the testing in the control site with the lower stimulus intensity to ensure a consistent measurement.

Appendix F

Publications and Presentations

Appendix 45. Publications and Presentations

Poster presentations

- **Neuropathic pain in treated leprosy patients in Ethiopia: a cross-sectional study**.
  14th World Congress on Pain, Milan, Italy August 27th – 31st, 2012
  Haroun OMO, Hietaharju A, Bizuneh E, Tesfaye F, Brandsma J.W, Haanpää M, Rice A.S.C, Lockwood D.N.J
- **Quantitative Sensory Testing Profiles in Leprosy Patients in Mumbai-India**.
  4th International Congress on Neuropathic Pain, Toronto, Canada May 23rd – 26th, 2013
  Haroun OMO, Pai VV, Shetty V, Pfau D, Bennett DLH, Maier C, Treede R-D, Rice ASC, Lockwood D.N.J
- **Neuropathic Pain in Leprosy Patients in Mumbai: A case control study**.
  18th International Leprosy Congress, Brussels, Belgium September 16th – 19th, 2013
  Haroun OMO, Khodke AS, Pai V, Shetty V, Pfau D, Bennett D, Maier C, Treede R-D, Rice ASC, Lockwood D.N.J

Accepted talk presentations

- **Symptom and quantitative sensory profiling in Leprosy patients with and without neuropathic pain: a case control study**.
  29th Biennial Conference of Indian Association of Leprologists on March 28-30, 2014 (cancelled)
- **Sensory profiling and nerve damage in Leprosy patients with and without neuropathic pain: insights into mechanisms of disease**.
  15th World Congress on Pain, Buenos Aires, Argentina, October 6-11, 2014.

Publications

- In process of submitting a manuscript titled "Comparability of detection and pain thresholds in different approaches: Approaches to simplify the DFNS QST protocol"

Appendix G

Others

Appendix 46. Univaiate logistic regression – Neuropathic pain

Independent variables	Proportion in the sample	Cases (%)	Odds ratio & (95% CI)	P. value
Skin lesions 1st symptoms				
No	28 (76.67%)	12 (46.15%)	1	**0.05**
Yes	62 (68.89%)	14 (53.85%)	0.38 (0.15–1.04)	
Burning 1st symptoms				
No	86 (95.55%)	23 (88.46%)	1	**0.04**
Yes	4 (44.45%)	3 (11.54%)	1.19 (0.17–2.86)	
Delay in presentation				
up to 6 month	44 (48.89%)	16 (61.59%)	1	**<0.001**
>6 months up to 1 year	11 (12.22%)	6 (23.08%)	1.22 (0.37–3.93)	
>1 year	35 (38.89%)	4 (15.83%)	0.13 (0.05–0.37)	
Diagnosis				
Newly diagnosed case	28 (31.11%)	2 (7.14%)	1	**<0.001**
Old case	62 (68.89%)	24 (38.17%)	8.21 (1.62–41.55)	
Duration of disease				
<6 months	11 (12.22%)	4 (36.36%)	1	**0.05**
6 months up to 1 year	12 (13.33%)	6(50.00%)	1.57 (0.33–9.30)	
>1 year up to 5 years	40 (44.44%)	29 (74.36%)	5.07 (1.22–21.06)	
>5 years	27 (30.00%)	20 (74.07%)	4.99 (1.12–22.41)	
Disability at diagnosis				
Absent	54 (60.00%)	9 (16.67%)	1	**<0.001**
Grade 1	24 (26.67%)	13 (54.17%)	2 (0.62–16.11)	
Grade 2	12 (13.33%)	29 (82.86%)	3.87 (1.31–11.38)	
On MDT treatment				
No	18 (20.00%)	1 (5.56%)	1	0.006
Yes	72 (20.00%)	25 (34.72%)	9 (1.04–78.31)	

Independent variables	Proportion in the sample	Cases (%)	Odds ratio & (95% CI)	P. value
Release from MDT				
No	44 (48.89 %)	39 (61.90%)	1	**<0.001**
Yes	46 (51.11 %)	20 (76.92%)	2 (1.71–5.92)	
Previous MDT				
No	65 (72.11 %)	14 (57.69%)	1	**0.05**
Yes	26 (27.78 %)	11 (42.31%)	2.6 (0.96–7.16)	
Leprosy reactions				
No	64 (71.11 %)	14 (53.85%)	1	**0.02**
Yes	26 (28.89 %)	20 (46.15%)	3 (1.12–8.39)	
Previous reaction				
No	50 (55.56%)	8 (30.77%)	1	**<0.001**
Yes	40 (44.45%)	18 (69.23%)	4 (1.51–12.14)	
No. of previous reactions				
0	50 (55.56%)	8 (30.77)	1	**0.04**
1-3	35 (38.89%)	17 (65.38%)	1.3 (0.13–13.34)	
>3	5 (5.56%)	1 (3.85%)	4.9 (1.81–13.55)	
Depression				
Absent	30 (33.71)	2 (7.69%)	1	**<0.001**
Present	59 (66.29)	24 (92.31%)	9.59 (2.08–44.14)	

Appendix 47. Multivariate logistic regression – Neuropathic pain

Variables	Crude OR& CI	Adjusted OR & CI	P. value
Depression			
Absent	1	1	**0.01**
Present	9.59 (2.08–44.14)	8 (1.17–33.68)	
Previous reactions			
No	1	1	0.07
Yes	4 (1.51–12.14)	3 (0.92 –9.11)	
Leprosy reactions			
Absent	1	1	0.4
Present	3 (1.12–8.39)	2 (0.50–5025)	

† Multivariate logistic regression of the association between variables and neuropathic pain

Appendix 48. Univaiate logistic regression – Depression

Independent variables	Proportion in the sample	Proportion with GHQ threshold score >3	Odds ratio & (95% CI)	P. value
Estimates of association between GHQ caseness and socio-demographic variables				
Sex				
Male	69 (76.67%)	44 (63.77%)	1	0.35
Female	21 (23.33%)	15 (75.00%)	1.70 (0.38–5.31)	
Age group				
<30 years	43 (47.78%)	27 (45.76%)	1	0.71
>30 years	47 (52.22%)	32 (54.24%)	1.19 (0.17–2.86)	
Education				
Illiterate	14 (15.56%)	9 (64.29%)	1	**0.04**
Primary	50 (55.56%)	37 (75.51%)	1.71 (0.48–6.11)	
Secondary	11 (12.22%)	3 (27.27%)	0.21 (0.04–1.16)	
High secondary	7 (7.78%)	4 (57.14%)	0.74 (0.12–4.73)	
College and above	8 (8.89%)	6 (75.00%)	0.74 (0.24–11.58)	
Marital status				
Married	60 (66.67%)	40 (67.80%)	1	0.67
Unmarried/widowed	30 (33.33%)	19 (63.33%)	1.22 (0.48–3.08)	
Estimates of association between GHQ caseness and clinical features				
Delay in presentation				
up to 6 month	44 (48.89%)	15 (62.50%)	1	**0.001**
>6 months up to 1 year	11 (12.22%)	12 (85.71%)	3.6 (0.65–19.90)	
>1 year	35 (38.89%)	32 (97.50%)	7.6 (2.72–20.90)	
Diagnosis				
Newly diagnosed case	28 (31.11%)	13 (46.43%)	1	**0.007**
Old case	62 (68.89%)	46 (75.41%)	3.54 (1.31–9.53)	

Independent variables	Proportion in the sample	Proportion with GHQ threshold score >3	Odds ratio & (95% CI)	P. value
Duration of disease				
<6 months	11 (12.22%)	4 (36.36%)	1	**0.05**
6 months up to 1 year	12 (13.33%)	6(50.00%)	1.57 (0.33–9.30)	
>1 year up to 5 years	40 (44.44%)	29 (74.36%)	5.07 (1.22–21.06)	
>5 years	27 (30.00%)	20 (74.07%)	4.99 (1.12–22.41)	
WHO classification				
MB	57 (63.33%)	40 (71.43%)	1	0.18
PB	33 (36.67%)	19 (57.58)	1.84 (0.73–4.60)	
Disability at diagnosis				
Absent	54 (60.00%)	6 (17.14%)	1	**0.001**
Present	36 (40.00%)	29 (82.86%)	3.87 (1.31–11.38)	
On MDT treatment				
No	18 (20.00%)	7 (38.89%)	1	**0.006**
Yes	72 (20.00%)	52 (73.24%)	4.3 (1.38–13.44)	
Leprosy reactions				
No	46 (71.11 %)	39 (61.90%)		0.17
Yes	26 (28.89 %)	20 (76.92%)	2.05 (0.71–5.92)	
Previous reaction				
No	50 (55.56%)	32 (80.00 %)	1	**0.02**
Yes	40 (44.45%)	36 (90.00%)	2.25 (1.13–8.21)	
No. of previous reactions				
0	50 (55.56%)	28 (56.00%)	1	0.06
1-3	35 (38.89%)	27 (79.41%)	3.03 (1.11–8.24)	
>3	5 (5.56%)	4 (80.00%)	3.14 (0.33–30.19)	

Independent variables	Proportion in the sample	Proportion with GHQ threshold score >3	Odds ratio & (95% CI)	P. value
Skin lesion O/E				
No skin lesion	20 (22.22%)	16 (84.21%)	1	0.06
Skin lesion	70 (77.78%)	43 (61.43%)	0.30 (0.08–1.16)	
Motor nerve impairment				
Absent	43 (47.78)	23 (53.49%)	1	**0.01**
Present	47 (52.22)	36 (78.26%)	3.13 (1.20–8.18)	
Ulnar neuropathy				
Absent	48 (53.33%)	25 (52.08%)	1	**0.001**
Present	42 (46.67%)	34 (82.93%)	4.46 (1.55–12.82)	
Sensory nerve impairment				
Absent	39 (43.33%)	22 (56.41%)		0.08
Present	51 (56.67%)	37 (74.00%)	2.20 (0.88–5.49)	
Clinical evidence of neuropathy				
Absent	36 (40%)	20 (55.56%)	1	0.07
Present	54 (60%)	39 (73.58%)	2.22 (0.88–5.58)	
Disability (current)				
Absent	40 (44.44%)	22 (55.00%)	1	**0.04**
Present	50 (55.56%)	37 (75.51%)	2.52 (1.00–6.38)	
Estimates of association between GHQ caseness and pain				
Current pain				
Absent	54 (60.00%)	29 (54.72%)		**0.005**
Present	36 (40.00%)	30 (83.33%)	4.14 (1.40–12.24)	

Independent variables	Proportion in the sample	Proportion with GHQ threshold score >3	Odds ratio & (95% CI)	P. value
Burning sensation				
Absent	67 (74.44%)	39 (59.09 %)		**0.01**
Present	23 (25.56%)	20 (86.96%)	4.62 (1.18–18.03)	
Electric shocks				
Absent	64 (71.11%)	35 (55.560 %)	1	**0.001**
Present	26 (28.89)	24 (92.31%)	9.60 (1.86–49.50)	
Tingling sensation				
Absent	58 (64.44%)	32 (56.14%)	1	0.007
Present	32 (35.56%)	36 (84.38%)	4.22 (1.35–13.22)	
Pins and needles sensation				
Absent	71 (78.89%)	42 (60.00%)		**0.01**
Present	19 (21.11%)	17 (89.47%)	5.66 (1.14–28.15)	
Numbness sensation				
Absent	69 (76.67%)	40 (58.82%)	1	0.007
Present	21 (23.33%)	19 (90.48%)	6.65 (1.33–33.27)	
Neuropathic pain				
Absent	64 (71.11%)	35 (55.56%)		**0.001**
Present	26 (28.89%)	24 (92.31%)	9.60 (1.86–49.50)	
Non-NP pain				
Absent	80 (88.89%)	53 (67.09%)	1	0.66
Present	10 (11.11%)	6 (60.00%)	1.07 (0.20–5.59)	
Pain				
Absent	54 (60.00%)	29 (54.72%)	1	**0.001**
Non-neuropathic pain	10 (11.11%)	6 (60.00%)	1.24 (0.31–4.91)	
Neuropathic pain	26 (28.89%)	24 (92.31%)	9.93 (2.12–46.35)	

Appendix 49. Multivariate logistic regression – Depression

Variables	Crude OR& CI	Adjusted OR & CI	P. value
Neuropathic pain			
Absent	1	1	**0.03**
Present	9.60 (1.86–49.50)	6.25 (1.17–33.57)	
Motor nerve impairment			
Absent	1	1	0.09
Present	3.13 (1.20–8.18)	4.21 (0.79–22.50)	
Skin lesion O/E			
Absent	1	1	0.20
Present	3.43 (0.08–1.16)	0.38 (0.85–1.68)	
On MDT treatment			
No	1	1	0.21
Yes	4.30 (1.38–13.44)	2.61 (0.58–11.98)	
Sensory nerve impairment			
Absent	1	1	0.28
Present	3.20 (0.88–5.49)	0.38 (0.07–2.15)	
Disease duration			
<1 year	1	1	0.36
>1 year	3.75 (1.32–10.61)	1.80 (0.51–6.42)	
Education			
Literate	1	1	0.51
Illiterate	1.11 (0.33–3.69)	0.61 (0.15–2.57)	
Disease diagnosis			
New case	1	1	0.83
Old case	3.54 (1.31–9.23)	0.86 (0.21–3.57)	

† Multivariate logistic regression of the association between variables and depression outcome

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Appendix 50. Pain-related definitions (IASP Taxonomy, 2014)

Pain-related definitions (IASP)

Allodynia: Pain due to a stimulus which does not normally provoke pain.

Analgesia: Absence of pain in response to stimulation which would normally be painful.

Anesthesia dolorosa: Pain in an area or region which is anesthetic.

Causalgia: A syndrome of sustained burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked.

Hyperalgesia: An increased response to a stimulus which is normally painful.

Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses.

Hyperpathia: A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Hypoalgesia: Diminished pain in response to a normally painful stimulus.

Hypoesthesia: Decreased sensitivity to stimulation, excluding the special senses.

Neuralgia: Pain in the distribution of a nerve or nerves.

Neuritis: Inflammation of a nerve or nerves.

Neuropathic Pain: Pain caused by a lesion or disease of the somatosensory nervous system

Neuropathy: A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

Nociceptor: A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli.

Nociceptive pain: Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

Noxious stimulus: A stimulus that is damaging or threatens damage to normal tissues.

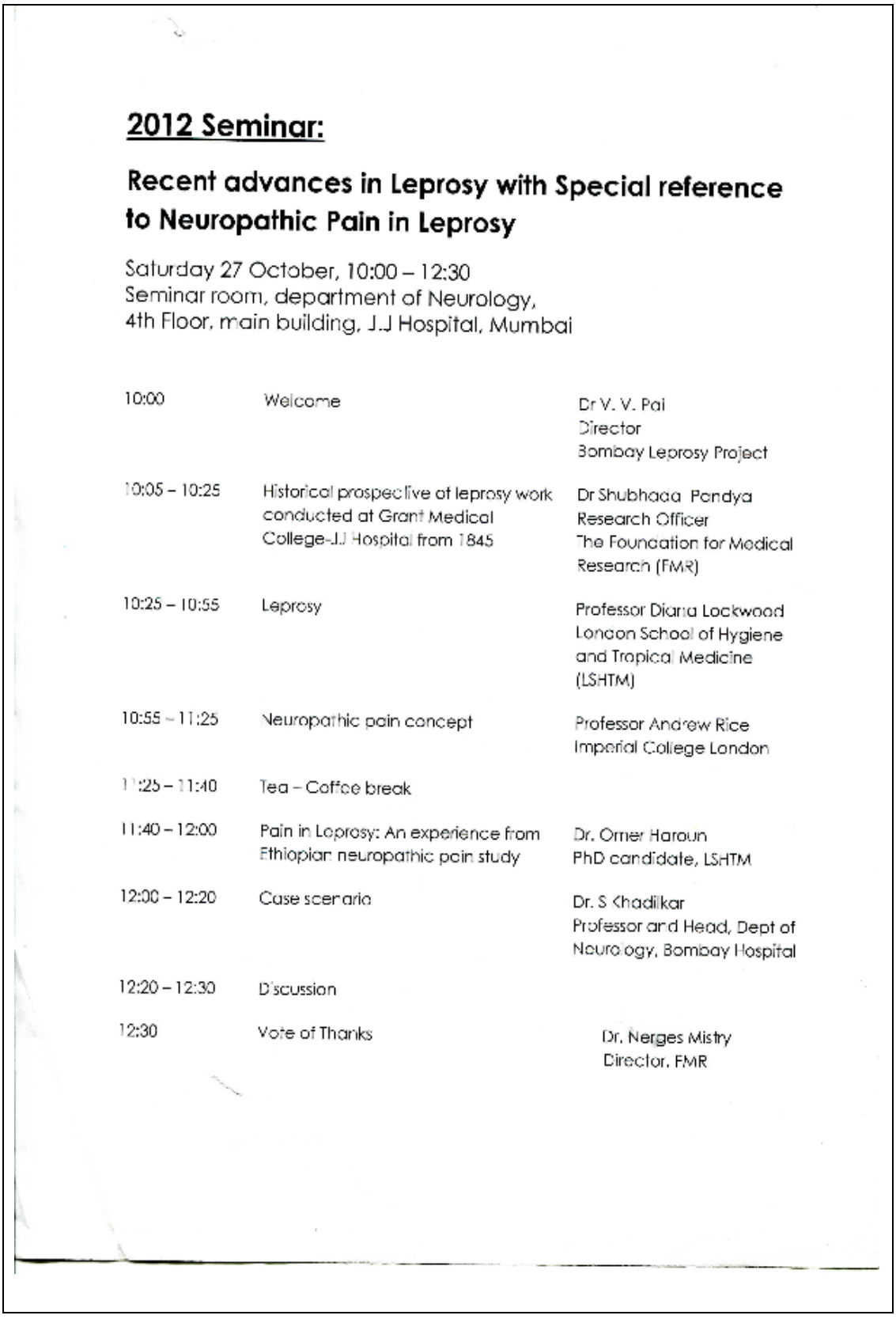
Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Pain Threshold: The minimum intensity of a stimulus that is perceived as painful.

Pain tolerance level: The maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation.

Paresthesia: An abnormal sensation, whether spontaneous or evoked.

Appendix 51. Neuropathic pain workshop – Mumbai



2012 Seminar:

Recent advances in Leprosy with Special reference to Neuropathic Pain in Leprosy

Saturday 27 October, 10:00 – 12:30
Seminar room, department of Neurology,
4th Floor, main building, J.J Hospital, Mumbai

10:00	Welcome	Dr V. V. Pai Director Bombay Leprosy Project
10:05 – 10:25	Historical prospective of leprosy work conducted at Grant Medical College-J.J Hospital from 1845	Dr Shubhada Pandya Research Officer The Foundation for Medical Research (FMR)
10:25 – 10:55	Leprosy	Professor Diana Lockwood London School of Hygiene and Tropical Medicine (LSHTM)
10:55 – 11:25	Neuropathic pain concept	Professor Andrew Rice Imperial College London
11:25 – 11:40	Tea – Coffee break	
11:40 – 12:00	Pain in Leprosy: An experience from Ethiopian neuropathic pain study	Dr. Omer Haroun PhD candidate, LSHTM
12:00 – 12:20	Case scenario	Dr. S Khadilkar Professor and Head, Dept of Neurology, Bombay Hospital
12:20 – 12:30	Discussion	
12:30	Vote of Thanks	Dr. Nerges Mistry Director, FMR

Appendix 52. DFNS-QST translation – Mumbai

AVENUE DIGITALS

Unit 1 & 2, Ground Floor, Vasan Eureka Bldg, Opp. Phoenix Mills, Senapati Bapat Marg, Lower Parel, Mumbai - 400 013. Tel : 2493 0224 / 2498 2057 / 6660 4455 Fax : 6660 4478
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Date 28 Sep 2017

To,
THE FOUNDATION FOR MEDICAL RESEARCH
84-A, R. G. THADANI MARG, WORLI,
MUMBAI - 400 018, INDIA.
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Document Translated : QST-instructions - Appendix - General Instructions for the volunteers/patients:

To Whom It May Concern:

This is to certify that Avenue Digitals has translated the QST-instructions - Appendix - General Instructions for the volunteers/patients document from Hindi - Marathi to English

The list of writers who have done the translations are as follows:

Serial No.	Name	Language (..... to English)
1.	Satyaprakash Mishra	Hindi
2.	Vinay Upasani	Marathi

Note: We will have not seen the original English document of QST instructions..

We confirm that the translation of QST-instructions - Appendix - General Instructions for the volunteers/patients document from hindi to english & marathi to English as specified above are to the best of our knowledge accurate and true translations from English.

Your's Sincerely,
For Avenue Digitals

(Ashwin Maheshwari)

Appendix 53. Studies on amitriptyline for the treatment of neuropathic pain

Condition	Authors, year	Study design	No of participants	Intervention	Duration	Primary outcome	Secondary outcome	Conclusion
Diabetes Mellitus (DM)	Max *et al.* 1987 (Max, 1987)	Double-blind, randomised placebo crossover study	29 patients	Amitriptyline (average 90mg) vs placebo	6 weeks	VAS pain intensity	HDS, POMS-D and DACL	Amitriptyline was superior to placebo
	Max *et al.* 1992 (Max et al., 1992)	Double-blind, randomised placebo crossover study	38 patients	Amitriptyline (average 105mg) vs desipramine (average 111mg) vs placebo	6 weeks	Rating pain intensity	Hamilton Depression Scale (HDS)	Amitriptyline was superior to placebo Similar effects of the amitriptyline & desipramine
	Verthem *et al.* 1997 (Vrethem et al., 1997)	Double-blind, randomised placebo crossover study	37 patients (33 completed)	Amitriptyline (75mg) vs maprotiline vs placebo	4 weeks	Pain relief scale	Comprehensive Psychological Pain Scale (CPRS)	Amitriptyline was superior to placebo
Post Herpetic Neuralgia (PHN)	Watson *et al.* 1985 (Watson and Evans, 1985)	Open-label cross-over	15 patients	Amitriptyline vs zimelidine	6 weeks	Pain relief scale	Depression	Amitriptyline was superior to Zimelidine
	Watson *et al.* 1992 (Watson et al., 1992)	Randomised, double-blind, crossover	35 patients	Amitriptyline vs maprotiline	6 weeks	Pain relief scale	Depression	Amitriptyline was superior to maprotiline
	Watson *et al.* 1998 (Watson et al., 1998)	Randomised, double-blind, crossover	33 patients (31 finished)	Amitriptyline vs nortriptyline	6 weeks	VAS pain intensity	Mood and satisfaction	Similar effects of the amitriptyline & nortript
	Radford *et al.* 2000 (Graff-Radford et al., 2000)	Double-blind, placebo-controlled, parallel study	49 patients	Amitriptyline	8 weeks	VAS pain intensity	MPQ and side-effects scale	Amitriptyline was superior to placebo
	Rowbotham *et al.* 2005 (Rowbotham et al., 2005)	Randomised, double-blind, parallel design	38 patients	Amitriptyline 150 mg vs imipramine 150mg vs fluoxetine 60mg	6 weeks	VAS pain intensity	Pain relief scale, BDI and QST	Similar effects of the three drugs

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Condition	Authors, year	Study design	No of participants	Intervention	Duration	Primary outcome	Secondary outcome	Conclusion
Phantom limb pain	Robinson *et al.* 2004 (Robinson et al., 2004)	Randomised, controlled, parallel trial	39 patients	Amitriptyline 10-125 mg vs placebo	6 weeks	NRS pain intensity	SF-MPQ, BPI interference scale	Similar effects of the amitriptyline and placebo
HIV/AIDS	Kieburtz *et al.* 1998 (Kieburtz et al., 1998)	Randomised, double-blind, parallel design	145 patients	Amitriptyline 25-100 mg vs. Mexiletine vs placebo	10 weeks	Gracely Pain Score (GP): The change in pain intensity at baseline and week 10		Neither Amitriptyline nor mexiletine provides significant pain relief in HIV neuropathy
	Shly JC *et al.* 1998 (Shlay et al., 1998)	Randomised, placebo controlled, parallel design	136 patients	Amitriptyline 25-75 mg (n=71) vs. Placebo (n=65)	14 weeks	Changes in mean pain score at base line & wk 14	Quality of life assessment	Amitriptyline was not more effective than placebo in relieving pain in HIV neuropathy
Chemotherapy induced neuropathy	Kautio *et al.* 2008	Double-blind, randomised, placebo-controlled, parallel design	44 patients (33 completed the study)	Amitriptyline 50mg vs placebo	8 weeks	Numerical rating pain intensity	Severity of mood, sleep and QOL: QOL, STAI and NPSI	Amitriptyline was superior to placebo
Malignancy neuropathic pain	Mercadante *et al.* 2002 (Mercadante et al., 2002)	Double-blind, randomised placebo crossover study	16 patients	Amitriptyline 50mg vs placebo	7 days	NRS pain intensity	Spitzer's QOL index, sleep, mood (NRS)	Amitriptyline was the same as placebo
Central post stroke pain	Leijon *et al.* 1989 (Leijon and Boivie, 1989)	Randomised placebo crossover study	15 patients	Amitriptyline 75mg vs. placebo	4 weeks	VRS pain intensity	Global rating scale and CPRS	Amitriptyline was superior to placebo
Spinal cord injury pain	Cardenas *et al.* 2002 (Cardenas et al., 2002)	Randomised, double-blind, parallel design	84 patients	Amitriptyline 125mg vs. placebo	6 week	NRS pain intensity	BPI, short form McGill pain qs.	Similar effects of the amitriptyline & placebo
Post mastectomy	Kalso *et al.* 1996 (Kalso et al., 1996)	Crossover study	15 patients	Amitriptyline 100mg vs. placebo	4 weeks	VAS and VRS pain relief	Anxiety and depression	Amitriptyline was superior to placebo

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Appendix 54. Thesis timeline

	Year																
	2010	**2011**				**2012**				**2013**				**2014**			
Quarter	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th	1st	2nd	3rd	4th
Planning and literature review																	
Refinement of PHD objectives																	
Study protocols																	
QST training and validation studies																	
Ethical approvals																	
Upgrading exam																	
Recruitment																	
Data Analysis																	
Thesis Writing																	
Submission																	
Viva																	